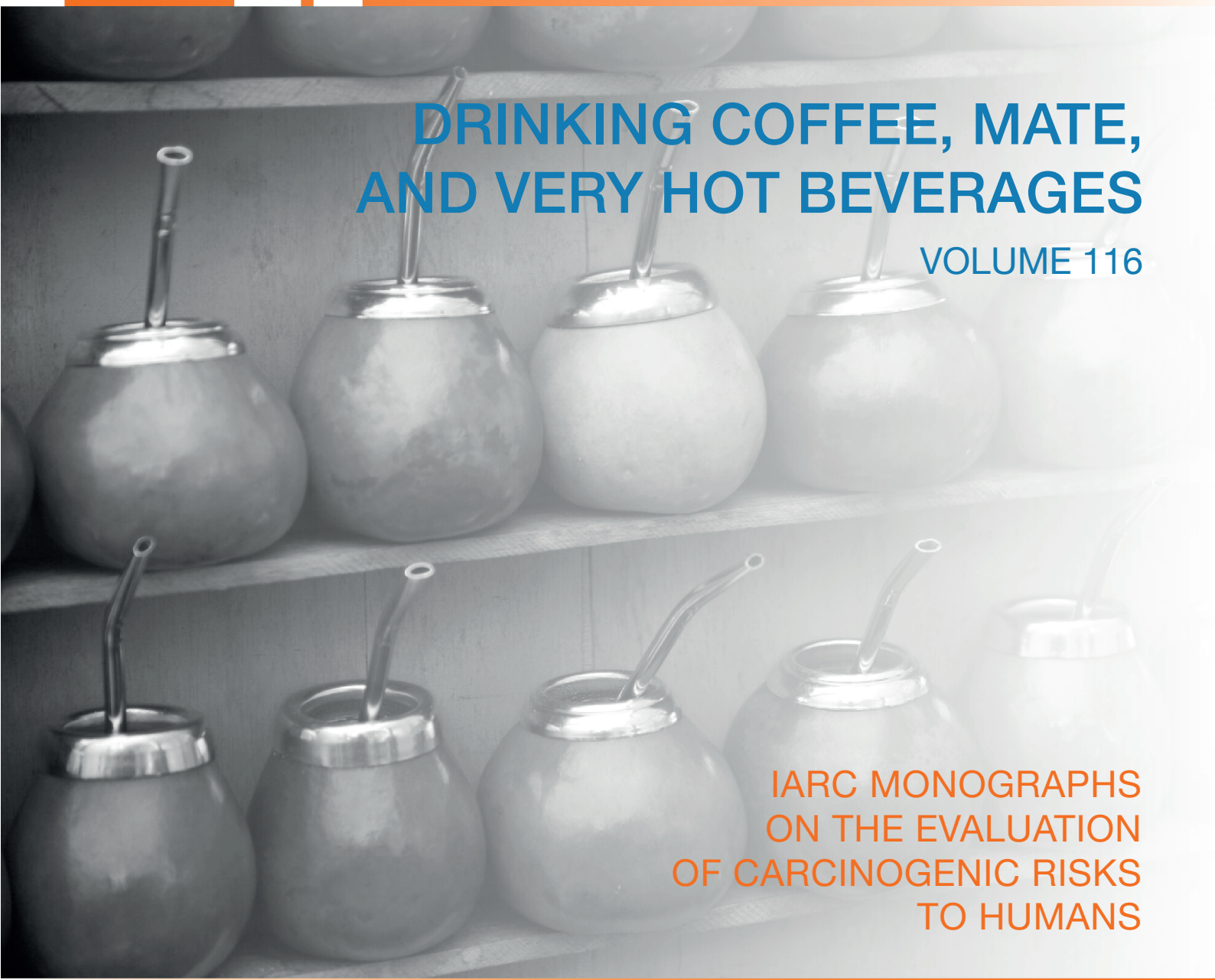
IARC MONOGRAPHS



DRINKING COFFEE, MATE, AND VERY HOT BEVERAGES

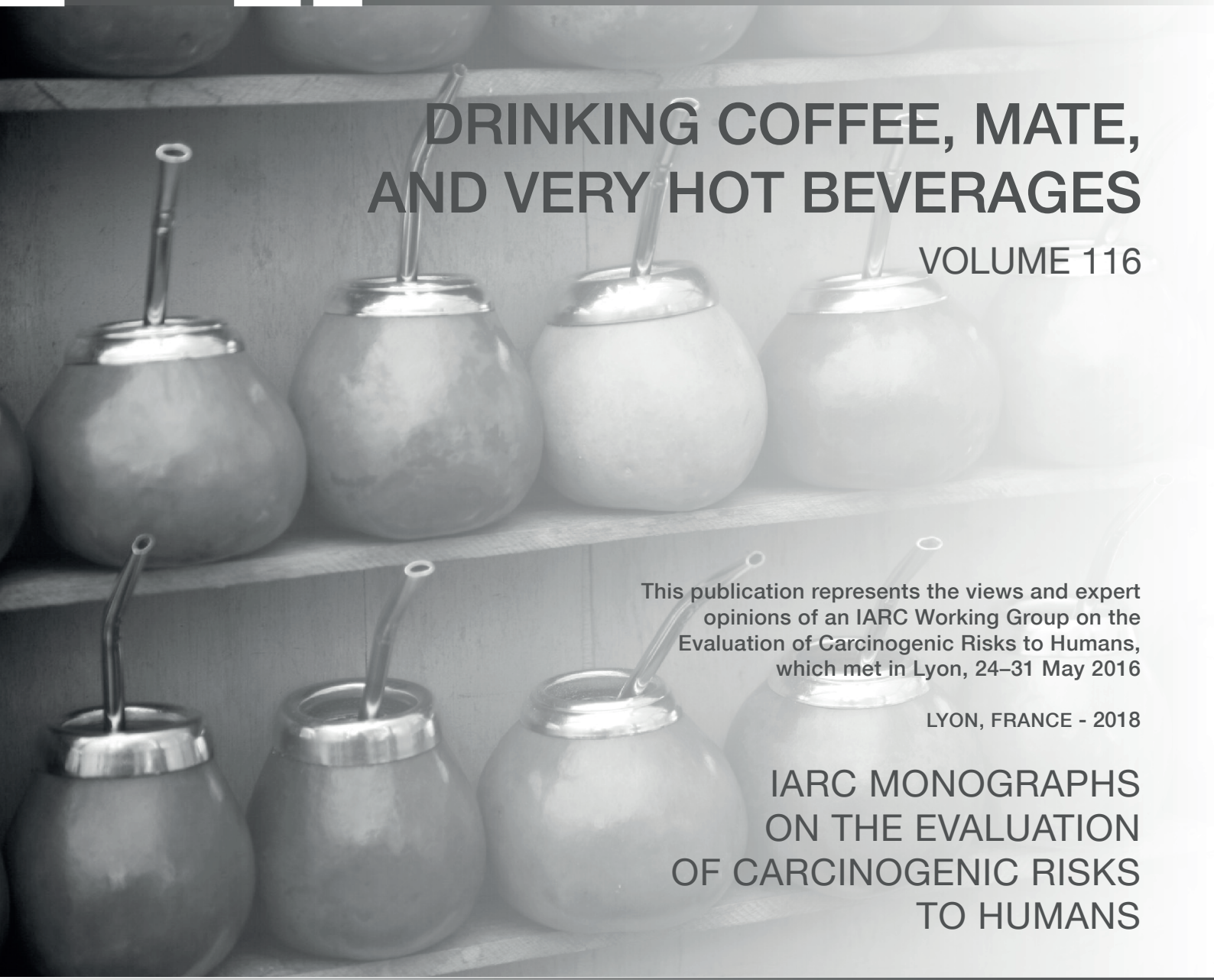
VOLUME 116

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS



DRINKING COFFEE, MATE, AND VERY HOT BEVERAGES

VOLUME 116

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 24–31 May 2016

LYON, FRANCE - 2018

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the European Commission Directorate-General for Employment, Social Affairs, and Inclusion, initially by the Unit of Health, Safety and Hygiene at Work, and since 2014 by the European Union Programme for Employment and Social Innovation "EaSI" (2014–2020) (for further information please consult: http://ec.europa.eu/social/easi). Support has also been provided since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the United States National Cancer Institute, the United States National Institute of Environmental Health Sciences, the United States Department of Health and Human Services, or the European Commission.

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

On-line publication, 13 June 2018

Distributed by WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel.: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int).

Corrigenda to the IARC Monographs are published online at http://monographs.iarc.fr/ENG/Publications/corrigenda.php
To report an error, please contact: editimo@iarc.fr

Co-funded by the European Union

IARC Library Cataloguing in Publication Data

Drinking coffee, mate, and very hot beverages / IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2016: Lyon, France)

(IARC monographs on the evaluation of carcinogenic risks to humans ; volume 116)

1. Carcinogens 2. Coffee – adverse effects 3. Ilex paraguariensis – adverse effects 4. Beverages – adverse effects 5. Hot Temperature – adverse effects 6. Risk Factors

I. International Agency for Research on Cancer II. Series

ISBN 978-92-832-0183-0 (NLM Classification: W1)
ISSN 1017-1606

CONTENTS

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Monographs* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

LIST OF PARTICIPANTS

Members [1]

Christina Bamia

Dept of Hygiene, Epidemiology and Medical Statistics, Medical School
National and Kapodistrian University of Athens
Athens
Greece

John A. Baron

Dept of Medicine and Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC
USA

Natasa Djordjevic

Dept of Pharmacology and Toxicology
University of Kragujevac
Kragujevac
Serbia

Adriana Farah

Nutrition Institute, Centre of Health Sciences
Federal University of Rio de Janeiro
Rio de Janeiro
Brazil

Elvira Gonzalez de Mejia

Dept of Food Science and Human Nutrition
University of Illinois
Urbana, IL
USA

[1] Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only. Invited Specialists do not serve as Meeting Chair or Subgroup Chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.
Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 4 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US$ 1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

Peter C. Hollman

Division of Human Nutrition
Wageningen University
Wageningen
The Netherlands

Manami Inoue

Dept of Health and Human Security
Graduate School of Medicine
University of Tokyo
Tokyo
Japan

Farhad Islami (unable to attend)

Surveillance and Health Services Research
American Cancer Society
Atlanta, GA
USA

Charles William Jameson

CWJ Consulting, LLC
Cape Coral, FL
USA

Farin Kamangar

Dept of Public Health Analysis
School of Community Health and Policy
Morgan State University
Baltimore, MD
USA

Siegfried Knasmüller

Institute of Cancer Research
Medical University of Vienna
Vienna
Austria

Dirk W. Lachenmeier (Subgroup Chair, Exposure Data)

Chemical and Veterinary Investigation Agency
Karlsruhe
Karlsruhe
Germany

David L. McCormick (Subgroup Chair, Cancer in Experimental Animals)

Illinois Institute of Technology Research Institute
Chicago, IL
USA

Elizabeth Milne

Cancer Epidemiology Group
Telethon Kids Institute
West Perth, WA
Australia

Igor Pogribny

Division of Biochemical Toxicology
National Center for Toxicological Research
Jefferson, AR
USA

Luis Felipe Ribeiro Pinto

Brazilian National Cancer Institute (INCA)
Rio de Janeiro
Brazil

Ivan I. Rusyn (Subgroup Chair, Mechanistic and Other Relevant Data)

College of Veterinary Medicine & Biomedical Sciences
Texas A&M University
College Station, TX
USA

Rashmi Sinha (Subgroup Chair, Cancer in Humans)

National Cancer Institute
Division of Cancer Epidemiology & Genetics
Bethesda, MD
USA

Leslie Stayner (Overall Chair)

Division of Epidemiology and Biostatistics
School of Public Health
University of Illinois at Chicago
Chicago, IL
USA

Mariana C. Stern

Norris Comprehensive Cancer Center
University of Southern California
Los Angeles, CA
USA

Alessandra Tavani

Mario Negri Institute of Pharmacological Research (IRCCS)
Milan
Italy

Piet van den Brandt

Dept of Epidemiology
Maastricht University
Maastricht
The Netherlands

Kathryn M. Wilson

Dept of Epidemiology
Harvard TH Chan School of Public Health
Boston, MA
USA

Invited Specialists

None

Representatives

Anne Morise

Risk Assessment Department
French Agency for Food, Environmental and Occupational Health & Safety (ANSES)
Maisons-Alfort
France

Observers [2]

Valentina Guercio [3]

Mario Negri Institute of Pharmacological Research (IRCCS)
Milan
Italy

[2] Each Observer agreed to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers did not serve as Meeting Chair or Subgroup Chair, draft any part of a Monograph, or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group Members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.
[3] Valentina Guercio attended as an Observer for the Mario Negri Institute of Pharmacological Research, Italy.

Thomas Hatzold [4]

Munich
Germany

Alan Leviton [5]

Children's Hospital
Boston, MA
USA

Frankie Phillips [6]

Exeter
England

Valentin Thomas [7]

University Paris Dauphine
Paris
France

Christian Wallmann [8]

Dept of Philosophy
School of European Culture and Languages
University of Kent
Canterbury, Kent
England

Michael Wilde [9]

Dept of Philosophy
School of European Culture and Languages
University of Kent
Canterbury, Kent
England

IARC/WHO Secretariat

Behnoush Abedi-Ardekani
Lamia Benbrahim-Tallaa *(Rapporteur, Mechanistic and Other Relevant Data)*
Véronique Bouvard *(Rapporteur, Exposure Data)*
Fatiha El Ghissassi *(Rapporteur, Mechanistic and Other Relevant Data)*
Yann Grosse *(Rapporteur, Cancer in Experimental Animals)*
Neela Guha *(Rapporteur, Cancer in Humans)*
Kathryn Guyton *(Rapporteur, Mechanistic and Other Relevant Data)*
Inge Huybrechts
Béatrice Lauby-Secretan
Dana Loomis *(Responsible Officer)*
Heidi Mattock *(Scientific Editor)*
Hwayoung Noh
Silvia Pisanu
Joseph Rothwell
Augustin Scalbert
Kurt Straif *(Head of Programme)*
Maria Zhivagui

[4] Thomas Hatzold was until 2015 employed by and still holds stock options from Mondelez International, a multinational confectionery, food, and beverage conglomerate with headquarters in Deerfield, IL, USA. He is an Observer for the Institute for Scientific Information on Coffee, an organization whose members include six of the major European coffee companies.
[5] Alan Leviton has provided consulting services for the National Coffee Association, a trade association, based in New York, USA. He is an Observer for the National Coffee Association.
[6] Frankie Phillips attended as a Freelance Dietitian and Nutrition Consultant.
[7] Valentin Thomas attended as an Observer for the University of Paris Dauphine, France.
[8] Christian Wallmann attended as an Observer for the University of Kent, England.
[9] Michael Wilde attended as an Observer for the University of Kent, England.

Administrative Assistance

Natacha Blavoyer
Marieke Dusenberg
Sandrine Egraz
Michel Javin
Helene Lorenzen-Augros

Post-meeting Assistance

Elaine Rowan (*Technical Editor*)

Post-meeting Scientific Assistance

Nilmara Oliveira Alves Brito
Badr Id Said
Marko Lukic

Production Team

Elisabeth Elbers
Fiona Gould
Solène Quennehen

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '... that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio et al., 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio et al., 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair

or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano et al., 2004).

The names and principal affiliations of participants are available on the *Monographs* programme web site (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano et al., 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare

preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data

Studies of cancer in humans

Studies of cancer in experimental animals

Mechanistic and other relevant data

Summary

Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production,

which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in

particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than

those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and

time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio et al., 1992; Toniolo et al., 1997; Vineis et al., 1999; Buffler et al., 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of

multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn et al., 1986; Tomatis et al., 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio et al., 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff et al., 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent

should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel et al., 1983; Gart et al., 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980; Gart et al., 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman et al., 1994; Dunson et al., 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of

historical controls, particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman et al., 1984; Fung et al., 1996; Greim et al., 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells

can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio et al., 1992; McGregor et al., 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests

have been published (Montesano et al., 1986; McGregor et al., 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals in vivo indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio et al., 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano et al., 1986; McGregor et al., 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen et al., 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem

plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme web site (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:**

The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity*:**

A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity*:**

The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity*:**

There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative

risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:**

The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:**

The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:**

The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:**

Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed,

especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

References

Bieler GS, Williams RL (1993). Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics*, 49:793–801. doi:10.2307/2532200 PMID:8241374

Breslow NE, Day NE (1980). Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ*, 32:5–338. PMID:7216345

Breslow NE, Day NE (1987). Statistical methods in cancer research. Volume II–The design and analysis of cohort studies. *IARC Sci Publ*, 82:1–406. PMID:3329634

Buffler P, Rice J, Baan R et al. (2004). Workshop on mechanisms of carcinogenesis: contributions of molecular epidemiology. Lyon, 14–17 November 2001. Workshop report. *IARC Sci Publ*, 157:1–27. PMID:15055286

Capen CC, Dybing E, Rice JM, Wilbourn JD (1999). Species differences in thyroid, kidney and urinary bladder carcinogenesis. Proceedings of a consensus conference. Lyon, France, 3–7 November 1997. *IARC Sci Publ*, 147:1–225. PMID:10627184

Cogliano V, Baan R, Straif K et al. (2005). Transparency in IARC Monographs. *Lancet Oncol*, 6:747. doi:10.1016/S1470-2045(05)70380-6

Cogliano VJ, Baan RA, Straif K et al. (2004). The science and practice of carcinogen identification and evaluation. *Environ Health Perspect*, 112:1269–1274. doi:10.1289/ehp.6950 PMID:15345338

Dunson DB, Chen Z, Harry J (2003). A Bayesian approach for joint modeling of cluster size and subunit-specific outcomes. *Biometrics*, 59:521–530. doi:10.1111/1541-0420.00062 PMID:14601753

Fung KY, Krewski D, Smythe RT (1996). A comparison of tests for trend with historical controls in carcinogen bioassay. *Can J Stat*, 24:431–454. doi:10.2307/3315326

Gart JJ, Krewski D, Lee PN et al. (1986). Statistical methods in cancer research. Volume III–The design and analysis of long-term animal experiments. *IARC Sci Publ*, 79:1–219. PMID:3301661

Greenland S (1998). Meta-analysis. In: Rothman KJ, Greenland S, editors. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins, pp. 643–673.

Greim H, Gelbke H-P, Reuter U et al. (2003). Evaluation of historical control data in carcinogenicity studies. *Hum Exp Toxicol*, 22:541–549. doi:10.1191/0960327103ht394oa PMID:14655720

Haseman JK, Huff J, Boorman GA (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol Pathol*, 12:126–135. doi:10.1177/019262338401200203 PMID:11478313

Hill AB (1965). The environment and disease: Association or causation? *Proc R Soc Med*, 58:295–300. PMID:14283879

Hoel DG, Kaplan NL, Anderson MW (1983). Implication of nonlinear kinetics on risk estimation in carcinogenesis. *Science*, 219:1032–1037. doi:10.1126/science.6823565 PMID:6823565

Huff JE, Eustis SL, Haseman JK (1989). Occurrence and relevance of chemically induced benign neoplasms in long-term carcinogenicity studies. *Cancer Metastasis Rev*, 8:1–22. doi:10.1007/BF00047055 PMID:2667783

IARC (1977). IARC Monographs Programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Preamble (IARC Intern Tech Rep No. 77/002).

IARC (1978). Chemicals with sufficient evidence of carcinogenicity in experimental animals – IARC Monographs Volumes 1–17 (IARC Intern Tech Rep No. 78/003).

IARC (1979). Criteria to select chemicals for IARC Monographs (IARC Intern Tech Rep No. 79/003).

IARC (1982). Chemicals, industrial processes and industries associated with cancer in humans (IARC Monographs, volumes 1 to 29). *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 4:1–292.

IARC (1983). Approaches to classifying chemical carcinogens according to mechanism of action (IARC Intern Tech Rep No. 83/001).

IARC (1987). IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. IARC Monogr Eval Carcinog Risks Hum Suppl, 7:1–440. Available from: http://publications.iarc.fr/139 PMID:3482203

IARC (1988). Report of an IARC Working Group to Review the Approaches and Processes Used to Evaluate the Carcinogenicity of Mixtures and Groups of Chemicals (IARC Intern Tech Rep No. 88/002).

IARC (1991). A consensus report of an IARC Monographs Working Group on the Use of Mechanisms of Carcinogenesis in Risk Identification (IARC Intern Tech Rep No. 91/002).

IARC (2004). Some drinking-water disinfectants and contaminants, including arsenic. IARC Monogr Eval Carcinog Risks Hum, 84:1–477. Available from: http://publications.iarc.fr/102 PMID:15645577

IARC (2005). Report of the Advisory Group to Recommend Updates to the Preamble to the IARC Monographs (IARC Intern Rep No. 05/001).

IARC (2006). Report of the Advisory Group to Review the Amended Preamble to the IARC Monographs (IARC Intern Rep No. 06/001).

McGregor DB, Rice JM, Venitt S (1999). The use of short-and medium-term tests for carcinogens and data on genetic effects in carcinogenic hazard evaluation. Consensus report. *IARC Sci Publ*, 146:1–18. PMID:10353381

Montesano R, Bartsch H, Vainio H et al., editors (1986). Long-term and short-term assays for carcinogenesis—a critical appraisal. *IARC Sci Publ*, 83:1–564. PMID:3623675

OECD (2002). Guidance notes for analysis and evaluation of chronic toxicity and carcinogenicity studies (Series on Testing and Assessment No. 35), Paris: OECD.

Peto R, Pike MC, Day NE et al. (1980). Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 2:Suppl: 311–426. PMID:6935185

Portier CJ, Bailer AJ (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam Appl Toxicol*, 12:731–737. doi:10.1016/0272-0590(89)90004-3 PMID:2744275

Sherman CD, Portier CJ, Kopp-Schneider A (1994). Multistage models of carcinogenesis: an approximation for the size and number distribution of late-stage clones. *Risk Anal*, 14:1039–1048. doi:10.1111/j.1539-6924.1994.tb00074.x PMID:7846311

Stewart BW, Kleihues P, editors (2003). World cancer report. Lyon: IARC.

Tomatis L, Aitio A, Wilbourn J, Shuker L (1989). Human carcinogens so far identified. *Jpn J Cancer Res*, 80:795–807. doi:10.1111/j.1349-7006.1989.tb01717.x PMID:2513295

Toniolo P, Boffetta P, Shuker DEG et al. (1997). Proceedings of the workshop on application of biomarkers to cancer epidemiology. Lyon, France, 20–23 February 1996. *IARC Sci Publ*, 142:1–318. PMID:9410826

Vainio H, Magee P, McGregor D, McMichael A (1992). Mechanisms of carcinogenesis in risk identification. IARC Working Group Meeting. Lyon, 11–18 June 1991. *IARC Sci Publ*, 116:1–608. PMID:1428077

Vainio H, Wilbourn JD, Sasco AJ et al. (1995). [Identification of human carcinogenic risks in IARC monographs] *Bull Cancer*, 82:339–348. PMID:7626841 [French]

Vineis P, Malats N, Lang M et al., editors (1999). Metabolic polymorphisms and susceptibility to cancer. *IARC Sci Publ*, 148:1–510. PMID:10493243

Wilbourn J, Haroun L, Heseltine E et al. (1986). Response of experimental animals to human carcinogens: an analysis based upon the IARC Monographs programme. *Carcinogenesis*, 7:1853–1863. doi:10.1093/carcin/7.11.1853 PMID:3769134

GENERAL REMARKS

This one-hundred-and-sixteenth volume of the *IARC Monographs* presents evaluations of the carcinogenic hazard to humans of drinking coffee, mate, and very hot beverages. A summary of the findings of this volume appears in *The Lancet Oncology* (Loomis et al., 2016).

The carcinogenicity of coffee was previously evaluated in Volume 51 of the *IARC Monographs* (IARC, 1991). After reviewing the data available at that time, the Working Group had classified coffee as *possibly carcinogenic to humans* (Group 2B) based on *limited evidence* in humans – derived from some 20 epidemiological case–control studies – that coffee causes cancer of the urinary bladder, and *inadequate evidence* in experimental animals. The same Working Group also concluded that there was *evidence suggesting lack of carcinogenicity* for cancers of the female breast and the colorectum.

In the current evaluation, based on a much larger volume of data comprising more than 1000 observational and experimental studies, the Working Group concluded there is *inadequate evidence* in humans and experimental animals for the carcinogenicity of coffee drinking. With the expanded literature, the Working Group focused their review on higher-quality epidemiological studies of cancer of the bladder and coffee drinking; these did not show a consistent association or a dose–response relationship. The Working Group judged that the positive associations between coffee drinking and cancer of the bladder observed in some studies were probably due to inadequate control for the confounding effects of tobacco smoking, a major risk factor for cancer of the bladder that is often strongly associated with coffee drinking. In considering the data now available for more than 20 other cancer sites in humans, the Working Group found *evidence suggesting lack of carcinogenicity* for cancers of the female breast, uterine endometrium, prostate, pancreas, and liver, and *inadequate evidence* in humans for cancers at all other sites. The Working Group's review of other relevant data found *strong evidence* in humans that coffee has antioxidant effects. As a result of this re-evaluation, the Working Group concluded that drinking coffee is *not classifiable as to its carcinogenicity to humans* (Group 3).

An earlier evaluation of the carcinogenicity of mate was also reported in Volume 51 (IARC, 1991). The evidence available at that time was obtained entirely from epidemiological case–control studies. In that review, the Working Group drew a distinction between mate itself and drinking hot mate, concluding that mate (without further specification) was *not classifiable as to its carcinogenicity to humans* (Group 3), but that drinking hot mate was *probably carcinogenic to humans* (Group 2A). Taking into account the previous evaluation, in addition to new data in humans and experimental animals, an Advisory Group that met in 2014 gave high priority to evaluating the carcinogenicity of drinking hot mate

and other hot beverages (Straif et al., 2014). In light of the evidence available at the present time, the current Working Group chose to evaluate the carcinogenicity of very hot beverages, including, but not limited to, mate. Epidemiological studies of cancer risk and drinking temperature for a variety of hot beverages, as well as co-carcinogenicity experiments in which hot liquids were administered to animals, were accordingly taken into consideration. The Working Group concluded that drinking very hot beverages (> 65 °C) is *probably carcinogenic to humans* (Group 2A) based on epidemiological studies showing *limited evidence* of a causal association with cancer of the oesophagus in humans and *limited evidence* in experimental animals. The Working Group noted that a causal relationship between consuming very hot beverages and cancer of the oesophagus is biologically plausible through mechanisms linking thermal injury to cancer. Drinking mate that is not very hot was classified in Group 3 (*not classifiable as to its carcinogenicity to humans*).

References

IARC (1991). Coffee, tea, mate, methylxanthines and methylglyoxal. *IARC Monogr Eval Carcinog Risks Hum*, 51:1–513. Available from: http://publications.iarc.fr/69 PMID:1674554

Loomis D, Guyton KZ, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, et al.; International Agency for Research on Cancer Monograph Working Group (2016). Carcinogenicity of drinking coffee, mate, and very hot beverages. *Lancet Oncol*, 17(7):877–8. doi:10.1016/S1470-2045(16)30239-X PMID:27318851

Straif K, Loomis D, Guyton K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. (2014). Future priorities for the IARC Monographs. *Lancet Oncol*, 15(7):683–4. doi:10.1016/S1470-2045(14)70168-8

DRINKING COFFEE

1. EXPOSURE DATA

Coffee seeds (known as beans) are contained in fruits from trees and shrubs grown naturally in the shade of eastern African forests encompassing Ethiopia and the islands of Madagascar and Mauritius, among other countries. Coffee has attracted the attention of explorers and botanists from all over the world from the 16th century, when the first coffee trees were reported in the literature (Charrier & Berthaud, 1987); in particular, many new species were discovered in the second half of the 19th century. The interest may have been partly due to its stimulating effects in animals and humans, compounded with its enchanting aroma after roasting. Today, it is known that different coffee species originated in different parts of Africa and that there are still species being discovered, some in Ethiopia (Farah & Ferreira dos Santos, 2015).

The year 575 AD is often cited as the date of the arrival of coffee on the Arabian peninsula from Ethiopia. Commercial and political links were at that time strengthening across the Red Sea (Wellman, 1961; IARC, 1991). Coffee cherries (*bun* or *bon*) were then probably only dried and chewed as a stimulant against fatigue. It was only by the middle of the 15th century that coffee as a beverage (*kahwah* in Arabic), an infusion of roasted and ground coffee beans cultivated in Yemen, near the harbour of Mocha, came into general use throughout the Ottoman empire. By the end of the 16th century it had crossed the Mediterranean Sea, and in less than a century it had spread throughout Europe and to the British colonies in North America (Wellman, 1961; IARC, 1991).

During the 17th century the cultivation of coffee spread to the Malabar coast of India and to Ceylon. From the beginning of the 18th century, seedlings of *Coffea arabica* L. cultivated in European glasshouses, as first described by Linnaeus in 1737 (Debry, 1989), were introduced to the Dutch West Indies and to the French, Portuguese, and Spanish colonies of America and Asia (Wellman, 1961; IARC, 1991; Davis et al., 2007; Farah & Ferreira dos Santos, 2015).

1.1 Identification of the agent

1.1.1 Botanical data

(a) Nomenclature

Botanical name: *Coffea arabica* L., *Coffea canephora* Pierre ex A. Froehner, and various other species in the genus *Coffea*

Family: Rubiaceae

Subfamily: Ixoroideae

Tribe: Coffeeae

Genus: *Coffea*

Subgenus: Coffea

Common names: coffee, Arabica coffee, Robusta coffee

GRIN (2016)

The coffee tree belongs to the botanical family Rubiaceae, with the genus *Coffea* being

Fig. 1.1 The coffee plant, *Coffea arabica* L.

The figure shows the leaves, fruits, and berries.
From Spohn (2015) with permission from Dr Roland Spohn, www.spohns.de

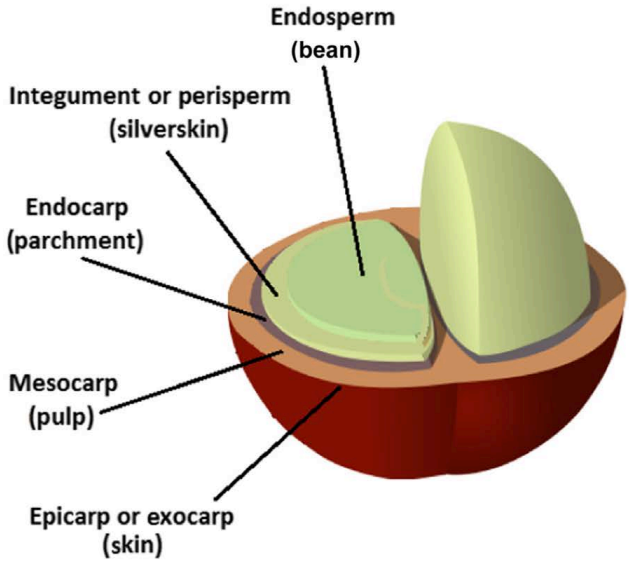
the most economically important member of this family (Murthy & Naidu, 2012). Because of the great variation in the types of coffee plants and seeds, botanists have failed to agree on a precise single system to classify them or even to designate some plants as true members of the *Coffea* genus. Although it is said that hundreds of species have been described, the National Center for Biotechnology Information (NCBI) in the USA and Davis et al. (2006; 2007) have described over 90 species within the *Coffea* genus, from which 25 have been more extensively studied (Davis et al., 2006; 2007; NCBI, 2014; Farah & Ferreira dos Santos, 2015). From these 25 species, only two have major commercial importance: *Coffea arabica* and *Coffea canephora*. It has been suggested that *C. arabica*, a tetraploid species ($2n = 4x = 44$), originated from natural hybridization between *C. canephora* and *C. eugenioides*, or ecotypes related to these two diploid ($2n = 2x = 22$) species (Charrier & Berthaud 1987; Lashermes et al., 1999; Anthony et al., 2002; Farah & Ferreira dos Santos, 2015).

(b) Description of the coffee plant

Coffee is an evergreen perennial plant. The shapes of the coffee tree and roots vary depending on the species and, in some cases, variety (Murthy & Naidu, 2012; FAO, 2014). In general, the coffee tree consists of an upright main shoot (trunk) with primary, secondary, and tertiary lateral branches. Naturally grown trees may be 4–6 m tall for *C. arabica* and 8–12 m for *C. canephora* (Illy & Viani, 2005).

Each leaf pair is opposite to the next leaf pair. Leaves appear shiny, wavy, and dark green in colour with conspicuous veins. In the axil of each leaf are four to six serial buds, which can develop into an inflorescence or secondary branches (Farah & Ferreira dos Santos, 2015; Fig. 1.1). The mature fruit, or "cherry" (Fig. 1.2), comprises: (1) skin (epicarp or exocarp), which is a red, dark

Fig. 1.2 Diagram of the coffee cherry fruit



Reproduced from Farah & Ferreira dos Santos (2015). The coffee plant and beans: introduction. In: Preedy V, editor. Coffee in health and disease prevention, 1st ed. San Diego (CA), USA: Academic Press; 5–10

pink or yellow monocellular layer covered with a waxy substance protecting the fruit; (2) pulp (mesocarp); (3) parchment or parch (endocarp); (4) silverskin, which is the seed coat composed mainly of polysaccharides (especially cellulose, hemicelluloses, and mannans); (5) two elliptical seeds (beans) containing the endosperm and embryo (CAC, 2009; Murthy & Naidu, 2012; Sánchez & Anzola, 2012; FAO, 2014; Farah & Ferreira dos Santos, 2015).

Arabica coffee grows optimally at altitudes of 550–1100 m in subtropical regions of latitudes 16–24° with well-defined rainy and dry seasons. The Brazilian regions of Minas Gerais and São Paulo, and Jamaica, Mexico, and Zimbabwe are examples of areas with these climate conditions (Illy & Viani, 2005). In the equatorial regions at latitudes below 10° coffee grows well at the higher altitudes of 1100–1900 m. Frequent rainfall causes almost continuous flowering, which results in two coffee harvesting seasons per year. Examples of countries that have this climate are Colombia, Costa Rica, Ethiopia, and Kenya (Illy & Viani, 2005).

C. canephora trees also grow at low elevations (from sea level to 900 m) in warmer climates in the equatorial regions at latitudes below 10°, and demonstrate higher resistance to diseases, but yield a beverage of inferior quality and lower market value compared to Arabica species. The species *Coffea liberica*, commanding less than 1% of the market, grows in warm climates and at low elevations; it is however susceptible to diseases and yields a beverage of poor quality (Illy & Illy, 1989; Hendre et al., 2008; FAO, 2014; Farah & Ferreira dos Santos, 2015; ICO, 2016).

1.2 Methods of production, uses, and preparation

1.2.1 Green coffee production

(a) Harvesting

Harvesting begins when about 80% of the fruits are ripe. Coffee cherries (ripe fruits) tend to yield better-quality beverages, whereas immature and overripe fruits yield defective low-quality beans (Toci & Farah, 2008). Harvesting may be undertaken manually or mechanically. Manual picking tends to yield better-quality beans (Farah, 2009; Filho et al., 2015).

(b) Post-harvest processing

Fig. 1.3 summarizes the steps involved in dry, semi-dry (or semi-wet/semi-washed), and wet methods used for coffee primary processing.

After being harvested, the fruits are either sorted manually or washed and separated in flotation tanks, followed by processing for the separation of the seeds from the rest of the fruit.

In the original dry processing method, harvested seeds are parched by sun exposure outdoors and/or by air dryers until the moisture content is about 10–12% (Trugo, 2003; Farah, 2009). Unless air dryers are available, protection from rain during the harvesting period is required to avoid the growth of microorganisms and to produce good-quality coffee (CAC, 2009; Farah, 2009). Once the fruits are dried, they are cleaned and the dried pericarp (endocarp, mesocarp, and epicarp) is removed mechanically (Fig. 1.2), leaving the mucilaginous material that envelops the seeds (silverskin) still adhering to their surface (Geromel et al., 2006; CAC, 2009; Farah, 2009). The product of dry processed fruits is called "natural" green coffee (CAC, 2009; Farah, 2009). The dry method is commonly used in Brazil and Africa (Farah & Ferreira dos Santos, 2015). Seeds produced by the dry method keep the silverskin adhered to their surface and have been valued in the market for the preparation of blends, as the silverskin confers more "body" or thickness to the brew (Borrelli et al., 2004).

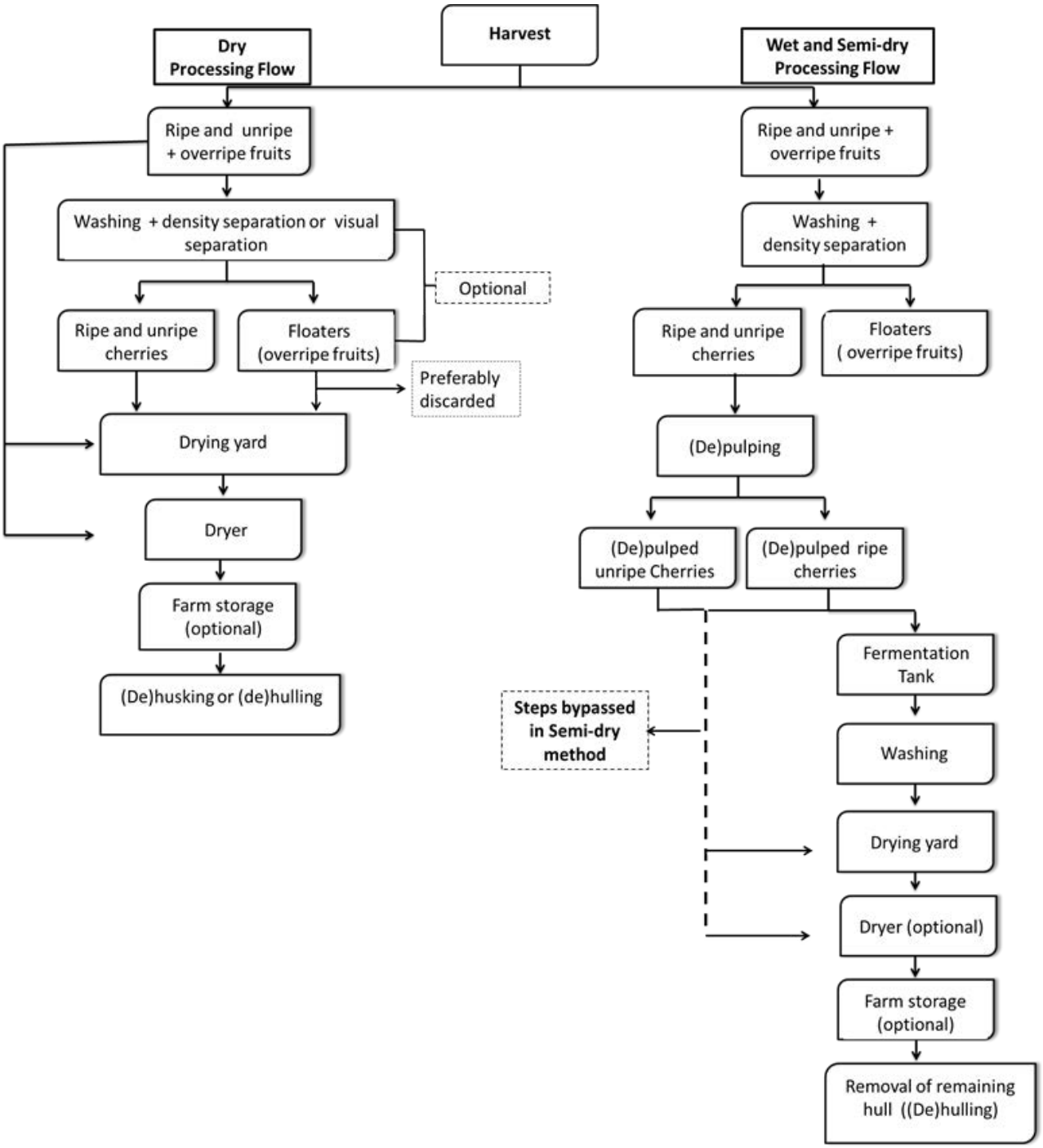
The wet process is more sophisticated and tends to generate a higher-quality beverage; generally only ripe cherries are processed this way. They can be selectively hand-picked or separated mechanically or in flotation tanks. Sorting is followed by mechanical (de)pulping, soaking, and fermenting in tanks, where the remaining pulp and silverskin are removed; acidity increases during this process and the pH may reduce to 4.5. The naked beans are washed and then dried in yards or in ventilated tables, possibly combined with hot air drying. After drying, the remaining part of the hull is often mechanically removed. Wet processing is frequently used in places where coffee is harvested by manual picking such as Asia, Central America, and Colombia; due to the higher market value, however, various farms in larger coffee-producing countries such as Brazil have also adopted this processing method. Wet-processed beans are called pulped coffees (Flament, 2002, Bee et al., 2005; Knopp et al., 2006; CAC 2009; Farah, 2009; Farah & Ferreira dos Santos, 2015).

At all steps of coffee processing, gram-negative and gram-positive bacteria, yeasts, and filamentous fungi are present at high levels. There has been a concern about the potential production of ochratoxin A and other mycotoxins by microorganisms during the fermentation in wet processing, when the natural growth of microorganisms can occur (see Section 1.4.2).

After the beans are treated by the dry or wet method, they are either stored or mechanically, manually, and/or electronically sized and sorted for quality control and commercialization. This process may be followed by an additional sorting with UV excitation.

Sorting yields coffee beans with extrinsic defects, such as stones, twigs, or other foreign matter, and intrinsic defects, such as immature,

Fig. 1.3 Coffee post-harvest processing: flow of dry, wet, and semi-dry/semi-washed methods



Reproduced from Farah & Ferreira dos Santos (2015). The coffee plant and beans: introduction. In: Preedy V, editor. Coffee in health and disease prevention, 1st ed. San Diego (CA), USA: Academic Press; 5–10

sour, or insect-damaged beans (Toci & Farah, 2008; Farah, 2009; Farah & Ferreira dos Santos, 2015). Avoiding undesirable contamination and the growth of microorganisms (especially mould) during harvesting, drying, and storage of the seeds is also critical. Defective beans are sold at a low price, roasted, blended with better-quality beans, and sold in the market as popular blends. The major concern here is the presence of moulded and oxidized defects, and therefore the potential presence of contaminants.

After marketing, green coffee beans are ready to undergo roasting. Optionally, they may be decaffeinated, steam-treated, or stored before roasting. If stored, this is another critical stage where the growth of microorganisms is common.

1.2.2 Decaffeination

Decaffeination is traditionally performed before roasting. For decaffeinated coffee, most countries require that the content of caffeine be reduced to less than 0.1% on a dry weight basis; however, decaffeinated coffees with up to 0.3% of caffeine can be found on the market. In addition to extracting caffeine, other substances are also extracted during the process including aroma precursors and bioactive compounds (Farah et al., 2006; Toci et al., 2006). As a result, decaffeinated products can taste very different from regular coffee.

Different solvents and adsorbent substances can be used for decaffeination, among which dichloromethane (see IARC, 1986, 1987, 2017), ethyl acetate (see IARC, 1979, 1987), edible fats and oils, supercritical carbon dioxide, and acid-activated carbon (used in extract decaffeination) are well known (IARC, 1991). The selectivity of solvents and adsorbent materials varies, along with the sensory result. Processes that do not employ an organic solvent are known as "water decaffeination". Currently, the industry in Europe and in the USA uses mostly water and supercritical carbon dioxide; the latter is employed at temperatures and pressures of 40–80 °C and 200–300 bar (i.e. above its critical point of 31.06 °C and 73.8 bar) for 5–30 hours (IARC, 1991). Dichloromethane or ethyl acetate are used in Central and South America, depending on the country.

1.2.3 Roasting, grinding, and packing

It is only during roasting that coffee acquires its characteristic aroma, a consequence of a dramatic change in chemical composition of the beans. The two main systems used for heat transfer in coffee roasters are conduction and convection. In roasters that use conduction, heat is transferred by direct contact with a hot surface and/or fire. In convection roasters heat is transferred by hot air circulation in the roasting chamber, distributing heat evenly. Most modern roasters work this way, and some use both convection and conduction. Convection roasters roast faster than conduction roasters, and this will have an influence on the chemical reactions that occur during the process (IARC, 1991; Holman, 2009; Soares et al., 2009; Fernandes, 2017). In addition to the different types of roasters, there are several variables that can be applied to the process such as time and temperature control.

During the roasting process the beans increase in volume, develop a brittle structure, and acquire a light to dark brown colour, while their composition changes dramatically as a consequence of pyrolysis, caramelization, and Maillard reactions. The roasting intensity will vary for different cultures and types of coffee. Roasting chamber temperatures generally vary over 190–270 °C, although the use of temperatures of 210–230 °C is more common in industry.

After cooling, which can be accelerated by quenching with vaporized water or a cool air stream, residual carbon dioxide trapped in the bean is slowly released over a period of days or up to 48 hours after grinding (IARC, 1991; Farah, 2012).

Coffee can be sold pre-ground and packaged after short degassing (2–4 hours) or under an initial slight vacuum in flexible bags (Viani, 1986). Unlike green beans, roasted coffee spoils relatively quickly if unprotected from oxygen and moisture; at ambient temperature, whole beans stale 4–6 weeks and ground coffee 2 weeks after roasting (Toci et al., 2013).

1.2.4 Brewing techniques

Brewing can be defined as the preparation of a beverage by "mixing, steeping, soaking, or boiling a solid in water" (Thesaurus, 2016). Coffee brewing is the process by which coffee soluble solids are extracted by water. Brewing techniques encompass a wide range of procedures used in different parts of the world, which are based on the types of coffee and roasting degrees traditionally used. Local cultural practices and the cup size used, associated with the variety of preparation methods, result in large differences in the chemical composition of the brew and a range of individual consumption patterns. Globalization has reduced cultural distances however, and a diversity of techniques and methods is available both for home preparation and in coffeehouses. An overview of the variety of coffee preparation methods is provided in Hatzold (2012).

In addition to the type of coffee and roasting degree, the particle size and the ratio of ground coffee to water vary considerably with techniques. Generally speaking, water temperature may vary from about 7–10 °C in cold brewing to 100 °C in boiling methods (see the monograph on Drinking Mate and Very Hot Beverages in the present volume for more information). After the extraction of coffee components, some techniques use filter paper to separate grounds from brew while others use a strainer, plunger, or no device at all. If no filter paper is used, the coffee will contain the diterpenes cafestol and kahweol (Urgert et al., 1995). The most common brewing techniques are described below.

(a) Decoction

(i) Boiled coffee

To prepare a boiled brew (most commonly consumed in northern Scandinavian countries), boiling water is poured onto coarsely ground roasted Arabica coffee and the decoction is boiled for up to 10 minutes. The decoction may also be allowed to sit without boiling. The brew is made at about 5% (weight/volume) [50 g coffee grounds in 1 L of water]. The ground coffee settles at the bottom and the brew is consumed. Cup volume is about 150 mL (IARC, 1991; van Dusseldorp et al., 1991; [expert knowledge of the Working Group]).

(ii) "Turkish" coffee

For coffee consumed in Greece, Turkey, parts of the Balkans, and parts of the Middle East, very finely ground coffee is brewed with sugar in a copper pot (*ibrik*) at about 8% w/v by gentle boiling. The ingredients are heated until a large bubble or foam is formed in the centre of the *ibrik*. The heat is interrupted and the process can be repeated up to three times. Cup volume is generally 60 mL (IARC, 1991).

(iii) Kopi tubruk

Another variation of boiled coffee is *kopi tubruk*, also called mud coffee. This is a common brewing method brought to Indonesia by Middle Eastern traders. The concentration is similar to "Turkish" coffee, but a medium to coarse grind is used instead of a fine grind. Coffee and sugar are placed in a cup or mug, boiling water is added, and the coffee is "cooked" until the grounds settle at the bottom. A variation is to heat water, coffee grounds, and sugar together and let them boil until the grounds settle. Cup/mug volume varies over 150–190 mL [expert knowledge of the Working Group].

(b) Infusion

In this technique roasted coarse coffee grounds are infused, usually followed by the use of a device to separate the grounds from the brew.

(i) Plunger pot

In this system, also called a "French press" or piston system, hot water is a poured over coarsely ground coffee with a concentration of about 4–10% (w/v), and a metal strainer is pushed down the coffee pot to separate the grounds from the brew after infusion. This system is used in Australia, Europe, and North America. A variation of this system uses a paper filter instead of a metal plunger. Cup/mug size varies over 150–190 mL (IARC, 1991) [expert knowledge of the Working Group].

(ii) Cold brewing

In this system, very coarsely ground coffee is placed in a receptacle with a lid. Cold to room-temperature water is poured over the ground coffee (about 12.5% w/v). The mixture is well stirred and the jar is covered and left for 12–24 hours. When brewed, the mixture is strained to remove solid residue. The resulting brew can be served cold or mixed with boiling water to serve hot. The main sensory characteristics of this brew are low acidity, gentleness, and sweetness [expert knowledge of the Working Group].

(c) Percolation

(i) Filtration

Filtered coffee is one of the most common brewing methods around the world; it is made by percolating pre-boiling water (95–98 °C) through medium-ground roasted coffee in a filter (usually paper but may be metal, nylon, or ceramic) set in a funnel. The brew drips into a warmed pot within about 2–5 minutes. The strength of the brew will vary with cultural habits, which includes roasting degree and coffee to water ratio of 7–14% w/v, which increases as the roasting degree becomes lighter. Light to medium roasts predominate in the USA, medium to dark roasts prevail in South America, and dark roasts are favoured in France and Italy. Cup size varies over 40–150 mL. Automatic coffee makers are available worldwide and have also been widely adopted by the food-services industry (IARC, 1991; [expert knowledge of the Working Group]).

(ii) Vaporization under pressure (moka pot)

In this technique water is heated to just above boiling point and forced by slight excess pressure through coarse medium-/dark-roasted coffee. Continuous recirculation over the coffee grounds occurs until the desired brew strength is reached. Ground coffee concentrations normally range over 8–12%. This method is traditional in Italian and Spanish households, and is becoming popular all over the world [expert knowledge of the Working Group].

(iii) Vaporization under pressure (espresso)

This method, which originated in Italy and is now popular worldwide, allows rapid extraction. In espresso machines, water at 92–95 °C is driven through a medium-/dark-roasted ground coffee packed bed by a pressure pump (8–12 bar) to extract soluble material over a period of 15–35 seconds. About 5–8 g of roasted coffee is used for each 25–60 mL cup. The extraction yield of coffee soluble solids from the roasted coffee is 18–26% with a soluble solids concentration in the cup of 20–60 g/L brew; 70–85% caffeine is recovered (Illy & Viani, 2005; Petracco, 2005; Corrochano et al., 2015). Automated methods for coffee preparation have gained popularity during the last decades, including fully automatic espresso-type machines that use coffee pods or capsules (Gloess et al., 2013).

1.2.5 Instant coffee production

Instant coffee is a dried water extract of roasted and ground coffee which readily dissolves in both cold and hot water, eliminating the need

for brewing equipment. The unit operations performed during the manufacture of instant coffee are the same as for roasted coffee, followed by extraction, concentration, and drying of the extract (to a maximum of 5% moisture by spray-drying or freeze-drying), followed by agglomeration, aromatization, and packaging of the powder. Packaging is performed under vacuum or in an inert atmosphere in jars or flexible bags, and the packaged product can be stable for more than two years if unopened (Viani, 1986; IARC, 1991).

1.2.6 Other beverages containing coffee

Coffee may also be sold as a "convenience" product in a ready-to-drink form in cans or aseptic carton packaging, typically premixed with milk or other ingredients (Waizenegger et al., 2011).

1.2.7 Other uses of coffee and coffee byproducts

Numerous other products containing coffee are available on the market. Coffee and all forms of coffee extracts or instant coffee may be used as an ingredient in various foods, such as the flavouring of chocolate or in various bakery products. Infusions may be prepared with coffee byproducts from post-harvesting processing (dry cherry pulp) or from coffee leaves. Coffee can also be consumed as chocolate-coated roasted coffee beans.

Non-traditional uses of coffee or coffee extracts include the use in food supplements. The US Dietary Supplements Label Database, for example, lists more than 100 products that contain the word "coffee" in the product name (NLM, 2016). Specifically, green coffee extract and roasted and green blends have been marketed for purported effects such as weight loss and intake of antioxidants. The methods of encapsulated green coffee extract production can be similar to those applied to instant coffee production. Decaffeinated hydroalcoholic extracts and alternative technologies are also available. Coffee silverskin is another byproduct of coffee production; its use for human consumption can be an alternative to its environmental disposal. The high fibre and antioxidant compound content means that use of coffee silverskin (as well as its extract) as a supplement for different purported purposes such as weight control or for antioxidant intake has been proposed (Borrelli et al., 2004; Narita & Inouye, 2012).

1.3 Exposure assessment and biological markers

This section reviews the methods used to assess coffee consumption and exposure to coffee components. Food consumption data, which are typically obtained by questionnaire, provide estimates of external exposures to coffee and related substances, while biological markers may be used to assess internal exposures.

1.3.1 Questionnaires

Dietary assessment methodologies are under continuous development in an attempt to improve the validity of dietary exposure data, while also profiting from rapid evolution in innovative technologies such as mobile applications, scan- and sensor-based technologies, and many other upcoming technologies (Illner et al., 2012). A comprehensive review of dietary assessment methodologies and technologies used in epidemiological studies is beyond the scope of this report, but can be found in Thompson & Subar (2013) and Slimani et al. (2015).

(a) Concepts, design, and applications

The majority of epidemiological studies investigating associations between coffee consumption and cancer risk have used a food frequency questionnaire (FFQ) to assess individual usual

coffee intake and/or particular coffee components (e.g. caffeine). The food frequency approach asks respondents to report their usual frequency of consumption of specific food items from a list covering a specific period of time. FFQs are typically used in epidemiological studies to assess "usual" dietary intake in individuals for several reasons. First, FFQs are the only feasible approach in case–control studies where usual diet (often in the distant past) must be ascertained retrospectively. Second, in large prospective cohort studies FFQs are often the instrument of choice because of their time- and cost-efficient characteristics, including low investigator burden and cost. The FFQ can be distributed by mail or online to a large number of participants, can be self-administered, may be optically scanned, computer assisted, or web-based, and is often pre-coded to facilitate data handling. Third, the FFQ has the advantage that it does not affect the respondent's eating behaviour and that usual individual intake is being requested (over a long timeframe), avoiding the need for repeated measurements.

Nevertheless, the completion of an FFQ may be a challenge for respondents as usual consumptions, and particularly portion sizes, are difficult to estimate precisely. The ability to quantify total dietary intake depends on the number of food items listed in the FFQ and on the level of detail collected within the questionnaire, whether or not portion sizes are included, what timeframe of intake or reference period is used, and, for caffeine intake specifically, the differentiation between caffeinated and decaffeinated coffee in the food list (Block et al., 1986; Rimm et al., 1992).

FFQs generally include 50–150 (mostly generic) food items, with the number of frequency categories varying according to the study objectives and designs. The appropriateness of the food list is crucial as the full variability of an individual's diet, which includes many foods and mixed dishes, cannot be captured by a finite food list.

Whether portion size information is also required depends on the study aims. Three different types of FFQ can be distinguished depending on the portion size information required in the questionnaire. If no portion size information is included then the questionnaire is called a qualitative or non-quantitative FFQ, while a questionnaire including detailed portion size information (e.g. in grams or number of units) is called a quantitative FFQ. Some questionnaires include several portion size categories (e.g. ≤ 1 cup; 2–3 cups; ≥ 4 cups) which the subject can choose from, and is called a semi-quantitative FFQ. Researchers have used methods to improve assessment of portion size (e.g. picture booklets to estimate cup size) in the studies included in this report (see Tables 1.1 and 1.2).

Some FFQs also include extra questions regarding food preparation methods (e.g. brewing method for coffee), and identification of the type (e.g. caffeinated versus decaffeinated) and brand of certain types of foods.

FFQs are used widely in case–control and cohort studies to assess associations between dietary intake and disease risk but, importantly, they are generally used for ranking subjects according to food or nutrient intake rather than for estimating absolute levels of intake (Beaton, 1994; Kushi, 1994).

The FFQs used in the epidemiological studies included in this report were developed with a broader aim than only coffee assessment; details regarding the type of coffee and/or preparation method were therefore often lacking. This limitation should be considered when comparing results from different regions/countries as quantities of coffee powder/beans used to brew a coffee may differ between countries and cultures, although this information is lacking in most studies.

(b) Validation and calibration

Assessments of the relative validity of a FFQ provide information about how well the instrument is measuring what it is intended to measure. This is evaluated by comparing dietary intake

Table 1.1 Summary of methods used in cohort studies investigating the relationship between coffee consumption and cancer risk

Study, country, reference	Information-collection method	Period of information collection	Respondents	Distinction between caffeinated/ decaffeinated	Exposure metrics
Melbourne Collaborative Cohort Study (MCCS), Australia (Ireland et al., 1994)	General: FFQ Coffee-specific questions: frequency of coffee consumption, consumption of milk with coffee	At baseline	24 500 women and 17 000 men aged 40–69 yr	No	1–3 cups/mo, 1 cup/wk, 2–4 cups/wk, 5–6 cups/wk, 1 cup/day, 2–3 cups/day, 4–5 cups/day, > 6 cups/day
The Singapore Chinese Health Study, Singapore (Ainslie-Waldman et al., 2014)	General: 165-item FFQ, in conjunction with the Singapore Food Composition Database for the ascertainment of 96 items including caffeine Coffee-specific questions: frequency of caffeinated coffee consumption Questionnaire not available	At baseline	63 257 Chinese men and women aged 45–74 yr	No	Never or hardly ever, 1–3 times/mo, once/wk, 2–3 times/wk, 4–6 times/wk, once/day, 2–3 times/day, 4–5 times/day, ≥ 6 times/day
Life Span Study, Japan (Sauvaget et al., 2002)	General: 22-item FFQ Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	40 349 Japanese men and women	No	1 cup/wk, 2–4 cups/wk, Almost daily, Do not eat/drink

Table 1.1 (continued)

Study, country, reference	Information-collection method	Period of information collection	Respondents	Distinction between caffeinated/ decaffeinated	Exposure metrics
Japan Public Health Center-based Prospective (JPHC) study, Japan (Makiuchi et al., 2016)	General: self-administered questionnaire including questions on beverage consumption Coffee-specific questions: circle the frequency of your average consumption of coffee; how many teaspoons of sugar do you use per cup of coffee?	At baseline	140 420 male and female Japanese subjects aged 40–69 yr at baseline	No	Studies using baseline questionnaire: Almost never 1–2 days/wk, 3–4 days/wk, 1–2 cups/day, 3–4 cups/day, > 5 cups/day Study using 5-year follow-up questionnaire: 0 cups/wk, 1–2 cups/wk, 3–4 cups/wk, 5–6 cups/wk, 1 cup/day 2–3 cups/day, 4–6 cups/day, 7–9 cups/day, 10 cups/day
Miyagi Cohort, Japan (Naganuma et al., 2008)	General: self-administered questionnaire with 36 food items and 4 beverages including coffee Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	25 279 men and 26 642 women 40–64 yr at baseline	No	Never, < 1 cup/day 1–2 cups/day, 3–4 cups/day, 5 cups/day
Japan Collaborative Cohort (JACC) study, Japan (Yamada et al., 2014)	General: self-administered questionnaire including questions on beverage consumption Coffee-specific questions: frequency of coffee consumption; addition of sugar and milk in coffee Questionnaire not available	At baseline	110 792 Japanese men and women aged 40–79 yr at baseline	No	Seldom or never, 1–2 cups/mo, 1–4 cups/wk, 1 cup/day, 2–3 cups/day, > 4 cups/day
Takayama city cohort, Japan (Oba et al., 2008)	General: 169- item FFQ Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	13 392 men and 15 695 women aged ≥ 35 yr	No	Never, > 1 cup mo to 4–6 cups/wk, > 1 cup/day

Table 1.1 (continued)

Study, country, reference	Information-collection method	Period of information collection	Respondents	Distinction between caffeinated/ decaffeinated	Exposure metrics
National Breast Screening Study (NBSS), Canada (Silvera et al., 2007)	General: 86-item FFQ Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	89 835 women, aged 40–59 yr	No	None, 0–1 cup/day, 2–3 cups/day, ≥ 4 cups/day
Health Professionals Follow-up study, USA (Wilson et al., 2011)	General: 130-item FFQ Coffee-specific questions: how frequently did you drink a cup of caffeinated coffee? How frequently did you drink a cup of decaffeinated coffee?	At baseline in 1986 and every 4 yr thereafter	47 911 male health professionals aged 40–75 yr at baseline	Yes	None, < 1 cup/day, 1–3 cups/day, 4–5 cups/day, 6 cups/day
Iowa Womens' Health Study, Iowa (Lueth et al., 2008)	General: 127-item FFQ Coffee-specific questions: number of cups per day for normal or decaffeinated coffee Questionnaire not available	At baseline	98 826 women in Iowa aged 55–69 yr at baseline	Yes	< 1/mo, 1–3 cups/mo, 1 cup/wk, 2–4 cups/wk, 5–6 cups/wk, 1 cup/day, 2–3 cups/day, 4–5 cups/day, 6 cups/day
NIH-AARP Diet and Health Study, USA (Dubrow et al., 2012)	General: 124-item FFQ Coffee-specific questions: how many cups of coffee caffeinated or decaffeinated did you drink? When you drank coffee, mark whether you usually drank caffeine-free or caffeine-containing types (didn't drink this beverage, more than half the time I drank caffeine-free, more than half the time I drank caffeine containing)	At baseline	3.5 million men and women from American Association of Retired Persons	Yes	10 frequency categories ranging from never to > 6 times/day
Black Women's Health study, USA (Boggs et al., 2010)	General: 68-item modified version of the National Cancer Institute Block FFQ, 85-item version in 2001 Coffee-specific questions: how often did you drink coffee with caffeine? How often did you drink decaffeinated coffee? Milk or cream in coffee	At baseline and after 6 yr	59 000 African-American women	Yes	Nine frequency categories ranging from never or 1 time/mo to 6 times/day

Table 1.1 (continued)

Study, country, reference	Information-collection method	Period of information collection	Respondents	Distinction between caffeinated/ decaffeinated	Exposure metrics
Nurses' Health Study and Nurses' Health Study 2, USA (Holick et al., 2010)	General: NHS1: 61-item semi-quantitative FFQ at baseline, after 130-item FFQ NHS2: 131-FFQ Coffee-specific questions: how often did you use coffee not decaffeinated (cups) in the precedent year?	At baseline and every 3 yr	121 700 female nurses 30–55 yr old at baseline (NHS1), 116 686 female nurses 25–42 yr old at baseline (NHS2)	Yes	0–1 cups/day, 2 cups/day, 3 cups/day, 4 cups/day, 5 cups/day
Prostate, Lung Colorectal and Ovarian (PLCO) cohort, USA (Dominianni et al., 2013)	General: 77-item FFQ, NIH Health Diet History Questionnaire (DHQ) in addition for coffee intake Coffee-specific questions: how many cups of coffee caffeinated or decaffeinated did you drink? How often was the coffee you drank decaffeinated? How often did you add sugar or honey to your coffee? Each time sugar or honey was added to your coffee how much was usually added? How often did you add artificial sweetener to your coffee? What kind of artificial sweetener do you usually use? How often was non-dairy creamer added to your coffee?	At baseline	154 901 men and women, aged 55–74 yr at baseline	Yes	None, < 1 cup/day, 1 cup/day, 2–3 cups/day, > 4 cups/day
Women's Health Initiative, USA (Giri et al., 2011)	General: questionnaires on demographic characteristics, medical history, family history, reproductive history, lifestyle/ behavioural factors, and quality of life Coffee-specific questions: do you usually drink coffee each day? Number of cups of coffee	At baseline and after 3 yr	93 676 women aged 50–79 yr at baseline	Yes	0 or 1 cup/day, 1 cup/day, 2–3 cups/day, 4 cups/day 4–5 cups/day > 6 cups/day
7th Day Adventists, USA (Phillips & Snowdon, 1983; Butler et al., 2008)	General: Lifestyle questionnaire, 51-item FFQ Coffee-specific questions: frequency of coffee consumption	At baseline	34 192 members of 7th Day Adventist church in California, > 25 yr old; non-Hispanic whites	No	< 1 cup 1–2 cups/day 3–4 cups/ day 5+ cups/day

Table 1.1 (continued)

Study, country, reference	Information-collection method	Period of information collection	Respondents	Distinction between caffeinated/ decaffeinated	Exposure metrics
Lutheran Brotherhood Insurance Study, USA (Murray et al., 1981)	General: FFQ Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	17 818 male, white policy holders, aged ≥ 35 yr, of the Lutheran Brotherhood Insurance Society	No	None < 1 cup/day 1–2 cups/day < 3 cups/day 3–4 cups/day, 5–6 cups/day, ≥ 7 cups/day
Leisure World Cohort, USA (Paganini-Hill et al., 2007)	General: FFQ Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	13 978 residents of Leisure World, California; men and women. The mean of age at entry was 75.0 yr for men and 73.8 yr for women	Yes	None < 1 cup/day 1 cup/day, 2–3 cups/day, ≥ 4 cups/day
Kaiser Permanente Medical Care Program Study, USA (Efird et al., 2004)	General: lifestyle questionnaire Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	182 357 Kaiser Foundation Health Plan members	No	≤ 6 cups/day, > 6 cups/day
Cancer Prevention Study II, USA (Hildebrand et al., 2013)	General: 66-item FFQ Coffee-specific questions: frequency of coffee consumption (currently and in the previous year)	At baseline	968 432; men and women (average age 57 yr)	Yes	< 1 cup/day, 1–2 cups/day, 3–4 cups/day, > 4 cups/day
Lutheran Brotherhood Insurance Study, USA (Murray et al., 1981)	General: FFQ Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	17 633 male white policy holders, aged ≥ 35 yr, of the Lutheran Brotherhood Insurance Society	No	< 3 cups/day 3–4 cups/day, 5–6 cups/day, ≥ 7 cups/day
The Glostrup Population Studies, Denmark (Sjøl et al., 1991)	General: standardized questionnaire for coffee consumption Coffee-specific questions: number of cups of coffee Questionnaire not available	At baseline	5207 Danish women	No	0–2 cups/day, 3–6 cups/day, > 7 cups/day
The ATBC study, Finland (Lai et al., 2013)	General: FFQ in conjunction with a validated comprehensive nutrient database Coffee-specific questions: how many cups did you drink per week or per day? Sugar, whipping cream, coffee cream, light cream, milk	At baseline	29 133 Finnish male smokers	No	Participants indicated the average number of cups of coffee consumed per day or per week in the previous year

Table 1.1 (continued)

Study, country, reference	Information-collection method	Period of information collection	Respondents	Distinction between caffeinated/ decaffeinated	Exposure metrics
Hu et al. (2008), Finland	General: lifestyle questionnaire Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline (seven independent cross-sectional population surveys were carried out in six geographical areas of Finland in 1972, 1977, 1982, 1987, 1992, 1997 and 2002)	62 015 Finish participants for seven surveys, aged 25–74 yr	No	0–1cups/day, 2–3 cups/day, 4–5 cups/day, 6–7 cups/day, ≥ 8 cups/day
Bidel et al. (2013), Finland	General: lifestyle questionnaire Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	60 041 Finnish men and women aged 26–74 yr	No	1–2 cups/day, 3–4 cups/day, 5–6 cups/day, 7–9 cups/day, ≥ 10 cups/day
Norwegian National Health Screening Service for CVD, Norway (Veierød et al., 1997)	General: semi-quantitative questionnaire with 54 questions obtained information on general meal pattern, amounts, frequencies and types of specified foods and beverages Coffee-specific questions: number of cups of coffee Questionnaire not available	At baseline	25 708 men and 25 049 women aged 16–56 yr at baseline attending a Norwegian health screening in 1977–1983	No	< 2 cups/day, 3–4 cups/day, 5–6 cups/day, > 7 cups/day
Norwegian Women and Cancer (NOWAC) study, Norway (Gavrilyuk et al., 2014)	General: questionnaire on health, lifestyle, and reproductive factors Coffee-specific questions: how many cups of each kind of coffee/tea do you usually drink? (filtered, boiled, instant) Do you use sugar, milk, or cream in coffee?	At baseline	97 926 women resident in Norway, aged 30–70 yr at baseline	No	≤ 1cup/day, 2–3 cups/day, 4–7 cups/day, ≥ 8 cups/day Almost never

Table 1.1 (continued)

Study, country, reference	Information-collection method	Period of information collection	Respondents	Distinction between caffeinated/ decaffeinated	Exposure metrics
Swedish Women's Lifestyle and Health cohort study, Sweden (Weiderpass et al., 2014)	General: self-administered FFQ Coffee-specific questions: how many cups per day or per week during the preceding year	At baseline	48 249 women residing in the Uppsala Health Care Region in Sweden between 1991 and 1992	No	No
Swedish Mammography Cohort, Sweden (Friberg et al., 2009)	General: 67-item FFQ Coffee-specific questions: how often do you drink coffee?	At baseline and after 7 yr	60 634 women born between 1914–1948 living in Uppsala County of Central Sweden, women born during 1917–1948 living in Västmanland county	No	1 cup/day, 2–3 cups/day, 4 cups/day
Västerbotten Intervention Project (VIP), Sweden (Norberg et al., 2010)	General: 84-item VIP FFQ (1992–1996), 64 items VIP FFQ (1997–2007) Coffee-specific questions: two questions on coffee, one for filtered and one for boiled coffee Questionnaire not available	At baseline	64 603 residents of the county of Västerbotten turning 40, 50, and 60 yr of age	No	Never, A few times/yr, 1–3 times/mo, 1 time/wk, 2–3 times/wk, 4–6 times/wk, 1 occasion/day, 2–3 occasions/day, 4 occasions/day
Swedish Twin Registry Study, Sweden (Isaksson et al., 2002)	General: lifestyle questionnaire Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	1884 men and women recruited in 1961, aged 36–75 yr	No	0–2 cups/day, 3–6 cups/day, ≥ 7 cups/day
Discacciati et al. (2013), Sweden	General: 96-item FFQ Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline	48 645 men aged 45–79 yr residing in Västmanland and Örebro counties in central Sweden	No	None, < 1 cup/day, 1–3 cups/day, 4–5 cups/day, ≥ 6 cups/day
Netherlands Cohort Study, Netherlands (Steevens et al., 2007)	General: FFQ including question about coffee intake (yes/no, how many cups per day) Coffee-specific questions: number of cups of coffee of coffee Questionnaire not available	At baseline	120 852 men and women aged 55–69 yr at baseline	No	0 – < 1 cups/day 1 – < 3 cups/day 3 to < 5 cups/day > 5 cups/day

Table 1.1 (continued)

Study, country, reference	Information-collection method	Period of information collection	Respondents	Distinction between caffeinated/ decaffeinated	Exposure metrics
Million Women Study, UK (Yang et al., 2015)	General: questionnaire on health, lifestyle, and reproductive factors Coffee-specific questions: How many teaspoons of sugar do you add to coffee? Do you add milk to your coffee?	At baseline and approximately after 3 yr	1.3 million middle-aged women	No	< 1 cup/day, 1–2 cups/day, 3–4 cups/day, ≥ 5 cups/day
Supplementation en Vitamines et Mineraux Antioxydants Study (SUVIMAX), France (Mennen et al., 2007; Hercberg et al., 2004)	General: 24 hours dietary recall Coffee-specific questions: indication of the portion size	At baseline and every 2 mo	7876 women aged 35–60 yr and 5141 men aged 45–60 yr	No	No
Fagherazzi et al. (2011), France	General: 208-item FFQ Coffee-specific questions: frequency of coffee consumption Questionnaire not available	At baseline and after 3 yr	67 703 women	Yes	≤ 1 cup/day, 1–3 cups/day, > 3 cups/day
EPIC, 10 European countries (Bhoo-Pathy et al., 2015)	General: Country-specific questionnaires: self-administered semi-quantitative FFQ (± 260 food items), dietary history questionnaires (> 600 food items), semi-quantitative food-frequency questionnaires combined with a food record Coffee-specific questions: number of cups of coffee Questionnaires not available	At baseline	521 448 men and women	Yes, except for Denmark and France	Different exposure metrics depending on the country
Multiethnic Cohort Study of Diet and Cancer (MEC) (Kolonel et al., 2000)	General: lifestyle questionnaire including diet history Coffee-specific questions: frequency of coffee consumption Do you add any of the following to coffee: cream or half and half; milk; non-diary cream; sugar or honey; sugar substitute	At baseline	215 000 men and women primarily of African-American, Japanese, Latino, native Hawaiian and Caucasian origin	Yes	Never or hardly never, Once a month, 2–3 times/mo, Once a week, 2–3 times/wk, 4–6 times/wk Once a day, 2–3 times/day, > 4 times/day

FFQ, food frequency questionnaire; mo, month(s); wk, week(s); yr, year(s)

Table 1.2 Summary description of methods used in cohort studies investigating the relationship between coffee consumption and cancer risk

Study, country, reference	Portion size	Specific components measured	Method validated for coffee consumption
Melbourne Collaborative Cohort Study (MCCS), Australia (Ireland et al., 1994)	No	No	No
Singapore Chinese Health Study, Singapore (Ainslie-Waldman et al., 2014)	Yes, three possible portion sizes	Daily caffeine intake	No
Life Span Study, Japan (Sauvaget et al., 2002)	No	No	Yes, correlation with 24 h diary: 0.51
Japan Public Health Center-based Prospective (JPHC) study, Japan[a] (Makiuchi et al., 2016)	No	No	Yes, Spearman correlation coefficient with diet record data: Baseline Q: 0.42 for men and 0.38 for women 5 yr follow-up Q: 0.75 in men and 0.80 in women
Miyagi Cohort, Japan (Naganuma et al., 2008)	No	No	Yes, Spearman rank correlation with 3-day diet records: 0.70
Japan Collaborative Cohort (JACC) study, Japan (Yamada et al., 2014)	No	No	Yes, Spearman rank correlation 12-day dietary record: 0.81
Takayama City Cohort, Japan (Oba et al., 2008)	No	No	No
National Breast Screening Study (NBSS), Canada (Silvera et al., 2007)	Yes	No	No
Health Professionals Follow-up study, USA (Wilson et al., 2011)	No	Daily caffeine intake	Yes, correlation with two week-long diet records: 0.93
Iowa Womens' Health Study, Iowa (Lueth et al., 2008)	No	Daily caffeine intake	Yes, correlation between caffeine intake estimates from dietary recalls and FFQ: 0.95
NIH-AARP Diet and Health Study, USA (Dubrow et al., 2012)	No	Daily caffeine intake	No
Black Women's Health study, USA (Boggs et al., 2010)	Yes (small, medium, or large)	Daily caffeine intake	Yes
Nurses' Health Study and Nurses' Health Study 2, USA (Holick et al., 2010)	No	Daily caffeine intake	Yes, Pearson correlation with 1 wk diet record: 0.93
Prostate, Lung Colorectal and Ovarian (PLCO) cohort, USA (Dominianni et al., 2013)	No	Daily caffeine intake	No
Women's Health Initiative, USA (Giri et al., 2011)	No	No	No
7th Day Adventists, USA (Phillips and Snowdon, 1983)	No	No	No
Leisure World Cohort, USA (Paganini-Hill et al., 2007)	No	No	No

Table 1.2 (continued)

Study, country, reference	Portion size	Specific components measured	Method validated for coffee consumption
Kaiser Permanente Medical Care Program Study, USA (Efird et al., 2004)	No	No	No
Cancer Prevention Study II, USA (Hildebrand et al., 2013)	No	No	No
Lutheran Brotherhood Insurance Study, USA (Murray et al., 1981)	No	No	No
Glostrup Population Studies, Denmark (Sjøl et al., 1991)	No	No	No
ATBC study, Finland[b] (Lai et al., 2013)	Yes, using a colour picture booklet (four possible portion sizes)	No	Yes, correlation with diet records: 0.72–0.79
Hu et al. (2008), Bidel et al. (2013) Finland	No	No	Yes, Spearman correlation with food records: 0.89 in men, 0.85 in women
Norwegian National Health Screening Service for CVD, Norway (Veierød et al., 1997)	No	No	No
Norwegian Women and Cancer (NOWAC) study, Norway (Gavrilyuk et al., 2014)	No	No	Yes, Spearman correlation with 24 h recall: 0.82
Swedish Women's Lifestyle and Health cohort study, Sweden (Weiderpass et al., 2014)	Yes (small, medium, or large)	Daily caffeine intake	Yes, Spearman correlation with weighted record: 0.60
Swedish Mammography Cohort, Sweden (Friberg et al., 2009)	No	No	Yes, Spearman correlation with weighted record: 0.60
Västerbotten Intervention Project (VIP)[b], Sweden (Norberg et al., 2010)	No	No	Yes, correlation with 24 h recall: 0.72–0.84
Swedish Twin Registry Study, Sweden (Isaksson et al., 2002)	No	No	No
Discacciati et al. (2013), Sweden	No	No	Yes, Spearman correlation with 24 h recall: 0.71
Netherlands Cohort Study, Netherlands (Steevens et al., 2007)	No	No	Yes, validated against a 9-day diet record
Million Women Study, UK (Yang et al., 2015)	No	No	No
Supplementation en Vitamines et Mineraux Antioxydants Study (SUVIMAX), France (Mennen et al., 2007)	Yes	No	Yes
Fagherazzi et al. (2011), France	Yes	Daily caffeine intake	No

Table 1.2 (continued)

Study, country, reference	Portion size	Specific components measured	Method validated for coffee consumption
EPIC, 10 European countries (Bhoo-Pathy et al., 2015)	Yes, except for Denmark, Italy, Norway, and Umeå (Sweden)	No	No
Multiethnic Cohort Study of Diet and Cancer (MEC), Hawai (Kolonel et al., 2000)	No	Daily caffeine intake	Yes, Spearman correlation with 24 h recall: 0.72

All studies in the table used retrospective dietary assessment methods to assess coffee exposure
Temperature at which the coffee was consumed was not assessed in any of these studies
[a] In the Japan Public Health Center-based Prospective (JPHC) study, canned coffee was also assessed as specific coffee type
[b] In the ATBC study, Norwegian Women and Cancer (NOWAC) study and the Västerbotten Intervention Project (VIP), the preparation method was specified as filtered or boiled
h, hour(s); wk, week(s); yr, year(s)

assessed using an FFQ to intake assessed in the same individuals using a reference method that is deemed to be superior, but that may be prohibitive to use in large epidemiological studies due to participant burden or cost.

To illustrate, in the National Institutes of Health–American Association of Retired Persons (NIH-AARP) cohort study, the FFQ used was validated against two non-consecutive 24-hour dietary recalls (Thompson et al., 2008). In a validation set of participants, Spearman correlations between 24-hour dietary recalls and the food frequency questionnaire were 0.80 for coffee, 0.64 for caffeinated coffee, and 0.48 for decaffeinated coffee (Thompson et al., 2008; Sinha et al., 2012). Further, data obtained through a semi-quantitative FFQ in the Health Professionals Follow-Up Study (HPFS) and the FFQs used in the different waves of the Nurses' Health Study have been tested for reproducibility in a subgroup of participants who completed two FFQs 1 year apart and two 1-week diet records 6 months apart during the intervening year. Pearson correlations between the average coffee intake, assessed by two 1-week diet records completed 6 months apart, and the baseline FFQ was 0.93 in the HPFS and 0.78 in the Nurses' Health Study (Holick et al., 2010).

In the European Prospective Investigation into Cancer and Nutrition (EPIC), dietary intakes over the previous year were assessed at enrolment through validated study centre specific questionnaires which also enquired about coffee intake. This method was reported to yield very good reliability of coffee consumption compared with repeated 24-hour recalls ($r = 0.70$) (Aleksandrova et al., 2015).

Calibration studies are used to calibrate a FFQ to a reference method using a regression model (e.g. an interviewer-led diet history or multiple 24-hour recalls). For example, the EPIC study used a computerized 24-hour diet recall method to calibrate dietary measurements across countries and to correct for systematic over- or underestimation of dietary intakes (Slimani et al., 2002).

Each epidemiological study included in Section 2 of this monograph has been examined to determine whether the FFQ used to assess coffee exposure has been validated.

(c) Cohort studies

A major strength of cohort studies in nutritional epidemiology is the ability to demonstrate a temporal relationship between dietary exposure and cancer risk, as all dietary assessments

are completed before diagnosis. This mitigates concerns related to recall bias and reverse causation. However, a limitation of many cohort studies is that exposures are often measured only once, usually during enrolment, whereas cancer cases develop over a long period of time. In the case of coffee consumption, however, there is a high correlation between successive measurements taken over time.

In the Nurses' Health Study (Willett et al., 1985; 1988), data were obtained at baseline in 1980 through a validated, self-administered, 61-item, semi-quantitative FFQ which was later expanded and applied every 4 years thereafter (Michels et al., 2005). Essentially the same validated, self-administered, semi-quantitative FFQ questionnaire with 131 items was used in the HPFS (Rimm et al., 1992). For each item, participants were asked to report their average use of each food and beverage over the preceding year. Consumption of caffeinated and decaffeinated coffee was measured in cups per day. Most analyses from the Nurses' Health Study and HPFS of coffee intake have used the cumulative average intake of coffee over time, incorporating information from the repeated questionnaires (Michels et al., 2005). [A strength of these studies was that the FFQs used were extensively validated and tested for reproducibility, demonstrating good validity for coffee intake estimations. A limitation was the lack of an assessment of preparation methods, which likely affects the concentration of different compounds in coffee.]

Sinha et al. (2012) used data from the NIH-AARP Diet and Health Study in which the National Cancer Institute's Diet History Questionnaire, a 124-item FFQ with information on the frequency of intake and portion sizes over the past year, was used. Coffee intake was assessed from 0 to 6 cups/day and participants were dichotomized according to whether they reported drinking caffeinated or decaffeinated coffee more than half the time. [A strength of this study was that the FFQs used were extensively validated against 24-hour dietary recalls, showing good validity of coffee estimates (Thompson et al., 2008). Limitations were the lack of an assessment of preparation methods, which likely affect the concentration of different compounds in coffee, and the fact that decaffeinated coffee drinkers were also defined on the basis of drinking either beverage more than half of the time, which could have led to misclassification.]

In the EPIC cohort study (Riboli et al., 2002; Aleksandrova et al., 2015), dietary intake over the 12 months before enrolment was measured by country-specific validated dietary questionnaires (88–266 food items, depending on the country), self-administered in most countries. A second dietary measurement was taken from an 8% random sample of the cohort (36 900 participants) using a computerized 24-hour diet recall method to calibrate dietary measurements across countries and to correct for systematic over- or underestimation of dietary intakes. [A major strength of this study was the large variability in dietary intake across populations and the use of a computerized 24-hour diet recall method to calibrate dietary measurements across countries. A limitation was the use of different dietary questionnaires in each participating country, requiring post-harmonization and calibration of the dietary data.]

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study (Lai et al., 2014), researchers used a self-administered, modified dietary history method to capture usual dietary intake 12 months before recruitment. The dietary history method included 276 food items and a picture booklet of photographs illustrating different portion sizes (Pietinen et al., 1988). To assess coffee consumption, participants were also asked to indicate their typical cup size. [A strength of this study was that the assessment of coffee intake was shown to be valid after comparison with food records. Another important advantage of this study was that information on coffee preparation methods was collected,

allowing exploration of whether the associations between coffee intake and disease risk differed by brewing method. A limitation was that no information was collected on whether intake of coffee was caffeinated or not, and coffee intake was only assessed a single time.]

In the Iowa Women's Health Study cohort, usual dietary intake during the previous year was assessed by a 127-item, validated, semi-quantitative, self-administered FFQ, virtually identical to that used in the 1984 survey of the Nurses' Health Study (Lueth et al., 2008). For decaffeinated coffee and regular coffee, the specified daily portion size was one cup (8 fluid ounces). The validity of the FFQ was evaluated by comparing nutrient values from the FFQ to those from the average of five 24-hour dietary recall surveys for 44 study participants. Reliability was assessed by repeating the FFQ after 3–6 months. [This study had several strengths, including the assessment of reliability and accuracy of the FFQ in the Iowa cohort and the possibility of allowing for multivariable adjustment due to the extensive FFQ. A limitation was the lack of an assessment of preparation methods, which likely affects the concentration of different compounds in coffee.]

In the Singapore Chinese Health Study, cohort members completed an in-person interview that included a validated 165-item FFQ that assessed coffee intake at nine predefined levels (Johnson et al., 2011). Decaffeinated coffee consumption was not assessed. [A strength of this study was that the FFQ was shown to be valid, while the fact that only a baseline assessment of self-reported coffee intake was available should be considered a limitation because of the potential for non-differential misclassification.]

In the Norwegian Women and Cancer (NOWAC) study the questions assessing coffee consumption varied according to the year of enrolment; women were asked about either their total coffee consumption or their consumption of filtered, boiled, and instant coffee (Gavrilyuk et al., 2014). The categories of coffee consumption in cups per day or week were also different in two versions of the questionnaire. Post-harmonization of the dietary data was therefore needed to create a common version of frequencies. Based on a 24-hour recall investigation in the NOWAC cohort, a standard cup size of 2.1 dL (7.1 oz) was assumed. [An advantage of this study was the broad range of exposures in the cohort and information on several coffee brewing methods. Limitations were the lack of information about decaffeinated coffee and preparation methods, which can also influence the level and properties of some coffee compounds.]

In the multiethnic, prospective, population-based Northern Manhattan Study (NOMAS), participants were administered a modified Block National Cancer Institute FFQ at baseline. Questions assessed the average consumption of decaffeinated and regular (caffeinated) coffee in units of medium cups according to nine different frequency categories (Gardener et al., 2013). [Despite the use of a validated and reliable Block FFQ, there were some limitations to the coffee exposure data. The analysis focuses on frequency of consumption and is not standardized for cup size. Although the FFQ was designed to measure average consumption over the previous year, dietary information was collected at one time (baseline) and information on duration of coffee consumption as well as changes during follow-up was lacking. Further, the questionnaire did not determine whether individuals were drinking boiled unfiltered or filtered coffee.]

In the Japan Collaborative Cohort Study (Yamada et al., 2014), information about coffee consumption and other lifestyle factors was obtained using a self-administered questionnaire. The question regarding coffee consumption was previously assessed by a validation study, which reported a strong agreement with 12-day weighted dietary records. [A limitation of this study was that only baseline data were collected; no details of coffee consumption,

such as the use of caffeinated or decaffeinated coffee and the method of coffee preparation (e.g. filtered or boiled), were collected.]

(d) Case–control studies

A description of the case–control studies included in this report is provided in Section 2. Case–control studies investigating the association between coffee intake and cancer risk are limited as they assess dietary intake after cancer has been diagnosed, which can lead to recall bias if intakes of the distant or recent past are assessed. In addition, for some cancer types, notably cancers of the digestive tract, patients may change their dietary intake with the potential to bias assessment of the usual coffee intake in the past. As a result, investigators usually ask cases included in their studies to recall dietary intake in a period before the diagnosis of cancer in an attempt to capture usual diet before diagnosis.

For these reasons, the approach used to assess dietary intake in the distant past is often conceptualized differently from the typical FFQs used in cohort studies by including extra questions to help the respondent remember details of past consumption. For example, in the Yale Study of Skin Health in Young People, Ferrucci et al. (2014) participants were first asked whether they drunk at least one cup of caffeinated coffee per week for at least 6 months. Those who responded affirmatively were then asked the age at which they began drinking caffeinated coffee at this frequency, as well as whether they were currently drinking it at least weekly or, if not, the age at which they had stopped. Thereafter, participants reported the average number of cups of coffee they drank per day and the number of years of consumption. [Even though the possibility of recall bias was still a limitation in this case–control study, this cognitive approach is considered an important strength in avoiding such bias.]

In the Western Australian Bowel Health Study (WABOHS), data on coffee consumption 10 years previously were collected by self-administered questionnaire (Green et al., 2014). The questions were adapted from the Arizona Tea Questionnaire, which was shown to have high test–retest reliability and high relative validity relative to 4-day food records. Data were collected on the frequency of consumption of hot caffeinated coffee, hot decaffeinated coffee, and iced coffee. [A limitation of this study was that asking participants to recall their dietary intake 10 years before may have affected the quality of recall, leading to increased likelihood of exposure misclassification which could bias the risk estimates towards the null.]

(e) Covariates of coffee consumption

The estimation of cancer risk associated with coffee intake may be influenced by other dietary and/or lifestyle factors that are correlated with coffee consumption. However, few studies investigated associations between coffee consumption and other lifestyle factors, which can vary depending on the population under study.

Freedman et al. (2012) investigated associations of coffee consumption with other dietary and lifestyle factors in the NIH-AARP Diet and Health Study in the USA. Coffee drinkers were more likely than non-drinkers of coffee to smoke cigarettes and also consume more alcoholic drinks and more red meat; coffee drinkers also tended to have lower levels of education, vigorous physical activity, and intake of fruits and vegetables (Freedman et al., 2012).

In a Japanese study, Yamada et al. (2014) reported that subjects who consumed high quantities of coffee were also more likely to be smokers, alcohol drinkers, and to regularly eat beef or pork, but were younger and better educated.

In the Singapore Chinese Health Study, Ainslie-Waldman et al. (2014) investigated differences in lifestyle and sociodemographic factors by the amount of coffee consumption. Among both men and women, a higher level of coffee consumption was associated with a higher prevalence of current smoking and alcohol

consumption, as well as lower proportions with a higher education or a history of diabetes. Those who drank more coffee also consumed more total energy but less fruit and vegetables. However, men who drank more than 4 cups of coffee per day had lower levels of BMI compared to those consuming < 1 cup per day.

The effect of coffee consumption on the risk of cancer may therefore be confounded by intake of other foods and lifestyle factors, in particular smoking status, but also drinking, BMI, meat consumption, and age. Adequate adjustment for these potential confounders is therefore essential, but only possible if researchers have included robust measures of exposure to these potential confounders and have used analytical methods that adequately adjust for these variables. Each study reviewed in this monograph, considered by cancer site in Section 2, has been examined in terms of ability to adequately adjust for potential confounders.

(f) Limitations

There was substantial heterogeneity across the studies reviewed by the Working Group due to a variety of factors, such as methods of dietary assessment and/or measurement, variable definitions (e.g. food groups, serving sizes), levels of detail (e.g. caffeinated versus decaffeinated), analytical categorizations (e.g. servings per week, grams per day), exposure contrasts (analytical cut-points and comparisons of intake levels), and degree of adjustment for potential confounding factors.

An important limitation in almost all epidemiological studies investigating the relationship between coffee consumption and cancer risk is the lack of details in the description of the coffee consumed. Descriptors such as the preparation method (e.g. filtered or not), the coffee concentration, and drinking temperature (see the monograph on Drinking Mate and Very Hot Beverages in the present volume) are almost always missing, although some of these factors could be important to consider in the relationship between coffee consumption and cancer risk. Another limitation is the reporting of the exposure assessment, which is sometimes insufficiently detailed to allow a critical and correct evaluation of the results reported (Lachat et al., 2016). These limitations in exposure assessment should be considered when interpreting the results reported in epidemiological studies.

(g) Biological markers

To date, very few studies have used biomarkers to estimate coffee intake in cancer epidemiological studies. However, the use of mass spectrometry techniques and metabolomic approaches has recently allowed the identification of several promising coffee biomarkers. A metabolomic analysis of baseline serum samples from participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial in the USA identified trigonelline, quinate, 1-methylxanthine and paraxanthine, along with *N*-2-furoylglycine and catechol sulfate, as potential biomarkers of coffee intake (Guertin et al., 2014). In a nested case–control study of colorectal cancer risk in the same cohort, plasma trigonelline and quinate concentrations were best correlated with coffee intake as assessed by FFQ (Guertin et al., 2015). Negative associations of these metabolites and several others with diagnosis of cancer of the colorectum were observed.

Biomarkers of coffee consumption have also been investigated through comparisons of coffee consumers and non-consumers in studies of free-living subjects. Dihydrocaffeic acid and its 3-glucuronide measured in 24-hour pooled urine were found to discriminate between high and low levels of coffee consumption with high sensitivity and specificity in a dietary intervention study in the UK, suggesting potential as markers of habitual coffee consumption (Lloyd et al., 2013). In the EPIC cohort, concentrations of 16 conjugated metabolites of phenolic acids, mostly glucuronide or sulfate esters, were

measured in 24-hour urine samples, and their levels were found to be correlated with both acute and regular coffee intake (Edmands et al., 2015). Dihydroferulic acid sulfate, feruloylquinic acid glucuronide, ferulic acid sulfate, and guaiacol glucuronide were the metabolites whose measured intensities best predicted the highest or lowest quintile of coffee intake. Coffee intake markers including non-phenolic metabolites were searched for in morning spot urine of 39 French coffee consumers from the Supplémentation en Vitamines et Minéraux Anti-oxydants (SUVIMAX) cohort (Rothwell et al., 2014). The intensities of several coffee-derived metabolites accurately classified consumers into high- and low-intake groups. The most effective of these were the diterpene atractyligenin glucuronide, the cyclic amino acid cyclo(isoleucyl-prolyl), and trignolline.

Several small, short-term intervention studies provided detailed information of coffee compounds found in blood or urine after coffee consumption. For example, urinary concentrations of trigonelline and the product of the coffee roasting process *N*-methylpyridinium best distinguished subjects given coffee from controls (Lang et al., 2011). Both compounds remained elevated in the urine of coffee consumers for at least two days after coffee consumption. Another coffee roasting product, *N*-2-furoylglycine, was identified as a promising biomarker of coffee intake in a metabolomic study based on spot urine profiles of five volunteers administered one cup of espresso coffee (Heinzmann et al., 2015). Trigonelline, caffeine, dimethylxanthine, methylxanthine, and ferulic acid in urine were also found to discriminate subjects administered a standardized dose of coffee from controls (Lang et al., 2013). [Dimethylxanthine and methylxanthine are metabolites of caffeine, so intake of other beverages containing caffeine (e.g. soft drinks, energy drinks, or tea) limit the specificity of caffeine and its metabolites as biomarkers of coffee intake.] Several other metabolites of chlorogenic acids were found to discriminate coffee consumers from controls. Dihydroferulic acid 4-*O*-sulfate and dihydrocaffeic acid 3-*O*-sulfate attained the highest plasma concentrations after coffee intake, while the latter compound and feruloylglycine were reported as the most effective urinary biomarkers of intake (Stalmach et al., 2009). Most of these coffee metabolites are eliminated within one day (Stalmach et al., 2009; Lang et al., 2013). [The rapid elimination of these metabolites should not be a limitation to using them as coffee biomarkers, due to the regular intake of coffee by most coffee consumers.]

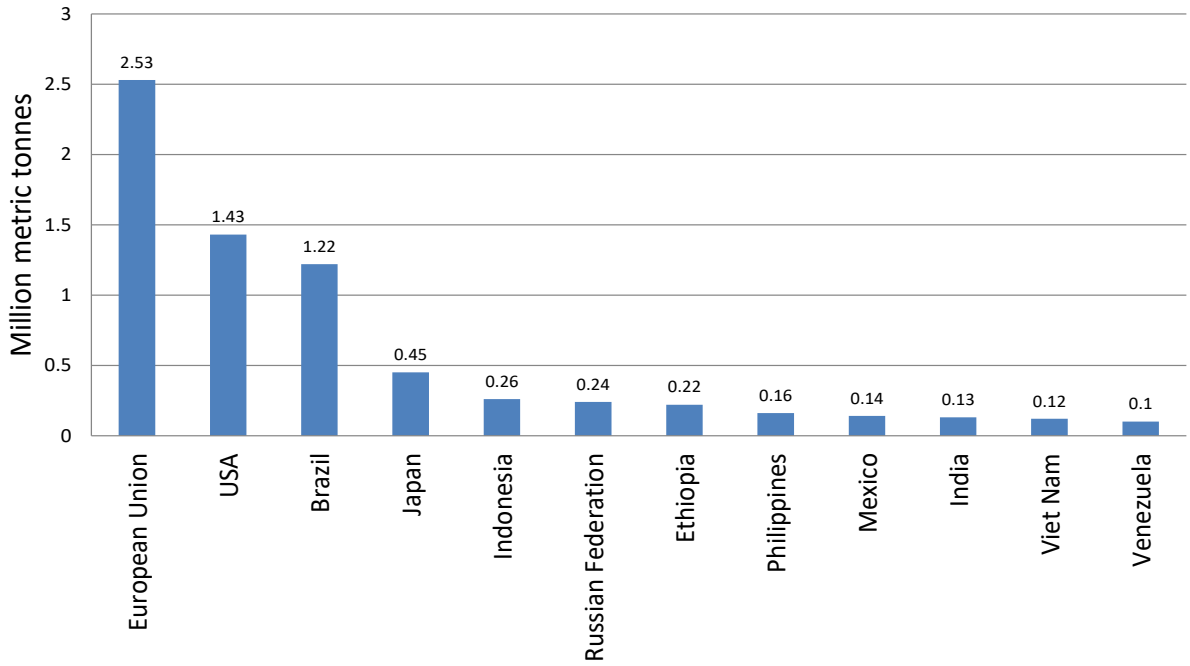
[The Working Group noted that the specificity of biomarkers for coffee drinking has not always been assessed as it relies on the known presence or absence of such compounds in other foods or beverages, and this information is not always available. In addition, some biomarkers might be specific to particular coffee brews, roasts, or varieties. The combinations of several biomarkers may provide clues regarding the type of coffee consumed (e.g. caffeinated vs decaffeinated coffee, varying degrees of roasting). The validity of biomarkers identified in clinical trials should be treated with caution and cannot necessarily be generalized to diverse free-living populations.]

1.3.2 Production and consumption volumes

Coffee production in 2015 was estimated to be about 9 million tonnes (ICO, 2016). In recent years, about two thirds of the world production has typically been Arabica coffee and one third Robusta. Brazilian production (mainly Arabica) accounted for 30%, followed by Viet Nam (19%, mainly Robusta), Colombia (9%, mainly Arabica), Indonesia (8%), and Ethiopia (4%), among others (ICO, 2016; USDA, 2016).

World coffee consumption in 2014 and 2015 was estimated to be about 9 million tonnes (ICO, 2016; USDA, 2016). Together, the European

Fig. 1.4 Total annual coffee consumption in 2014, in selected countries or regions with high consumption



From International Coffee Organization (ICO, 2016)

Union countries are responsible for 28% of the world coffee consumption. Because of their large territorial extension and populations associated with high consumptions, the USA and Brazil are the individual countries with the highest consumption, accounting for about 16% and 13% of total world consumption, respectively. Japan (5.6%) and the Russian Federation (2.2%) follow (ICO, 2016; Fig. 1.4).

The consumption of decaffeinated coffee as a percentage of total consumption in 2009 was estimated as being highest in Spain (17%), USA (16%), UK (13%), Netherlands (12%), and Belgium/Luxembourg (10%). In all other countries the percentage was below 10% (ITC, 2012).

Coffee consumption at the population level can be measured in several ways. Data on the amounts of coffee in international trade are typically expressed in terms of disappearance, defined as net imports into a country, estimated by the difference between gross imports and re-exports (ICO, 2016). An estimate of per capita coffee consumption can be obtained by dividing disappearance (typically reported in kilograms per year) by population. This indicator is primarily useful for ranking countries with respect to relative levels of consumption. Disappearance data for trade in green coffee beans indicate that the Nordic countries Finland, Norway, Denmark, and Iceland and Austria are leading consumers of coffee by this measure (Table 1.3). Other important consumers are Switzerland, Montenegro, Sweden, Lebanon and Germany (ICO, 2016). Historical consumption data from 2011 to 2014 (ICO, 2016) show a modest increase in worldwide consumption, with stagnation in countries with a high per capita consumption, mainly in Europe. A few countries in Central America, Mexico, and South America also showed this trend. Increasing consumption is observed in countries that are

Table 1.3 Annual coffee consumption per person from disappearance data for green coffee beans (10 highest consuming countries, 2013)

Country	Arithmetic mean consumption (kg/person per year)
Finland	12.07
Norway	9.01
Denmark	8.75
Austria	8.74
Iceland	8.43
Switzerland	8.29
Montenegro	7.61
Sweden	7.33
Lebanon	6.97
Germany	6.92

With permission from the International Coffee Organization (unpublished work)

currently lower per capita consumers, situated mainly in Asia, Oceania and Africa. Examples are Egypt, India, Indonesia, Philippines, Saudi Arabia, Thailand, Turkey, and Viet Nam.

The preceding estimates of per capita consumption of traded coffee beans may not reflect the amounts of coffee beverage consumed by individuals, however. Individual-level consumption of coffee beverages is assessed by dietary surveys (see Section 1.3.1) or specialized surveys of coffee drinking. An important consideration in survey data is that the proportion of coffee drinkers in a given population is less than 100%, with that proportion varying between and within countries. Consequently, average consumption among all respondents tends to be less than the average among coffee drinkers only. The latter quantity corresponds most closely to dose and is comparable to the exposure indicators typically used in epidemiological studies. Table 1.4 presents survey data on the average coffee consumption of adult coffee drinkers in countries with available data. A limitation of such survey data is that they are not available for all countries and the details available within countries may not be comparable. Data in Table 1.4 were obtained from a FFQ for the USA (NCA, 2016), 24-hour recall for Europe (EFSA, 2011), and purchasing data for Brazil (ABIC, 2016). Consumption is organized by range of consumption and average amount consumed daily. Based on these assessments, the highest individual coffee consumption is in Denmark followed by the USA, Netherlands, and Germany. There is also a very large individual variation (23–1914 g/day). [The Working Group noted that the data from the different countries, including within Europe, were collected from different sources with differences in years and types of questionnaires, among others.]

1.4 Chemical constituents

1.4.1 Major constituents

An overview of compounds present in green, roasted, brewed, instant, and decaffeinated coffees was provided in the previous *IARC Monograph* on coffee (IARC, 1991). More recent updates have been published (Farah, 2012; Oestreich-Janzen, 2013).

The compounds in coffee are typically classified into non-volatile and volatile fractions. The non-volatile compounds include water, carbohydrates and fibre, proteins and free amino acids, lipids, minerals (40% potassium), organic acids,

Table 1.4 Mean daily coffee beverage consumption among coffee drinkers in selected countries

Country, year	Arithmetic mean[d] (mL/day)	Range[d] (mL/day)	Proportion of consumers within population (%)
Denmark, NR[a]	846	86–1914	83
USA, 2016[b]	740[e]	NR	57 consuming on previous day, 76 in previous year
Netherlands, 2007–2010[a]	573	100–1253	75
Germany, NR[a]	539	100–1199	82
Sweden, 2010–2011[a]	431	75–875	78
Latvia, 2004[a]	309	90–650	83
Ireland, NR[a]	259	23–783	54
Brazil, 2016[c]	222	NR	54
Italy, 2005–2006[a]	108	20–240	89
Romania, 2005–2006[a]	93	11–253	68
UK, NR[a]	147	9–552	34

[a] European Food Safety Association (EFSA, 2011)
[b] National Coffee Association (NCA, 2016)
[c] Brazilian Coffee Industry Association (ABIC, 2016)
[d] Converted to L/day with a density of 1.0
[e] Reported mean of 2.96 cups/day converted to g/day assuming 250 g/cup
NR, not reported

chlorogenic acids, trigonelline, and caffeine. The volatile fraction may contain more than 950 different compounds from chemical classes such as furans and pyrans, pyrazines, pyrroles, ketones, phenols, hydrocarbons, alcohols, aldehydes, pyridines, and other compounds (IARC, 1991; Farah, 2012). An overview of the composition of roasted coffee seeds is provided in Table 1.5. Minor compounds such as 16-*O*-methylcafestol and kahweol (Monakhova et al., 2015) or minor chlorogenic acid compounds (Farah & Donangelo, 2006) vary between Arabica and Robusta species.

As a natural product, the chemical composition of coffee may vary to a wide degree depending on the species and degree of maturation, as well as soil composition, climate, agricultural practices, and storage conditions (Farah, 2012). For example, the caffeine content in coffee beverages (including decaffeinated beverages) may range over 0.3–380 mg/100 mL (Farah, 2012; Lachenmeier et al., 2013); the niacin content may range over about 10–40 mg/100 mL (Adrian & Frangne, 1991); and cafestol may be present in quantities of 2–5 mg/100 mL (Zhang et al., 2012). Table 1.6 presents the typical composition of coffee brew from medium-roasted coffee beans.

Caffeine is thought to be one of the principal components with pharmacological effects in coffee, and its mild stimulating effect may be the reason for the popularity of this beverage (Lachenmeier et al., 2012). According to a review by the European Food Safety Authority (EFSA), a standard cup of coffee in Europe has a caffeine concentration of about 38–69 mg/100 mL; an average of 45 mg/100 mL was used for intake assessment (EFSA, 2015).

For further details on caffeine, see IARC (1991).

1.4.2 Other constituents and contaminants

Some compounds found in coffee have known toxic properties and, in some cases, carcinogenic effects. Coffee constituents and contaminants that have been evaluated by IARC and classified as *possibly carcinogenic to humans* (Group 2B) or higher are shown in Table 1.7. These include heating-induced compounds benzo[*a*]pyrene

Table 1.5 Chemical composition of roasted *Coffea arabica* and *Coffea canephora* seeds

Compounds	Concentration[a] (g/100 g)	
	Coffea arabica	*Coffea canephora*
Carbohydrates/fibre		
Sucrose	4.2–tr	1.6–tr
Reducing sugars	0.3	0.3
Polysaccharides (arabinogalactan, mannan, and glucan)	31–33	37
Lignin	3.0	3.0
Pectins	2.0	2.0
Nitrogenous compounds		
Protein	7.5–10	7.5–10
Free amino acids	ND	ND
Caffeine	1.1–1.3	2.4–2.5
Trigonelline	1.2–0.2	0.7–0.3
Nicotinic acid	0.016–0.026	0.014–0.025
Lipids		
Coffee oil (triglycerides with unsaponifiables)	17.0	11.0
Diterpene esters	0.9	0.2
Minerals	4.5	4.7
Acids and esters		
Chlorogenic acids	1.9–2.5	3.3–3.8
Aliphatic acids	1.6	1.6
Quinic acid	0.8	1.0
Melanoidins	25	25

[a] Content varies according to cultivar, agricultural practices, climate, soil composition, methods of analysis, and roasting degree
ND, not detected; tr, trace
Reproduced from Farah (2012). Coffee Constituents. Coffee: Wiley-Blackwell; 2012. p. 21–58

(Group 1), acrylamide (Group 2A), acetaldehyde and furan (both Group 2B), the mycotoxins aflatoxin (Group 1) and ochratoxin A (Group 2B), and pesticides DDT, captafol (both Group 2A), and dichlorvos (Group 2B).

The prevalence of mycotoxins, notably aflatoxins and ochratoxin A, in green coffee beans is high (Soliman, 2002; Paterson et al., 2014). In tropical and subtropical regions where coffee is grown, ochratoxin A and aflatoxin B_1 are produced by *Aspergillus* species. Contamination will vary not only with country but with individual farms, depending on manufacturing practices. It has been speculated that with climate change aflatoxin may gain importance as a hazard to coffee production (Paterson et al., 2014).

The high temperatures of coffee roasting significantly decrease aflatoxin and ochratoxin A levels in coffee; reductions of the concentration of ochratoxin A by more than 90% have been observed, depending on the degree of roasting (Soliman, 2002; Romani et al., 2003; Ferraz et al., 2010).

Few studies have assessed the levels of ochratoxin A in coffee beverages. Only trace levels of ochratoxin A (< 1 µg/L) were detected in ready-to-drink coffee (Noba et al., 2009), and ochratoxin A has been detected in instant coffee (IARC, 1991; Vecchio et al., 2012). Although aflatoxin has been detected in green and roasted coffee beans (Soliman, 2002), data on aflatoxin occurrence in brewed coffee are unavailable (Vieira et al., 2015).

Another group of coffee contaminants are biogenic amines, which may be produced by microorganisms in defective beans or during storage. Putrescine, spermidine, and spermine

Table 1.6 Typical chemical composition per 100 mL of coffee brew from medium roasted coffee

Constituent[a]	Concentration (mg/100 mL)
Caffeine	50–380
Chlorogenic acids	35–500
Trigonelline	40–50
Soluble fibre	200–800
Protein	100
Lipids	0.8
Minerals	250–700
Niacin	10
Melanoidins	500–1500

[a] Brew composition varies according to blend, roasting degree, grind, and method of preparation
From Farah (2012)

Table 1.7 Summary of IARC-evaluated compounds that may be present in coffee

Agent	*IARC Monographs* evaluation of carcinogenicity			*IARC Monographs* Volume (year of publication in print)
	In animals	In humans	IARC Group	
Acetaldehyde	Sufficient	Inadequate	2B	71 (1999)
Acrylamide	Sufficient	Inadequate	2A	60 (1994)
Aflatoxins	Sufficient	Sufficient	1	100F (2012)
Benzo[*a*]pyrene	Sufficient	No data	1	100F (2012)
Caffeic acid	Sufficient	No data	2B	56 (1993)
Captafol	Sufficient	No data	2A	53 (1991)
DDT and associated compounds	Sufficient	Limited	2A	113 (2018)
Dichlorvos	Sufficient	Inadequate	2B	53 (1991)
Dichloromethane	Sufficient	Limited	2A	110 (2017)
Furan	Sufficient	Inadequate	2B	63 (1995)
Methyl isobutyl ketone	Sufficient	No data	2B	101 (2013)
Ochratoxin A	Sufficient	Inadequate	2B	56 (1993)

are considered to be major amines in coffee. Tyramine (one of the most toxic amines), cadaverine, and others are considered to be minor amines in coffee (Farah, 2012).

While roasting largely destroys contaminants such as mycotoxins and thermolabile pesticide residues that may exist in the green coffee, several heat-induced contaminants may be formed during roasting. These include acetaldehyde (Uebelacker & Lachenmeier, 2011), furan (Wenzl et al., 2007; Petisca et al., 2013; Lachenmeier, 2015), acrylamide (Lantz et al., 2006; Guenther et al., 2007), and polycyclic aromatic hydrocarbons (PAHs) including benzo[*a*]pyrene (Houessou et al., 2007). It has been reported that lower roasting temperatures and shorter roasting times tend to reduce the formation of PAHs and acrylamide (Guenther et al., 2007; Houessou et al., 2007; Soares et al., 2009).

Among the heat-induced contaminants in coffee, only furan has been systematically studied; it occurs in every coffee brew at about 40–100 µg/L depending on the preparation method (Waizenegger et al., 2012). The average furan intake per cup of coffee was estimated as 0.12 µg/kg body weight (Lachenmeier, 2015). In an experimental study, Houessou et al. (2007) reported total PAH concentrations of < 1 µg/L

in brewed coffee. [The Working Group noted the absence of systematic survey data on PAHs in coffee beans or coffee brews.]

Some cohort studies have reported coffee as one of the largest contributor to acrylamide intake (e.g. Larsson et al., 2009; Wilson et al., 2012). [Other data indicated that fried potatoes and bread products are the major contributors to the dietary exposures of acrylamide for most countries (JECFA, 2011). The Working Group noted that the populations in some cohort studies may therefore have been biased towards groups with a high consumption of coffee relative to fried foods.]

References

ABIC (2016). Indicadores da indústria de café no Brasil – 2015. Available from: http://abic.com.br/estatisticas/indicadores-da-industria/indicadores-da-industria-2015/ [Portuguese]

Adrian J, Frangne R (1991). Synthesis and availability of niacin in roasted coffee. *Adv Exp Med Biol*, 289:49–59. doi:10.1007/978-1-4899-2626-5_4 PMID:1897406

Ainslie-Waldman CE, Koh WP, Jin A, Yeoh KG, Zhu F, Wang R, et al. (2014). Coffee intake and gastric cancer risk: the Singapore Chinese health study. *Cancer Epidemiol Biomarkers Prev*, 23(4):638–47. doi:10.1158/1055-9965.EPI-13-0886 PMID:24608187

Aleksandrova K, Bamia C, Drogan D, Lagiou P, Trichopoulou A, Jenab M, et al. (2015). The association of coffee intake with liver cancer risk is mediated by biomarkers of inflammation and hepatocellular injury: data from the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*, 102(6):1498–508. doi:10.3945/ajcn.115.116095 PMID:26561631

Anthony F, Combes C, Astorga C, Bertrand B, Graziosi G, Lashermes P (2002). The origin of cultivated Coffea arabica L. varieties revealed by AFLP and SSR markers. *Theor Appl Genet*, 104(5):894–900. doi:10.1007/s00122-001-0798-8 PMID:12582651

Beaton GH (1994). Approaches to analysis of dietary data: relationship between planned analyses and choice of methodology. *Am J Clin Nutr*, 59(1) Suppl: 253S–61S. PMID:8279436

Bee S, Brando CHJ, Brumen G, Carvalhaes N, Kolling-Speer I, Speer K, et al. (2005). The raw bean. In: Illy A, Viani R, editors. Espresso coffee, the science of quality. Elsevier Academic Press; pp. 87–178. doi:10.1016/B978-012370371-2/50004-4

Bhoo-Pathy N, Peeters PH, Uiterwaal CS, Bueno-de-Mesquita HB, Bulgiba AM, Bech BH, et al. (2015). Coffee and tea consumption and risk of pre- and post-menopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Breast Cancer Res*, 17(15):15–0521. doi:10.1186/s13058-015-0521-3 PMID:25637171

Bidel S, Hu G, Jousilahti P, Pukkala E, Hakulinen T, Tuomilehto J (2013). Coffee consumption and risk of gastric and pancreatic cancer–a prospective cohort study. *Int J Cancer*, 132(7):1651–9. doi:10.1002/ijc.27773 PMID:22886387

Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L (1986). A data-based approach to diet questionnaire design and testing. *Am J Epidemiol*, 124(3):453–69. PMID:3740045

Boggs DA, Palmer JR, Stampfer MJ, Spiegelman D, Adams-Campbell LL, Rosenberg L (2010). Tea and coffee intake in relation to risk of breast cancer in the Black Women's Health Study. *Cancer Causes Control*, 21(11):1941–8. doi:10.1007/s10552-010-9622-6 PMID:20680436

Borrelli RC, Esposito F, Napolitano A, Ritieni A, Fogliano V (2004). Characterization of a new potential functional ingredient: coffee silverskin. *J Agric Food Chem*, 52(5):1338–43. doi:10.1021/jf034974x PMID:14995143

Butler TL, Fraser GE, Beeson WL, Knutsen SF, Herring RP, Chan J, et al. (2008). Cohort profile: the Adventist Health Study-2 (AHS-2). *Int J Epidemiol*, 37(2):260–5. doi:10.1093/ije/dym165 PMID:17726038

CAC (2009). Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Report of the 3rd session of the Codex Committee on Contaminants in Foods, Proposed Draft Code of Practice for the Prevention and Reduction of Ochratoxin A Contamination in Coffee, Appendix VI, page 73. Agenda Item 8. ALINORM 09/32/41.

Charrier A, Berthaud J (1987). Botanical classification of coffee. In: Clifford MN, Willson KC, editors. Coffee botany, biochemistry and production of beans and beverage. Connecticut, USA: the AVI publishing company, Inc., 1985. pp. 13–47.

Corrochano BR, Melrose JR, Bentley AC, Fryer PJ, Bakalis S (2015). A new methodology to estimate the steady-state permeability of roast and ground coffee in packed beds. *J Food Eng*, 150:106–16. doi:10.1016/j.jfoodeng.2014.11.006

Davis AP, Chester M, Maurin O, Fay MF (2007). Searching for the relatives of Coffea (Rubiaceae, Ixoroideae): the circumscription and phylogeny of Coffeeae based on plastid sequence data and morphology. *Am J Bot*, 94(3):313–29. doi:10.3732/ajb.94.3.313 PMID:21636404

Davis AP, Govaerts R, Bridson DM, Stoffelen P (2006). An annotated taxonomic conspectus of the genus *Coffea* (Rubiaceae). *Bot J Linn Soc*, 152(4):465–512. doi:10.1111/j.1095-8339.2006.00584.x

Debry G (1989). Le Café [Coffee], Nancy, France: Centre de Nutrition Humaine. [French]

Discacciati A, Orsini N, Andersson SO, Andrén O, Johansson JE, Mantzoros CS, et al. (2013). Coffee consumption and risk of localized, advanced and fatal prostate cancer: a population-based prospective study. *Ann Oncol*, 24(7):1912–8. doi:10.1093/annonc/mdt105 PMID:23508823

Dominianni C, Huang WY, Berndt S, Hayes RB, Ahn J (2013). Prospective study of the relationship between coffee and tea with colorectal cancer risk: the PLCO Cancer Screening Trial. *Br J Cancer*, 109(5):1352–9. doi:10.1038/bjc.2013.434 PMID:23907431

Dubrow R, Darefsky AS, Freedman ND, Hollenbeck AR, Sinha R (2012). Coffee, tea, soda, and caffeine intake in relation to risk of adult glioma in the NIH-AARP Diet and Health Study. *Cancer Causes Control*, 23(5):757–68. doi:10.1007/s10552-012-9945-6 PMID:22457000

Edmands WM, Ferrari P, Rothwell JA, Rinaldi S, Slimani N, Barupal DK, et al. (2015). Polyphenol metabolome in human urine and its association with intake of polyphenol-rich foods across European countries. *Am J Clin Nutr*, 102(4):905–13. doi:10.3945/ajcn.114.101881 PMID:26269369

Efird JT, Friedman GD, Sidney S, Klatsky A, Habel LA, Udaltsova NV, et al. (2004). The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors. *J Neurooncol*, 68(1): 57–69. doi:10.1023/B:NEON.0000024746.87666.ed PMID:15174522

EFSA (2011). The EFSA comprehensive European Food Consumption Database. Parma, Italy: European Food Safety Authority. Available from: http://www.efsa.europa.eu/en/food-consumption/comprehensive-database.

EFSA (2015). Scientific Opinion on the safety of caffeine. Panel on Dietetic Products, Nutrition and Allergies *EFSA J*, 13(5):4120.

Fagherazzi G, Touillaud MS, Boutron-Ruault MC, Clavel-Chapelon F, Romieu I (2011). No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study. *Public Health Nutr*, 14(7):1315–20. doi:10.1017/S1368980011000371 PMID:21466740

FAO (2014). Arabica coffee manual for Lao PDR 2005, January 2014. FAO Corporate Document Repository. Rome, Italy: Food and Agriculture Organization of the United Nations. Available from: http://www.fao.org/docrep/008/ae939e/ae939e00.htm.

Farah A (2009). Coffee as a speciality and functional beverage. In: Paquin P, editor. Functional and speciality beverage technology. 1st ed. Cambridge, UK: Woodhead Publishing Series in Food Science, Technology and Nutrition. doi:10.1533/9781845695569.3.370

Farah A (2012). Chapter 2: Coffee constituents. In: Chu Y-F, editor. Coffee: emerging health effects and disease prevention. Oxford, UK: Wiley-Blackwell. doi:10.1002/9781119949893.ch2

Farah A, de Paulis T, Moreira DP, Trugo LC, Martin PR (2006). Chlorogenic acids and lactones in regular and water-decaffeinated arabica coffees. *J Agric Food Chem*, 54(2):374–81. doi:10.1021/jf0518305 PMID:16417293

Farah A, Donangelo CM (2006). Phenolic compounds in coffee. *Braz J Plant Physiol*, 18(1):23–36. doi:10.1590/S1677-04202006000100003

Farah A, Ferreira dos Santos T (2015). The coffee plant and beans: an introduction. In: Preedy VR, editor. Coffee in health and disease prevention. San Diego (CA), USA: Academic Press; pp. 5–10. doi:10.1016/B978-0-12-409517-5.00001-2

Fernandes F (2017). Chapter 8, Roasting. In: Farah A, editor. Coffee: chemistry, quality and health implications. London, UK: Royal Society of Chemistry.

Ferraz MB, Farah A, Iamanaka BT, Perrone D, Copetti MV, Marques VX, et al. (2010). Kinetics of ochratoxin A destruction during coffee roasting. *Food Contr*, 21(6):872–7. doi:10.1016/j.foodcont.2009.12.001

Ferrucci LM, Cartmel B, Molinaro AM, Leffell DJ, Bale AE, Mayne ST (2014). Tea, coffee, and caffeine and early-onset basal cell carcinoma in a case-control study. *Eur J Cancer Prev*, 23(4):296–302. doi:10.1097/CEJ.0000000000000037 PMID:24841641

Filho GRS, Vieira HD, Rodrigues WP, Partelli FL (2015). Comparison between manual and semi-mechanical harvest of coffee fruit in mountainous areas. *Afr J Agric Res*, 10(28):2724–30. doi:10.5897/AJAR2014.9356

Flament I (2002). Coffee flavor chemistry. West Sussex, England: John Wiley & Sons, Ltd.

Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R (2012). Association of coffee drinking with total and cause-specific mortality. *N Engl J Med*, 366(20):1891–904. doi:10.1056/NEJMoa1112010 PMID:22591295

Friberg E, Orsini N, Mantzoros CS, Wolk A (2009). Coffee drinking and risk of endometrial cancer–a population-based cohort study. *Int J Cancer*, 125(10):2413–7. doi:10.1002/ijc.24543 PMID:19585497

Gardener H, Rundek T, Wright CB, Elkind MS, Sacco RL (2013). Coffee and tea consumption are inversely associated with mortality in a multiethnic urban population. *J Nutr*, 143(8):1299–308. doi:10.3945/jn.112.173807 PMID:23784068

Gavrilyuk O, Braaten T, Skeie G, Weiderpass E, Dumeaux V, Lund E (2014). High coffee consumption and different brewing methods in relation to postmenopausal endometrial cancer risk in the Norwegian women and cancer study: a population-based prospective study. *BMC Womens Health*, 14(1):48–14. doi:10.1186/1472-6874-14-48 PMID:24666820

Geromel C, Ferreira LP, Guerreiro SM, Cavalari AA, Pot D, Pereira LF, et al. (2006). Biochemical and genomic analysis of sucrose metabolism during coffee (Coffea arabica) fruit development. *J Exp Bot*, 57(12):3243–58. doi:10.1093/jxb/erl084 PMID:16926239

Giri A, Sturgeon SR, Luisi N, Bertone-Johnson E, Balasubramanian R, Reeves KW (2011). Caffeinated coffee, decaffeinated coffee and endometrial cancer risk: a prospective cohort study among US postmenopausal women. *Nutrients*, 3(11):937–50. doi:10.3390/nu3110937 PMID:22254087

Gloess AN, Schönbächler B, Klopprogge B, Lucio D, Chatelain K, Bongartz A, et al. (2013). Comparison of nine common coffee extraction methods: instrumental and sensory analysis. *Eur Food Res Technol*, 236(4):607–27. doi:10.1007/s00217-013-1917-x

Green CJ, de Dauwe P, Boyle T, Tabatabaei SM, Fritschi L, Heyworth JS (2014). Tea, coffee, and milk consumption and colorectal cancer risk. *J Epidemiol*, 24(2):146–53. doi:10.2188/jea.JE20130063 PMID:24531002

GRIN (2016). Germplasm Resources Information Network. Beltsville (MD), USA: United States Department of Agriculture. Available from: https://www.ars-grin.gov/, accessed 22 January 2016.

Guenther H, Anklam E, Wenzl T, Stadler RH (2007). Acrylamide in coffee: review of progress in analysis, formation and level reduction. *Food Addit Contam*, 24(Suppl 1):60–70. doi:10.1080/02652030701243119 PMID:17687700

Guertin KA, Loftfield E, Boca SM, Sampson JN, Moore SC, Xiao Q, et al. (2015). Serum biomarkers of habitual coffee consumption may provide insight into the mechanism underlying the association between coffee consumption and colorectal cancer. *Am J Clin Nutr*, 101(5):1000–11. doi:10.3945/ajcn.114.096099 PMID:25762808

Guertin KA, Moore SC, Sampson JN, Huang WY, Xiao Q, Stolzenberg-Solomon RZ, et al. (2014). Metabolomics in nutritional epidemiology: identifying metabolites associated with diet and quantifying their potential to uncover diet-disease relations in populations. *Am J Clin Nutr*, 100(1):208–17. doi:10.3945/ajcn.113.078758 PMID:24740205

Hatzold T (2012). Introduction. In: Chu Y-F, editor. Coffee: emerging health effects and disease prevention. Oxford, UK: Wiley-Blackwell.

Heinzmann SS, Holmes E, Kochhar S, Nicholson JK, Schmitt-Kopplin P (2015). 2-Furoylglycine as a candidate biomarker of coffee consumption. *J Agric Food Chem*, 63(38):8615–21. doi:10.1021/acs.jafc.5b03040 PMID:26357997

Hendre PS, Phanindranath R, Annapurna V, Lalremruata A, Aggarwal RK (2008). Development of new genomic microsatellite markers from robusta coffee (Coffea canephora Pierre ex A. Froehner) showing broad cross-species transferability and utility in genetic studies. *BMC Plant Biol*, 8(1):51. doi:10.1186/1471-2229-8-51 PMID:18447947

Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, et al. (2004). The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med*,164(21):2335–42.doi:10.1001/archinte.164.21.2335 PMID:15557412

Hildebrand JS, Patel AV, McCullough ML, Gaudet MM, Chen AY, Hayes RB, et al. (2013). Coffee, tea, and fatal oral/pharyngeal cancer in a large prospective US cohort. *Am J Epidemiol*, 177(1):50–8. doi:10.1093/aje/kws222 PMID:23230042

Holick CN, Smith SG, Giovannucci E, Michaud DS (2010). Coffee, tea, caffeine intake, and risk of adult glioma in three prospective cohort studies. *Cancer Epidemiol Biomarkers Prev*, 19(1):39–47. doi:10.1158/1055-9965.EPI-09-0732 PMID:20056621

Holman JP (2009). Heat transfer. Chapters 5 and 6. New York, USA: McGraw-Hill Book Company.

Houessou JK, Maloug S, Leveque AS, Delteil C, Heyd B, Camel V (2007). Effect of roasting conditions on the polycyclic aromatic hydrocarbon content in ground Arabica coffee and coffee brew. *J Agric Food Chem*, 55(23):9719–26. doi:10.1021/jf071745s PMID:17941690

Hu G, Tuomilehto J, Pukkala E, Hakulinen T, Antikainen R, Vartiainen E, et al. (2008). Joint effects of coffee consumption and serum gamma-glutamyltransferase on the risk of liver cancer. *Hepatology*, 48(1):129–36. doi:10.1002/hep.22320 PMID:18537182

IARC (1979). Some halogenated hydrocarbons. *IARC Monogr Eval Carcinog Risk Chem Hum*, 20:1–609. Available from: http://publications.iarc.fr/38 PMID:296120

IARC (1986). Some halogenated hydrocarbons and pesticide exposures. *IARC Monogr Eval Carcinog Risk Chem Hum*, 41:1–407. Available from: http://publications.iarc.fr/59 PMID:3473020

IARC (1987). Overall evaluations of carcinogenicity: an updating of *IARC Monographs* volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7:1–440. Available from: http://publications.iarc.fr/139 PMID:3482203

IARC (1991). Coffee, tea, mate, methylxanthines and methylglyoxal. *IARC Monogr Eval Carcinog Risks Hum*, 51:1–513. Available from: http://publications.iarc.fr/69 PMID:1674554

IARC (2017). Some chemicals used as solvents and in polymer manufacture. *IARC Monogr Eval Carcinog Risks Hum*, 110:1–276. Available from: http://publications.iarc.fr/547.

ICO (2016). Historical data on the global coffee trade. London, UK: International Coffee Organization. Available from: http://www.ico.org/new_historical.asp?section=Statistics, accessed February 2016.

Illner AK, Freisling H, Boeing H, Huybrechts I, Crispim SP, Slimani N (2012). Review and evaluation of innovative technologies for measuring diet in nutritional epidemiology. *Int J Epidemiol*, 41(4):1187–203. doi:10.1093/ije/dys105 PMID:22933652

Illy A, Viani R (2005). Espresso coffee: the science of quality. 2nd ed. Elsevier Academic Press.

Illy F, Illy R (1989). Dal Caffe al Espresso. Milano, Italy: A. Mondadoni [Italian].

Ireland P, Jolley D, Giles G, O'Dea K, Powles J, Rutishauser I, et al. (1994). Development of the Melbourne FFQ: a food frequency questionnaire for use in an Australian prospective study involving an ethnically diverse cohort. *Asia Pac J Clin Nutr*, 3(1):19–31. PMID:24351203

Isaksson B, Jonsson F, Pedersen NL, Larsson J, Feychting M, Permert J (2002). Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer*, 98(3):480–2. doi:10.1002/ijc.10256 PMID:11920604

ITC (2012). The coffee guide. Trade practices of relevance to exporters in coffee-producing countries. Demand – decaffeinated coffee. International Trade Centre. Available from: http://www.thecoffeeguide.org/coffee-guide/the-markets-for-coffee/.

JECFA (2011). Safety evaluation of certain contaminants in food. WHO Food Additives Series: 63. Geneva, Switzerland: Joint FAO/WHO Expert Committee on Food Additives, World Health Organization. Available from: http://www.inchem.org/documents/jecfa/jecmono/v63je01.pdf.

Johnson S, Koh WP, Wang R, Govindarajan S, Yu MC, Yuan JM (2011). Coffee consumption and reduced risk of hepatocellular carcinoma: findings from the Singapore Chinese Health Study. *Cancer Causes Control*, 22(3):503–10. doi:10.1007/s10552-010-9725-0 PMID:21258859

Knopp S, Bytof G, Selmar D (2006). Influence of processing on the content of sugars in green Arabica coffee beans. *Eur Food Res Technol*, 223(2):195–201. doi:10.1007/s00217-005-0172-1

Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, et al. (2000). A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. *Am J Epidemiol*, 151(4):346–57. doi:10.1093/oxfordjournals.aje.a010213 PMID:10695593

Kushi LH (1994). Gaps in epidemiologic research methods: design considerations for studies that use food-frequency questionnaires. *Am J Clin Nutr*, 59(1) Suppl: 180S–4S. PMID:8279420

Lachat C, Hawwash D, Ocké MC, Berg C, Forsum E, Hörnell A, et al. (2016). Strengthening the Reporting of Observational Studies in Epidemiology-Nutritional Epidemiology (STROBE-nut): An Extension of the STROBE Statement. *PLoS Med*, 13(6):e1002036. doi:10.1371/journal.pmed.1002036 PMID:27270749

Lachenmeier DW (2015). Furan in coffee products: a probabilistic exposure estimation. In: Preedy VR, editor. Coffee in health and disease prevention. San Diego, USA: Academic Press; pp. 887–93. doi:10.1016/B978-0-12-409517-5.00098-X

Lachenmeier DW, Steffen C, el-Atma O, Maixner S, Löbell-Behrends S, Kohl-Himmelseher M (2012). What is a food and what is a medicinal product in the European Union? Use of the benchmark dose (BMD) methodology to define a threshold for "pharmacological action". *Regul Toxicol Pharmacol*, 64(2):286–95. doi:10.1016/j.yrtph.2012.08.017 PMID:22960033

Lachenmeier DW, Wegert K, Kuballa T, Schneider R, Ruge W, Reusch H, et al. (2013). Caffeine intake from beverages in German children, adolescents, and adults. *J Caffeine Res*, 3(1):47–53. doi:10.1089/jcr.2013.0008

Lai GY, Weinstein SJ, Albanes D, Taylor PR, McGlynn KA, Virtamo J, et al. (2013). The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers. *Br J Cancer*, 109(5):1344–51. doi:10.1038/bjc.2013.405 PMID:23880821

Lai GY, Weinstein SJ, Albanes D, Taylor PR, Virtamo J, McGlynn KA, et al. (2014). Association of serum α-tocopherol, β-carotene, and retinol with liver cancer incidence and chronic liver disease mortality. *Br J Cancer*, 111(11):2163–71. doi:10.1038/bjc.2014.365 PMID:25314058

Lang R, Dieminger N, Beusch A, Lee YM, Dunkel A, Suess B et al. (2013). Bioappearance and pharmacokinetics of bioactives upon coffee consumption. *Anal Bioanal Chem*, 405(26):8487–503. doi:10.1007/s00216-013-7288-0 PMID:23982107

Lang R, Wahl A, Stark T, Hofmann T (2011). Urinary *N*-methylpyridinium and trigonelline as candidate dietary biomarkers of coffee consumption. *Mol Nutr Food Res*, 55(11):1613–23. doi:10.1002/mnfr.201000656 PMID:21618426

Lantz I, Ternité R, Wilkens J, Hoenicke K, Guenther H, van der Stegen GH (2006). Studies on acrylamide levels in roasting, storage and brewing of coffee. *Mol Nutr Food Res*, 50(11):1039–46. doi:10.1002/mnfr.200600069 PMID:17054100

Larsson SC, Akesson A, Wolk A (2009). Long-term dietary acrylamide intake and risk of epithelial ovarian cancer in a prospective cohort of Swedish women. *Cancer Epidemiol Biomarkers Prev*, 18(3):994–7. doi:10.1158/1055-9965.EPI-08-0868 PMID:19223560

Lashermes P, Combes M-C, Robert J, Trouslot P, D'Hont A, Anthony F, et al. (1999). Molecular characterisation and origin of the Coffea arabica L. genome. *Mol Gen Genet*, 261(2):259–66. doi:10.1007/s004380050965 PMID:10102360

Lloyd AJ, Beckmann M, Haldar S, Seal C, Brandt K, Draper J (2013). Data-driven strategy for the discovery of potential urinary biomarkers of habitual dietary exposure. *Am J Clin Nutr*, 97(2):377–89. doi:10.3945/ajcn.112.048033 PMID:23269817

Lueth NA, Anderson KE, Harnack LJ, Fulkerson JA, Robien K (2008). Coffee and caffeine intake and the risk of ovarian cancer: the Iowa Women's Health Study. *Cancer Causes Control*, 19(10):1365–72. doi:10.1007/s10552-008-9208-8 PMID:18704717

Makiuchi T, Sobue T, Kitamura T, Ishihara J, Sawada N, Iwasaki M, et al. (2016). Association between green tea/coffee consumption and biliary tract cancer: A population-based cohort study in Japan. *Cancer Sci*, 107(1):76–83. doi:10.1111/cas.12843 PMID:26530716

Mennen L, Hirvonen T, Arnault N, Bertrais S, Galan P, Hercberg S (2007). Consumption of black, green and herbal tea and iron status in French adults. *Eur J Clin Nutr*, 61(10):1174–9. doi:10.1038/sj.ejcn.1602634 PMID:17299492

Michels KB, Willett WC, Fuchs CS, Giovannucci E (2005). Coffee, tea, and caffeine consumption and incidence of colon and rectal cancer. *J Natl Cancer Inst*, 97(4):282–92. doi:10.1093/jnci/dji039 PMID:15713963

Monakhova YB, Ruge W, Kuballa T, Ilse M, Winkelmann O, Diehl B, et al. (2015). Rapid approach to identify the presence of Arabica and Robusta species in coffee using 1H NMR spectroscopy. *Food Chem*, 182:178–84. doi:10.1016/j.foodchem.2015.02.132 PMID:25842325

Murray SS, Bjelke E, Gibson RW, Schuman LM (1981). Coffee consumption and mortality from ischemic heart disease and other causes: results from the Lutheran Brotherhood study, 1966–1978. *Am J Epidemiol*, 113(6):661–7. doi:10.1093/oxfordjournals.aje.a113145 PMID:7234854

Murthy PS, Naidu MM (2012). Sustainable management of coffee industry by-products and value addition — a review. *Resour Conserv Recycling*, 66:45–8. doi:10.1016/j.resconrec.2012.06.005

Naganuma T, Kuriyama S, Kakizaki M, Sone T, Nakaya N, Ohmori-Matsuda K, et al. (2008). Coffee consumption and the risk of oral, pharyngeal, and esophageal cancers in Japan: the Miyagi Cohort Study. *Am J Epidemiol*, 168(12):1425–32. doi:10.1093/aje/kwn282 PMID:18974083

Narita Y, Inouye K (2012). High antioxidant activity of coffee silverskin extracts obtained by the treatment of coffee silverskin with subcritical water. *Food Chem*, 135(3):943–9. doi:10.1016/j.foodchem.2012.05.078 PMID:22953809

NCA (2016). National coffee drinking trends 2016. New York, USA: National Coffee Association of USA. Available from: http://www.ncausa.org/.

NCBI (2014). Coffea. Taxonomy Browser. Bethesda (MD), USA: National Center for Biotechnology Information. Available from: http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=13442, accessed January 2016.

NLM (2016). Coffee. Dietary supplements labels database. Bethesda (MD), USA: United States National Library of Medicine. Available from: https://www.dsld.nlm.nih.gov/dsld/index.jsp, accessed 28 March 2016.

Noba S, Uyama A, Mochizuki N (2009). Determination of ochratoxin a in ready-to-drink coffee by immunoaffinity cleanup and liquid chromatography-tandem mass spectrometry. *J Agric Food Chem*, 57(14):6036–40. doi:10.1021/jf900546p PMID:19537783

Norberg M, Wall S, Boman K, Weinehall L (2010). The Västerbotten Intervention Programme: background, design and implications. *Glob Health Action*, 3(1):10. doi:10.3402/gha.v3i0.4643 PMID:20339479

Oba S, Nagata C, Nakamura K, Takatsuka N, Shimizu H (2008). Self-reported diabetes mellitus and risk of mortality from all causes, cardiovascular disease, and cancer in Takayama: a population-based prospective cohort study in Japan. *J Epidemiol*, 18(5):197–203. doi:10.2188/jea.JE2008004 PMID:18753735

Oestreich-Janzen S (2013). Chemistry of coffee. Reference module in chemistry, molecular sciences and chemical engineering. Elsevier Inc. doi:10.1016/B978-0-12-409547-2.02786-4

Paganini-Hill A, Kawas CH, Corrada MM (2007). Non-alcoholic beverage and caffeine consumption and mortality: the Leisure World Cohort Study. *Prev Med*, 44(4):305–10. doi:10.1016/j.ypmed.2006.12.011 PMID:17275898

Paterson RRM, Lima N, Taniwaki MH (2014). Coffee, mycotoxins and climate change (2014). *Food Res Int*, 61:1–15. doi:10.1016/j.foodres.2014.03.037

Petisca C, Perez-Palacios T, Farah A, Pinho O, Ferreira IMPL (2013). Furans and other volatile compounds in ground roasted and espresso coffee using headspace solid-phase microextraction: Effect of roasting speed. *Food Bioprod Process*, 91(3):233–41. doi:10.1016/j.fbp.2012.10.003

Petracco M (2005). The cup. In: Illy A, Viani R, editors. Espresso coffee: the science of quality. Elsevier Academic Press; pp. 259–89. doi:10.1016/B978-012370371-2/50008-1

Phillips RL, Snowdon DA (1983). Association of meat and coffee use with cancers of the large bowel, breast, and prostate among Seventh-Day Adventists: preliminary results. *Cancer Res*, 43(5 Suppl):2403s–8s. PMID:6831464

Pietinen P, Hartman AM, Haapa E, Räsänen L, Haapakoski J, Palmgren J, et al. (1988). Reproducibility and validity of dietary assessment instruments. I. A self-administered food use questionnaire with a portion size picture booklet. *Am J Epidemiol*, 128(3):655–66. PMID:2458036

Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. (2002). European Prospective Investigation

into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr*, 5(6B):1113–24. doi:10.1079/PHN2002394 PMID:12639222

Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC (1992). Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol*, 135(10):1114–26, discussion 1127–36. PMID:1632423

Romani S, Pinnavaia GG, Dalla Rosa M (2003). Influence of roasting levels on ochratoxin a content in coffee. *J Agric Food Chem*, 51(17):5168–71. doi:10.1021/jf030116p PMID:12903986

Rothwell JA, Fillâtre Y, Martin JF, Lyan B, Pujos-Guillot E, Fezeu L, et al. (2014). New biomarkers of coffee consumption identified by the non-targeted metabolomic profiling of cohort study subjects. *PLoS ONE*, 9(4):e93474. doi:10.1371/journal.pone.0093474 PMID:24713823

Sánchez DA, Anzola C (2012). Chemical characterization of the coffee silverskin (Coffea arabica) in varieties Colombia and Caturra. *Rev Colomb Quim*, 41(2):211–26.

Sauvaget C, Allen N, Hayashi M, Spencer E, Nagano J (2002). Validation of a food frequency questionnaire in the Hiroshima/Nagasaki Life Span Study. *J Epidemiol*, 12(5):394–401. doi:10.2188/jea.12.394 PMID:12395883

Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE (2007). Intake of coffee and tea and risk of ovarian cancer: a prospective cohort study. *Nutr Cancer*, 58(1):22–7. doi:10.1080/01635580701307945 PMID:17571963

Sinha R, Cross AJ, Daniel CR, Graubard BI, Wu JW, Hollenbeck AR, et al. (2012). Caffeinated and decaffeinated coffee and tea intakes and risk of colorectal cancer in a large prospective study. *Am J Clin Nutr*, 96(2):374–81. doi:10.3945/ajcn.111.031328 PMID:22695871

Sjøl A, Grunnet K, Schroll M (1991). Secular trends in serum cholesterol, high density lipoproteins and triglycerides 1964–1987. *Int J Epidemiol*, 20(1):105–13. doi:10.1093/ije/20.1.105 PMID:2066206

Slimani N, Freisling H, Illner AK, Huybrechts I (2015). Methods to determine dietary intake. Chapter 4. In: Lovegrove JA, Hodson L, Sharma S, Lanham-New SA, editors. Nutrition research methodologies. Wiley-Blackwell; pp. 48–70. Available from: http://eu.wiley.com/WileyCDA/WileyTitle/productCd-EHEP003370.html.

Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel-Chapelon F, Lotze G, et al. (2002). European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. *Public Health Nutr*, 5(6B):1125–45. doi:10.1079/PHN2002395 PMID:12639223

Soares C, Farah A, Fernandes F, Casal S, Fernandes J (2009). Influence of the roasting conditions on the formation of acrylamide in Brazilian coffee: preliminary results. In: Proceedings of the 22nd International Conference on Coffee Science, ASIC 2008, Campinas, Brazil; pp. 239–241.

Soliman KM (2002). Incidence, level, and behavior of aflatoxins during coffee bean roasting and decaffeination. *J Agric Food Chem*, 50(25):7477–81. doi:10.1021/jf011338v PMID:12452679

Spohn R (2015). Water colour of Coffea arabica, Engen, Germany: Dr. Roland Spohn, Botanik-Fotoarchiv, Illustration, Malerei.

Stalmach A, Mullen W, Barron D, Uchida K, Yokota T, Cavin C, et al. (2009). Metabolite profiling of hydroxycinnamate derivatives in plasma and urine after the ingestion of coffee by humans: identification of biomarkers of coffee consumption. *Drug Metab Dispos*, 37(8):1749–58. doi:10.1124/dmd.109.028019 PMID:19460943

Steevens J, Schouten LJ, Verhage BAJ, Goldbohm RA, van den Brandt PA (2007). Tea and coffee drinking and ovarian cancer risk: results from the Netherlands Cohort Study and a meta-analysis. *Br J Cancer*, 97(9):1291–4. doi:10.1038/sj.bjc.6604008 PMID:17923877

Thesaurus (2016). Brewing. Online dictionary. Available from: http://www.dictionary.com/browse/brewing, accessed 11 February 2016.

Thompson FE, Kipnis V, Midthune D, Freedman LS, Carroll RJ, Subar AF, et al. (2008). Performance of a food-frequency questionnaire in the US NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study. *Public Health Nutr*, 11(2):183–95. doi:10.1017/S1368980007000419 PMID:17610761

Thompson FE, Subar AF (2013). Dietary assessment methodology. In: Coulston AM, Boushey CJ, Ferruzzi MG, editors. Nutrition in the prevention and treatment of disease. 3rd ed. Elsevier Academic Press. doi:10.1016/B978-0-12-391884-0.00001-9

Toci A, Farah A, Trugo LC (2006). Effect of decaffeination using dichloromethane on the chemical composition of arabica and robusta raw and roasted coffees. *Quim Nova*, 29(5):965–71. doi:10.1590/S0100-40422006000500015

Toci AT, Farah A (2008). Volatile compounds as potential defective coffee beans' markers. *Food Chem*, 108(3):1133–41. doi:10.1016/j.foodchem.2007.11.064 PMID:26065781

Toci AT, Neto VJ, Torres AG, Farah A (2013). Changes in triacylglycerols and free fatty acids composition during storage of roasted coffee. *Lebensm Wiss Technol*, 50(2):581–90. doi:10.1016/j.lwt.2012.08.007

Trugo L (2003). Coffee analysis. In: Caballero B, Trugo LC, Finglas P, editors. Encyclopedia of food science and nutrition. Volume 3. 2nd ed. Oxford, UK: Academic Press. doi:10.1016/B0-12-227055-X/00271-6

Uebelacker M, Lachenmeier DW (2011). Quantitative determination of acetaldehyde in foods using automated digestion with simulated gastric fluid followed by headspace gas chromatography. *J Autom Methods Manag Chem*, 2011:907317. doi:10.1155/2011/907317 PMID:21747735

Urgert R, van der Weg G, Kosmeijer-Schuil TG, van de Bovenkamp P, Hovenier R, Katan MB (1995). Levels of the cholesterol-elevating diterpenes cafestol and kahweol in various coffee brews. *J Agric Food Chem*, 43(8):2167–72. doi:10.1021/jf00056a039

USDA (2016). Coffee: world market and trade. June 2016. United States Department of Agriculture, Foreign Agricultural Service. Available from: http://apps.fas.usda.gov/psdonline/circulars/coffee.pdf.

van Dusseldorp M, Smits P, Lenders JW, Thien T, Katan MB (1991). Boiled coffee and blood pressure. A 14-week controlled trial. *Hypertension*, 18(5):607–13. doi:10.1161/01.HYP.18.5.607 PMID:1937663

Vecchio A, Mineo V, Planeta D (2012). Ochratoxin A in instant coffee in Italy (2012). *Food Contr*, 28(2):220–3. doi:10.1016/j.foodcont.2012.04.029

Veierød MB, Thelle DS, Laake P (1997). Diet and risk of cutaneous malignant melanoma: a prospective study of 50,757 Norwegian men and women. *Int J Cancer*, 71(4):600–4. doi:10.1002/(SICI)1097-0215(19970516)71:4<600::AID-IJC15>3.0.CO;2-F PMID:9178814

Viani R (1986). Coffee. Ullmann's encyclopedia of industrial chemistry. Volume A7. Weinheim, Germany: VCH Verlagsgesellschaft; pp. 315–39.

Vieira T, Cunha S, Casal S (2015). Chapter 25: Mycotoxins in coffee. In: Preedy V, editor. Coffee in health and disease prevention. Academic Press, Elsevier; pp. 225–33. doi:10.1016/B978-0-12-409517-5.00025-5

Waizenegger J, Castriglia S, Winkler G, Schneider R, Ruge W, Kersting M, et al. (2011). Caffeine exposure in children and adolescents consuming ready-to-drink coffee products. *J Caffeine Res*, 1(4):200–5. doi:10.1089/jcr.2011.0024

Waizenegger J, Winkler G, Kuballa T, Ruge W, Kersting M, Alexy U, et al. (2012). Analysis and risk assessment of furan in coffee products targeted to adolescents. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*, 29(1):19–28. doi:10.1080/19440049.2011.617012 PMID:22035212

Weiderpass E, Sandin S, Lof M, Oh JK, Inoue M, Shimazu T, et al. (2014). Endometrial cancer in relation to coffee, tea, and caffeine consumption: a prospective cohort study among middle-aged women in Sweden. *Nutr Cancer*, 66(7):1132–43. doi:10.1080/01635581.2014.948214 PMID:25181598

Wellman FL (1961). Coffee: botany, cultivation and utilization. London, UK: Leonard Hill.

Wenzl T, Lachenmeier DW, Gökmen V (2007). Analysis of heat-induced contaminants (acrylamide, chloropropanols and furan) in carbohydrate-rich food. *Anal Bioanal Chem*, 389(1):119–37. doi:10.1007/s00216-007-1459-9 PMID:17673989

Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, et al. (1988). The use of a self-administered questionnaire to assess diet four years in the past. *Am J Epidemiol*, 127(1):188–99. doi:10.1093/oxfordjournals.aje.a114780 PMID:3337073

Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. (1985). Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*, 122(1):51–65. PMID:4014201

Wilson KM, Giovannucci E, Stampfer MJ, Mucci LA (2012). Dietary acrylamide and risk of prostate cancer. *Int J Cancer*, 131(2):479–87. doi:10.1002/ijc.26383 PMID:21866549

Wilson KM, Kasperzyk JL, Rider JR, Kenfield S, van Dam RM, Stampfer MJ, et al. (2011). Coffee consumption and prostate cancer risk and progression in the Health Professionals Follow-up Study. *J Natl Cancer Inst*, 103(11):876–84. doi:10.1093/jnci/djr151 PMID:21586702

Yamada H, Kawado M, Aoyama N, Hashimoto S, Suzuki K, Wakai K, et al.; JACC Study Group (2014). Coffee consumption and risk of colorectal cancer: the Japan Collaborative Cohort Study. *J Epidemiol*, 24(5):370–8. doi:10.2188/jea.JE20130168 PMID:24857957

Yang TO, Crowe F, Cairns BJ, Reeves GK, Beral V (2015). Tea and coffee and risk of endometrial cancer: cohort study and meta-analysis. *Am J Clin Nutr*, 101(3):570–8. doi:10.3945/ajcn.113.081836 PMID:25733642

Zhang C, Linforth R, Fisk ID (2012). Cafestol extraction yield from different coffee brew mechanisms. *Food Res Int*, 49(1):27–31. doi:10.1016/j.foodres.2012.06.032

2. CANCER IN HUMANS

2.1 Cancer of the bladder

2.1.1 Cohort studies

See Table 2.1, Fig 2.1, Fig. 2.2, and Fig. 2.3.

This section summarizes the results of the Working Group's review of prospective cohort studies that reported on the association between drinking coffee and the risk of cancer of the bladder. One study that reported on bladder cancer mortality as an end-point (Snowdon & Phillips, 1984) was excluded, as the role of coffee in cancer etiology cannot be distinguished from its role in cancer progression or response to treatment. Also excluded are three studies, two of the same cohort, that did not report estimates of association (Schulte et al., 1985, 1986; Whittemore et al., 1985).

When reviewing the available studies, the Working Group considered two important criteria in evaluating how informative each was. One was appropriate adjustment for tobacco smoking, given that this is an important bladder cancer risk factor and is often reported to be correlated with coffee drinking. The other was consideration of sensitivity analyses excluding patients diagnosed too close to the start of the cohort; patients with bladder cancer might be likely to change their coffee drinking habits, which might lead to bias in the analyses. Studies that conducted such sensitivity analyses and adjusted for tobacco smoking were therefore considered to be the most informative, and are discussed first. Studies that adjusted for smoking but did not conduct sensitivity analyses, as well as one study that did neither, are then discussed. Overall, studies with a large sample size are considered more informative as measures of association will tend to be more precise; we therefore discuss larger studies first, followed by smaller studies.

In the following paragraphs the cohort studies that were considered the most informative by the Working Group are described. These studies were given more weight in the evaluation.

In the Netherlands Cohort Study (Zeegers et al., 2001), 569 incident cases of cancer of the urinary bladder were identified. Among men, the relative risk for the highest level of intake (≥ 7 cups/day) compared with the lowest (0 to < 2 cups/day) was 1.33 (95% CI, 0.94–1.90), with an estimate per 1 cup/day of coffee of 1.04 (95% CI, 1.00–1.09). The test for trend was not statistically significant (*P* for trend, 0.06). Among women, the relative risk for the highest level (≥ 5 cups/day) was 0.36 (95% CI, 0.18–0.72), with an estimate per 1 cup/day of 0.83 (95% CI, 0.72–0.96). A statistically significant test for trend (*P* for trend, < 0.01) was reported. Sensitivity analyses excluding cases diagnosed in the first 1–2 years of follow-up did not change results. [The limitations of this study were the lack of consideration of coffee drinking history and lack of stratification by smoking status.]

Table 2.1 Cohort studies on cancer of the bladder and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zeegers et al. (2001) Netherlands, 1986 (enrolment), 1992 (follow-up)	3500, Netherlands Cohort Study, men and women (aged 55–69 yr), case–cohort approach Exposure assessment method: FFQ (non-validated coffee questions, self-administered, frequency and amount), caffeinated coffee only (low consumption of decaffeinated)	Urinary bladder: ~96% TCC	*Coffee consumption among men (cups/day)*			Age, numbers of cigarettes/day, years of cigarette smoking	Strengths: prospective, large number of cases, detailed questionnaire including 19 beverages, both men and women included, complete follow-up data Limitations: no drinking history; no follow-up information
			0 to < 2	23	0.89 (0.51–1.54)		
			2 to < 3	32	0.72 (0.45–1.13)		
			3 to < 4	61	1.27 (0.87–1.87)		
			4 to < 5	119	1.00		
			5 to < 6	72	0.98 (0.68–1.4)		
			6 to < 7	91	1.25 (0.89–1.76)		
			≥ 7	93	1.33 (0.94–1.90)		
			Per 1 cup/day	NR	1.04 (1.00–1.09)		
			Coffee consumption among women (cups/day)				
			0 to < 2	11	1.23 (0.56–2.73)		
			2 to < 3	13	0.84 (0.4–1.76)		
			3 to < 4	20	1.00		
			4 to < 5	17	0.44 (0.22–0.86)		
			≥ 5	17	0.36 (0.18–0.72)		
			Per 1 cup/day	NR	0.83 (0.72–0.96)		
Ros et al. (2011) 10 European countries, 1992–2000 (enrolment), follow-up varied by country	233 236 (67 914 men and 165 322 women), EPIC, subjects aged 25–70 yr Exposure assessment method: validated FFQ, frequency and amount considered	Urinary bladder: UCC	*Coffee consumption (mL/day)*			Age, sex, centre, smoking status, duration of smoking, lifetime intensity of smoking, energy intake from fat and non-fat sources	Strengths: prospective large cohort, extensive set of potential confounders, possible to distinguish between low- and high-risk urothelial bladder cancers Limitations: no history of coffee drinking, no information about type of coffee studied, results not stratified by sex or smoking, no follow-up information on exposure
			T1: < 429 (men), 250 (women)	133	1.00		
			T2: 429–874 (men), 250–469 (women)	179	1.11 (0.88–1.41)		
			T3: ≥ 875 (men), ≥ 500 (women)	201	1.11 (0.85–1.43)		
			Continuous for every 100 mL increase (observed)	380	1.00 (0.98–1.03)		
			Trend test *P* value, 0.5				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Michaud et al. (1999) USA, 1986 (enrolment), 1996 (last follow-up)	47 909; HPFS, male health professionals aged 40–75 yr in all 50 states, predominantly white Exposure assessment method: validated FFQ by mail, regular and decaffeinated coffee, frequency/serving size assessed	Urinary bladder: 90% TCC	*Decaffeinated coffee consumption*			Geographic region, age, pack-years of smoking, current smoking status, energy intake, intake of fruits and vegetables, intake of all other beverages (water, milk, juice, soda, lemonade, tea, alcohol)	Strengths: prospective, follow-up information every 2 yr Limitations: restricted to mostly white professional men in USA (no women included), no history of intake
			< 1 cup/mo	106	1.00		
			1 cup/mo–6 cups/wk	65	0.94 (0.69–1.29)		
			1–3 cups/day	72	1.20 (0.87–1.65)		
			≥ 4 cups/day	9	0.83 (0.41–1.66)		
			Trend test *P* value, 0.47				
			Coffee consumption				
			Per 240 mL of daily intake	252	0.93 (0.85–1.02)		
			< 1 cup/mo	75	1.00		
			1 cup/mo–6 cups/wk	56	0.97 (0.68–1.37)		
			1–3 cups/day	98	1.00 (0.73–1.37)		
			≥ 4 cups/day	23	0.79 (0.48–1.30)		
			Trend test *P* value, 0.56				
Nagano et al. (2000) Japan, 1979–1981 (enrolment), 1980–1993 (follow-up)	38 540 atomic bomb survivors, Life Span Study (men and women) Exposure assessment method: frequency only by self-administered questionnaire	Urinary bladder	*Coffee consumption frequency (times/wk)*			Age, sex, radiation dose, smoking status and cigarettes/day, education level, BMI, calendar time	Strengths: prospective Limitations: modest numbers, not representative of all Japanese population, no information on serving sizes, consumption history, or types of coffee
			0	25	1.00		
			1–4	32	0.73 (0.43–1.25)		
			≥ 5	32	0.90 (0.52–1.56)		
			Trend test *P* value, 0.78				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jacobsen et al. (1986) Norway, 1964 (enrolment), 1967 (questionnaire), follow-up until 1978	16 555; two cohorts of Norwegian men (population sample and brothers of migrants to the USA); spouses and siblings of individuals enrolled in a case–control study of gastrointestinal cancer were included Exposure assessment method: validated self-administered questionnaire with follow-up	Urinary bladder	*Coffee consumption (cups/day): men only* ≤ 2 > 7 Trend test *P* value, 0.88	 20 10	 1.00 0.98 (NR)	Age, residence, smoking status, cigarettes/day	Strengths: prospective, sensitivity analyses considering time between diagnosis and baseline Limitations: no assessment of duration of coffee drinking, unclear reference period for coffee intake, coffee type only coffee (decaffeinated/instant not commonly consumed)
Stensvold & Jacobsen (1994) Norway, 1977–1982 (enrolment), follow-up until 1990	43 973 men and women aged 35–54 yr participating in cardiovascular screening programme Exposure assessment method: validated self-administered FFQ	Urinary bladder: ICD-7, 181	*Coffee consumption (cups/day): men* ≤ 4 5–6 ≥ 7 Per 2 cup/day increase *Coffee consumption (cups/day): women* ≤ 4 5–6 ≥ 7 Per 2 cup/day increase	 13 8 19 NR 3 5 5 NR	 1.00 0.70 1.50 1.13 (0.87–1.49) 1.00 2.10 2.40 1.22 (0.73–2.05)	Age, cigarettes per day, county of residence	Strengths: population-based, included participants in different parts of Norway Limitations: no assessment of duration of coffee intake or type of coffee/preparation method, modest sample size

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sugiyama et al. (2017) Japan, 1990–2007 (Miyagi), 1994–2008 (Ohsaki)	73 346 (38 646 Miyagi, 34 700 Ohsaki) men and women aged 40–79 yr, cohorts were pooled for analyses Exposure assessment method: validated self-administered FFQ	Urinary bladder: ICD-O-3 C67–67.9	*Coffee consumption (cups/day)*			Sex, age, BMI, history of hypertension, diabetes mellitus, myocardial infarction, stroke, job status, years of education, smoking status and cigarettes/ day, alcohol consumption, green tea consumption, time spent walking	Strengths: prospective, large cohorts, use of population-based registries Limitations: no history of drinking coffee assessed, no follow-up information (only baseline), no information on brewing or type of coffee, no occupational exposures assessed, very few cases
			Never	63	1.00		
			Occasionally	130	1.22 (0.90–1.66)		
			1–2	65	0.88 (0.61–1.26)		
			≥ 3	16	0.56 (0.32–0.99)		
			Trend test *P* value, 0.04				
		Urinary bladder: ICD-O-3 C67–67.9	*Coffee consumption (cups/day) stratified by smoking: never smokers*				
			Never	19	1.00		
			Occasionally	35	1.46 (0.82–2.58)		
			1–2	13	0.97 (0.47–2.01)		
			≥ 3	2	0.62 (0.14–2.72)		
			Coffee consumption (cups/day) stratified by smoking: former or current smokers				
			Never	38	1.00		
			Occasionally	83	1.22 (0.83–1.81)		
			1–2	48	0.95 (0.61–1.47)		
			≥ 3	13	0.61 (0.32–1.17)		

Table 2.1 (continued)

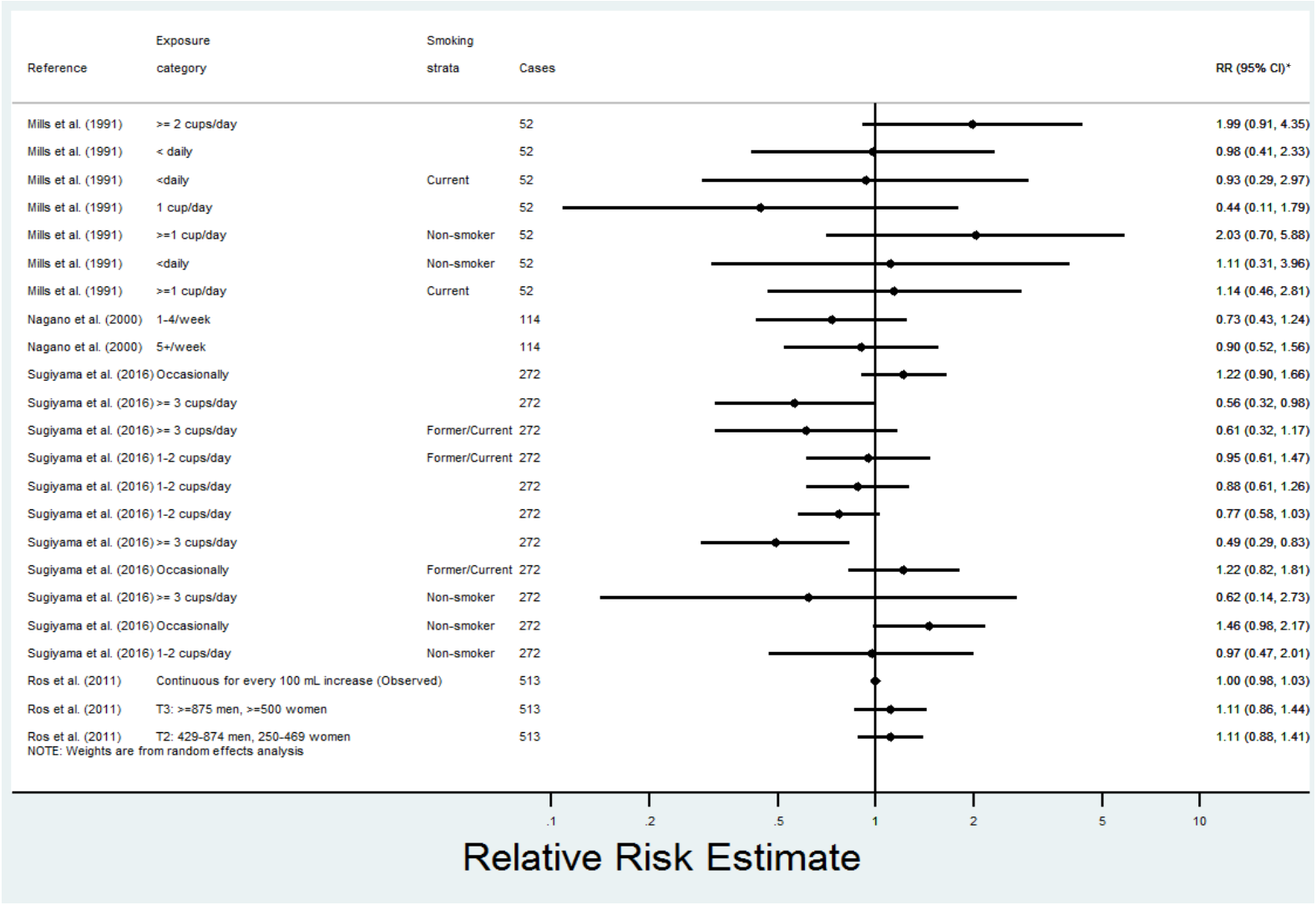
Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kurahashi et al. (2009) Japan 1990, 1993 (enrolment), 2005 (follow-up)	133 084 (65 660 men, 67 424 women), JPHC, 104 440 residents of 11 public health centre areas across Japan of age 40–69 yr included Exposure assessment method: validated, self-administered questionnaire assessing frequency/amount (no decaffeinated coffee considered)	Urinary bladder	*Coffee consumption among men*			Age, area of recruitment, smoking status/ pack-years, alcohol drinking, green tea	Decaffeinated coffee is rare in Japan; no other cancers reported in this paper Strengths: prospective, catchment area includes most of the country, stratification by sex and smoking Limitations: no assessment of drinking history, modest numbers (especially for stratified analyses)
			Almost never	50	1.00		
			1–4 times/wk	52	1.26 (0.84–1.88)		
			1–2 cups/day	43	1.53 (0.98–2.37)		
			≥ 3 cups/day	19	1.37 (0.75–2.51)		
			Trend test *P* value, 0.09				
			Coffee consumption among women				
			Almost never	19	1.00		
			1–4 times/wk	15	1.03 (0.51–2.07)		
			≥ 1 cup/day	8	0.55 (0.23–1.33)		
			Trend test *P* value, 0.23				
			Coffee frequency among men stratified by smoking status				
			Among never smokers				
			Almost none	6	1.00		
			1–4 times/wk	9	1.89 (0.67–5.32)		
			≥ 1 cup/day	11	2.48 (0.88–7.05)		
			Among former smokers				
			Almost none	13	1.00		
			1–4 times/wk	13	1.25 (0.58–2.71)		
			≥ 1 cup/day	16	2.09 (0.96–4.54)		
			Among current smokers				
			Almost none	29	1.00		
			1–4 times/wk	30	1.11 (0.65–1.9)		
			≥ 1 cup/day	33	1.13 (0.65–1.97)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chyou et al. (1993) Hawaii (Oahu), 1965–1968 (enrolment), 15 years of follow-up	7355 Japanese men born during 1900–1919 (no other criteria mentioned) Exposure assessment method: 24-hour recall questionnaire (no decaffeinated coffee considered)	Urinary bladder	*Coffee consumption (cups/wk)* ≤ 1 2–4 ≥ 5 Trend test *P* value, 0.174	 5 5 86	 1.00 3.52 (1.02–12.2) 2.07 (0.84–5.12)	Age, pack-years smoking	Strengths: prospective, good assessment of cancers Limitations: modest sample size, only assessed past 24 hours of intake not long-term history of drinking, few criteria listed for study eligibility, only men
Mills et al. (1991) USA (California), 1974 (recruitment), 1976 (survey), 1982 (end of follow-up)	34 198 non-Hispanic white members of Seventh-day Adventist church in California, > 25 yr old Exposure assessment method: self-administered 51-item FFQ and lifestyle questionnaire (no decaffeinated coffee considered)	Urinary bladder: 92% TCC	*Coffee intake frequency (cups/day)* Never < 1 1 ≥ 2 Trend test *P* value, 0.13 *Coffee frequency among never smokers (cups/day)* Never < 1 ≥ 1 *Coffee frequency among past/current smokers (cups/day)* Never < 1 ≥ 1	 26 7 2 12 NR NR NR NR NR	 1.00 0.98 (0.41–2.31) 0.44 (0.11–1.83) 1.99 (0.91–4.34) 1.00 1.11 (0.31–3.95) 2.03 (0.70–5.87) 1.00 0.93 (0.29–2.96) 1.14 (0.46–2.80)	Age, sex, smoking	Strengths: prospective, men and women included Limitations: no assessment of duration of coffee drinking, population studied does not traditionally drink coffee so intake of coffee might be a proxy for other changes from traditional Adventist lifestyle

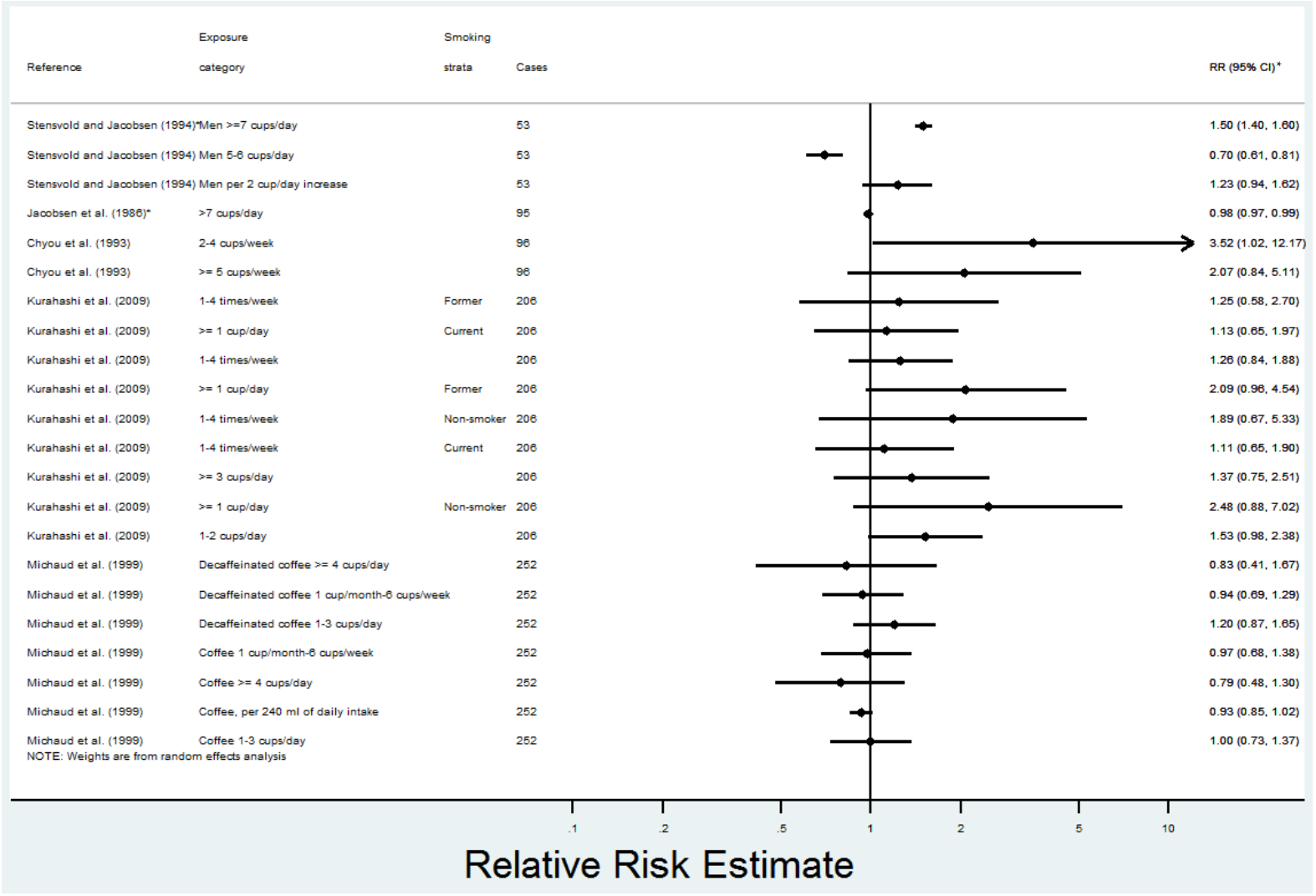
BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-up Study; ICD-7, International Classification of Disease - Revision 7; ICD-O-3, International Classification of Disease – Oncology Revision 3; JPHC, Japan Public Health Center-based Prospective; mo, month(s); NR, not reported; TCC, transitional cell carcinoma; UCC, urothelial cell carcinoma; wk, week(s); yr, year(s)

Fig. 2.1 Relative risk estimate for coffee and bladder cancer cohorts: both sexes



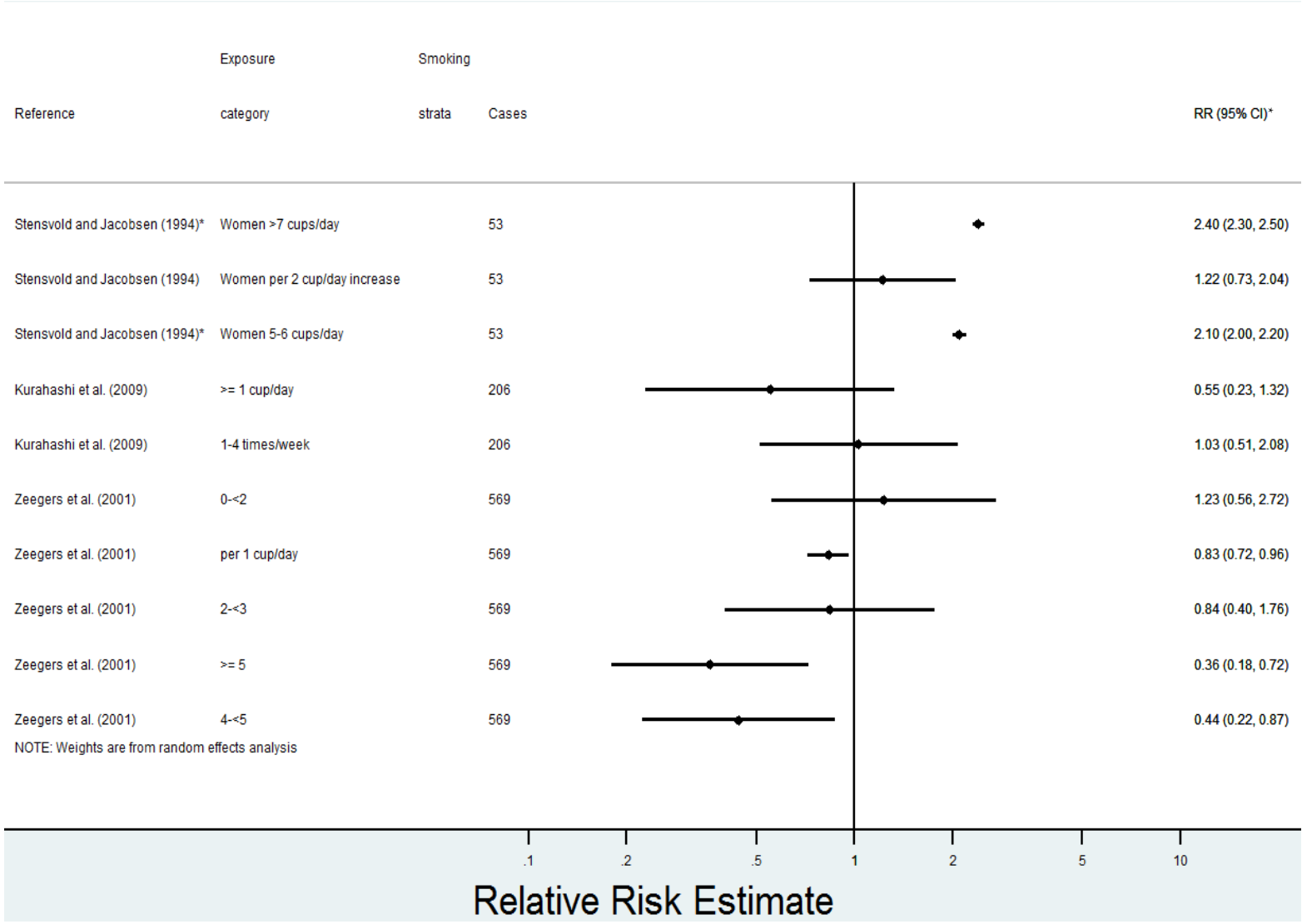
* CIs were forced to display on the plot
Compiled by the Working Group

Fig. 2.2 Relative risk estimate for coffee and bladder cohorts: men only



* CIs were forced to display on the plot
Compiled by the Working Group

Fig. 2.3 Relative risk estimate for coffee and bladder cohorts: women only



* CIs were forced to display on the plot
Compiled by the Working Group

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, 513 incident cases were identified during 1992–2000 (Ros et al., 2011). The relative risk for every 100 mL of coffee increase was 1.0 (95% CI, 0.98–1.03). The relative risk for the highest level of coffee intake (≥ 875 mL/day for men and ≥ 500 mL/day for women) compared with the lowest level (< 429 mL/day for men and < 250 mL/day for women) was 1.11 (95% CI, 0.85–1.43, *P* for trend, 0.5). Sensitivity analyses excluding cases diagnosed within 2 years of recruitment did not change results. Stratification of cases by high (≥ T1, CIS, WHO grade 3) or low (Ta grade 1, Ta grade 2) risk of progression also yielded comparable results. [Limitations noted were: stratified results by smoking were conducted and mentioned but estimates not shown; a lack of consideration of coffee-drinking history; and no follow-up data on coffee drinking.]

In the Health Professionals Follow-up Study (HPFS) (Michaud et al., 1999) 252 incident cases of bladder cancer were identified during 1986–1996. The relative risk for the highest level of caffeinated coffee intake (≥ 4 cups/day) compared with the lowest (< 1 cup/month) was 0.79 (95% CI, 0.48–1.30), with no evidence of dose–response and trend (*P* for trend, 0.56). Similarly, for decaffeinated coffee the relative risk for the highest level of coffee (≥ 4 cups/day) compared with the lowest (< 1 cup/month) was 0.83 (95% CI, 0.41–1.66), with no evidence of dose–response and trend (*P* for trend, 0.47). Sensitivity analyses excluding cases diagnosed during the first 3 years of the study did not change findings. [A weakness was the lack of consideration of coffee-drinking history.]

In the Life Span Study of atomic bomb survivors in Japan (Nagano et al., 2000), 114 incident cases of bladder cancer were identified between 1979 and 1983 (83 men and 31 women). The relative risk for the highest level of intake (> 5 times/week) compared with never drinkers was 0.90 (95% CI, 0.52–1.56), with no evidence of dose–response or trend (*P* for trend, 0.78). Sensitivity analyses excluding cases diagnosed during the first 2 years after a postal survey (a total of 96 cases) yielded the same results. [A weakness of this study was the limited assessment of coffee consumption with no quantity/serving, history of intake, or follow-up data provided.]

In a study that included 94 bladder cancer cases diagnosed within two Norwegian cohorts of men (Jacobsen et al., 1986), the relative risk for the highest level of intake (> 7 cups/day) compared with the lowest (≤ 2 cups/day) was 0.98. No confidence intervals were provided. Similar estimates were obtained for women, although no adjustment for smoking was possible among them. Excluding cases diagnosed in the first 4 years of the cohorts yielded comparable results. [Weaknesses of this study were the lack of assessment of coffee-drinking history, no follow-up data regarding coffee, and no stratification of results by smoking. Even though decaffeinated coffee or instant coffee were not assessed, it was indicated that these were rarely consumed at the time of the study.]

In the Norwegian National Health Screening Service for cardiovascular disease (Stensvold & Jacobsen, 1994) a total of 53 incident cases of cancer of the bladder (40 men and 13 women) were identified. Among men the relative risk per 2 cups/day increase in coffee drinking was [1.13 (95% CI, 0.87–1.49)]; among women the corresponding relative risk was [1.22 (95% CI, 0.73–2.05)] [the paper reports coefficients for these estimates, which were exponentiated here]. Analyses using tertiles of coffee intake are presented without confidence intervals. Sensitivity analyses for the first 2 years of diagnoses in cohort were performed. [A main weakness was the modest sample size, particularly for women, and lack of consideration of duration of coffee intake.]

In the following, cohort studies that reported results for coffee intake but were given less weight by the Working Group are described.

A study that combined data from the Miyagi Cohort Study and the Ohsaki Cohort Study in Japan, including 272 bladder cancer cases, was reported (Sugiyama et al., 2017). The relative risk for the highest consumption level (≥ 3 cups/day) compared with never drinkers was 0.56 (95% CI, 0.32–0.99; *P* for trend, 0.04). When stratifying individuals by smoking status, the relative risks for the same comparisons were 0.62 (95% CI, 0.14–2.72) for never smokers and 0.61 (95% CI, 0.32–1.17) for former or current smokers, with a test of interaction *P* = 0.99. Interaction analyses were also performed for sex, age, body mass index (BMI), diabetes, and alcohol; no evidence of effect modification was obtained for any of these variables. [The number of cases was small for stratified analyses, especially among never smokers.]

In the Japan Public Health Center-based Prospective (JPHC) study 206 (164 men and 42 women) bladder cancer cases were identified (Kurahashi et al., 2009). Among men, the hazard ratio for the highest category of coffee intake (≥ 3 cups/day) compared with those who consumed almost no coffee was 1.37 (95% CI, 0.75–2.51; *P* for trend, 0.09). [No evidence of a dose–response relationship was observed.] Among women the hazard ratio for the highest category of intake (≥ 1 cup/day) compared with almost none was 0.55 (95% CI, 0.23–1.33; *P* for trend, 0.23). Among never smoking men, the hazard ratio for the highest category (≥ 1 cup/day) compared with almost no coffee drinking was 2.48 (95% CI, 0.88–7.05), 2.09 (95% CI, 0.96–4.54) among former smokers, and 1.13 (95% CI, 0.65–1.97) among current smokers. A test of interaction was not statistically significant. [The main weaknesses were the modest sample size among never smokers, and the lack of coffee-drinking history and follow-up exposure data.]

In a prospective study conducted in Hawaii, 96 men with bladder cancer were identified (Chyou et al., 1993). The relative risk for high (≥ 5 cups/week) compared with low (≤ 2 cups/week) intake was 2.07 (95% CI, 0.84–5.12; *P* for trend, 0.174). There was no evidence of a dose–response relationship. A previous study reported on a subset of these men (Nomura et al., 1986). [A limitation of this study was the fact that coffee intake was assessed via 24 hour recalls, which may not be representative of long-term coffee drinking. The numbers of cases in lower-intake categories were very small.]

A total of 52 bladder cancer cases were identified within the Seventh-day Adventist Church Cohort study conducted in California (Mills et al., 1991). The relative risk for the highest level of intake (≥ 2 cups/day) compared with never drinkers was 1.99 (95% CI, 0.91–4.34; *P* for trend, 0.13) with little evidence of a dose–response relation. Analyses stratifying by smoking status showed that the relative risk for the highest category (≥ 1 cup/day) compared with never drinkers was 2.03 (95% CI, 0.70–5.87) among never smokers and 1.14 (95% CI, 0.46–2.80) among past or current smokers. [Key limitations were overall small numbers (especially among never smokers with only 25 cases), an unclear definition of smoking variables in regression, and a concern for potential underreporting of tobacco consumption.]

In the Iowa Women's Health Study 112 incident bladder cancer cases were identified between 1986 and 1998 among postmenopausal women (Tripathi et al., 2002). The relative risk for the highest frequency of coffee intake (≥ 4 times/day) compared with the lowest (never or < 1 time/month) was 1.59 (95% CI, 0.95–2.68). [Since it was not clear whether smoking was included as a confounder, the Working Group decided not to include this study for final evaluation.]

2.1.2 Case–control studies

See Table 2.2.

The Working Group identified 64 case–control studies that reported on associations

Table 2.2 Case–control studies on cancer of the bladder and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cole (1971) USA (Massachusetts), 1966–1968	Cases: 470 population-based, pathology logs of hospitals in the area were used Controls: 500 population-based using residents lists, matched to cases by sex and year of birth Exposure assessment method: interviewer-administered questionnaire, frequency and amount of coffee, unclear validation	Urinary bladder: TCC and SCC	*Coffee intake among men (cups/day)*			Age, cigarette smoking (cigarettes smoked/day), occupation	Also presented analyses stratified by age and sex, although numbers were very small; among men the association was stronger for older men, and among women it was stronger for women aged 60–74 yr Strengths: population-based, adequate sample size, consideration of occupational exposures Limitations: no information on drinking history or types of coffee consumed, no confidence intervals shown for RR in dose–response analyses, small numbers for some stratified analyses
			< 1	29	1.00		
			1	86	1.34 (NR)		
			2–3	146	1.18 (NR)		
			≥ 4	84	1.31 (NR)		
			≥ 1 vs < 1	316	1.24 (0.80–1.93)		
			Coffee intake among women (cups/day)				
			< 1	9	1.00		
			1	19	1.60 (NR)		
			2–3	50	3.76 (NR)		
			≥ 4	22	2.19 (NR)		
			≥ 1 vs < 1	100	2.58 (1.30–5.10)		
			Coffee intake among non-smokers without high-risk occupations (cups/day)				
			< 1	10	1.00		
			1	31	2.18 (NR)		
			2–3	37	1.84 (NR)		
			≥ 4	12	2.60 (NR)		
Fraumeni et al. (1971) USA (New Orleans), 1958–1964	Cases: 493; NR see Dunham et al. (1968) Controls: 527; NR see Dunham et al. (1968) Exposure assessment method: Questionnaire; see Dunham et al. (1968)	Urinary bladder	*Daily consumption coffee (cups/day)*			Age, cigarette smoking	Strengths: both white and black subjects Limitations: no confidence intervals shown for most estimates
			Any amount vs none	NR	1.50		
			Daily consumption of coffee among white men (cups/day)				
			0 (reference)	5	1.00		
			1–2	85	1.40 (NR)		
			3–4	76	1.96 (NR)		
			≥ 5	99	1.66 (NR)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Fraumeni et al. (1971) (cont.)			*Daily consumption of coffee among black men (cups/day)*				
			0 (reference)	6	1.00		
			1–2	23	2.13 (NR)		
			3–4	27	2.90 (NR)		
			≥ 5	13	2.10 (NR)		
			Daily consumption of coffee (cups/day)				
			Any daily amount vs none (all men)	323	1.95 (NR)		
			Any daily amount vs none (white men)	260	1.78 (NR)		
			Any daily amount vs none (black men)	63	2.10 (NR)		
			Daily consumption of coffee among white women (cups/day)				
			0 (reference)	14	1.00		
			1–2	45	0.70 (NR)		
			3–4	29	0.47 (NR)		
			≥ 5	24	0.32 (NR)		
			Trend test *P* value, 0.04				
			Daily consumption of coffee among black women (cups/day)				
			0 (reference)	2	1.00		
			1–2	27	10.00 (NR)		
			3–4	10	4.58 (NR)		
			≥ 5	8	2.30 (NR)		
			Trend test *P* value, 0.04				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Fraumeni et al. (1971) (cont.)			*Daily consumption of coffee among all women (cups/day)*				
			Any daily amount vs none (all women)	147	1.19 (NR)		
			Daily amount vs none (white women)	98	0.51 (NR)		
			Daily amount vs none (black women)	45	5.65 (NR)		
			Trend test *P* value, 0.04				
			Daily consumption coffee (cups/day)				
			Never smokers (blacks)	NR	1.00		
			Ever smokers (blacks)	NR	3.56 (NR)		
			Never smokers (whites)	NR	1.00		
			Ever smokers (whites)	NR	0.67 (NR)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Simon et al. (1975) USA (Massachusetts, Rhode Island), 1965–1971	Cases: 135 hospital-based Controls: 390 hospital-based, identified via discharge lists of same hospitals as cases, free of urinary tract problems (no selection made related to other diseases) Exposure assessment method: mailed questionnaire, validation unclear (both regular and decaffeinated coffee considered)	Urinary bladder	*Coffee consumption among non- and light smokers (cups/day)* 0 to < 1 ≥ 1 *Coffee consumption among moderate to heavy smokers (cups/day)* 0 to < 1 ≥ 1	 9 76 1 45	 1.0 1.7 (0.8–3.5) 1.0 3.7 (0.6–23.6)	None	Strengths: Assessed coffee drinking strength and history Limitations: hospital-based, controls not excluded based on non-urinary tract disease that may also affect coffee drinking (GI diseases), small numbers in stratified analyses, no estimates provided adjusting for smoking, women only

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mettlin & Graham (1979) USA (Buffalo, New York), 1957–1965	Cases: 569 hospital-based Controls: 1025 hospital-based, admitted to same hospital as cases with non-neoplastic complaints, no matching performed Exposure assessment method: questionnaire, validation unclear, administered in person, frequency/amount of coffee	Urinary bladder: ICD-188	*Coffee consumption among men (cups/day)*			Cigarettes smoked/ day	Same patient population as described by Bross & Tidings (1973) Strengths: adequate sample size with large number of controls Limitations: hospital-based, no drinking history, controls may include patients with disorders that affect coffee drinking, number of women for smoking stratified analyses was small (not presented here)
			< 1	24	1.00		
			1	56	1.38 (NR)		
			2	73	1.16 (NR)		
			3	76	2.11 (NR)		
			> 3	124	1.64 (NR)		
		Urinary bladder	*Coffee consumption among women (cups/day)*				
			< 1	15	1.00		
			1	25	0.83 (NR)		
			2	34	1.03 (NR)		
			3	13	1.25 (NR)		
			> 3	24	0.81 (NR)		
			Coffee consumption among men and women (cups/day)			Sex, cigarettes smoked/day	
			< 1	39	1.00		
			1	81	1.15 (NR)		
			2	107	1.11 (NR)		
			3	89	1.82 (NR)		
			> 3	148	1.30 (NR)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mettlin & Graham (1979) (cont.)			*Coffee consumption among light-smoking (< half a pack/day) men (cups/day)*			Cigarettes smoked/ day	
			< 1	16	1.00		
			1	28	1.28 (0.58–2.82)		
			2	34	0.98 (0.46–2.09)		
			3	30	2.18 (0.97–4.93)		
			> 3	26	1.40 (0.62–3.15)		
			Coffee consumption among light-smoking (< half a pack/day) women (cups/day)				
			< 1	14	1.00		
			1	24	0.80 (0.33–1.93)		
			2	30	0.93 (0.40–2.19)		
			3	12	1.17 (0.40–3.47)		
			> 3	15	0.66 (0.25–1.74)		
Wynder & Goldsmith (1977) USA (various states), 1969–1974	Cases: 732 hospital-based, from 17 hospitals in New York (majority), Houston, Los Angeles, Miami, Birmingham, New Orleans, Virginia Controls: 732 hospital-based, patients without history of tobacco-related conditions, matched to cases by sex, race, hospital status, age at diagnosis Exposure assessment method: questionnaire, in-person interview, frequency and amount	Urinary bladder	*Coffee (cups/day)*			Smoking	Strengths: adequate numbers, includes cases from various regions of the USA Limitations: controls may include patients with diseases that affect coffee intake, few details of statistical analyses, no history of coffee drinking considered
			None/ occasionally	NR	1.0		
			1–3	NR	1.4 (0.8–2.3)		
			4–6	NR	1.9 (1.0–3.6)		
			≥ 7	NR	2.0 (0.8–4.9)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Howe et al. (1980) Canada (Nova Scotia, Newfoundland, British Columbia), 1974–1976	Cases: 632 population-based, identified through cancer registries Controls: 632 population-based, neighbourhood controls, matched to cases by age and sex Exposure assessment method: interviewer-administered questionnaire	Urinary bladder	*Lifetime average total coffee for men (cups/day)*			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, diabetes, education, aspirin, artificial sweetener	Strengths: coffee drinking history and coffee types, included men and women, comprehensive consideration of confounders Limitations: small numbers for stratified analyses
			Never drinker	NR	1.0		
			1–2	NR	[1.6 (1.0–2.6)]		
			3–4	NR	[1.3 (0.7–2.3)]		
			> 4	NR	[1.5 (0.8–2.8)]		
			Lifetime average total coffee for women (cups/day)			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, kidney infection, diabetes	
			Never drinker	NR	1.0		
			1–2	NR	[0.7 (0.3–1.5)]		
			3–4	NR	[1.7 (0.6–4.8)]		
			> 4	NR	[1.3 (0.4–4.1)]		
			Lifetime average instant coffee for men (cups/day)			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, education, aspirin, artificial sweetener, regular coffee	
			Never drinker	NR	1.0		
			1–2	NR	[1.5 (1.0–2.3)]		
			3–4	NR	[1.7 (0.9–3.3)]		
			> 4	NR	[1.5 (0.7–3.1)]		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Howe et al. (1980) (cont.)			*Lifetime average instant coffee for women (cups/day)*			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, kidney infection, diabetes, regular coffee	
			Never drinker	NR	1.0		
			1–2	NR	[1.1 (0.5–2.5)]		
			3–4	NR	[1.2 (0.3–5.1)]		
			> 4	NR	[1.2 (0.2–5.5)]		
			Lifetime average regular coffee for men (cups/day)			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, education, aspirin, artificial sweetener, instant coffee	
			Never drinker	NR	1.0		
			1–2	NR	[2.0 (1.1–3.4)]		
			3–4	NR	[1.5 (0.8–2.7)]		
			> 4	NR	[1.8 (1.0–3.5)]		
			Lifetime average regular coffee for women (cups/day)			Cigarettes smoked, smoking status, lifetime pipe use, inhales pipe smoke heavily, occupation, use of non-public water supply, bladder infection, kidney infection, diabetes, instant coffee	
			Never drinker	NR	1.0		
			1–2	NR	[0.4 (0.2–8.0)]		
			3–4	NR	[0.7 (0.2–14)]		
			> 4	NR	[0.7 (0.2–16)]		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Howe et al. (1980) (cont.)			*Lifetime average instant coffee for non-smoking women (cups/day)*			NR	
			≤ 2	NR	1.0		
			> 2	NR	1.4 (0.4–4.4)		
Morrison et al. (1982) USA (Boston), UK (Manchester), Japan (Nagoya), 1976–1978	Cases: 1666 population-based, identified through hospitals Controls: 2229 population-based, randomly identified, matched to cases by age and sex Exposure assessment method: questionnaire (no information about validation) administered in person	Urinary bladder	*Coffee (cups/day): all studies combined*			Age, sex, study area, cigarette smoking	Strengths: large sample size, comprehensive exposure assessment, consideration of occupational exposure and other confounders Limitations: not all analyses are shown, no confidence intervals provided for most of the estimates
			< 1	514	1.0		
			> 1	903	1.0 (0.8–1.2)		
			Coffee (cups/day): Boston study, men only				
			< 1	23	1.0		
			1	98	0.8 (NR)		
			2	95	0.7 (NR)		
			3	82	0.9 (NR)		
			4	41	0.8 (NR)		
			5	19	0.8 (NR)		
			≥ 6	65	1.5 (NR)		
			Coffee (cups/day): Boston study, women only				
			< 1	20	1.0		
			1	59	0.8 (NR)		
			2	38	0.6 (NR)		
			3	19	1.7 (NR)		
			4	12	0.9 (NR)		
			5	10	0.7 (NR)		
			≥ 6	7	1 (NR)		
			Coffee (cups/day): Manchester study, men only				
			< 1	224	1.0		
			1	85	1.1 (NR)		
			2	40	0.9 (NR)		
			3–4	27	0.9 (NR)		
			≥ 5	12	0.8 (NR)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Morrison et al. (1982) (cont.)			*Coffee (cups/day): Manchester study, women only*				
			< 1	79	1.0		
			1	46	1.4 (NR)		
			2	8	0.4 (NR)		
			3–4	14	1.2 (NR)		
			≥ 5	5	1 (NR)		
			Coffee (cups/day): Nagoya study, men only				
			< 1	116	1.0		
			1	43	1.0		
			2	38	1.2		
			3–4	20	1.3		
			≥ 5	7	1.9		
			Coffee (cups/day): Nagoya study, women only				
			< 1	52	1.0		
			1	11	0.7		
			> 2	2	0.7		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hartge et al. (1983) USA (10 geographical regions), 1977–1978	Cases: 2982 population-based, identified through SEER cancer registries Controls: 5782 population-based, identified through RDD or Medicare records, frequency matched to cases on age, sex, and geographical distribution Exposure assessment method: interviewer-administered questionnaire, different types of coffee and frequency of drinking assessed	Urinary bladder	*Coffee drinking history*			Sex, age, race, geographic area, tobacco history (based on cigarettes/day and smoking status)	Strengths: large sample size, thorough confounding assessment, years of coffee drinking assessed Limitations: modest numbers in some stratified analyses, small number in reference group
			Never drinker	98	1.0		
			Ever drinker	2809	1.4 (1.1–1.8)		
			Men: never drinker	58	1.0		
			Men: ever drinker	2139	1.6 (1.2–2.2)		
			Women: never drinker	40	1.0		
			Women: ever drinker	670	1.2 (0.8–1.7)		
			Coffee consumption (cups/wk) among men				
			≤ 7	397	1.0		
			7.1–14	389	0.9 (0.8–1.1)		
			41.1–21	381	1.0 (0.8–1.2)		
			21.1–35	493	1.1 (0.9–1.3)		
			35.1–49	195	1.0 (0.8–1.3)		
			49.1–63	109	1.2 (0.9–1.6)		
			63.1–155	148	1.5 (1.1–1.9)		
			Coffee consumption (cups/wk) among women				
			≤ 7	164	1.0		
			7.1–14	161	0.9 (0.7–1.2)		
			41.1–21	110	0.8 (0.6–1.1)		
			21.1–35	133	0.9 (0.7–1.2)		
			35.1–49	49	0.7 (0.5–1.1)		
			49.1–63	21	0.9 (0.5–1.7)		
			63.1–155	26	0.8 (0.4–1.4)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hartge et al. (1983) (cont.)			*Coffee drinking status by smoking status among men*				
			Non-smokers	NR	–		
			Never drinkers	159	1.0		
			Ever drinkers	NR	1.5 (0.9–2.5)		
			Past smokers	NR	–		
			Never drinkers	62	1.0		
			Ever drinkers	NR	1.4 (0.8–2.6)		
			Smokers	NR	–		
			Never drinkers	56	1.0		
			Ever drinkers	NR	2.1 (1.2–3.9)		
			Coffee drinking high/low by smoking status among men				
			Non-smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	21	4.2 (1.7–10.0)		
			Past smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	208	1.3 (1–1.8)		
			Smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	302	1.2 (1–1.6)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hartge et al. (1983) (cont.)			*Coffee drinking status by smoking status among women*			Sex, age, race, geographical area, amount of tobacco	
			Non-smokers	NR	–		
			Never drinkers	121	1.0		
			Ever drinkers	NR	0.9 (0.6–1.5)		
			Past smokers	NR	–		
			Never drinkers	13	1.0		
			Ever drinkers	NR	3.0 (0.8–12.0)		
			Smokers	NR	–		
			Never drinkers	27	1.0		
			Ever drinkers	NR	1.3 (0.6–2.9)		
			Coffee drinking high/low by smoking status among women				
			Non-smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	24	0.4 (0.2–1.5)		
			Past smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	25	1.7 (0.7–4.2)		
			Smokers	NR	–		
			≤ 49 cups/wk	NR	1.0		
			Ever drinkers (> 49 cups/wk)	67	1 (0.6–1.7)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sturgeon et al. (1994) USA (10 geographical regions), 1977–1978	Cases: 1860; see Hartge et al. (1983) Controls: 3934; see Hartge et al. (1983) Exposure assessment method: questionnaire; see Hartge et al. (1983)	Urinary bladder: TCC	*Coffee consumption (cups/wk) by tumour grade*			Age, sex, cigarette use (status and cigarettes/day), history of urinary infections, history of bladder stones, artificial sweetener, family history of urinary tract cancer, high-risk occupation, race, education	Same study as Hartge et al. (1983) Strengths: large sample size, thorough confounding assessment, years of coffee drinking assessed, very comprehensive and thorough analyses Limitations: modest numbers for stage and grade combined analyses
			Grade I, consumption < 50	326	1.0		
			Grade I, consumption ≥ 50	49	1.3 (0.9–1.8)		
			Grade II, consumption < 50	578	1.0		
			Grade II, consumption ≥ 50	87	1.3 (1.0–1.7)		
			Grade III/IV, consumption < 50	562	1.0		
			Grade III/IV, consumption ≥ 50	61	1.4		
			RR for coffee (cups/wk) by tumour stage				
			Non-invasive, consumption < 50	983	1.0		
			Non-invasive, consumption ≥ 50	147	1.4 (1.1–1.7)		
			Invasive overall, consumption < 50	522	1.0		
			Invasive overall, consumption ≥ 50	68	1.2 (0.9–1.6)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sturgeon et al. (1994) (cont.)			*RR for coffee (cups/wk) by tumour grade and stage*				
			Non-invasive low grade, consumption < 50	668	1.0		
			Non-invasive low grade, consumption ≥ 50	109	1.4 (1.1–1.8)		
			Non-invasive high grade, consumption < 50	156	1.0		
			Non-invasive high grade, consumption ≥ 50	15	1.3 (0.7–2.2)		
			Invasive low grade, consumption < 50	197	1.0		
			Invasive low grade, consumption ≥ 50	23	1.0 (0.6–1.5)		
			Invasive high grade, consumption < 50	293	1.0		
			Invasive high grade, consumption ≥ 50	43	1.4 (1.0–2.0)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kantor et al. (1988) USA (10 geographical regions), 1977–1978	Cases: 2915; see Hartge et al. (1983) Controls: 5782; see Hartge et al. (1983) Exposure assessment method: questionnaire; see Hartge et al. (1983)	Urinary bladder: SCC	*Coffee consumption (cups/wk)*			Sex, age, cigarette smoking	Strengths: consideration of tumour subtypes, large sample size for TCC Limitations: very small numbers for SCC and adenocarcinoma, small number in reference group (never drinkers)
			0–7	9	1.0		
			8–21	12	0.9 (0.3–2.2)		
			22–49	13	1.4 (0.5–3.5)		
			50–63	3	2.1 (0.4–10.8)		
			≥ 64	2	1.1 (0.1–6.6)		
		Urinary bladder: adenocarcinomas	*Coffee consumption (cups/wk)*				
			0–7	5	1.0		
			8–21	13	2.1 (0.7–6.9)		
			22–49	11	2.8 (0.8–9.5)		
			50–63	1	2.7 (0.1–48.7)		
			≥ 64	2	5.2 (0.5–58.1)		
			Trend test *P* value, 0.049				
		Urinary bladder: TCC	*RR for coffee (cups/wk)*				
			0–7	625	1.0		
			8–21	932	1.0 (0.9–1.1)		
			22–49	761	1.1 (0.9–1.2)		
			50–63	110	1.4 (1.0–1.8)		
			≥ 64	153	1.5 (1.1–1.9)		
			Trend test P value, < 0.01				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rebelakos et al. (1985) Greece (Athens), 1980–1982	Cases: 300 hospital-based Controls: 300 hospital-based, different hospitals from cases (majority traumatic fractures or conditions) Exposure assessment method: interviewer-administered questionnaire (no information about validation), amount and duration recorded	Urinary bladder: 93% TCC	*Coffee consumption (cups/day): men and women*			Age, sex, smoking status	Strengths: proper adjustment Limitations: moderate size, but too small for stratified analyses by sex (few women), no consideration of drinking history, no mention of other confounders other than age and smoking, different types of coffee not specified
			0	25	1.0		
			1	62	1.2 (0.8–2.2)		
			2	150	1.7 (1.0–2.8)		
			3	36	2.7 (0.9–8.2)		
			≥ 4	24	0.7 (0.2–2.7)		
			> 2 vs < 2 (including 0)	210	1.7 (1.2–2.3)		
			Coffee consumption (cups/day): men				
			0	15	1.0		
			1	41	1.1 (0.5–2.3)		
			2	133	1.5 (0.8–2.7)		
			3	32	4.0 (1.2–13.4)		
			≥ 4	22	0.5 (0.1–2.5)		
			> 2 vs < 2 (including 0)	187	1.7 (1.2–2.4)		
			Coffee consumption (cups/day): women				
			0	10	1.0		
			1	21	2.0 (0.9–5.0)		
			2	15	2.1 (0.9–5.0)		
			3	0	0.0 (0.0–0.0)		
			≥ 4	2	2.0 (0.2–23.6)		
			> 2 vs < 2 (including 0)	17	1.6 (0.8–3.2)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Claude et al. (1986) Germany (Lower Saxony), 1977–1982	Cases: 431 hospital-based Controls: 431 hospital-based, identified in urology ward and for older individuals from elderly homes in town, matched to cases 1:1 by age and sex Exposure assessment method: questionnaire administered in person, frequency of intake recorded, different types (ground, regular, decaffeinated) of coffee considered	Urinary bladder	*Consumption of ground coffee (cups/day): men*			Smoking	Strengths: adequate numbers Limitations: hospital-based, possible bias due to selection of hospital-based controls with urological diseases, duration of intake not considered
			0	NR	1.00		
			1–2	NR	1.42 (0.70–2.80)		
			3–4	NR	1.39 (0.70–2.60)		
			> 4	NR	2.29 (0.40–11.60)		
			Drinker vs non-drinker	NR	1.57 [(0.60–3.80)]		
			Consumption of ground coffee (cups/day): women				
			0	NR	1.00		
			1–2	NR	1.26 (0.80–2.00)		
			3–4	NR	1.89 (0.50–6.60)		
			> 4	NR	2.18 (0.50–10.00)		
			Drinker vs non-drinker	NR	0.99 [(1.00–1.00)]		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kunze et al. (1992) Germany (Lower Saxony), 1977–1985	Cases: 675 hospital-based Controls: 675 hospital-based, identified in urology ward, matched by age and sex (64% of men had hyperplasia of the prostate, 73% women had lower urinary infections) Exposure assessment method: questionnaire administered in person, frequency of intake recorded, different types (ground, regular, decaffeinated) of coffee considered	Urinary bladder: lower urinary tract cancers, majority bladder but also others	*Coffee consumption (cups/day): women* 0 1–2 3–4 ≥ 5 *Coffee consumption (cups/day): men* 0 1–2 3–4 ≥ 5	 NR 47 60 24 NR 168 205 102	 1.0 1.4 (0.7–3.0) 2.4 (1.0–5.4) 2.7 (0.9–7.8) 1.0 1.3 (0.8–2.0) 1.5 (0.95–2.3) 2.0 (1.2–3.3)	Smoking status, pack-years	Extension of a study reported by Claude et al. (1986), so includes patients reported in this previous study Strengths: adequate numbers Limitations: hospital-based, possible bias due to selection of hospital-based controls with urological diseases, no history of coffee drinking considered

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jensen et al. (1986) Denmark (Copenhagen), 1979–1981	Cases: 371 population-based Controls: 771 population-based, matched to cases by sex, age, and residential area Exposure assessment method: questionnaire administered in person, frequency of intake recorded, different types (ground, regular, decaffeinated, instant) of coffee considered, drinking history and amount	Urinary bladder: majority TCC	*Coffee consumption*			Age, smoking status, lifetime cigarette exposure (pack-years)	Strengths: adequate sample size, comprehensive questionnaire Limitations: no information on validation of questionnaire, modest numbers for reference category for stratified analyses by sex
			Men per L/day	NR	[1.1 (0.9–1.4)]		
			Women per L/day	NR	[1.1 (0.7–1.9)]		
			Coffee consumption (mL/day): men				
			0	15	1.0		
			1–499 (0–2 cups)	69	0.9 (0.5–1.9)		
			500–999 (2–4 cups)	90	0.8 (0.4–1.6)		
			1000–1499 (4–6 cups)	56	0.9 (0.4–1.8)		
			≥ 1500 (> 6 cups)	50	1 (0.5–2.1)		
			Trend test *P* value, 0.83				
			Coffee consumption (mL/day): women				
			0	4	1.0		
			1–499 (0–2 cups)	20	1.9 (0.6–6.7)		
			500–999 (2–4 cups)	33	1.2 (0.4–3.5)		
			1000–1499 (4–6 cups)	15	1.6 (0.4–6.0)		
			≥1500 (> 6 cups)	13	2.7 (0.7–10.9)		
			Trend test *P* value, 0.37				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kabat et al. (1986) USA (various states), 1976–1983	Cases: 152; see Wynder & Goldsmith (1977) Controls: 492; see Wynder & Goldsmith (1977) Exposure assessment method: questionnaire; see Wynder & Goldsmith (1977)	Urinary bladder	*Brewed coffee consumption (cups/day): men*			None	Strengths: focus on non-smokers (important given the strong confounding effect of smoking), large catchment area across the USA Limitations: hospital-based controls (which may introduce bias if they had diseases that affect coffee intake), small numbers for some of the coffee drinking categories
			None/occasional	40	1.00		
			1–2	18	0.91 (0.48–1.71)		
			3–4	15	1.38 (0.69–2.79)		
			5–6	3	1.38 (0.34–5.59)		
			≥ 7	0	0.46 (0.03–8.47)		
			Brewed coffee consumption (cups/day): women				
			None/occasional	40	1.00		
			1–2	24	1.51 (0.84–2.72)		
			3–4	8	0.81 (0.35–1.88)		
			5–6	2	0.66 (0.14–3.10)		
			≥ 7	2	2.43 (0.41–14.34)		
			Decaffeinated coffee consumption (cups/day): men				
			None/occasional	60	1.00		
			1–2 cups/day	14	1.07 (0.54–2.11)		
			3–4 cups/day	2	0.40 (0.09–1.71)		
			≥ 5 cups/day	0	0.27 (0.02–4.10)		
			Decaffeinated coffee consumption (cups/day): women				
			None/occasional	62	1.00		
			1–2	9	0.50 (0.24–1.07)		
			3–4	5	0.73 (0.26–2.01)		
			≥ 5	0	0.58 (0.03–11.82)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Piper et al. (1986) USA (New York), 1975–1980	Cases: 165 population-based, identified through cancer registry Controls: 165 population-based, identified through RDD, paired to cases by strata defined by age and residence Exposure assessment method: telephone questionnaire, no information about validation, regular coffee only	Urinary bladder	*Coffee consumption (cup-years) among women* Non-drinker 1–50 51–100 ≥ 101	 NR NR NR	 1.0 0.9 (0.5–2.3) 1.9 (0.8–4.6) 2.1 (0.7–6.3)	Race, level of education, smoking (pack-years), phenacetin drugs use, bladder infection, thyroid uptake procedure	Strengths: population-based, adequate control for confounders Limitations: narrow focus on young women, no history of coffee drinking studied
Iscovich et al. (1987) Argentina (La Plata), 1983–1985	Cases: 117 hospital-based, 60% of registered cases for catchment area Controls: 117 hospital-based (16% digestive system problems, 17% heart disease, 12% hypertension), 2:1 ratio: one recruited from same hospitals, another from the neighbourhood of the case Exposure assessment method: in-person questionnaire, coffee frequency and amount considered	Urinary bladder	*Coffee consumption (cups/day)* 0 1 2 ≥ 3 Trend test *P* value, < 0.05	 35 24 16 24	 1.00 1.08 (NR) 4.45 (NR) 12 (NR)	Age, average cigarettes smoked	Strengths: case recruitment comparable to a population-based study Limitations: modest numbers, use of hospital-based controls that included disorders that may affect coffee intake (thus leading to potential biases that may inflate ORs), no confidence intervals presented, no history of coffee drinking considered

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ciccone & Vineis (1988) Italy (Torino), 1978–1983	Cases: 512 hospital-based Controls: 594 hospital-based, patients with urological or surgical conditions (~20% from 'other surgical departments'; no other information provided), no information on matching to cases Exposure assessment method: in-person questionnaire (unclear validation), coffee history and frequency of intake	Urinary bladder	*Current consumption (cups/day): men*			Age, smoking status, lifelong use of cigarettes, high-risk occupations	Strengths: stratification by smoking Limitations: hospital-based (therefore concern about bias introduced), very small numbers for stratified analyses
			Non-drinker	88	1.0		
			1	93	0.8 (0.5–1.3)		
			2	122	1.0 (0.7–1.5)		
			3	122	1.2 (0.8–1.8)		
			≥ 4	87	0.8 (0.5–1.2)		
			Consumption (cups/day) 10 yr before diagnosis: men				
			Non-drinker	39	1.0		
			1	65	1.2 (0.7–2.1)		
			2	97	1.5 (0.9–2.5)		
			3	104	1.1 (0.7–1.8)		
			≥ 4	139	1.1 (0.6–1.8)		
			Current consumption (cups/day): women			Age, smoking status, lifelong use of cigarettes	
			Non-drinkers	8	1.0		
			1	17	1.4 (0.5–3.8)		
			2	12	1.0 (0.4–3.0)		
			3	8	0.7 (0.2–2.2)		
			≥ 4	7	0.8 (0.2–2.6)		
			Consumption (cups/day) 10 yr before diagnosis: women				
			0–1	16	1.0		
			2	13	0.9 (0.4–2.3)		
			3	8	0.5 (0.2–1.5)		
			≥ 4	15	1.4 (0.6–3.5)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ciccone & Vineis (1988) (cont.)			*Current consumption (cups/day): non-smoking men*			Age, high-risk occupations	
			Non-drinker	3	1.0		
			1	6	1.1 (0.2–5.4)		
			2	5	1.9 (0.4–9.3)		
			3	5	4.4 (0.8–25.1)		
			Consumption (cups/day) 10 yr before diagnosis: non-smoking men			Age, smoking, high-risk occupations	
			Non-drinker	2	1.0		
			1	4	1.6 (0.2–10.4)		
			2	5	2.7 (0.4–17)		
			≥ 3	5	4.9 (0.8–31.6)		
			Current consumption (cups/day): non-smoking women			Age	
			Non-drinker	7	1.0		
			1	11	1.1 (0.4–3.3)		
			2	7	0.9 (0.3–3.2)		
			≥ 3	6	0.5 (0.1–1.5)		
		Urinary bladder: no information provided on histological types	*Consumption (cups/day) 10 yr before diagnosis: non-smoking women*				
			0–1	12	1.0		
			2	6	0.9 (0.3–2.6)		
			3	5	0.7 (0.2–2.2)		
			≥ 4	8	1.5 (0.6–3.5)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Risch et al. (1988) Canada (South Central Ontario), 1979–1982	Cases: 835 population-based, identified through hospital registries or regional tumour registry Controls: 781 population-based identified from population listings, matched by sex, birth year, area of residence Exposure assessment method: questionnaire, in-person interview (no information about validation), different types (ground, instant, instant decaffeinated, espresso) of coffee considered, frequency and lifetime use considered	Urinary bladder	*Ever coffee drinking of total coffee: men*			Lifetime smoking history (pack-years), history of diabetes	Strengths: large sample size, comprehensive questionnaire, consideration of non-smokers, different types of coffee and lifetime use Limitations: sample size not shown for different strata in analyses, no tests for trend shown
			Ever drinker	NR	0.86 (0.59–1.25)		
			Ever drinker, non-smokers	NR	1.69 (0.30–9.59)		
			Ever drinker, non-user of artificial sweetener	NR	0.64 (0.38–1.06)		
			Ever coffee drinking of total coffee: women				
			Ever drinker	NR	1.87 (1.03–3.40)		
			Ever drinker, non-smokers	NR	2.05 (0.69–6.15)		
			Ever drinker, non-user of artificial sweetener	NR	2.55 (1.05–6.22)		
			Average consumption of total coffee (cups/day): men				
			None	NR	1.00		
			> 1–3	NR	1.04 (0.76–1.41)		
			> 3–6	NR	1.15 (0.82–1.62)		
			> 6	NR	0.91 (0.58–1.44)		
			Total lifetime intake	NR	0.95 (0.85–1.06)		
			Average consumption of total coffee (cups/day): women				
			None	NR	1.00		
			> 1–3	NR	0.96 (0.57–1.61)		
			> 3–6	NR	1.85 (0.98–3.50)		
			> 6	NR	1.11 (0.46–2.71)		
			Total lifetime intake	NR	1.16 (0.88–1.53)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Risch et al. (1988) (cont.)			*Ever drinker of ground coffee: men*				
			Ever	NR	1.02 (0.78–1.33)		
			Total lifetime intake	NR	0.95 (0.85–1.08)		
			Ever drinker of ground coffee: women				
			Ever	NR	1.15 (0.75–1.76)		
			Total lifetime intake	NR	1.11 (0.83–1.48)		
			Ever drinker of instant coffee: men				
			Ever	NR	0.93 (0.74–1.18)		
			Total lifetime intake	NR	0.94 (0.83–1.07)		
			Ever drinker of instant coffee: women				
			Ever	NR	0.97 (0.65–1.47)		
			Total lifetime intake	NR	0.95 (0.73–1.25)		
			Ever drinker of instant decaffeinated coffee: men				
			Ever	NR	1.12 (0.83–1.51)		
			Total lifetime intake	NR	0.91 (0.76–1.10)		
			Ever drinker of instant decaffeinated coffee: women				
			Ever	NR	1.5 (0.90–2.52)		
			Total lifetime intake	NR	1.2 (0.87–1.67)		
			Ever drinker of espresso coffee: men				
			Ever	NR	1.64 (0.96–2.79)		
			Total lifetime intake	NR	1.29 (0.96–1.74)		
			Ever drinker of espresso coffee: women				
			Ever	NR	1.50 (0.59–3.78)		
			Total lifetime intake	NR	1.75 (0.91–3.39)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Slattery et al. (1988a) USA (Utah), 1977–1983	Cases: 332 population-based, cases identified through population-based cancer registry Controls: 686 population-based, identified through RDD or social security administration roster (Medicare), frequency matched by age and sex Exposure assessment method: questionnaire, in-person survey, lifetime coffee (only caffeinated)	Urinary bladder	*Caffeinated coffee (cups/wk)*			Smoking status (never, ex, current)	Possible overlap with Slattery et al. (1988b) Strengths: population-based, cases identified via registry Limitations: very unique population with majority of Mormons (distinctive coffee drinking and smoking habits)
			Never drinkers	NR	1.00		
			1–15	NR	1.32 (0.88–2.00)		
			16–30	NR	0.80 (0.50–1.26)		
			> 30	NR	1.28 (0.76–2.17)		
			Caffeinated coffee (cups/wk): never smokers			None	
			Never drinkers	NR	1.00		
			1–15	NR	1.42 (0.69–2.90)		
			16–30	NR	1.36 (0.55–3.35)		
			> 30	NR	1.50 (0.39–2.17)		
			Caffeinated coffee (cups/wk): smokers				
			Never drinkers	NR	1.00		
			1–15	NR	1.36 (0.88–2.10)		
			16–30	NR	0.88 (0.56–1.39)		
			> 30	NR	1.54 (0.98–2.44)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Slattery et al. (1988b) USA (Utah), 1977–1983	Cases: 419 population-based, identified through population-based cancer registry Controls: 889 population-based, identified through RDD or social security administration roster (Medicare), 2:1 ratio of controls to cases, frequency matched by age, sex Exposure assessment method: questionnaire, in-person survey, lifetime coffee (only caffeinated)	Urinary bladder	*Consumption of caffeinated coffee, number of 8 oz servings (~1 cup)/wk*			Age, sex, diabetes, bladder infections, cigarette smoking (smoking status, pack-years)	Strengths: population-based, cases identified via registry Limitations: very unique population with majority of Mormons (distinctive coffee drinking and smoking habits)
			0	164	1.00		
			1–20	99	1.23 (0.88–1.72)		
			21–40	93	1.05 (0.73–1.51)		
			> 40	58	1.60 (1.00–2.56)		
			Consumption of caffeinated coffee, number of 8 oz servings (~1 cup)/wk				
			0	354	1.00		
			≥ 1	62	1.04 (0.73–1.48)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Clavel & Cordier (1991) France 1984–1987	Cases: 781 hospital-based Controls: 781 hospital-based controls, identified in same hospitals as cases (non-cancer, no symptoms of bladder cancer), matched by sex, age, place of residence Exposure assessment method: in-person questionnaire, different types (regular, instant, caffeinated, decaffeinated) of coffee considered, history of consumption (average daily consumption since age 18)	Urinary bladder	*Average daily coffee consumption (cups/day): men and women*			Age, hospital, residence, smoking status	Strengths: large sample size, several types of coffee studied Limitations: hospital-based, 21% of controls had gastrointestinal disease and 30% men with heart disease problems (which may affect coffee intake), sample sizes too small for stratified analyses (too many cells with number of subjects < 10), no combined analyses shown
			0	12	1.00		
			1–4	488	1.24 (0.56–2.74)		
			5–7	61	1.46 (0.6–3.51)		
			> 7	27	2.94 (1.06–8.15)		
			Average daily coffee consumption (cups/day): non-smoking women			Age, hospital, residence	
			0	3	1.00		
			1	7	1.00		
			2	16	0.99 (0.34–2.93)		
			3	13	1.51 (0.48–4.74)		
			> 3	15	2.29 (0.59–8.86)		
			Average daily coffee consumption (cups/day): non-smoking men				
			0	1	1.00		
			1	3	0.97 (0.08–11.43)		
			2	9	2.93 (0.31–30.35)		
			≥ 3	29	5.10 (0.59–43.86)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
D'Avanzo et al. (1992) Italy (Milan), 1985–1990	Cases: 555 hospital-based from Milan and Pordenone Controls: 855 hospital-based, recruited in same hospitals as cases (no urological and non-cancer patients, no specific diseases excluded were listed) Exposure assessment method: validated in-person questionnaire, regular and decaffeinated coffee	Urinary bladder	*Regular coffee duration of drinking (yr), both sites combined*			Age, sex, education level, smoking (status, cigarettes/ day), alcohol, occupation	Same design as La Vecchia et al. (1989a) so probably some overlap of cases Strengths: validated questionnaire, consideration of duration of drinking Limitations: possible bias introduced by use of hospital-based controls, many of whom may have had disease that affect coffee intake
			Non-drinkers	71	1.0		
			< 30	219	1.2 (0.9–1.7)		
			≥ 30	267	1.4 (0.9–2.2)		
			Trend test *P* value, < 0.05				
			Regular coffee drinking status, both sites combined				
			Non-drinkers	71	1.0		
			Drinkers	484	1.3 (1.0–1.8)		
			Trend test *P* value, > 0.05				
			Regular coffee drinking frequency (cups/day), both sites combined				
			Non-drinkers	71	1.0		
			1	126	1.2 (0.8–1.7)		
			2	167	1.4 (0.9–2.0)		
			3	109	1.5 (1.0–2.2)		
			≥ 4	82	1.4 (0.9–2.2)		
			Trend test *P* value, > 0.05				
			Decaffeinated coffee drinking status, both sites combined				
			Non-drinkers	519	1.0		
			Drinkers	39	1.5 (0.9–2.4)		
			Trend test *P* value, > 0.05				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nomura et al. (1991) USA (Hawaii), 1977–1986	Cases: 261 population-based, identified at 7 hospitals Controls: 522 population-based, identified from state survey, matched to cases by sex, ethnic group, age, residence Exposure assessment method: validated in-person questionnaire, frequency and quantity of coffee (regular, decaffeinated, brewed, instant, and all combinations of these) considered	Urinary bladder	*Coffee consumption, all types (cup-years): men*			Pack-years of smoking	Strengths: validated and thorough coffee drinking assessment, including years of consumption Limitations: no adjustment for race, analyses of different coffee types not adjusted for each other
			Non-drinker	7	1.0		
			Drinker	188	0.8 (0.3–2.0)		
			1–49	34	0.6 (0.2–1.6)		
			50–109	74	0.9 (0.4–2.3)		
			≥ 110	80	1.0 (0.4–2.7)		
			Trend test *P* value, 0.12				
			Coffee consumption, regular ground (cup-years): men				
			Non-drinker	10	1.0		
			Drinker	185	0.9 (0.4–2.0)		
			1–39	46	0.9 (0.4–2.0)		
			40–89	58	0.9 (0.4–2.1)		
			≥ 90	81	1.0 (0.4–2.3)		
			Trend test *P* value, 0.72				
			Coffee consumption, instant (cup-years): men				
			Non-drinker	106	1.0		
			Drinker	89	1.0 (0.7–1.4)		
			1–14	37	0.8 (0.5–1.3)		
			≥ 15	52	1.2 (0.8–1.9)		
			Trend test *P* value, 0.26				
			Coffee consumption, instant decaffeinated (cup-years): men				
			Non-drinker	144	1.0		
			Drinker	51	1.3 (0.8–2.0)		
			1–4	26	1.5 (0.8–2.6)		
			≥ 5	25	1.1 (0.6–1.9)		
			Trend test *P* value, 0.82				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nomura et al. (1991) (cont.)			*Coffee consumption, all types (cup-years): women*				
			Non-drinker	6	1.0		
			Drinker	60	0.8 (0.3–2.6)		
			1–49	24	0.9 (0.3–2.9)		
			50–109	24	0.9 (0.2–2.9)		
			≥ 110	12	0.5 (0.5–2.1)		
			Trend test *P* value, 0.26				
			Coffee consumption, regular ground (cup-years): women				
			Non-drinker	9	1.0		
			Drinker	57	0.7 (0.2–1.9)		
			1–39	20	0.7 (0.2–2.1)		
			40–89	29	0.8 (0.3–3.6)		
			≥ 90	8	0.3 (0.1–1.0)		
			Trend test *P* value, 0.02				
			Coffee consumption, instant (cup-years): women				
			Non-drinker	32	1.0		
			Drinker	34	1.8 (0.9–3.3)		
			1–14	22	1.8 (0.9–3.7)		
			≥ 15	12	1.6 (0.6–4.0)		
			Trend test *P* value, 0.46				
		Urinary bladder: 98% bladder cancer, 83% of which were SCC or TCC	*Coffee consumption, instant decaffeinated (cup-years): women*				
			Non-drinker	53	1.0		
			Drinker	13	0.6 (0.3–1.2)		
			1–4	7	0.5 (0.2–1.4)		
			≥ 5	6	0.6 (0.2–1.6)		
			Trend test *P* value, 0.3				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Escolar Pujolar et al. (1993) Spain (Cadiz, Barcelona, Madrid, Guipuzkoa, Bizcaya), 1983–1986	Cases: 497 hospital-based but with good population coverage, 51% identified using registries Controls: 1113, ~50% hospital-based (excluding urological, diabetes, heart or circulatory, cancer of respiratory or upper gastrointestinal tract), matched for sex, age, province of residence; other ~50% were population-based controls identified from electoral rolls Exposure assessment method: in-person questionnaire, unclear validation, coffee (regular, instant, decaffeinated) history/ frequency considered	Urinary bladder	*Coffee consumption status and frequency (cups/wk): men*			Smoking (cigarettes/day), occupation, consumption of artificial sweeteners, age, province of residence Smoking status, consumption of artificial sweeteners, age, province of residence	Strengths: adequate sample size, comprehensive assessment of coffee drinking (taking into account frequency, amount, and duration), stratification by smoking Limitations: use of hospital-based controls may introduce bias, very small numbers for stratified analyses by smoking
			Non-drinker (reference)	34	1.00		
			Ex-drinker	42	1.22 (0.69–2.15)		
			Current drinker	362	0.96 (0.62–1.49)		
			Drinker	404	0.98 (0.64–1.52)		
			2–7	138	0.99 (0.63–1.57)		
			8–14	130	0.95 (0.59–1.51)		
			≥ 15	135	1.02 (64.0–1.63)		
			Coffee consumption status and frequency (cups/wk): women				
			Non-drinker (reference)	5	1.00		
			Ex-drinker	6	0.87 (0.20–3.77)		
			Current drinker	48	0.98 (0.31–3.14)		
			2–7	17	1.02 (0.29–3.58)		
			8–14	24	1.14 (0.34–3.85)		
			≥ 15	13	0.71 (0.20–2.56)		
			Coffee lifelong consumption in cups (thousands): women				
			0	3	1.00		
			1–10	6	1.47 (0.29–7.58)		
			10–20	13	1.80 (0.41–7.90)		
			20–30	9	2.03 (0.43–9.70)		
			30–40	10	1.47 (0.31–6.89)		
			≥ 40	12	1.39 (0.31–6.25)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Escolar Pujolar et al. (1993) (cont.)			*Coffee consumption status and frequency (cups/wk): non-smoking men*			Smoking (cigarettes/day), occupation, consumption of artificial sweeteners, age, province of residence	
			Non-drinker	3	1.00		
			Ex-drinker	1	0.61 (0.06–6.26)		
			Current drinker	24	2.78 (0.78–9.87)		
			Drinker	25	2.41 (0.68–8.46)		
			2–7	10	2.22 (0.57–8.66)		
			8–14	10	3.11 (0.79–12.27)		
			≥ 15	5	1.87 (0.41–8.47)		
			Coffee lifelong consumption in cups (thousands): men				
			0 cups	28	1.00		
			1–10	70	1.09 (0.63–1.87)		
			10–20	86	0.91 (0.54–1.54)		
			20–30	69	1.11 (0.65–1.90)		
			30–40	52	0.99 (0.56–1.74)		
			≥ 40	128	1.14 (0.69–1.90)		
			Coffee lifelong consumption in cups (thousands): non-smoking men				
			0 cups	3	1.00		
			1–10	5	1.74 (0.38–7.95)		
			10–20	6	2.42 (0.55–10.66)		
			20–30	5	2.67 (0.57–12.45)		
			30–40	4	3.67 (0.70–19.25)		
			≥ 40	5	2.08 (0.44–9.86)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena et al. (1993) USA (west New York), 1979–1985	Cases: 351 hospital-based, recruited at most hospitals in the area (Buffalo, Niagara Falls, Rochester) Controls: 855 population-based neighbourhood controls in same counties as cases Exposure assessment method: in-person questionnaire, validated for some of the factors via telephone recalls, coffee (regular, decaffeinated, instant, perk) frequency only	Urinary bladder: TCC	*Coffee consumption (cups/day)*			Age, education, cigarette smoking (pack-years), other liquids, sodium, carotene, calories	Strengths: adequate sample size, use of population-based controls, hospital-based cases with ample catchment area (comparable to population-based cases) Limitations: no history of coffee consumption recorded, patients too ill to participate or deceased were not included, many controls declined to participate because the survey was too long
			0–1	60	1.0		
			2	62	1.3 (0.8–2.0)		
			3–4	114	1.6 (1.1–2.3)		
			≥ 5	115	2.1 (1.3–3.2)		
			Trend test *P* value, < 0.001				
			Coffee consumption (cups/day) for non-smokers aged > 65 yr				
			0–1	NR	1.0		
			2	NR	2.3		
			3–4	NR	3.3		
			≥ 5	NR	6.4		
			Trend test *P* value, 0.02				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena et al. (1993) (cont.)			*Coffee consumption (cups/day) by coffee type: men*			Age, education	
			0–1, any type	60	1.0		
			2–4 decaffeinated, instant	25	1.8 (1.0–3.2)		
			≥ 5 decaffeinated, instant	2	0.4 (0.9–1.8)		
			2–4 decaffeinated, perk	8	1.0 (0.5–2.4)		
			≥ 5 decaffeinated, perk	7	2.8 (1.0–7.8)		
			2–4 regular, instant	29	1.5 (0.9–2.5)		
			≥ 5 regular, instant	19	1.6 (0.9–3.0)		
			2–4 regular, perk	114	1.5 (1.0–2.1)		
			≥ 5 regular, perk	87	2.5 (1.7–3.8)		
			Coffee consumption (cups/day) among those aged < 65 yr			Age, education, cigarette smoking pack-years, other liquids, sodium, carotene, calories	
			0–1	NR	1.0		
			2	NR	1.3 (0.7–2.7)		
			3–4	NR	1.4 (0.7–2.6)		
			≥ 5	NR	1.9 (1.0–3.7)		
			Trend test *P* value, 0.03				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vena et al. (1993) (cont.)			*Coffee consumption (cups/day) among those aged > 65 yr*				
			0–1	NR	1.0		
			2	NR	1.3 (0.7–2.2)		
			3–4	NR	1.7 (1.0–2.8)		
			≥ 5	NR	2.2 (1.2–4.1)		
			Trend test *P* value, < 0.01				
			Coffee consumption (cups/day) among non-smokers aged < 65 yr				
			0–1	NR	1.0		
			2	NR	0.6		
			3–4	NR	1.0		
			≥ 5	NR	1.6		
			Trend test *P* value, 0.08				
Momas et al. (1994) France (Herault district), 1987–1989	Cases: 219 population-based, identified via cancer registry Controls: 792 population-based selected via electoral rolls Exposure assessment method: in-person or mailed questionnaire, duration and changes in coffee intake	Urinary bladder	*Lifelong coffee drinking (cups)*			Lifelong tobacco smoking (cigarettes equivalent), spice consumption, age, occupation, residence, vegetable consumption, lifelong alcohol drinking, birthplace, saccharin	Strengths: population-based study, consideration of coffee duration Limitations: very small numbers for reference category used, only considered lifelong coffee intake (not frequency)
			< 365	8	1.0		
			365–25 000	36	1.6 (0.6–3.8)		
			25 001–60 000	59	1.6 (0.6–3.8)		
			> 60 000	58	4.1 (1.7–10.0)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bruemmer et al. (1997) USA (Washington), 1987–1990	Cases: 262 population-based cases identified via cancer registry (SEER) Controls: 405 population-based, identified via RDD Exposure assessment method: telephone interview questionnaire, coffee (regular, decaffeinated) frequency and amount of intake considered only	Urinary bladder: invasive or non-invasive (in situ or papillary)	*Coffee consumption (cups/day): women*			Age, county, smoking status (never, former, current)	Pack-years was not found to be a confounder, so it was not added Strengths: population-based, consideration of decaffeinated Limitations: modest numbers (especially for women), no consider of duration of intake or amounts, participants < 65 yr
			None	11	1.0		
			≤ 3	21	0.5 (0.2–1.2)		
			> 3–6	20	0.5 (0.5–1.3)		
			> 6	8	0.6 (0.2–1.9)		
			Trend test *P* value, 0.46				
			Coffee consumption (cups/day): men				
			None	24	1.0		
			≤ 3	50	1.1 (0.5–2.1)		
			> 3–6	77	1.7 (0.9–3.4)		
			> 6	51	1.2 (0.6–2.3)		
			Trend test *P* value, 0.38				
			Decaffeinated coffee consumption: women				
			≤ 1 cup/mo	39	1.0		
			> 1 cup/mo – 1 cup/wk	12	1.6 (0.7–3.6)		
			> 7 cups/wk	9	2.1 (0.8–5.3)		
			Trend test *P* value, 0.08				
			Decaffeinated coffee consumption: men				
			≤ 1 cup/mo	148	1.0		
			> 1 cup/mo – 1 cup/wk	31	1.4 (0.8–2.6)		
			> 7 cups/wk	23	0.9 (0.5–1.8)		
			Trend test *P* value, 0.85				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Donato et al. (1997) Italy (Brescia), 1991–1992	Cases: 172 hospital-based Controls: 578 hospital-based identified from three hospitals (prostate adenoma, urolithiasis, obstructive uropathy), male controls were age-matched (not possible for women) Exposure assessment method: in-person validated questionnaire, coffee quantity and frequency considered	Urinary bladder	*Coffee consumption status and frequency:* women			Age, residence, education, date of interview, smoking (lifetime cigarettes smoked), alcohol	Strengths: good representation of underlying case population Limitations: hospital-based controls (not clear if the diseases included may affect coffee intake), very tiny numbers for stratified analyses by sex (women)
			Non-drinker	2	1.0		
			Ex-drinker	0	–		
			Current drinker	35	5.2 (1.0–30.4)		
			1–2 cups/day	27	4.3 (0.8–23.9)		
			3–4 cups/day	8	4.9 (0.7–33.0)		
			Coffee consumption status and frequency: men				
			Non-drinker	7	1.0		
			Ex-drinker	6	2.7 (0.7–10.3)		
			Current drinker	122	2.6 (1.1–6.1)		
			1–2 cups/day	66	2.3 (0.9–5.6)		
			3–4 cups/day	44	2.8 (1.1–7.4)		
			≥ 5 cups/day	11	4.5 (1.2–16.8)		
			Trend test *P* value, > 0.1				
Pohlabeln et al. (1999) Germany (Hesse), 1989–1992	Cases: 300 hospital-based Controls: 300 hospital-based (identified from same hospitals as cases), matched to cases on sex, age, area of residence Exposure assessment method: questionnaire, in-person interview, coffee frequency and amount considered	Urinary bladder	*Coffee amount: men and women*			Smoking status and pack-years	With more thorough adjustment for smoking, weaker ORs were observed for coffee intake. Restricting analyses to urinary bladder yielded similar results. Strengths: thorough adjustment by smoking, stratification by smoking Limitations: hospital-based (therefore concerns about potential bias), very small number of women
			Heavy consumption	NR	1.52 (0.39–5.93)		
			Coffee frequency (cups/day): men				
			≤ 1	53	1.00		
			2–4	128	1.51 (0.95–2.39)		
			≥ 5	58	1.59 (0.87–2.91)		
			Coffee frequency (cups/day): women				
			≤ 1	11	1.00		
			2–4	40	1.28 (0.50–3.31)		
			≥ 5	10	1.25 (0.29–5.30)		
			Coffee frequency (cups/day): non-smokers			NR	
			≤ 1	8	1.00		
			2–4	15	2.29 (0.82–6.36)		
			≥ 5	1	0.69 (0.07–6.86)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Geoffroy-Perez & Cordier (2001) France, 1984–1987	Cases: 765 hospital-based Controls: 765 hospital-based (free of cancer, respiratory diseases, and bladder cancer symptoms), matched to cases based on hospital, sex, age, area of residence Exposure assessment method: questionnaire, in person interview, drinking history, frequency and amounts	Urinary bladder	*Frequency of coffee intake (mL/wk): men*			Age, centre, place of residence, smoking status, pack-years	Strengths: large sample size, duration of drinking was taking into account Limitations: concern about controls with disease that may affect coffee intake (GI diseases, cardiovascular)
			≤ 1050	83	1.00		
			1051–2050	116	1.45 (0.97–2.16)		
			2051–2400	133	1.54 (1.04–2.28)		
			2401–2800	127	1.62 (1.08–2.40)		
			> 2800	134	1.42 (0.94–2.14)		
			Trend test *P* value, 0.14				
			Frequency of coffee intake (mL/wk): women			Age, centre, place of residence, smoking status	
			≤ 1150	20	1.00		
			1151–2100	38	1.40 (0.63–3.12)		
			2101–2600	28	1.25 (0.53–2.98)		
			> 2600	19	0.74 (0.28–1.96)		
			Trend test *P* value, 0.63				
			Frequency of coffee intake (mL/wk): non-smoking women			Age, centre, place of residence	
			≤ 1100	13	1.00		
			1101–2100	25	1.67 (0.66–4.21)		
			2101–2550	9	1.11 (0.35–3.51)		
			> 2550	19	1.28 (0.45–3.63)		
			Trend test *P* value, 0.69				
			Frequency of coffee intake (mL/wk): non-smoking men				
			≤ 1050	7	1.00		
			1051–2050	8	1.41 (0.43–4.65)		
			2051–2600	28	3.78 (1.36–10.47)		
			> 2600	11	2.49 (0.73–8.49)		
			Trend test *P* value, 0.02				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Woolcott et al. (2002) Canada, 1992–1994	Cases: 927 population-based, identified via registry Controls: 2494 hospital-based, identified through RDD, frequency matched to cases on age and sex distribution of the combined case series (bladder, colon, rectum) Exposure assessment method: mailed questionnaire, coffee (brewed, iced) considered	Urinary bladder: ICD-9 188	*Coffee frequency (cups/day) for all individuals*			Age, sex, education level, smoking (ever, current, cumulative, intensity), energy intake, calcium, fibre, beer	Strengths: population-based, large sample size Limitations: controls were matched to other cancer cases, few cases were non-smokers
			< 1	150	1.00		
			1–2	320	1.03 (0.81–1.32)		
			3–4	278	0.88 (0.68–1.13)		
			≥ 5	165	1.06 (0.79–1.42)		
			Trend test *P* value, 0.76				
			Coffee frequency (cups/day): never smokers				
			< 1	NR	1.00		
			1–2	NR	1.46 (0.91–2.35)		
			3–4	NR	1.25 (0.73–2.13)		
			≥ 5	NR	1.84 (0.80–4.22)		
			Trend test *P* value, 0.23				
			Coffee frequency (cups/day): ever smokers				
			< 1	NR	1.00		
			1–2	NR	0.90 (0.67–1.20)		
			3–4	NR	0.77 (0.58–1.03)		
			≥ 5	NR	0.92 (0.66–1.27)		
			Trend test *P* value, 0.39				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Radosavljević et al. (2003) Serbia, 1997–1999	Cases: 130 hospital-based Controls: 130 hospital-based (no urological malignancies or diseases that change diet), same hospital as cases, matched 1:1 by sex, age, place of residence Exposure assessment method: FFQ, unclear validation and administration, patterns of consumption and changes in diet in the past 10 yr considered	Urinary bladder: 93% TCC	*Coffee intake* *Coffee intake*	NR NR	1.46 (1.05–2.01) 1.55 (1.24–1.94)	Smoking soda, spirit, mineral water, skim milk, yogurt, frequency of daily urination Smoking	Limitations: hospital-based, concern about controls; units of coffee intake not clear
Ugnat et al. (2004) Canada (British Columbia, Alberta, Saskatchewan, Manitoba), 1994–1997	Cases: 549 population-based controls identified as part of a larger population-based study (NECSS) Controls: 1099 population-based matched to cases by distribution of age, identified randomly from health insurance plan lists or RDD Exposure assessment method: mailed questionnaire, unclear validation	Urinary bladder	*Coffee consumption* < 1 cup/mo ≥ 1 cup/mo – ≤ 1 cup/day 2–3 cups/day ≥ 4 cups/day Trend test *P* value, 0.0001 *Coffee frequency (cups/day): non-smokers* < 4 > 4	 34 89 214 210 NR NR	 1.00 1.13 (0.69–1.83) 1.56 (0.99–2.46) 1.77 (1.11–2.82) 1.00 6.17 (1.73–21.96)	Age, province, education, pack-years of smoking, tea NR	Strengths: population-based, adequate sample Limitations: no consideration of duration of intake of coffee, not clear if test of trend corresponds to adjusted or unadjusted model

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wakai et al. (2004) Japan (Nagoya), 1994–2000	Cases: 124 hospital-based cases identified from database of outpatients Controls: 620 hospital-based, randomly selected from outpatients in database without cancer, matched by age, sex, year of visit Exposure assessment method: self-administered questionnaire but checked by interviewer, frequency of coffee intake	Urinary bladder: 90% TCC	*Coffee consumption (cups/day)* Almost never Occasionally 1 2 ≥ 3 Trend test *P* value, 0.68	 26 23 28 26 21	 1.00 0.93 (0.52–1.66) 0.82 (0.47–1.44) 1.07 (0.59–1.94) 1.14 (0.58–2.23)	Age, sex, year of first visit, pack-years cigarette smoking	Less than 3% of cases drank high levels of coffee Limitations: hospital-based, (therefore potential for bias among controls depending on cause of outpatient visit), no lifetime consumption of coffee considered, few confounders considered
De Stefani et al. (2007) Uruguay, 1996–2000	Cases: 255 hospital-based Controls: 501 hospital-based (excluding diseases related to tobacco, alcohol or recent changes in diet), identified at same hospital as cases, frequency matched by age, sex, and residence Exposure assessment method: in-person questionnaire, coffee drinking history considered	Urinary bladder: TCC	*Coffee with milk (cups/wk)* Never drinkers 1–6 ≥ 7 Trend test *P* value, 0.01 *Pure coffee consumption (cups/wk)* Never drinkers 1–6 ≥ 7 Trend test *P* value, 0.03 *Total coffee consumption (cups/wk)* Never drinkers 1–6 ≥ 7 Trend test *P* value, < 0.01	 135 70 24 135 22 15 135 84 36	 1.0 1.5 (1–2.2) 1.9 (1–3.7) 1.0 1.6 (0.8–3.1) 2.0 (0.9–4.4) 1.0 1.5 (1.1–2.2) 2.1 (1.2–3.6)	Age, sex, residence, urban/rural status, family history of bladder cancer, BMI, occupation, smoking status, years since quitting smoking, number of cigarettes smoked per day, mate, soft drinks, milk, tea	Some overlap in patients between this study and that by Balbi et al. (2001) Limitations: data regarding drinking history mentioned but not provided

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Covolo et al. (2008) Italy (Brescia), 1997–2000	Cases: 197 hospital-based Controls: 211 hospital-based, identified at same hospital as cases (patients with urological non-neoplastic diseases), frequency matched to cases on age, period of recruitment, and hospital Exposure assessment method: in-person questionnaire, coffee (with milk, cappuccino, decaffeinated) lifetime consumption	Urinary bladder	*Coffee consumption (cups/day)* Non-drinkers 1–3 > 3 *Coffee consumption (cups/day): heavy smokers* Non-drinkers 1–3 > 3 *Coffee consumption (cups/day): non-smokers* Non-drinkers 1–3 > 3 *Coffee consumption (cups/day): light smokers* Non-drinkers 1–3 > 3	 26 125 77 12 86 27 5 10 2 9 29 17	 1.00 0.76 (0.41–1.41) 1.25 (0.59–2.67) 1.00 1.45 (0.56–3.70) 1.46 (0.49–4.36) 1.00 0.42 (0.01–1.77) 0.35 (0.04–2.99) 1.00 0.47 (0.16–1.35) 3.04 (0.77–11.97)	Age, education, PAHs and AA exposure, cumulative lifetime smoking (pack-years)	Genotype data also collected: GSTM1, GSTT1, GSTP1, NAT1, NAT2, SULTIA1, XRCC1–3, XPD. Combined estimates of genotypes and coffee were presented, but no tests of interaction. Strengths: Lifetime history of coffee use Limitations: Hospital-based controls (therefore concern about possible bias introduced by changes in coffee consumption), very small numbers in stratified analyses by smoking, very modest sample size for GxE interaction analyses

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jiang et al. (2008) USA (Los Angeles), 1987–1999	Cases: 1586 population-based, identified via cancer registry (SEER) Controls: 1586 population-based, identified via neighbourhoods of cases, matched to cases by age, sex, and race Exposure assessment method: in-person questionnaire, both regular and decaffeinated coffee considered	Urinary bladder	*Coffee consumption (cups/day)* 0 < 1 1–2 3–4 5–6 ≥ 7 Trend test *P* value, 0.052	 129 49 501 467 226 210	 1.00 1.15 (0.71–1.85) 1.04 (0.78–1.38) 1.21 (0.89–1.64) 1.19 (0.95–1.68) 1.38 (0.95–2.00)	Level of education, use of NSAIDs, intake of carotenoids, years as hairdresser/ barber, cigarette smoking status, duration of smoking, intensity of smoking, age, sex, race	Strengths: population-based, large sample size Limitations: no long-term history of consumption of coffee, only recent (2 yr before diagnosis)
Villanueva et al. (2009) Spain (Barcelona, Valles/Bages, Alicante, Tenerife, Asturias), 1998–2001	Cases: 1219 hospital-based Controls: 1271 hospital-based, identified from same hospitals as cases (disease unrelated to bladder cancer risk factors), individually matched to cases by sex, age and residence Exposure assessment method: questionnaire, computer-assisted interview, coffee assessment included age started and stopped drinking, and average intake per day during adult life	Urinary bladder	*Coffee consumption (cups/day)* Never Ever 1 2 3 ≥ 4 Trend test *P* value, 0.082 *Coffee consumption (cups/day): current smokers* Never Ever 1 2 3 ≥ 4 Trend test *P* value, 0.559	 120 1016 336 303 223 154 46 468 130 143 105 90	 1.00 1.25 (0.95–1.64) 1.24 (0.92–1.66) 1.11 (0.82–1.51) 1.57 (1.13–2.19) 1.27 (0.88–1.81) 1.00 1.20 (0.72–2.01) 1.14 (0.65–2.00) 1.20 (0.68–2.09) 1.39 (0.77–2.53) 1.13 (0.61–2.09)	Age, sex, area, intensity of smoking (cigarettes/day)	Strengths: large sample size, large representation of hospitals in this area, coffee drinking history Limitations: hospital-based controls could induce bias if they altered coffee drinking due to disease (does not seem likely in this case)

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Villanueva et al. (2009) (cont.)			*Coffee consumption (cups/day): former smokers*				
			Never	34	1.00		
			Ever	423	1.85 (1.16–2.95)		
			1	152	1.92 (1.16–3.17)		
			2	128	1.62 (0.97–2.70)		
			3	94	2.36 (1.36–4.11)		
			≥ 4	49	1.57 (0.86–2.90)		
			Trend test *P* value, 0.176				
			Coffee consumption (cups/day): never smokers				
			Never	40	1.00		
			Ever	125	0.85 (0.53–1.35)		
			1	54	0.91 (0.53–1.56)		
			2	32	0.61 (0.34–1.10)		
			3	24	1.06 (0.53–2.13)		
			≥ 4	15	1.23 (0.55–2.76)		
			Trend test *P* value, 0.961				
Wang et al. (2013a) USA (Houston, Texas), 1999–ongoing	Cases: 1007 hospital-based Controls: 1299 clinic-based, identified at clinics in the area for annual health check-ups Exposure assessment method: in-person questionnaire, coffee (regular, decaffeinated) frequency and amount	Urinary bladder: TCC	*Frequency of all coffee intake (servings/day)*			Age, sex, ethnicity, energy intake, smoking status	Assessed polymorphisms in UGT enzymes Strengths: large sample size Limitations: no lifetime history of coffee assessed
			Never	155	1.00		
			0.1–1.9	271	1.13 (0.87–1.47)		
			≥ 2	581	1.14 (0.90–1.46)		
			Trend test *P* value, 0.336				
			Frequency of regular coffee intake (servings/day)				
			Never	288	1.00		
			0.1–1.9	235	0.91 (0.72–1.15)		
			≥ 2	484	0.92 (0.74–1.13)		
			Trend test *P* value, 0.426				
			Frequency of decaffeinated coffee intake (servings/day)				
			Never	717	1.00		
			0.1–1.9	94	1.75 (1.28–2.41)		
			≥ 2	196	1.37 (1.09–1.73)		
			Trend test *P* value, 0.001				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Turati et al. (2015) Italy (Aviano, Pordenone, Milan, Naples, Catania), 2003–2014	Cases: 690 hospital-based Controls: 655 hospital-based (with acute, non-neoplastic diseases unrelated to smoking and alcohol or long-term diet changes) identified from same network of hospitals as cases, matched by study centre, sex, and age Exposure assessment method: in-person questionnaire, coffee (regular, cappuccino, decaffeinated) frequency of consumption, age at starting and quitting, changes in drinking during life, and average lifetime coffee drinking estimated	Urinary bladder	*Average lifetime coffee drinking (cups/day)*			Age, sex, study centre, year of interview, smoking (status and cigs/day among current smokers)	Strengths: thorough exposure assessment Limitations: use of hospital-based controls, although it is noted that most diseases among controls seem unrelated to coffee intake
			0 to < 1	57	1.00		
			1 to < 2	142	1.30 (0.83–2.03)		
			2 to < 3	166	0.90 (0.58–1.38)		
			3 to < 4	149	1.16 (0.74–1.82)		
			≥ 4	176	1.73 (1.08–2.77)		
			1 cup/day increase	NR	1.06 (0.99–1.14)		
			Trend test *P* value, 0.049				
			Coffee drinking status				
			Never	30	1.00		
			Ex	42	1.21 (0.61–2.40)		
			Current	618	1.25 (0.74–2.10)		
			Lifetime coffee drinking (1 cup/day increase) by age			Age, sex, study centre, year of interview, tobacco smoking, education, alcohol, BMI, family history of bladder cancer, history of cystitis	
			Age < 65 yr	NR	1.09 (0.99–1.21)		
			Age > 65 yr	NR	1.05 (0.95–1.16)		
			Lifetime coffee drinking (1 cup/day increase) by sex				
			Men	NR	1.05 (0.98–1.14)		
			Women	NR	1.14 (0.90–1.45)		
			Lifetime coffee drinking (1 cup/day increase) by smoking status				
			Never smokers	NR	1.18 (0.96–1.46)		
			Ex-smokers	NR	1.07 (0.97–1.19)		
			Current smokers	NR	1.03 (0.92–1.15)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Turati et al. (2015) (cont.)			*Duration of coffee drinking (yr)*			Age, sex, study centre, year of interview, smoking (status and cigarettes/day among current smokers)	
			≤ 35	146	1.00		
			36–44	172	1.13 (0.79–1.63)		
			45–51	174	1.17 (0.79–1.72)		
			≥ 52	185	1.20 (0.80–1.79)		
			10-yr increase	NR	1.03 (0.95–1.13)		
			Coffee drinking frequency (cups/day)				
			0 to < 1	99	1.00		
			1 to < 2	128	1.13 (0.77–1.68)		
			2 to < 3	161	0.86 (0.60–1.24)		
			3 to < 4	146	1.15 (0.78–1.69)		
			≥ 4	156	1.28 (0.85–1.94)		
			1 cup/day increase	NR	1.03 (0.96–1.10)		
			Trend test *P* value, 0.305				
			Age at starting drinking (yr)				
			< 20	267	1.00		
			≥ 20	380	1 (0.78–1.28)		

AA, aromatic amines; BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; GI, gastrointestinal; ICD, International Classification of Disease; mo, month(s); NECSS, Canadian National Enhanced Cancer Surveillance System; NR, not reported; NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons; RDD, random-digit dialling; RR, relative risk; SCC, squamous cell carcinoma; SEER, Surveillance, Epidemiology and End Results; TCC, transitional cell carcinoma; UGT, UDP-glucuronosyltransferase; vs, versus; wk, week(s); yr, year(s)

between coffee intake and risk of cancer of the bladder. In reviewing the literature, the Working Group considered the following criteria when determining which studies would be informative for evaluation of the association between risk of bladder cancer and coffee consumption.

1. Sample size, which impacts statistical power. As there were a large number of studies published on this topic, the Working Group focused its review on studies had a minimum of 100 cases.
2. Case and control selection: hospital-based versus population-based control selection. Depending on the inclusion criteria for hospital controls, these individuals may have diseases that could potentially lead to modification in coffee intake, making them less representative of the underlying population to which the cases should be compared, and therefore result in selection biases. In particular, studies that included hospital-based controls with gastrointestinal diseases and cardiovascular disorders were considered potentially problematic. The Working Group considered whether studies had specifically listed which diseases were included among hospital-based controls, or provided some indication that diseases that may affect coffee intake had been excluded. The Working Group gave more weight to population-based studies.
3. Adjustment for potential confounding factors, in particular tobacco smoking. Given that smoking is a strong risk factor for bladder cancer and tends to be highly correlated with coffee intake in many populations, the Working Group considered only studies that evaluated smoking variables as possible confounders. Although adjustment for other confounders was also favourably considered and noted (e.g. occupational exposure), none of the other risk factors were deemed as important as tobacco smoking.

Based on the criteria described above, of the 64 studies identified: seven studies were excluded due to having a case sample size of < 100 (Sullivan, 1982; Mommsen et al., 1983a; González et al., 1985; Restrepo et al., 1989; Bento & Barros, 1997; Lu et al., 1999; Kobeissi et al., 2013); one study was excluded because no potential confounders were considered (Demirel et al., 2008); four studies were excluded because risk estimates were not reported (Morgan & Jain, 1974; Mommsen et al., 1983b; Wynder et al., 1985; Akdaş et al., 1990); one study was excluded because smoking was not adjusted for (Bravo et al., 1986); one study was excluded because no units were provided for the estimates of association (Boada et al., 2015); and five studies were excluded because they included cases and controls already included in other studies (Bross & Tidings, 1973; Mettlin & Graham, 1979; Marrett et al., 1983; Ohno et al., 1985; La Vecchia et al., 1989a).

The Working Group organized studies for discussion into four main groups defined in Sections 2.1.2 (a)–(d). Given that studies with larger sample sizes are likely to be more informative, larger studies are described first followed by studies with smaller sample sizes.

(a) Population-based studies

The population-based case–control studies that reported results for coffee intake and were considered informative by the Working Group are described in the following. These studies were given more weight in the evaluation than those described in Section 2.1.1 (b)–(d).

Hartge et al. (1983) conducted a study in the USA (2982 cases, 5782 controls) that reported a positive association between ever drinking coffee and risk of bladder cancer among men (OR, 1.6; 95% CI, 1.2–2.2), women (OR, 1.2; 95% CI, 0.8–1.7) and for both combined (OR, 1.4; 95% CI, 1.1–1.8). When various levels of coffee consumption were considered, the only statistically significant association was for men drinking over 63 cups of coffee per week (OR, 1.5; 95%

CI, 1.1–1.9) [equivalent to roughly 9 cups/day]. No dose–response relationship was evident for either men or women. Similarly, there was no association with duration of coffee drinking. When stratifying men by smoking status, no differences in the magnitude of estimates were observed when comparing ever drinkers to never drinkers. However, when comparing drinkers of large quantities to drinkers of smaller quantities (≤ 49 cups/week), a stronger significant positive association was observed among never smokers [numbers of subjects were smaller and confidence intervals very wide], whereas positive associations of smaller magnitude were observed among past or current smokers. Results were less pronounced among women, and none of the estimates was statistically significant. A subsequent study by Kantor et al. (1988) reported estimates by subtyping cases by three histological types; significant trends for positive associations with risk of adenocarcinomas or transitional cell carcinomas (TCC) for men and women combined were reported, although only the estimate for the highest intake (> 64 cups/week) versus lowest (0–7 cups/week) was statistically significant for TCC (OR, 1.5; 95% CI, 1.1–1.9; *P* for trend, < 0.01 [numbers for adenocarcinomas were extremely low (32 cases)]. There was no evidence of trend or statistically significant point estimates for squamous cell carcinomas [numbers were too small to interpret]. Another extension of the study by Sturgeon et al. (1994) considered subtypes of cases defined by tumour stage and grade. Positive associations of similar magnitude were observed for high versus low intake of coffee among non-invasive and invasive bladder cancer, as well as when stratifying cases by grade (I, II, or III/IV). Even though some of the estimates were statistically significant in some strata and not others, all estimates were of comparable magnitude.

Morrison et al. (1982) reported a study that combined data from three population-based case–control studies in Boston, USA (587 cases, 528 controls), Manchester, UK (541 cases, 725 controls), and Nagoya, Japan (289 cases, 586 controls) for a total of 1666 cases and 2229 controls. On pooling the three studies, there was no association for drinking ≥ 1 cup/day versus less (OR, 1.0; 95% CI, 0.8–1.2). Results stratifying by study area did not show consistent evidence of a dose–response relationship [confidence intervals for estimates were not reported for any of the study-specific results].

Jiang et al. (2008) conducted a study in Los Angeles County, California, USA (1586 cases, 1586 controls). They reported a positive association for heavy coffee drinking (≥ 7 cups/day) versus non-drinkers with an odds ratio of 1.38 (95% CI, 0.95–2.00). There was weak evidence of a dose–response relationship (*P* for trend, 0.052). [The limitations included a lack of consideration of coffee-drinking history; only coffee consumption from 2 years before diagnosis was considered.]

A population-based study was performed in Ontario, Canada (Woolcott et al., 2002) involving 927 cases and 2494 controls. No associations were noted when considering all individuals combined; positive associations were however observed among never smokers, although the estimates were not statistically significant and there was no consistent dose–response trend. No evidence of positive associations was observed among ever smokers. [The limitations of this study include the fact that controls were recruited for multiple cancers and matching for bladder cancer might not be optimal. Further, only 15% of cases were non-smokers ($n = 139$), which limits power for smoking-stratified analyses.]

Risch et al. (1988) (835 cases, 781 controls) reported that ever drinkers of coffee had an odds ratio of 0.86 (95% CI, 0.59–1.25) in men and 1.87 (95% CI, 1.03–3.4) in women. Restricting analyses to non-smokers yielded positive associations for both men and women, but neither was statistically significant. Analyses that considered several categories of frequency of coffee intake showed little evidence for a dose–response

relationship or association for men or women. Similarly, estimates were close to null when considering ground, decaffeinated, or instant coffee. For total lifetime intake or ever intake of espresso coffee, positive associations were noted for both men and women; neither reached statistical significance, however, with a lifetime intake odds ratio of 1.29 (95% CI, 0.96–1.74) for men and 1.75 (95% CI, 0.91–3.39) for women. [No tests for trend were presented. Smoking adjustment only included pack-years of smoking, raising concerns about residual confounding.]

Howe et al. (1980) reported on a study based in Nova Scotia, Newfoundland, and British Columbia in Canada, involving 632 cases and 632 controls. A non-statistically significant positive association between the highest level of lifetime average consumption (> 4 cups/day) of total coffee and risk of bladder cancer when compared with never drinkers was reported (OR, 1.5; 95% CI, 0.8–2.8 for men and OR, 1.3; 95% CI, 0.4–4.1 for women). No tests of trend were presented, and there was no evidence of a dose–response relationship. Separate risk estimates are also presented for instant coffee and regular coffee, for men and women individually. A positive association was reported for regular coffee for men (> 4 cups/day vs never drinkers: OR, 1.8; 95% CI, 1.0–3.5), but there was weak evidence of a dose–response relationship. Analyses restricted to non-smokers were conducted only among women and an odds ratio of 1.4 (95% CI, 0.4–4.4) was reported for a lifetime average of > 2 cups/day compared with ≤ 2 cups/days. [Numbers were very small for some of the cells in stratified analyses. All odds ratios and confidence intervals were estimated by the Working Group.]

Ugnat et al. (2004) (549 cases, 1099 controls) conducted a population-based case–control study in Canada (British Columbia, Alberta, Saskatchewan, and Manitoba provinces) and reported a positive association with high intake of coffee (≥ 4 cups/day vs < 1 cup/month: OR, 1.77; 95% CI, 1.11–2.82; *P* for trend, < 0.001), with evidence of a dose–response relationship. [It is unclear from the publication if the test for trend corresponds to the unadjusted or adjusted estimates.] It is mentioned in the text that a positive association was found among non-smokers (≥ 4 cups/day vs < 1 cup/month: OR, 6.17; 95% CI, 1.73–21.96). [The number of cases in these analyses was not reported. Further, the low response rates of cases and controls raise some concern about possible bias introduced by responders. Only pack-years for smoking adjustment were considered, raising concern about residual confounding.]

Cole (1971) (470 cases, 500 controls) conducted a population-based case–control study in Massachusetts, USA. Positive associations between coffee intake and risk of bladder cancer were reported (> 4 cups/day vs < 1 cup/day: OR, 1.31 for men and 2.19 for women) [no confidence intervals or a test for trend were presented], with weak evidence for a dose–response trend. The odds ratio for drinking > 1 cup/day versus < 1 cup/day was 1.24 (95% CI, 0.8–1.93) among men and 2.58 (95% CI, 1.30–5.10) among women. When restricting analyses to non-smokers without high-risk occupational exposure and comparing the highest intake (> 4 cups/day) to the lowest (< 1 cup/day), an odds ratio of 2.6 for men and women combined was reported [no confidence intervals were provided, and the reference category comprised only 10 cases].

Jensen et al. (1986) (371 cases, 771 controls) conducted a population-based case–control study in Copenhagen, Denmark and reported no association between coffee intake and risk of bladder cancer; per L/day of coffee intake, odds ratios were 1.1 (95% CI, 0.9–1.4) for men and 1.1 (95% CI, 0.7–1.9) for women. Analyses considering quintiles showed estimates close to 1 for men, with no evidence of dose–response or trend (*P* for trend, 0.83). In contrast, positive associations were reported among women for all categories in comparison to never drinkers with an odds ratio of 2.7 (95% CI, 0.7–10.9) for the

highest category (> 1500 mL/day or > 6 cups), but there was no evidence of a dose–response relationship and the trend was not statistically significant (*P* for trend, 0.37). [It was noted that the reference category for this analysis among women had only 4 cases and the highest category had only 13 cases.] No differences in age at which coffee drinking started or in duration of coffee drinking were observed between cases and controls, and changes over time of the quantity of coffee consumed were similar for both cases and controls; however, no estimates were shown.

Slattery et al. (1988a) reported the results of a population-based case–control study conducted in Utah, USA (332 cases, 686 controls). A non-statistically significant positive association with caffeinated coffee (> 30 cups/week vs 1–15 cups/week OR, 1.28; 95% CI, 0.76–2.17) was reported, without evidence of a dose–response relationship. Different models adjusting for different smoking variables yielded comparable results, with the exception of a model that adjusted for 'years stopped smoking' that yielded null results (> 30 cups/week vs 1–15 cups/week OR, 1.07; 95% CI, 0.62–1.85). Another paper published on the same study (Slattery et al., 1988b) with slightly larger numbers also reported a non-statistically significant association with no consistent dose–response relationship (> 40 servings/week vs never drinkers OR, 1.6; 95% CI, 1.00–2.56). In this study there was no evidence of an association between consumption of decaffeinated coffee and risk of bladder cancer. [It was noted in the study that a substantial proportion of the Utah population belongs to the Mormon church, which forbids the consumption of coffee and tea as well as alcohol and tobacco; there is therefore the potential for underreporting of both coffee and smoking, which might lead to bias and residual confounding.]

Bruemmer et al. (1997) reported on a population-based study in Washington, USA (262 cases, 405 controls). The odds ratio comparing the highest category of regular coffee intake (> 6 cups/day) with non-drinkers was 1.2 (95% CI, 0.6–2.3) for men and 0.6 (95% CI, 0.2–1.9) among women. There was no evidence of a dose–response relationship and no statistically significant trends. When considering decaffeinated coffee, the comparable odds ratios were 0.9 (95% CI, 0.5–1.8) for men and 2.1 (95% CI, 0.8–5.3) for women [there were only 9 cases in the highest intake category]. There was no evidence of a trend among men; there was however a suggestion of a trend among women with an estimate of 1.6 (95% CI, 0.7–3.6; *P* for trend, 0.08) for the middle category. [The Working Group noted that this study only included men and women of age up to 65 years and the models only adjusted for smoking status, raising concerns over residual confounding.]

Nomura et al. (1991) reported on a study conducted in Hawaii, USA (261 cases, 522 controls). For 'cup-years' of coffee consumed among men, estimates of association for all types of coffee combined or for regular ground coffee were around 1.0 with no evidence of a dose–response relationship or trend. For both regular and decaffeinated instant coffee, some estimates were > 1 but there was no evidence of a dose–response relationship. Among women, for all types of coffee combined and regular ground coffee there were inverse associations for the highest intake categories (regular ground coffee OR, 0.3; 95% CI, 0.1–1.0 for > 90 cup-years compared with non-drinkers), but the trend was only statistically significant for regular ground coffee ($P = 0.02$). [The number of cases in the highest intake category was 8 and there were 9 non-drinkers.] For regular instant coffee and decaffeinated instant coffee some of the estimates were either > 1.0 or < 1.0; none were statistically significant however, and there was no evidence of a dose–response relationship or trend. [There was no evidence that different coffee types were mutually adjusted, and there was no adjustment for race even though this was a multiethnic study.

Adjustment for smoking only included pack-years, raising concerns about potential residual confounding.]

Momas et al. (1994) reported on a study conducted in the Herault district, France (219 cases, 792 controls). They reported an odds ratio for lifelong coffee drinking of 4.1 (95% CI, 1.7–10.0) for > 60 000 cups compared with < 365 cups. Whereas estimates for lower strata were smaller, there was no clear dose–response relationship. [No estimates of trend were reported. It was also noted that the reference category had only 8 cases and that adjustment for smoking only included lifelong smoking (cigarettes equivalent), raising concerns about residual confounding.]

Piper et al. (1986) reported results from a population-based case–control study of bladder cancer in women (aged 20–49 years) conducted in New York State (165 cases, 165 controls). The odds ratio for drinking more than 101 cup-years compared with non-drinkers was 2.1 (95% CI, 0.7–6.3). [No test for trend estimate or counts for each exposure level were presented. Adjustment for smoking only included pack-years, raising concerns about residual confounding.]

(b) Hospital-based case-control studies that used population-based controls

Hospital-based case–control studies that used population-based controls and reported results for coffee intake are discussed in the following. The Working Group considered these studies to be slightly less informative than those described in Section 2.1.2 (a) above, and they were correspondingly given less weight in the evaluation.

Escolar Pujolar et al. (1993) reported findings from a study conducted in Spain (497 cases, 1113 controls). They reported no evidence of association between frequency of coffee consumption and risk of bladder cancer among men, with all estimates close to 1.0. The highest versus lowest intake level odds ratio among women was 0.71 (95% CI, 0.20–2.56), but there was no evidence of a dose–response trend. When considering lifelong consumption in number of cups, the odds ratio for 40 000 cups versus none was 1.14 (95% CI, 0.69–1.9) for men and 1.39 (95% CI, 0.31–6.25) for women. Analyses restricted to non-smoking men or women showed positive associations, although neither were significant [the numbers of cases for many of the strata among men were < 10, and all of the strata among women were < 10]. [The Working Group noted that very small numbers were employed in the stratified analyses by smoking. Smoking adjustment may not have been adequate, as only cigarettes/day for men and smoking status for women were considered.]

Vena et al. (1993) reported results from a study carried out in western New York, USA (351 hospital-based cases, 855 population-based controls). When comparing the highest intake category (≥ 5 cups/day) to the lowest (0–1 cup/day) they reported an odds ratio of 2.1 (95% CI, 1.3–3.2), and there was evidence of a dose–response relationship with a significant trend (*P* for trend, <0.001). When restricting analyses to non-smokers there was also evidence of a positive association, and among those > 65 years old there was evidence of a dose–response relationship and a significant trend (*P* for trend, 0.02). Positive associations were also noted for decaffeinated instant, decaffeinated perk, regular instant, and regular perk, although these analyses were only adjusted for age and education. [Among the weaknesses of this study were the low response rates which, combined with the fact that deceased subjects or those too ill to participate were not included, raises concerns about possible bias. Many of the controls declined to participate, which could also introduce a bias. Many of the strata evaluated had very small numbers. Subject numbers for analyses stratifying by smoking status were not shown. Adjustment for smoking only considered pack-years which might not be adequate, raising concerns about residual confounding.]

(c) Hospital-based case-control studies that excluded diseases that may affect coffee intake

Hospital-based case–control studies that used hospital-based controls and reported results for coffee intake are described in the following. The Working Group considered these studies less informative than those described in Sections 2.2.1 (a) and (b) above, and so were given less weight in the evaluation.

Villanueva et al. (2009) reported on a hospital-based study conducted in Spain (1219 cases, 1271 controls). The odds ratio for the highest level of consumption (≥ 4 cups/day) compared with never drinkers was 1.27 (95% CI, 0.88–1.81; *P* for trend, 0.082) and there was no consistent dose–response relationship. They also reported estimates stratified by smoking status; the odds ratios for the highest intake versus never drinkers were > 1.0 among never, former, and current smokers, but there was no consistent dose–response relationship for any of the groups and none of the trend tests were significant. [Smoking adjustment only included smoking intensity, so residual confounding cannot be ruled out.]

Wang et al. (2013a) reported on a hospital-based case–control study conducted in Houston, Texas, USA (1007 cases, 1299 controls). When comparing the highest intake level of all types of coffee combined (> 2 servings/day) with never drinkers, the odds ratio was 1.14 (95% CI, 0.9–1.46; *P* for trend, 0.336). There was no evidence for a dose–response relationship. When considering decaffeinated coffee only, the comparable odds ratio was 1.37 (95% CI, 1.09–1.73; *P* for trend, 0.001); however, there was no evidence of a dose–response relationship, with the middle category estimate being larger than the highest category. Estimates for regular coffee only were no near 1.0. [Controls were individuals attending clinics for annual check-ups; there is therefore concern that their coffee-drinking habits are not representative of the underlying population. Adjustment for smoking only included smoking status, raising concerns about residual confounding.]

Turati et al. (2015) reported on a hospital-based study conducted in Italy (690 cases, 655 controls). When considering the average lifetime intake, the odds ratio for the highest versus the lowest category was 1.73 (95% CI, 1.08–2.77) and 1.06 for a 1 cup/day increase (95% CI, 0.99–1.14). There was no consistent evidence of a dose–response trend, and the trend test *P* value was 0.049. Estimates for current drinking did not show statistically significant associations or evidence of a dose–response relationship. However, when analyses were restricted to non-smokers there was an odds ratio of 1.18 (95% CI, 0.96–1.46), whereas estimates were around 1.0 among ex-smokers or current smokers. Comparable analyses performed with lifetime coffee drinking showed similar odds ratios (close to 1.0) across the three categories of smoking. There was no significant association observed between years of drinking or age at which coffee drinking began.

Rebelakos et al. (1985) conducted a study in Greece (300 cases, 300 controls) and reported that drinking > 2 cups/day compared with < 2 cups/day had an odds ratio of 1.7 (95% CI, 1.2–2.3). Results stratifying by sex showed estimates of similar magnitude, although they were only significant among men. Analyses comparing cups/day to never drinkers showed no evidence of a dose–response relationship. [The Working Group noted that sample size among women was very small (these analyses were therefore underpowered) and that adjustment for smoking only considered smoking status, raising concerns about residual confounding.]

De Stefani et al. (2007) conducted a hospital-based study in Uruguay (255 cases, 501 controls) and reported an odds ratio for the highest intake (≥ 7 cups/week) and intermediate intake of coffee (1–6 cups/week) compared with never drinkers of 2.1 (95% CI, 1.2–3.6) and 1.5 (95% CI, 1.1–2.2), respectively, with a *P* for

trend of <0.01. Similar estimates were observed when considering pure coffee or coffee with milk. [Diseases among controls were listed; it is unclear whether some of them could affect coffee intake, raising concerns about possible bias in estimates.]

(d) Hospital-based case-control studies that used controls with diseases that may affect coffee intake, or where no information was provided

Hospital-based case–control studies that used hospital-based controls and included diseases that may have affected coffee intake, or studies for which it is not clear if other diseases were considered (raising concerns about biased estimates), are described in the following. The Working Group considered these studies to be less informative than those described in Sections 2.1.2 (a)–(c) above, and gave them little weight in the evaluation.

Clavel & Cordier (1991) conducted a hospital-based study in France (781 cases, 781 controls), reporting positive associations for all individuals combined and for non-smoking men and women separately. [All analyses were conducted using never drinkers as the reference, and subject numbers for this category are < 10 for both men and women non-smokers (1 and 3, respectively); all estimates are therefore very unstable. Adjustment for smoking was performed using smoking status only, which may lead to residual confounding. More than 50% of controls had a disease that may affect coffee intake, leading to biased estimates.]

Geoffroy-Perez & Cordier (2001) reported on a hospital-based study conducted in France (765 cases, 765 controls). When comparing the highest intake category with the lowest, they reported an odds ratio of 1.42 (95% CI, 0.94–2.14) among men and 0.74 (95% CI, 0.28–1.96) among women. There was no evidence for a dose–response trend for either men or women. When restricting analyses to non-smokers, positive associations were observed for both men and women without consistent evidence of a dose–response relationship. [For analyses of non-smokers, the reference category had 7 cases for men and 13 cases for women. Control subjects had conditions that could affect coffee drinking habits (approximately 20% had gastrointestinal diseases and close to 30% had cardiovascular diseases), leading to concerns about possible selection bias.]

Kunze et al. (1992) reported on a hospital-based study carried out in Germany (675 cases, 675 controls) which found an odds ratio for the highest category of intake (> 5 cups/day) compared with never drinkers of 2.0 (95% CI, 1.2–3.3) for men and 2.7 (95% CI, 0.9–7.8) for women. There was also some evidence of a positive dose–response relationship, but no test for trend was provided. A previous report was published by Claude et al. (1986), reporting on a subset of these patients. [A main limitation of this study was the use of controls with urological diseases, such as hyperplasia of the prostate in men and urinary infections in women, which may affect their liquid intake and possibly introduce a bias in the estimates.]

Wynder & Goldsmith (1977) reported findings from a hospital-based study conducted in the USA (732 cases, 732 controls). Compared with individuals with no or occasional intake, the odds ratio for those who consumed ≥ 7 cups/day was 2.0 (95% CI, 0.8–4.9). [No definition of the smoking variable used for controlling confounding was provided. Controls with diseases that may affect coffee intake were not excluded, raising concerns about bias.] An expanded study (Kabat et al., 1986) included some of these cases as well as additional cases recruited later (152 cases, 492 controls). No association between consumption of brewed coffee or decaffeinated coffee and risk of bladder cancer was observed for either sex, with all estimates being very close to unity and based on very small numbers. [The Working Group noted the very small numbers for stratified analyses, the same

concerns as for the parent study by Wynder & Goldsmith (1977).]

Mettlin & Graham (1979) reported results from a hospital-based study performed in the USA (569 cases, 1025 controls) which showed that consumption of ≥ 3 cups/day compared with < 1 cup/day was associated with an odds ratio of 1.30 for men and women combined [no confidence intervals were provided]. The corresponding results for men and women separately were 1.64 and 0.81. Among men classified as relatively light smokers (< half a pack/day) there was still a positive association, whereas for women classified as relatively light smokers there was a slight inverse association. Neither estimate was statistically significant, and there was no evidence of a dose–response relationship [no definition of diseases among controls]. A previous report by Bross & Tidings (1973) reported on the same patients in this study.

D'Avanzo et al. (1992) reported results from a hospital-based study performed in Italy (555 cases, 855 controls). The odds ratio for the highest intake level of regular coffee (≥ 4 cups/day) compared with non-drinkers was 1.4 (95% CI, 0.9–2.2; *P* for trend, > 0.05), with no evidence of a dose–response relationship. Coffee drinking for ≥ 30 years compared with no coffee drinking yielded an odds ratio of 1.4 (95% CI, 0.9–2.2), whereas drinking coffee for < 30 years had an odds ratio of 1.2 (95% CI, 0.9–1.7; *P* for trend, < 0.05). [The strengths of this study include consideration of drinking history.] A non-statistically significant positive association was also reported for decaffeinated ever drinking versus never drinking. [No specific diseases excluded from controls were listed, raising concerns about possible bias.]

Ciccone & Vineis (1988) reported on a hospital-based study in Italy (512 cases, 594 controls); none of the estimates were statistically significant. Analyses stratifying by smoking were presented, but subject numbers were very small. [No information was provided about the conditions of the controls.]

Fraumeni et al. (1971) reported on a study conducted in the USA (493 cases, 527 controls), a reanalysis of a previous study conducted by Dunham et al. (1968). A positive association was found for black men and women (statistically significant in women only), without evidence of a dose–response relationship. Positive associations were seen for white and black men, but neither was statistically significant. Overall, there was no consistent dose–response relationship [no confidence intervals were presented].

Pohlabeln et al. (1999) conducted a hospital-based study in Germany (300 cases, 300 controls). When comparing the highest intake level of coffee (≥ 5 cups/day) with the lowest (≤ 1 cup/day), the odds ratios were 1.59 (95% CI, 0.87–2.91) for men and 1.25 (95% CI, 0.29–5.30) for women. There was no evidence of a dose–response relationship, as estimates for the middle category (2–4 cups/day) were either higher than or similar to the highest category. No test for trend was provided. They also reported analyses among non-smokers, but numbers were too small to be meaningful. [Among male controls, 41% had prostatic adenoma and 30% had kidney stones. Among women, 13% had urinary infections and 62% had kidney stones. The Working Group considered that it is feasible that patients with prostate adenoma may have changed coffee-drinking habits due to increased urination, raising concerns about possible bias.]

Covolo et al. (2008) reported on a hospital-based study carried out in Italy (197 cases, 211 controls). Comparing the highest level of coffee intake (> 3 cups/day) with non-coffee drinkers resulted in an odds ratio of 1.25 (95% CI, 0.59–2.67). There was no evidence of a dose–response relationship and no test for trend presented. Results were also stratified by smoking, but numbers of non-smokers were too small to be meaningful. Interactions were presented for the examined polymorphisms in metabolism enzymes, but no details of test of interaction were presented. [The Working Group was concerned

about bias introduced by patient controls, as well as the small numbers in many categories.]

Donato et al. (1997) reported on another hospital-based study in Italy (172 cases, 578 controls). Among men, the odds ratio for comparing the lowest (1–2 cups/day), intermediate (3–4 cups/day), and highest intake level (≥ 5 cups/day) with non-drinkers were 2.3 (95% CI, 0.9–5.6), 2.8 (95% CI, 1.1–7.4), and 4.5 (95% CI, 1.2–16.8), respectively, without a statistically significant trend (*P* for trend, >0.1). Among women, the estimates for the lowest (1–2 cups/day) and highest (3–4 cups/day) coffee intake levels compared with non-coffee drinkers were 4.3 (95% CI, 0.8–23.9) and 4.9 (95% CI, 0.7–33.0), respectively. [Numbers for some of the categories were very small, in particular non-drinkers. Controls included several benign urological diseases (prostate adenoma, urolithiasis, obstructive uropathy), and it is not clear if these disorders affect coffee intake. Prostate adenoma could affect coffee intake, raising concerns about bias in the results.]

Simon et al. (1975) conducted a hospital-based study in the USA (135 cases, 390 controls) and reported non-statistically significant positive associations among non-smokers/light smokers and also among moderate–heavy smokers. [Subject numbers for this analysis were very low.]

Radosavljević et al. (2003) conducted a hospital-based study in Serbia (130 cases, 130 controls) and reported an odds ratio for coffee intake of 1.46 (95% CI, 1.05–2.01). [The units associated with the reported odds ratios are not clear from the paper. The smoking variable used was not defined, so there is concern over residual confounding. It is not clear if the diseases among controls may have influenced coffee intake, leading to bias.]

Wakai et al. (2004) reported results from a study conducted in Japan (124 cases, 620 controls). The odds ratio for comparing the highest level of coffee intake (≥ 3 cups/day) with the lowest (almost never) was 1.14 (95% CI, 0.58–2.23). There was no evidence of a dose–response trend and the trend test was not statistically significant.

Iscovich et al. (1987) conducted a hospital-based study in Argentina with 117 cases and 234 controls (117 hospital and 117 neighbourhood). The odds ratios for consumption of 1 cup/day, 2 cups/day or ≥ 3 cups/day compared with non-drinkers were 1.08, 4.45, and 12, respectively. [No confidence intervals or test for trend were provided. Hospital controls included patients with digestive system problems (16%), heart disease (17%), and hypertension diseases (12%), all of which could affect coffee drinking and lead to bias.]

2.1.3 Meta-analyses and pooled analyses

Sala et al. (2000) conducted a pooled analyses of coffee intake and bladder cancer among non-smokers that included ten case–control studies carried out in Europe, including Rebelakos et al. (1985), Jensen et al. (1986), Ciccone & Vineis (1988), Clavel & Cordier (1991), Kunze et al. (1992), Escolar Pujolar et al. (1993), Donato et al. (1997), and Pohlabeln et al. (1999), discussed in Section 2.1.2 above. These ten studies involved a total of 564 cases and 2929 controls. The pooled odds ratio from comparing the highest intake level (≥ 10 cups/day) with never drinkers was 1.8 (95% CI, 1.0–3.3), with no evidence of a dose–response relationship or a significant trend. When stratifying studies by types of controls among studies that used hospital-based controls, the odds ratio was 3.2 (95% CI, 1.4–7.3) with a *P* for trend of 0.05. Among studies that used population-based controls, the odds ratio was 0.7 (95% CI, 0.2–2.0) with a *P* for trend of 0.3 [the number of cases in the highest category among population-based controls was 4]. Similar estimates were observed when further stratifying by sex although, among women, the odds ratio for population-based controls was > 1.0. Analyses taking into account duration of consumption in years (six studies) showed an

odds ratio for the longest duration compared with never drinkers of 0.9 (95% CI, 0.6–1.2).

Wu et al. (2015) conducted a meta-analysis that included 25 case–control (15 419 cases and 23 585 controls) and five prospective studies (753 cases and 236 343 controls). The overall pooled odds ratio for all studies was 1.33 (95% CI, 1.19–1.48), and heterogeneity was present (P = 0.008; I^2 = 38.4%). For case–control studies, the combined odds ratio was 1.37 (95% CI, 1.22–1.53) and also showed heterogeneity (P = 0.017; I^2 = 37.1%). For cohort studies the corresponding odds ratio was 1.10 (95% CI, 0.78–1.54) with less heterogeneity (P = 0.112; I^2 = 44%). Subgroup analyses were performed for various characteristics, such as type of control (hospital, population, or both). The meta-analysis odds ratio for studies that used hospital-based controls (20 studies) was 1.44 (95% CI, 1.21–1.72); for studies that used population-based controls (12 studies), the meta-analysis odds ratio was 0.98 (95% CI, 0.63–1.52). While studies based in Europe or America had comparable meta-analysis odds ratios of approximately 1.3, studies from Asia had an odds ratio of 1.0 (95% CI, 0.7–1.4). [Of the 11 cohort studies with data available, Wu et al. (2015) only included 4; there are also 6 other studies that were published during the period considered in this meta-analysis that were not included.]

2.2 Cancer of the pancreas

The Working Group reviewed all of the pertinent cohort studies (including nested case–control or case–cohort studies), case–control studies, and pooled and meta-analyses that assessed the association between coffee consumption and cancer of the pancreas.

Studies were excluded if statistical analyses were not adjusted for smoking, since it is an important potential confounder (Jick & Dinan, 1981; Kessler, 1981; Goldstein, 1982; Heuch et al., 1983; Snowdon & Phillips, 1984; Hsieh et al., 1986; Jacobsen et al., 1986; Mack et al., 1986; Norell et al., 1986; Wynder et al., 1986; Raymond et al., 1987; Pfeffer et al., 1989; Mizuno et al., 1992; Kalapothaki et al., 1993; Gullo et al., 1995; Kokic et al., 1996; Mori et al., 1999). We also excluded studies that did not provide sufficient information regarding risk estimates associated with coffee intake (Kinlen & McPherson, 1984; Baghurst et al., 1991, Chan et al., 2009).

If the 14 cohort studies included in a pooled analysis by Genkinger et al. (2012) are counted individually, then evidence from 20 individual cohort studies is available. In addition, 22 case–control studies were available that controlled for smoking, 14 of which were population-based and 8 hospital-based. For the reviewed studies, detailed information is presented in Table 2.3 for cohort studies and Table 2.4 for case–control studies.

2.2.1 Cohort studies

See Table 2.3.

A nested case–control analysis of a cohort study investigated pancreatic cancer mortality in a follow-up of 50 000 male former college students (Whittemore et al., 1983). There were 84 deaths from pancreatic cancer. Data on coffee and tea consumption and other variables were collected during a physical examination at the college. No statistically significant association with coffee consumption was noted; after adjustment for smoking, age, college, and class year the relative risk was 1.1 (95% CI, 0.7–1.9) when comparing those drinking ≥ 2 cups/day with those drinking < 2 cups/day.

In a Hawaiian cohort study of the association between cancer incidence and coffee consumption, 7355 Japanese men were followed for a minimum of 14 years from the time of collection of a 24-hour dietary recall during 1965–1968 (Nomura et al., 1986). This is an update of an earlier study by the same group (Nomura et al., 1981). Incidence rates were adjusted for age or

Table 2.3 Prospective cohort studies on cancer of the pancreas and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Whittemore et al. (1983) USA, 1962–1966 (enrolment), mortality until 1978	50 000 (84 cases): college alumni, male students who entered Harvard University during 1916–1950 or University of Pennsylvania during 1931–1940 Exposure assessment method: questionnaire	Pancreas	*Current coffee drinking (cups/day)* < 2 ≥ 2	 60 24	 1.0 1.1 (0.7–1.9)	Age, smoking, college, class year	Strengths: nested case–control with 4 controls per case, matched on birth year Limitations: fatal cancer only, small number of cases, limited exposure information
Nomura et al. (1986) USA (Hawaii), 1965–1968 (enrolment), incidence until July 1983	7355 (21 cases): Japanese men born during 1900–1919 on Hawaiian Island of Oahu, aged 45–68 yr at baseline Exposure assessment method: 24-hour diet recall	Pancreas	*Current coffee drinking (cups/day)* 0 1–2 3–4 ≥ 5 Trend test *P* value, 0.41	 2 7 7 5	 1.00 1.16 2.08 1.63	Age, smoking	Strengths: prospective design Limitations: very small number of cases, intake based on 24-hour recall, limited confounder information
Hiatt et al. (1988) USA, 1978–1984 (enrolment), incidence 6 yr	122 894 (49 cases): members (men and women) of the Kaiser Permanente Medical Care Program in Northern California who had a multiphasic health check-up during 1978–1984, mean age at baseline 41 yr Exposure assessment method: questionnaire	Pancreas	*Current coffee drinking (cups/day)* 0 < 1 1–3 ≥ 4	 NR NR NR NR	 1.0 0.8 (0.3–2.6) 0.9 (0.4–2.1) 0.7 (0.2–1.9)	Age, sex, ethnicity, smoking, alcohol consumption, diabetes, blood glucose	Strengths: prospective design Limitations: short follow-up, small number of cases

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mills et al. (1988) USA, 1976 (enrolment), mortality 1976–1982 (6 yr)	34 198 (40 cases), non-Hispanic white Californian Seventh-day Adventists, men and women, aged ≥ 25 yr Exposure assessment method: questionnaire	Pancreas	*Coffee drinking status*			Age, smoking, sex, consumption of meat and eggs	Strengths: prospective design Limitations: fatal cancer only, low number of cases due to short follow-up, only dichotomous exposure to coffee (few heavy coffee drinkers), generalizing findings to general population limited
			Not current	NR	1.00		
			Current	NR	2.21 (0.61–7.99)		
Friedman & van den Eeden (1993) USA, incidence 1964–1988	175 000 (450 cases, 2687 controls in nested case–control analysis), members (men and women) of the Kaiser Permanente Medical Care Program in Northern California Exposure assessment method: questionnaire, focusing on large volumes of consumption	Pancreas	*Current coffee drinking (cups/day)*			Age, sex, smoking, race, examination site, date of first check-up	Part of substantial multiple-comparison analysis Strengths: large cohort study, with relatively large number of cases Limitations: very limited exposure information (single coffee intake question of "Do you usually drink over 6 cups of coffee per day?")
			≤ 6	NR	1.00		
			> 6	NR	0.95 (0.73–1.22)		
			Trend test *P* value, 0.672				
Zheng et al. (1993) USA, 1966 (enrolment), mortality 1966–1986 (20 yr)	17 633 (57 cases), white men aged ≥ 35 yr, policy holders of the Lutheran Brotherhood Life Insurance Society (LBS) Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day)*			Age, smoking, alcohol consumption	Strengths: prospective design Limitations: fatal cancer only, small number of cases
			< 3	21	1.0		
			3–4	18	0.6 (0.3–1.2)		
			5–6	12	0.7 (0.4–1.6)		
			≥ 7	5	0.9 (0.3–2.4)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shibata et al. (1994) USA, 1981–1985 (enrolment), incidence 1981–1990 (9 yr)	13 979 (65 cases), men and women, mean age at entry (standard deviation) 75.0 yr (men) and 73.8 yr (women) Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day)* < 1 1 2–3 ≥ 4	 7 16 35 5	 1.00 1.82 (0.75–4.43) 1.67 (0.74–3.77) 0.88 (0.28–2.80)	Age, sex, smoking	Strengths: prospective design Limitations: upper–middle socioeconomic class considered only, small number of cases, limited confounder information
Stensvold & Jacobsen (1994) Norway, 1977–1982 (enrolment), incidence until 1990 (average 10.1 yr)	42 973 (41 cases) men and women aged 35–54 yr, living in three counties in different parts of Norway, participating in a cardiovascular screening programme organized by the National Health Screening Service Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day): women* ≤ 4 ≥ 5 *Current coffee drinking (cups/day): men* ≤ 4 5–6 ≥ 7	 6 9 9 9 8	 1.0 1.2 1.0 1.0 0.6	Age, smoking, residence	Strengths: prospective design, sex-specific analyses Limitations: small number of pancreas cancer cases overall, and sex-specific, very few subjects drinking 0–1 cups/day, limited confounder information, multiple comparisons (15 cancer sites analysed)

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Harnack et al. (1997) USA, 1986 (enrolment), incidence 1986–1994 (9 yr)	33 976 (66 cases) women living in Iowa aged 55–69 yr (Iowa Women's Health Study), 99% of cohort was white Exposure assessment method: FFQ	Pancreas	*Coffee (cups/wk)*			Age, smoking	Comparison of results in never smokers with total cohort suggests residual confounding by smoking. Updated version of this study (with inverse association) is reported in pooled analysis of Genkinger et al. (2012) Strengths: population-based cohort, validated FFQ (from NHS), prospective design precludes recall bias, separate results for never smokers Limitations: low number of cases, limited confounder information
			≤ 7	11	1.00		
			8–17.5	20	1.91 (0.92–40.00)		
			> 17.5	35	2.15 (1.08–4.30)		
			Trend test *P* value, 0.03				
			Coffee consumption (cups/wk): never smokers			Age	
			≤ 7	10	1.00		
			8–17.5	11	1.36 (0.58–3.20)		
			> 17.5	17	1.74 (0.80–3.80)		
			Trend test *P* value, 0.17				
Michaud et al. (2001) USA, 1980 (NHS enrolment), 1986 (HPFS enrolment), 1980–1996 (NHS incidence), 1986–1998 (HPFS, incidence)	88 799 in NHS (158 female cases), 47 794 in HPFS (130 male cases) Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day): women*			Age, sex, smoking, BMI, diabetes, cholecystectomy, energy intake, period	Strengths: validated FFQ (from NHS), large cohorts with detailed information, able to control for multiple confounders Limitations: limited to health professionals
			0	39	1.00		
			< 1	10	0.72 (0.36–1.44)		
			1	14	0.71 (0.38–1.30)		
			2–3	52	0.88 (0.58–1.34)		
			> 3	43	0.88 (0.56–1.38)		
			Trend test *P* value, 0.92				
			Current coffee drinking (cups/day): men				
			0	47	1.00		
			< 1	36	1.04 (0.67–1.61)		
			1	10	0.48 (0.24–0.95)		
			2–3	31	0.89 (0.56–1.40)		
			> 3	6	0.37 (0.16–0.88)		
			Trend test *P* value, 0.04				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Michaud et al. (2001) (cont.)			*Current coffee drinking (cups/day)*				
			0	86	1.00		
			< 1	46	0.94 (0.65–1.36)		
			1	24	0.60 (0.38–0.94)		
			2–3	83	0.88 (0.65–1.21)		
			> 3	49	0.62 (0.27–1.43)		
			Trend test *P* value, 0.35				
Isaksson et al. (2002) Sweden 1961 (enrolment), 1969–1997 (incidence, 16 yr median)	21 884 (131 cases), Swedish Twin Registry cohort: male and female same-sexed twin pairs born during 1886–1925 and both living in Sweden in 1961 Exposure assessment method: questionnaire	Pancreas	*Current coffee drinking (cups/day)*			Age, sex, smoking	Strengths: 90% of the pancreas tumours were histologically confirmed Limitations: no incidence data in period 1961–1969, limited dietary and confounder information
			0–2	29	1.00		
			3–6	95	0.91 (0.60–1.38)		
			≥ 7	7	0.39 (0.17–0.89)		
Lin et al. (2002) Japan, 1988–1990 (enrolment), mortality until 1997 (8.1 yr average)	110 792, JACC (46 465 men and 64 327 women), inhabitants of 45 areas throughout Japan aged 40–79 yr at baseline Exposure assessment method: questionnaire	Pancreas	*Current coffee drinking: men*			Age, smoking pack-years	According to authors, the association between coffee consumption and pancreatic cancer risk was similar for non-smokers and current smokers (data not shown) Strengths: large cohort study with relatively large number of cases Limitations: fatal cancer only, no data on histological confirmation, small proportion drinking larger amounts of coffee with very few drinking > 4 cups/day, limited confounder information
			0	35	1.00		
			1–2 cups/mo	12	0.74 (0.37–1.49)		
			1–4 cups/wk	19	0.58 (0.32–1.08)		
			1 cup/day	8	0.59 (0.26–1.33)		
			2–3 cups/day	11	0.75 (0.36–1.59)		
			≥ 4 cups/day	5	3.19 (1.22–8.35)		
			Trend test *P* value, 0.79				
			Current coffee drinking: women				
			0	27	1.00		
			1–2 cups/mo	12	1.27 (0.64–2.54)		
			1–4 cups/wk	11	0.74 (0.36–1.50)		
			1 cup/day	9	0.94 (0.44–2.01)		
			2–3 cups/day	2	0.31 (0.07–1.33)		
			≥ 4 cups/day	1	1.8 (0.24–13.66)		
			Trend test *P* value, 0.21				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Stolzenberg-Solomon et al. (2002) Finland, 1985–1988 (enrolment), incidence until 1997 (10.2 yr median)	27 111 (163 cases), participants ATBC, smoking men aged 50–69 yr residing in southwestern Finland, randomized to receive supplements or placebo Exposure assessment method: FFQ	Pancreas	*Coffee consumption (g/day)* ≤ 321.4 450 624.9 878.6 > 878.6 Trend test *P* value, 0.62	 NR NR NR NR NR	 1.00 1.48 (0.89–2.46) 1.12 (0.61–2.03) 1.72 (1.01–2.86) 0.95 (0.54–1.68)	Age, smoking years	Strengths: detailed and validated FFQ Limitations: male smokers only, few people with low intake of coffee
Khan et al. (2004) Japan, mortality 1984–2002 (mean 13.8 yr for men, 14.8 yr for women)	3158 (25 fatal cases), subjects aged ≥ 40 yr using the resident registries of Hokkaido, Japan (1524 men and 1634 women) Exposure assessment method: questionnaire	Pancreas	*Coffee drinking: men* Non/occasional ≥ several times/wk Coffee drinking: women Non/occasional ≥ several times/wk	 NR NR NR NR	 1.0 0.6 (0.2–2.2) 1.0 0.2 (0–1.8)	Age, smoking Age, health status, health education, health screening, smoking	Limitations: no data on histological confirmation, very small number of cases, fatal cases only, limited control for confounders

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Luo et al. (2007) Japan, incidence 1990–2003 (mean 11 yr)	102 137 (233 cases), JPHC Study, conducted in 11 public health centre-based areas throughout Japan among residents aged 40–69 yr (48 783 men and 53 354 women) Exposure assessment method: FFQ	Pancreas	*Current coffee drinking: men*			Age, sex, smoking, BMI, physical activity, alcohol, diabetes, cholelithiasis, study area, green tea	Strengths: large number of incident cases Limitations: no data on histological confirmation, relatively few people with high coffee intake
			Rarely	54	1.0		
			1–2 cups/wk	30	1.0 (0.6–1.5)		
			3–4 cups/wk	15	0.8 (0.5–1.5)		
			1–2 cups/day	25	0.7 (0.4–1.1)		
			≥ 3 cups/day	11	0.6 (0.3–1.1)		
			Trend test *P* value, 0.04				
			Current coffee drinking: women				
			Rarely	38	1.0		
			1–2 cups/wk	16	0.9 (0.5–1.7)		
			3–4 cups/wk	14	1.7 (0.9–3.1)		
			1–2 cups/day	24	1.3 (0.8–2.3)		
			≥ 3 cups/day	6	1.3 (0.5–3.3)		
			Trend test *P* value, 0.2				
			Current coffee drinking: men and women combined				
			Rarely	92	1.0		
			1–2 cups/wk	46	1.0 (0.7–1.4)		
			3–4 cups/wk	29	1.1 (0.7–1.7)		
			1–2 cups/day	49	0.9 (0.6–1.3)		
			≥ 3 cups/day	17	0.8 (0.4–1.3)		
			Trend test *P* value, 0.4				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nilsson et al. (2010) Sweden, incidence 1992–2007 (median 6 yr)	64 603 (74 cases), prospective cohort study from the VIP, subjects aged 40–60 yr at start Exposure assessment method: FFQ	Pancreas	*All coffee (cups/day)*			Age, sex, smoking, BMI, education, physical activity	Strengths: distinction between filtered and boiled coffee Limitations: small number of cases, no data on histological confirmation
			< 1	5	1.00		
			1–3	41	1.18 (0.47–3.02)		
			≥ 4	28	1.50 (0.57–3.92)		
			Coffee intake, filtered method (cups/day)				
			< 1	23	1.00		
			1–3	38	0.85 (0.50–1.44)		
			≥ 4	13	0.88 (0.44–1.76)		
			Coffee intake, boiled method (cups/day)				
			< 1	42	1.00		
			1–3	24	1.68 (1.01–2.81)		
			≥ 4	8	2.51 (1.15–5.50)		
Nakamura et al. (2011) Japan, mortality 1992–1997 (5 yr)	30 826 (14 241 men and 16 585 women; 52 fatal cases) residents of Takayama, Gifu Prefecture, Japan, aged ≥ 35 yr Exposure assessment method: FFQ	Pancreas	*Current coffee drinking: men*			Age, smoking, BMI, diabetes	Limitations: small number of cases, only fatal cases, no histological confirmation, low coffee intake levels
			Never	14	1.00		
			> 1 cup/mo to 4–6 cups/wk	11	0.67 (0.29–1.55)		
			≥ 1 cup/day	8	0.44 (0.15–1.29)		
			Trend test *P* value, 0.08				
			Current coffee drinking: women				
			Never	9	1.00		
			> 1 cup/mo to 4–6 cups/wk	5	0.62 (0.2–2)		
			≥ 1 cup/day	4	0.68 (0.17–2.78)		
			Trend test *P* value, 0.71				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Genkinger et al. (2012) USA, Canada, Netherlands, Sweden, Australia, incidence 1980–2005 (varies by cohort)	853 894 (317 828 men, 536 066 women) and 2185 cases (1047 men, 1138 women); pooling of 14 prospective cohort studies (including ATBC, BCDDP, CNBSS, CPS-II, CTS, COSM, HPFS, IWHS, MCCS, NLCS, NYSC, NHS, PLCO, SMC) Exposure assessment method: FFQ	Pancreas	*Coffee consumption (g/day): men and women*			Age, smoking, alcohol consumption, diabetes, BMI, energy intake, year of enrolment	When the case definition was limited to adenocarcinomas (n = 1554), no statistically significant association was observed with intake of coffee. Strengths: large size with high number of cases, enabling analyses of broad exposure range and possibility to evaluate effect modification Limitations: none
			0	149	1.00		
			0.01 to < 150	135	1.16 (0.84–1.6)		
			150 to < 400	316	1.01 (0.82–1.25)		
			400 to < 900	738	1.08 (0.89–1.31)		
			≥ 900	257	1.10 (0.81–1.48)		
			Continuous for 237 g/day increase	1595	1.01 (0.97–1.04)		
			Trend test P value, 0.71				
			Coffee consumption (g/day): men				
			0	54	1.00		
			0.01 to < 150	79	1.53 (1.03–2.26)		
			150 to < 400	163	1.02 (0.73–1.43)		
			400 to < 900	411	1.15 (0.84–1.58)		
			≥ 900	130	0.95 (0.67–1.36)		
			Continuous for 237 g/day increase	837	0.98 (0.95–1.01)		
			Trend test P value, 0.06				
			Coffee consumption (g/day): women				
			0	95	1.00		
			0.01 to < 150	56	0.87 (0.53–1.43)		
			150 to < 400	153	1.00 (0.76–1.32)		
			400 to < 900	327	1.04 (0.8–1.34)		
			≥ 900	127	1.18 (0.71–1.98)		
			Continuous for 237 g/day increase	758	1.04 (0.97–1.11)		
			Trend test P value, 0.5				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bidel et al. (2013) Finland, incidence 1972–2006 (mean 18 yr)	60 041 (29 159 men and 30 882 women; 235 cases) from six geographic areas of Finland, random sampling of the population aged 25–74 yr, stratified by area, sex, and 10-year age group Exposure assessment method: mailed, self-administered questionnaire	Pancreas	*Current coffee drinking (cups/day): men*			Age, smoking, study year, education, alcohol consumption, physical activity, diabetes, tea, BMI	Coffee cup size was small (100 mL) Strengths: prospective design with long follow-up (precluding recall bias), sex-specific analyses possible, wide range of coffee intake analysed
			0	9	1.00		
			1–2	14	0.72 (0.30–1.71)		
			3–4	32	0.76 (0.35–1.67)		
			5–6	38	0.64 (0.29–1.41)		
			7–9	20	0.72 (0.31–1.68)		
			≥ 10	16	0.80 (0.30–1.95)		
			Trend test *P* value, 0.91				
			Current coffee drinking (cups/day): women				
			0	3	1.00		
			1–2	11	1.30 (0.36–4.77)		
			3–4	33	1.29 (0.39–4.31)		
			5–6	40	1.21 (0.36–4.07)		
			7–9	16	1.52 (0.42–5.43)		
			≥ 10	3	0.71 (0.14–3.63)		
			Trend test *P* value, 0.88				
Bhoo-Pathy et al. (2013) 10 European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK), 1992–2000 (enrolment), follow-up varied by country (mean 11.6 years)	477 312 (865 cases), EPIC cohort Exposure assessment method: FFQ	Pancreas	*Total coffee: country-specific quartiles*			Age, sex, centre, and age at diagnosis, height, weight, smoking status, history of diabetes, education, physical activity, energy intake, red meat, processed meat, alcohol, tea, soft drink, fruit, and vegetable intake	Median total coffee intake ranged from 92 mL/day in Italy to 900 mL/day in Denmark. Decaffeinated coffee also showed no association. Strengths: large study size and number of cases, with large variation in coffee intake, coffee intake calibrated with 24-hour recall Limitations: method and source of follow-up not described for most countries
			Non-drinker	52	1.09 (0.8–1.5)		
			Q1 (ref)	237	1.00		
			Q2	214	1.11 (0.92–1.34)		
			Q3	196	0.99 (0.81–1.21)		
			Q4	166	1.07 (0.86–1.33)		
			Continuous for 100 mL/day increase	865	1.00 (0.97–1.02)		
			Trend test *P* value, 0.925				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Guertin et al. (2016) USA, enrolment (NA), follow-up incidence until 2006	457 366 (1541 cases with exocrine pancreas cancer); NIH-AARP Diet and Health Study, participants aged 50–71 yr residing in one of six US states or two metropolitan areas Exposure assessment method: FFQ	Pancreas	*Current coffee drinking (cups/day): men*			Age, smoking, diabetes, race/ ethnicity, BMI, highest level of education, alcohol consumption, health status, use of nutritional supplements, current marital status, physical activity, history of cardiovascular disease, family history of cancer, energy intake, nutrient density-adjusted intakes of fruits, vegetables, folate, protein, saturated fat, total fat	The association did not differ by tobacco smoking or self-reported history of diabetes. Strengths: large study size and number of cases
			0	71	1.00		
			< 1	153	1.14 (0.86–1.52)		
			1	146	1.02 (0.76–1.35)		
			2–3	427	1.05 (0.81–1.36)		
			4–5	142	1.06 (0.79–1.43)		
			≥ 6	54	1.21 (0.84–1.75)		
			Trend test *P* value, 0.55				
			Current coffee drinking (cups/day): women				
			0	58	1.00		
			< 1	81	0.91 (0.65–1.28)		
			1	112	1.12 (0.82–1.55)		
			2–3	218	1.01 (0.75–1.35)		
			4–5	53	0.89 (0.60–1.3)		
			≥ 6	26	1.38 (0.85–2.22)		
			Trend test *P* value, 0.53				

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BCDDP, Breast Cancer Detection Demonstration Project; BMI, body mass index; CNBSS, Canadian National Breast Screening Study; CI, confidence interval; COSM, Cohort of Swedish Men; CPS-II, Cancer Prevention Study; CTS, California Teacher's Study; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-up Study; IWHS, Iowa Women's Health Study; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; JPHC, Japan Public Health Center-based Prospective; MCCS, Melbourne Collaborative Cohort Study; mo, month(s); NA, not available; NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health–Association of American Retired Persons; NLCS, Netherlands Cohort Study; NR, not reported; NYSC, New York State Cohort; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort; VIP, Västerbotten Intervention Project; wk, week(s); yr, year(s)

both age and smoking, using the entire cohort as the standard population. No significant association was reported between coffee drinking and risk of pancreatic cancer after adjusting for smoking (*P* for trend, 0.41). [The Working Group noted the very low number of cases; in addition, dietary information was based on a single 24-hour recall.]

A cohort study in northern California investigated a 6-year follow-up of pancreatic cancer incidence among 122 894 men and women who had completed a questionnaire collecting data on coffee, tea, smoking, and alcohol use during 1978–1984 (Hiatt et al., 1988). There were 49 cases of pancreatic cancer. A multivariate analysis identified no increased pancreatic cancer risk associated with increasing coffee consumption.

A cohort study (Mills et al., 1988) of 34 198 non-Hispanic, white Californian Seventh-day Adventists followed participants for 6 years after their completion of a questionnaire determining exposure to several risk factors, including coffee consumption, in 1976. Forty deaths from pancreatic cancer were reported. Multivariate analyses using the Cox proportional hazards model resulted in a relative risk for current coffee consumption versus no coffee consumption, adjusted for age, sex, and smoking, of 2.21 (95% CI, 0.61–7.99). [The Working Group noted that the distribution of coffee drinking in this population is unusual because there are few drinkers of larger quantities of coffee; only 17–18% of the population drank ≥ 2 cups/day.]

Friedman & van den Eeden (1993) conducted a nested case–control study within the Kaiser–Permanente cohort study, consisting of people who had received multiphasic health check-ups in the San Francisco Bay Area. Measurement of coffee intake was limited to one yes-or-no question in a questionnaire focusing on heavy consumption: "Do you usually drink over 6 cups of coffee per day?" As part of an exploratory analysis of 779 characteristics, coffee intake was also analysed. After multivariate adjustment, drinking > 6 cups/day of coffee was not associated with increased pancreatic cancer risk (RR, 0.95; 95% CI, 0.73–1.22).

Via the Lutheran Brotherhood Life Insurance Society (LBS) cohort, Zheng et al. (1993) studied risk factors for pancreatic cancer mortality in a cohort study of 17 633 white men in the USA who responded to a mailed questionnaire in 1966 and were followed up until 1986 for mortality. After 20 years of follow-up, 57 fatal pancreatic cancer cases were identified. Coffee consumption at baseline (current coffee drinking) was measured using a food frequency questionnaire (FFQ). Coffee was not related to pancreatic cancer mortality; the relative risk for those drinking ≥ 7 cups/day was 0.9 (95% CI, 0.3–2.4) compared with those drinking < 3 cups/day.

Shibata et al. (1994) examined risk factors for pancreatic cancer in a cohort study of 13 979 men and women resident within a retirement community in USA. After 9 years of follow-up, 65 incident cases of pancreatic cancer were identified. Coffee consumption at baseline was measured using a FFQ. Coffee was not related to pancreatic cancer risk; the relative risk for those drinking ≥ 4 cups/day compared with those drinking < 1 cup/day was 0.88 (95% CI, 0.28–2.80).

As part of a larger study on coffee drinking and cancer incidence, Stensvold & Jacobsen (1994) studied a cohort of 21 735 men and 21 238 women aged 35–54 years. The study population participated in a cardiovascular screening in three counties in Norway during 1977–1982. After an average follow-up period of 10.1 years, 41 incident cases were identified. Data on coffee habits at baseline were based on information from a self-administered FFQ. No statistically significant association was found between coffee drinking and incidence of cancer of the pancreas. In men, the relative risk for those drinking ≥ 7 cups/day compared with ≤ 4 cups/day was 0.6 (no confidence interval given) [coffee consumption is high in Norway]. In women, the relative

risk for those drinking ≥ 5 cups/day compared with those drinking ≤ 4 cups/day was 1.2. [The Working Group noted that the reference group could include individuals who consumed significant amounts of coffee.]

Harnack et al. (1997) examined the relationship between coffee consumption and pancreatic cancer incidence in the Iowa Women's Health Study cohort. Data were available from 33 976 women aged 55–69 years in 1986 who responded to a mailed questionnaire and who were followed until 1994 (9 years) for cancer incidence. Coffee intake at baseline was estimated using a validated FFQ. The relative risk for those drinking ≥ 17.5 cups/week compared with those drinking ≤ 7 cups/week was 2.15 (95% CI, 1.08–4.30; *P* for trend, 0.03). Among never smokers, the relative risk for the same consumption levels was not statistically significant at 1.74 (95% CI, 0.80–3.80; *P* for trend, 0.17). [The Working Group noted that an updated version of this study with a longer follow-up, but with an inverse association, is reported in the pooled analysis of Genkinger et al. (2012).]

Michaud et al. (2001) used data on coffee intake from semiquantitative FFQs administered at baseline in the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS), and in subsequent follow-up questionnaires. In both the NHS and HPFS, repeated measurements for coffee intake were accounted for in the analysis. The HPFS included 44 794 men, while there were data available on 88 799 women from the NHS. Results revealed a significant inverse association in men (RR for those drinking > 3 cups/day compared with those drinking 0 cups/day was 0.37; 95% CI, 0.16–0.88; *P* for trend, 0.04), and no association in women (RR, 0.88; 95% CI, 0.56–1.38; *P* for trend, 0.92). No associations between decaffeinated coffee or caffeine intake and pancreatic cancer, overall or by sex, were evident. [Data from the NHS and HPFS were included in the pooled analysis of Genkinger et al. (2012).]

Isaksson et al. (2002) studied the association between coffee consumption and pancreatic cancer incidence in a cohort study of twins established in 1958 and followed up by the Swedish Twin Registry. At 1961 (baseline), self-administered questionnaires regarding lifestyle factors were mailed. The analysis included 12 204 women and 9680 men who responded to these questionnaires. For those who consumed ≥ 7 cups/day compared with those who reported ≤ 2 cups/day, the relative risk of pancreatic cancer was 0.39 (95% CI, 0.17–0.89). [The Working Group noted that no incidence follow-up data were available for the period 1961–1969.]

Lin et al. (2002) evaluated the association between coffee consumption and pancreatic cancer mortality in a large-scale prospective cohort study, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study). At baseline, a self-administered questionnaire was used to estimate coffee consumption. During the follow-up period (mean 8.1 years), 225 pancreatic cancer deaths were identified. Overall, coffee intake was not associated with fatal pancreatic cancer. While the relative risks were inverse for those drinking up to 3 cups/day of coffee compared with non-consumers of coffee (0 cups/day), the corresponding relative risk was positive and statistically significant (RR, 3.19; 95% CI, 1.22–8.35) for men who consumed ≥ 4 cups/day of coffee. A similar, but less-pronounced pattern of risks was observed among women. [The Working Group noted that, there was only limited control for confounders.]

Stolzenberg-Solomon et al. (2002) examined the association between coffee and exocrine pancreatic cancer in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study cohort in Finland among 27 111 male smokers aged 50–69 years. Coffee intake was estimated with a self-administered FFQ given at baseline (1985–1988). Compared with those drinking ≤ 321.4 mL/day of coffee, the relative risk for those drinking > 878.6 g/day was 0.95 (95% CI,

0.54–1.68; *P* for trend, 0.62). [The Working Group noted that coffee consumption was not very low in the reference group. Data from this study were included in the pooled analysis of Genkinger et al. (2012).]

Khan et al. (2004) studied the association between coffee drinking and pancreatic cancer mortality in a cohort study (1984–2002) in Hokkaido, Japan, among 1524 men and 1634 women aged 40 years and over at the beginning of the study period. Baseline coffee consumption was assessed with a questionnaire. During follow-up until 2002, 25 fatal cases were detected. There was no significant association between coffee drinking and the incidence of pancreatic cancer in men or women. [The Working Group noted the extremely low number of cases in sex-specific analyses.]

Luo et al. (2007) examined the association between coffee drinking and the risk of pancreatic cancer in a large population-based cohort study in Japan (JPHC study). A total of 233 incident cases of pancreatic cancer were identified. Baseline coffee consumption was assessed with a FFQ. Coffee drinking was not significantly associated with the risk of pancreatic cancer in men and women combined (*P* for trend, 0.4). Among men, but not among women, there was a significant trend towards lower risk with increasing coffee intake; the relative risk for ≥ 3 cups/day versus rarely drinking coffee was 0.6 (95% CI, 0.3–1.1; *P* for trend, 0.04).

Nilsson et al. (2010) investigated total, filtered, and boiled coffee consumption in relation to the risk of incident cancer in a prospective cohort study from the ongoing, population-based Västerbotten Intervention Project (VIP) established in 1985 in Sweden. Consumption of filtered and boiled coffee was assessed using a FFQ. Total and filtered coffee were not associated with risk of pancreatic cancer, but boiled coffee was positively associated with a relative risk of 2.51 for ≥ 4 cups/day versus < 1 cups/day (95% CI, 1.15–5.50; *P* for trend, 0.006). When coffee intake was modelled as a continuous variable, there was significant heterogeneity between filtered and boiled coffee (*P* for trend, 0.013) with an elevated risk for boiled coffee.

Nakamura et al. (2011) evaluated the association between coffee consumption and risk of death from pancreatic cancer in a prospective cohort study in Takayama, Japan. Coffee intake was estimated with a self-administered FFQ distributed at baseline. There was no significant association between intake of coffee and the risk of pancreatic cancer death; when comparing subjects drinking ≥ 1 cup/day versus never drinkers of coffee, the relative risk was 0.44 (95% CI, 0.15–1.29; *P* for trend, 0.08) among men and 0.68 (95% CI, 0.17–2.78; *P* for trend, 0.71) among women. [The Working Group noted the very small numbers of cases in sex-specific analyses.]

Genkinger et al. (2012) performed a pooled analysis of primary data from 14 cohort studies as part of the Prospective Studies of Diet and Cancer Pooling Project, a large international consortium. These studies included: the ATBC; Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP); Canadian National Breast Screening Study (CNBSS); Cancer Prevention Study II Nutrition Cohort (CPS II); California Teachers Study (CTS); Cohort of Swedish Men (COSM); Health Professionals Follow-up Study (HPFS); Iowa Women's Health Study (IWHS); Melbourne Collaborative Cohort Study (MCCS); the Netherlands Cohort Study (NLCS); New York State Cohort (NYSC); Nurses' Health Study (NHS); Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; and Swedish Mammography Cohort (SMC). Baseline coffee consumption was measured with FFQs as applied in each of the cohorts. Estimated coffee intake levels were converted into grams/day to avoid heterogeneity due to different cup sizes between countries. Coffee consumption was not associated with pancreatic cancer risk overall, and there was no indication of a dose–response association in categorical or

continuous analyses. When comparing intake of ≥ 900 g/day with 0 g/day, the pooled relative risk was 1.10 (95% CI, 0.81–1.48) with a *P* value of 0.08 in a test for between-study heterogeneity. There was no indication of a differential association by sex (*P* value, 0.69 in test for between-study heterogeneity due to sex). The pooled relative risks among women were 1.18 (95% CI, 0.71–1.98; *P* value in test for between-studies heterogeneity, 0.01) and among men 0.95 (95% CI, 0.67–1.36; *P* value in test for between-studies heterogeneity, 0.83). Although not statistically significant, a suggestion of heterogeneity due to differences in the percentage of current smokers in the female cohorts was present (*P* value for between-studies heterogeneity, 0.12). Expressed per increment of 237 mL/day, the pooled relative risk was 1.01 (95% CI, 0.97–1.04) for women and men combined with a *P* value for between-studies heterogeneity of 0.05. The large size of the pooled analysis also permitted evaluation of the effect of modification by other variables; however, there was no evidence of interaction by evaluated lifestyle or cohort characteristics. Among never smokers (525 cases), the relative risk was 1.04 (95% CI, 0.95–1.15) per 237 mL/day. [The large size of this pooled analysis of individual data with a high number of cases enabled analyses of broad exposure ranges and the possibility of evaluating effect modification.]

Bidel et al. (2013) examined the association between coffee and pancreatic cancer in a cohort study in six areas in Finland among 29 159 men and 30 882 women aged 25–74 years at baseline. Coffee intake was estimated with a self-administered questionnaire. Incident cancer cases were identified through the country-wide Finnish Cancer Registry. Coffee consumption was not associated with an increased risk of pancreatic cancer in men, women, or both sexes combined. The hazard ratio of pancreatic cancer incidence for ≥ 10 cups/day of coffee compared with non-drinkers was 0.80 (95% CI, 0.30–1.95; *P* for trend, 0.91) for men, and 0.71 (95% CI, 0.14–3.63; *P* for trend, 0.88) for women, and 0.82 (95% CI, 0.38–1.76; *P* for trend, 0.95) for men and women combined.

Bhoo-Pathy et al. (2013) analysed the relationship between coffee intake and pancreatic cancer in the EPIC cohort conducted in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK. The cohort included 477 312 participants without cancer who completed a FFQ during 1992–2000 and were followed up for cancer incidence. Estimated coffee intake from the FFQ was calibrated with a 24-hour recall. Median total coffee intake ranged from 92 mL/day in Italy to 900 mL/day in Denmark. Consumption of total coffee, caffeinated, and decaffeinated coffee intake were not associated with risk of pancreatic cancer. For total coffee, the hazard ratio of pancreatic cancer risk for the highest versus the lowest quartile of consumption was 1.07 (95% CI, 0.86–1.33; *P* for trend, 0.925). Hazard ratios for caffeinated and decaffeinated coffee were similar. Continuous analyses for increments of 100 mL/day did not show any increase or decrease in risk of pancreatic cancer for all coffee types. No material changes in risk estimates were observed when beverages were grouped using EPIC cohort-wide categories instead of country-specific intake. Associations between coffee intake and pancreatic cancer were generally similar across subgroups as defined by sex, age group, smoking status, and BMI categories.

Guertin et al. (2016) used data from the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study. At baseline, participants were aged 50–71 years and resided in one of six US states or two metropolitan areas. For this analysis, 457 366 participants (275 328 men and 182 038 women) with non-missing data on coffee intake and smoking were included. Cancer cases were identified by linkage of the NIH-AARP cohort to 11 state cancer registries and the National Death

Index. Intakes of coffee and predominant type of coffee consumed were assessed with a FFQ. Although models adjusted only for age and sex suggested a statistically significant higher risk of pancreatic cancer with higher coffee intake, the association was substantially attenuated after extensive adjustment for smoking. Adjustment for additional covariates did not appreciably alter risk estimates. In the fully adjusted model, the hazard ratio of pancreatic cancer risk for men drinking ≥ 6 cups/day of coffee versus 0 cups/day was 1.21 (95% CI, 0.84–1.75; *P* for trend, 0.55); for women, the corresponding hazard ratio was 1.38 (95% CI, 0.85–2.22; *P* for trend, 0.53). The association did not vary with tobacco smoking or self-reported history of diabetes.

2.2.2 Case–control studies

See Table 2.4.

(a) Population-based case–control studies

Severson et al. (1982) based their study on 22 cases aged 40–79 years from a registry that was part of the Surveillance, Epidemiology and End Results (SEER) Program in Seattle, Washington, USA during 1977–1980, and on a random population sample of controls (n = 485). Next of kin were interviewed for most of the cases (20), whereas personal interviews were obtained for controls. The odds ratio for current versus not current coffee drinking was 1.0 (95% CI, 0.2–4.5). [This study was published as a letter, which contained few details.]

In the study of Gold et al. (1985), 201 cases (94 men, 107 women) with pancreatic cancer from 16 hospitals in Baltimore, Maryland, USA were included in a matched analysis. Of the 201, 25% had a personal interview. Two control groups were used: a matched hospital series (for age, race, sex, hospital, date of admission) from which patients with other cancers were excluded; and a population-based group that was chosen by random-digit dialling (RDD), matched by age, race, sex, and telephone exchange, and interviewed by telephone. Participation was about 50% of eligible individuals in both control series. No significant associations were found between pancreatic cancer and coffee drinking when using hospital- or population-based controls. The relative risks for those drinking ≥ 3 cups/day versus 0 cups/day, while controlling for smoking status, were 1.68 (95% CI, 0.71–3.95) when using population controls and 1.52 (95% CI, 0.68–3.43) with hospital controls.

A small study by Gorham et al. (1988) of 30 cases and 47 controls was based only on death certificates in Imperial County, California, USA, during 1978–1984. Controls were matched for age, sex, race, and year of death; cancer patients were excluded. The estimated relative risk for pancreatic cancer mortality associated with consumption of ≥ 3 cups/day compared with < 3 cups/day of coffee was 2.7, which dropped to 1.9 and was non-significant after adjustment for smoking. [The Working Group noted that only 30 of 51 deaths from pancreatic cancer were included; hospital records were not examined.]

A case–control study in the USA involved 212 cases identified from death certificates and 220 population-based controls contacted by RDD and matched to cases by age within 5 years (Olsen et al., 1989). Family members (usually widow or spouse) were interviewed on the case's use of cigarettes, alcohol, coffee, and other dietary factors 2 years before the death of the patient or before interview for controls. Coffee intake was not associated with pancreatic cancer mortality (OR for ≥ 7 cups/day versus < 1 cup/day, 0.60; 95% CI, 0.27–1.27.

Farrow & Davis (1990) conducted a case–control study with 148 cases and 188 controls among married men in Washington State, USA. Cases residing in three counties of Washington State, aged 20–74 years at diagnosis, were identified from the SEER Program. Population-based controls, matched to cases by age, were contacted by RDD. Information about each

Table 2.4 Case–control studies on cancer of the pancreas and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacMahon et al. (1981b) USA, 1974–1979	Cases: 367 admitted to one of 11 hospitals Controls: 644 hospital-based, other patients treated in same hospitals as cases (excluding diseases of biliary tract, pancreas, CVD, diabetes, respiratory or bladder cancer, peptic ulcer) Exposure assessment method: interview	Pancreas	*Coffee consumed (cups/day)* 0 1–2 ≥ 3 Trend test *P* value, 0.001	 20 153 194	 1.0 1.8 (1.0–3.0) 2.7 (1.6–4.7)	Age, sex, smoking	Strengths: comparable catchment area of cases and controls Limitations: many controls had gastrointestinal problems and may therefore have reduced their coffee intake, response rates moderate, interviewers not blinded for case/control status
Severson et al. (1982) USA, 1977–1980	Cases: 22 from SEER registry in Seattle, aged 40–79 yr at diagnosis Controls: 485 population-based, randomly selected from population in which cases arose, aged 40–79 yr Exposure assessment method: interview	Pancreas	*Coffee drinking status* Not current Current	 NR NR	 1.0 1.0 (0.2–4.5)	Age, sex, smoking	Strengths: population-based study Limitations: very small number of cases, cases information from two living patients and 20 from next-of-kin because of death, limited exposure information
Wynder et al. (1983) USA, 1977–1981	Cases: 275 aged 20–80 yr, admitted to 17 hospitals in 6 major cities Controls: 7994 hospital-based controls, matched on age, race, sex, room status from same hospital as cases (diseases, some cancers, not associated with tobacco) Exposure assessment method: interview	Pancreas	*Coffee consumed (cups/day): men* 0 1 2 3–5 ≥ 6 *Coffee consumed (cups/day): women* 0 1 2 3–5 ≥ 6	 26 15 34 50 28 25 19 25 36 17	 1.00 0.80 (0.40–1.48) 1.10 (0.68–1.95) 1.00 (0.59–1.59) 1.00 (0.59–1.79) 1.0 0.90 (0.48–1.64) 0.90 (0.51–1.59) 0.90 (0.53–1.50) 1.00 (0.52–1.83)	Age, smoking Age, smoking	Strengths: relatively large series with detailed control for smoking Limitations: hospital-based controls, reduced response rates in cases and controls

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kinlen & McPherson (1984) UK, 1952–1954	Cases: 216 aged > 40 yr, derived from an earlier study by Stocks (1957) conducted in 1952–1954 in greater Liverpool area and north Wales Controls: 432 hospital-based, cancer controls from Stocks study (excluding smoking-related and GI tract cancer, and ovarian cancer), matching on sex, age, residence area Exposure assessment method: interview	Pancreas	*Coffee drinking status: men* Never Weekly Daily *Coffee drinking status: women* Never Weekly Daily	 69 22 18 55 29 23	 1.00 0.87 (0.48–1.54) 0.93 (0.49–1.76) 1.00 1.28 (0.71–2.28) 0.86 (0.86–1.58)	Age, tea, smoking Age, smoking, tea	Strengths: adjustment for tea Limitations: hospital-based, little information about cases, no information about response rates, limited exposure information
Gold et al. (1985) USA, 1978–1980	Cases: 201 from 16 major hospitals in Baltimore area Controls: 201 population-based, matched by age, race, sex and telephone exchange, plus 201 hospital-based (other cancers excluded) controls matched for age, race, sex, hospital, date of admission Exposure assessment method: interview (often with next of kin)	Pancreas	*Coffee consumed (cups/day): population controls* 0 1–2 ≥ 3 *Coffee consumed (cups/day): hospital controls* 0 1–2 ≥ 3	 18 91 88 18 91 88	 1.00 1.37 (0.59–3.18) 1.68 (0.71–3.95) 1.00 1.43 (0.65–3.14) 1.52 (0.68–3.43)	Age, sex, smoking	Strengths: relatively large case series with two types of control groups Limitations: large difference in proportion of proxy interviews between cases (75%) and controls (0%), different response rates between cases and controls

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Falk et al. (1988) USA, 1979–1983	Cases: 363 incident cases from hospitals in Louisiana Controls: 1234 admitted to same hospital as cases, matched on sex, age, race Exclusions: chronic conditions (cancers, diabetes, CVD, digestive diseases, respiratory diseases) suspected to be related to lifestyle or diet Exposure assessment method: questionnaire	Pancreas	*Coffee consumed (cups/day): women*			Age, smoking, alcohol consumption, intake of fruit, income	Strengths: questionnaire instead of interview Limitations: hospital-based, interview for 50% of cases and 13% of controls through next of kin (potential for recall bias)
			0	32	1.00		
			1–2	58	0.67		
			3–4	35	0.69		
			5–7	15	0.96		
			≥ 8	20	0.92		
			Coffee consumed (cups/day): men				
			0	34	1.00		
			1–2	64	0.66		
			3–4	34	0.53		
			5–7	23	0.67		
			≥ 8	48	1.39		
Gorham et al. (1988) USA, 1978–1984	Cases: 30 fatal pancreatic cancer cases identified from death certificates in Imperial County, California Controls: 47 controls identified from death certificates (excluding deaths from cancer), matching on age, sex, race and year of death Exposure assessment method: questionnaire	Pancreas	*Coffee consumed (cups/day)*			Age, smoking	Strengths: comparison of fatal cases with dead controls should lead to less information bias, interviewers blinded with respect to cause of death Limitations: only 30 of 51 deaths from pancreatic cancer were included, hospital records were not examined, information from next of kin, median length of time between death and date of interview was 6 yr in cases and controls
			< 3	7	1.0		
			≥ 3	16	1.9		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Clavel et al. (1989) France, 1982–1985	Cases: 161 cases (98 men) with diagnosed cancer of exocrine pancreas from public hospitals in Paris (102 of 161 cases histologically verified); mean age at diagnosis was 62 yr in men and 64 yr in women Controls: 268 hospital-based controls, matched on age, sex, hospital, interviewer; 129 controls had other cancers (excluding biliary, liver, stomach, oesophagus, respiratory and bladder cancers) and 139 had non-neoplastic disorders Exposure assessment method: interview	Pancreas	*Coffee consumed (cups/day): women* 0 1 2–3 ≥ 4 Trend test *P* value, 0.006 *Coffee consumed (cups/day): men* 0 1 2–3 ≥ 4 Trend test *P* value, 0.14	 4 24 29 6 6 35 44 15	 1.00 3.94 (0.85–18.22) 6.71 (1.47–30.65) 9.56 (1.29–70.71) 1.00 1.07 (0.30–3.88) 1.45 (0.41–5.04) 2.08 (0.49–8.86)	Age, ethnicity, education, alcohol consumption, smoking	Unusually high risks were seen in women and in persons who had never drank alcohol. Strengths: study of interaction with alcohol Limitations: hospital–based, interviewers not blinded, proportion of subjects born outside France was higher among cases than controls (but was adjusted for in analyses), possible interview bias in study period due to widely publicized study by MacMahon et al. (1981b)
Cuzick & Babiker (1989) UK, 1983–1986	Cases: 216 cases (30% histologically verified) from Leeds, London, Oxford Controls: 279, mix of hospital-based (212) and population-based (67) controls from same three areas Exposure assessment method: questionnaire	Pancreas	*Coffee consumed currently (cups/day)* 0 1–2 3–4 ≥ 5 Trend test *P* value, 0.23 *Coffee consumed 10 yr previously (cups/day)* 0 1–2 3–4 ≥ 5 Trend test *P* value, 0.43	 97 77 19 23 117 69 18 12	 1.00 0.87 0.63 1.37 1.00 0.93 0.85 0.77	Age, smoking, sex	Strengths: analyses of coffee consumption 10 yr previously Limitations: mostly hospital-based

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Olsen et al. (1989) USA, 1980–1983	Cases: 212 aged 40–84 yr identified from death certificates in Minneapolis–St Paul area Controls: 220 population-based white men contacted by RDD, matched to cases by age within 5 yr Exposure assessment method: FFQ	Pancreas	*Coffee consumed (cups/day)* < 1 1–3 4–6 ≥ 7	 29 60 74 49	 1.00 0.50 (0.26–1.00) 0.72 (0.37–1.45) 0.60 (0.27–1.27)	Age, smoking, education, diabetes, meat intake, intake of vegetables	Strengths: dead cases are compared with dead controls, comparable information more likely Limitations: information obtained from next of kin
Farrow & Davis (1990) USA, 1982–1986	Cases: 148 men from SEER, Washington State, aged 20–74 yr Controls: 188 population-based controls contacted by RDD, matched to cases by age Exposure assessment method: interview	Pancreas	*Coffee consumed (cups/day)* 0 1–2 3–5 ≥ 6	 18 27 55 62	 1.0 0.7 (0.3–1.7) 1.0 (0.4–2.2) 1.1 (0.5–2.4)	Age, smoking, race, education, energy-adjusted intake of protein and calcium	Strengths: surrogate interviews for all cases and controls, comparable information more likely Limitations: information obtained from next of kin, interviews were held 2.0–4.5 yr after the diagnosis

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jain et al. (1991) Canada, 1983–1986	Cases: 249 diagnosed in 20 hospitals in Toronto Controls: 505 population-based, matched by sex and age from population lists Exposure assessment method: diet history interview	Pancreas	*Lifetime coffee consumption (cup-years)* 0 ≤ 39 40–110 ≥ 110 Continuous for 100 cup-years	 25 69 76 76 229	 1.00 0.94 (0.47–1.89) 0.90 (0.45–1.79) 0.90 (0.44–1.81) 0.96 (0.77–1.19)	Age, sex, smoking, residence, proxy/ direct interview, energy intake, fibre	Further analysis by type of coffee (regular, instant, caffeinated, decaffeinated) also showed no evidence of an effect. Strengths: relatively large study with dietary history interview; lifetime history estimates of coffee, tea and alcohol consumption Limitations: low response rates, interview 3 mo after diagnosis with high case fatality rate, different proportions of cases and controls interviewed by proxy (possibly leading to bias), 194 of 249 cases interviewed by proxy (62% with spouse, 31% with daughters and sons, and 7% with others), 194 of 505 controls interviewed by proxy (72% with spouse, 19% with daughters and sons, and 9% with others)
Ghadirian et al. (1991) Canada, 1984–1988	Cases: 179 aged 35–79 yr, diagnosed in 19 hospitals located in greater Montreal Controls: 239 population-based matched for age, sex, and place of residence selected randomly from RDD Exposure assessment method: questionnaire, interviews	Pancreas	*Cumulative lifetime coffee consumption* Quintile 1 Q2 vs Q1 Q3 vs Q1 Q4 vs Q1 Q5 vs Q1 Trend test *P* value, 0.53	 NR NR NR NR NR	 1.00 0.44 0.82 0.51 0.55 (0.19–1.62)	Age, sex, smoking, education, respondent type	Further analysis by type of coffee (regular, instant, caffeinated, decaffeinated) also showed no evidence of an effect. Strengths: lifetime coffee drinking and coffee drinking patterns (e.g. with meals) were studied Limitations: large difference in proportion of interviews by proxy between cases (75%) and controls (17%)

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bueno de Mesquita et al. (1992) Netherlands, 1984–1987	Cases: 176 aged 35–79 yr in central part of the Netherlands Controls: 487 population-based controls aged 35–79 yr from municipal population registries in the same area, frequency matched to the age-and-sex distribution of the cases Exposure assessment method: interviewer-administered questionnaire on lifetime frequency	Pancreas	*Cumulative lifetime coffee consumption (L)* < 6 193 < 9 012 < 11 840 ≥ 11 840 Trend test *P* value, 0.06	 26 23 17 24	 1.00 0.72 (0.36–1.43) 0.37 (0.18–0.79) 0.58 (0.28–1.20)	Age, sex, smoking, respondent type, energy intake, intake of vegetables, tea	The suggestion of an inverse dose–response relationship with the lifetime consumption of coffee was not present in the analysis of direct responders only. Further analysis by type of coffee (regular, instant, caffeinated, decaffeinated) showed no evidence of an association. Strengths: lifetime coffee drinking Limitations: possible selection bias due to relatively large difference in response rate between cases and controls and different proportion of proxy interviews between cases (42%) and controls (29%)
Lyon et al. (1992) USA, 1984–1987	Cases: 149 with pancreatic adenocarcinoma or carcinoma, from Utah Cancer Registry, aged 40–79 years Controls: 363 population-based controls, frequency matched to the distribution of cases by age, sex, and county of residence at the time of diagnosis Exposure assessment method: questionnaire, telephone interview with proxies	Pancreas	*Cumulative lifetime coffee consumption (cups)* 0–2000 2001–50 000 ≥ 50 000 Trend test *P* value, < 0.001	 38 44 40	 1.00 1.34 (0.78–2.29) 2.38 (1.16–4.85)	Age, sex, smoking, religion	Strengths: for all cases and controls, surrogate interviews were held with next of kin (comparable information more likely) Limitations: non-response rate among controls was higher than among cases, surrogate information obtained from next of kin (information less reliable)

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zatonski et al. (1993) Poland, 1985–1988	Cases: 110 identified through hospitals and the Cancer Registry located in the Opole Voivodeship Oncological Clinic Controls: 195 population-based controls from same area, frequency matched on age, sex, place of residence Exposure assessment method: interviewer-administered questionnaire on lifetime frequency of the consumption of specific beverages per age period	Pancreas	*Cumulative lifetime coffee consumption (L)* 0 < 417 < 1916 ≥ 1916 Trend test *P* value, 0.042	 58 17 18 16	 1.00 0.61 (0.30–1.23) 0.63 (0.30–1.30) 0.48 (0.22–1.02)	Age, sex, smoking, education	Strengths: substantial proportion of never drinkers of coffee Limitations: large difference in proportion of proxy interviews between cases (71%) and controls (0%) leading to information bias, few subjects drinking large amounts of coffee
Partanen et al. (1995) Finland, 1984–1987	Cases: 662 identified at the Finnish Cancer Registry Controls: 1770 from Finnish Cancer Registry (1014 stomach, 441 colon, 315 rectum cancer) Exposure assessment method: questionnaire, mail questionnaire, coffee use 20 yr before diagnosis considered, obtained from next of kin	Pancreas	*Coffee consumed 20 yr previously (cups/day)* None/ occasional 1–3 4–6 > 6	 24 104 273 91	 1.00 0.83 (0.50–1.38) 0.96 (0.59–1.56) 0.71 (0.41–1.20)	Age, sex, smoking	Consumption of coffee is high in Finland, with few people who never or occasionally drink coffee. ORs were lower (but NS) when rectum cancers were used as controls only, as opposed to colon cancer controls only (OR close to 1). Strengths: size, surrogate interviews were held with next of kin for all cases and controls (comparable information more likely) Limitations: use of cancer controls possibly related to coffee consumption, surrogate information obtained from next of kin (information less reliable), response rates in cases or controls were not provided

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nishi et al. (1996) Japan, 1987–1992	Cases: 141 pancreas cancer diagnosed at Sapporo Medical University and its affiliated hospitals Controls: 282 population-based controls from Hokkaido, matched for sex, age and place of residence Exposure assessment method: cases interviewed and controls received a questionnaire	Pancreas	*Coffee consumed (cups/day): men*			Age, smoking	Reports a U-shape curve, with extra meta-analyses. Strengths: population-based Limitations: cases were interviewed but controls received a questionnaire (possibly leading to information bias), limited control for confounders
			0	NR	1.00		
			Occasionally	NR	0.18 (0.07–0.43)		
			1–2	NR	0.53 (0.27–1.07)		
			≥ 3	NR	0.93 (0.44–1.96)		
			Coffee consumed (cups/day): women				
			0	NR	1.00		
			Occasionally	NR	0.53 (0.20–1.38)		
			1–2	NR	0.70 (0.31–1.58)		
			≥ 3	NR	1.37 (0.46–4.14)		
Silverman et al. (1998) USA, 1986–1989	Cases: 436 among 30–79-year-old residents of areas covered by cancer registries in Atlanta, Detroit, and 10 New Jersey counties Controls: 2003, random sample from general population, frequency matched on age, race, sex, and study area Exposure assessment method: interview (sometimes with next of kin) with FFQ	Pancreas	*Coffee consumed (cups/day): men*			Age, race, study area, smoking, alcohol consumption, diabetes, BMI, energy intake, cholecystectomy, income	Strengths: size, high proportion of direct interviews
			≤ 1	53	1.0		
			2	57	1.1 (0.7–1.7)		
			3	31	1.0 (0.6–1.7)		
			4–5	23	0.8 (0.4–1.4)		
			≥ 6	28	0.9 (0.5–1.7)		
			Non-drinker (reference)	26	1.0		
			Ever	192	0.9 (0.5–1.4)		
			Coffee consumed (cups/day): women				
			≤ 1	65	1.0		
			2	52	1.0 (0.7–1.6)		
			3	26	0.7 (0.4–1.1)		
			4–5	32	1.0 (0.6–1.7)		
			≥ 6	15	1.0 (0.5–2.2)		
			Non-drinker (reference)	23	1.0		
			Ever	190	1.4 (0.9–2.4)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Villeneuve et al. (2000) Canada, 1994–1997	Cases: 583 aged 30–76 yr from eight provincial cancer registries confirmed Controls: 4813 population-based, frequency matched on age and sex Exposure assessment method: FFQ	Pancreas	*Coffee consumed: men*			Age, province of residence, smoking, alcohol consumption, energy intake, fat intake	Proxy interviews for 24% of cases but 0% of controls. Strengths: large study Limitations: large difference in proportion of proxy interviews between cases and controls, leading to information bias
			< 3 cups/mo	34	1.00		
			1–6 cups/wk	33	1.23 (0.71–2.13)		
			1 cup/day	33	0.70 (0.40–1.22)		
			2–3 cups/ day	124	1.11 (0.72–1.71)		
			≥ 4 cups/day	91	1.23 (0.78–1.97)		
			Coffee consumed (cups/day): women			Age, province of residence, smoking, alcohol consumption, energy intake, fat intake, number of live births	
			< 3 cups/mo	43	1.00		
			1–6 cups/wk	29	0.90 (0.52–1.57)		
			1 cup/day	40	1.00 (0.61–1.65)		
			2–3 cups/ day	85	0.81 (0.53–1.33)		
			≥ 4 cups/day	55	1.02 (0.63–1.66)		
Turati et al. (2011a) Italy, 1983–2008	Cases: 688, pooling of data from two hospital-based case–control studies in Milan (362 cases, 1983–1992) and Pordenone (326 cases, 1992–2008) Controls: 2204, hospital-based controls (admitted to the same hospitals as cases for acute conditions other than neoplasia or diseases of the digestive tract), frequency matched with cases by age and sex Exposure assessment method: questionnaire	Pancreas	*Coffee consumed (cups/day)*			Age, sex, smoking, year of enrolment, education, BMI, alcohol consumption, diabetes	Includes results from La Vecchia et al. (1987) by pooling two case–control studies. No heterogeneity by age, sex, smoking, other covariates. No association with decaffeinated coffee. Strengths: large pooled study with investigation of effect modifiers Limitations: hospital-based controls
			0	78	1.00		
			≤ 1	171	1.41 (1.02–1.94)		
			≤ 2	199	1.29 (0.94–1.77)		
			≤ 3	133	1.23 (0.88–1.72)		
			> 3	107	1.46 (1.02–2.10)		
			Continuous for 1 cup/ day	610	1.05 (0.98–1.11)		
			Trend test *P* value, 0.232				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Azeem et al. (2013) Czech Republic, 2006–2009	Cases: 309 (180 men, 129 women) from three hospitals in three regions Controls: 220 (123 men, 97 women) population-based, matched on age, sex, health status and region Exposure assessment method: questionnaire, interview, measurements of anthropometric data	Pancreas	*All types of coffee consumed*			Age, sex, smoking, BMI, education, physical activity, alcohol consumption, tea	Limitations: interviewers were not blinded, no indication of the cancer diagnosis method, response rates unknown
			0–1 cup/wk	53	1.00		
			> 1 cup/wk – 2 cups/day	202	1.02 (0.60–1.75)		
			≥ 3 cups/day	38	0.78 (0.36–1.66)		

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; FFQ, food frequency questionnaire; GI, gastrointestinal; mo, month(s); NR, not reported; NS, not significant; OR, odds ratio; RDD, random-digit dialling; SEER, Surveillance, Epidemiology and End Results; vs, versus; wk, week(s); yr, year(s)

man's consumption of coffee and other exposures was collected in a telephone interview with his wife. Coffee was not significantly associated with pancreatic cancer risk; the odds ratio for ≥ 6 cups/day versus 0 cups/day was 1.1 (95% CI, 0.5–2.4). [The Working Group noted that the deliberate use of surrogate interviewees enhanced comparability of information of cases and controls; nevertheless, both could have suffered from misclassification. This problem may have been aggravated as a result of the long period (2–4.5 years) between the times of diagnosis and interviews with spouses, who were required to recall exposure details of more than 3 years before diagnosis.]

Jain et al. (1991) described results obtained in a population-based case–control study carried out in Toronto, Canada, as part of the IARC-SEARCH programme. A quantitative diet history was used to estimate the lifetime consumption of different types of coffee for 249 cases and 505 controls. A total of 194 cases were interviewed by proxy. A proxy control was obtained for each case interviewed by proxy. Odds ratio estimates for quartiles of coffee consumption or per 100 cup-years increment showed no evidence of an association between coffee intake and pancreatic cancer risk. The odds ratio for ≥ 110 cup-years versus 0 cup-years was 0.90 (95% CI, 0.44–1.81). The odds ratio for an increment of 100 cup-years was 0.96 (95% CI, 0.77–1.19). Further analysis by type of coffee (regular, instant, caffeinated, and decaffeinated) also showed no evidence of an association.

Ghadirian et al. (1991) described results from another Canadian case–control study that was part of IARC-SEARCH. A total of 179 cases, aged 35–79 years, were diagnosed in 19 hospitals located in Greater Montreal. Population-based controls (239) matched for age, sex, and place of residence were selected by the RDD method or randomly from the telephone directory. There was an inverse association (*P* for trend, 0.53) between cumulative lifetime coffee consumption in quintiles and pancreatic cancer risk (Q5 vs Q1 OR, 0.55; 95% CI, 0.19–1.62). Similar results were evident in analyses by type of coffee consumed. The authors noted that proxy respondents reported higher amounts of total coffee intake compared with direct respondents for all subjects combined. [The Working Group noted a large difference in proportion of interviews by proxy between cases (75%) and controls (17%), leading to possible information bias.]

Bueno de Mesquita et al. (1992) conducted a case–control study on pancreatic cancer and coffee consumption in the Netherlands as part of IARC-SEARCH. Pancreatic cancer cases (alive or dead) were 35–79 years of age, newly diagnosed between 1984 and 1987, and living in the central part of the Netherlands at the time of diagnosis of cancer of the exocrine pancreas. Population-based controls were obtained from municipal population registries in the area and matched to the age–sex distribution of the cases. A quantitative diet history was used to estimate the lifetime consumption of total coffee and of different types of coffee for 176 cases and 487 controls. The results for lifetime drinking of coffee indicated an inverse dose–response association between coffee intake and risk of pancreatic cancer, with the test for trend approaching statistical significance (*P* for trend, 0.06). The odds ratio for ≥ 11 840 L coffee per life versus < 6193 L coffee per life was 0.58 (95% CI, 0.28–1.20). The suggestion of an inverse dose–response relationship with the lifetime consumption of coffee was not present in the analysis of direct responders only. [The Working Group noted that possible selection bias may have occurred due to relatively large differences in the response rate between cases and controls. The different proportions of proxy interviews between cases and controls (42% versus 29%) could also contribute to information bias.]

Lyon et al. (1992) conducted a population-based case–control study of 149 cases of cancer of the exocrine pancreas (excluding

insulinomas) and 363 controls in Utah, USA. All information was obtained from proxy respondents for cases and controls. Pancreatic cancer risk increased with the amount of coffee drunk with an odds ratio of 2.38 (95% CI, 1.16–4.85) for those having at least 50 000 lifetime cups (*P* for trend, < 0.001) compared with those having 0–2000 lifetime cups. Positive associations were also observed for users of regular and decaffeinated coffee, but were stronger in magnitude for users of decaffeinated coffee than users of regular coffee. [The Working Group noted many limitations of this study. The non-response rate among controls (23%) was higher than among cases (12%), which might have led to selection bias. Since all information was obtained from proxy respondents, it is possible that there was a difference in the type of proxy respondents available for the cases compared with the controls. Approximately 5% more spouses were available as proxies for the controls than for the cases, whereas about 7% more children or children's spouses were available as proxies for the cases than for the controls, possibly resulting in information bias.]

Zatonski et al. (1992) conducted a case–control study on the association between pancreatic cancer and coffee consumption in Poland as part of IARC-SEARCH. Of the 110 cases, 32 were interviewed directly and a proxy interview was available for 78. All 195 controls were interviewed directly following the very low acceptance rate among proxy controls found in a pilot study. Lifetime coffee drinking was estimated for total coffee and different types of coffee. Compared with never drinkers of coffee, the odds ratio of risk of pancreatic cancer for ≥ 1916 L of coffee per life was 0.48 (95% CI, 0.22–1.02). A significant trend test (*P* for trend, 0.042) was observed, which remained when the analyses were limited to directly interviewed subjects only and when consumption of tea was additionally adjusted for. [The Working Group noted a large difference in the proportion of proxy interviews between cases and controls, which may have led to information bias.]

Nishi et al. (1996) conducted a case–control study in Hokkaido, Japan, employing 141 cases with cancer of the pancreas and 282 controls (2 for each case) matched for sex, age, and place of residence. This is an update of an earlier study by Goto et al. (1990). To estimate coffee intake, cases were interviewed by a trained interviewer while a 'self-rating questionnaire' was distributed to the controls. Consumption of coffee was not significantly associated with risk of pancreatic cancer; the odds ratio for ≥ 3 versus 0 cups/day was 0.93 (95% CI, 0.44–1.96) among men and 1.37 (95% CI, 0.46–4.14) among women. [The Working Group noted that cases were interviewed but controls received a questionnaire, possibly leading to information bias. There was also limited control for confounders.]

Silverman et al. (1998) conducted a population-based case–control study of pancreatic cancer diagnosed in Atlanta, Detroit, and in 10 New Jersey counties, USA, from August 1986 to April 1989. Reliable dietary histories were obtained for 436 patients and 2003 general-population control subjects aged 30–79 years. Men who were regular coffee drinkers experienced no overall increased risk, whereas women who were regular drinkers had a non-significant 40% increased risk of pancreatic cancer as compared with non-drinkers of coffee. Among coffee drinkers, neither a gradient in risk with increasing amount of coffee consumed or increased risk with any amount of consumption was observed for either men or women.

Villeneuve et al. (2000) conducted a population-based case–control study of pancreatic cancer diagnosed in eight Canadian provinces as part of the Canadian National Enhanced Cancer Surveillance System (NECSS) project. Cases (n = 583) aged 30–76 years were identified from eight provincial cancer registries. Population-based controls (4813), frequency-matched for age and sex, were selected from health insurance

plans using stratified random sampling or RDD, depending on province. Coffee intake was estimated using a FFQ. Among cases, 24% were proxy interviews with next of kin; among controls the corresponding percentage was 0. Coffee intake was not significantly associated with pancreatic cancer risk in either men or women. The odds ratio for ≥ 4 cups/day versus < 3 cups/month in men was 1.23 (95% CI, 0.78–1.97); in women the respective association was 1.02 (95% CI, 0.63–1.66). [The Working Group noted a large difference in proportion of proxy interviews between cases and controls, which may have led to information bias.]

Azeem et al. (2013) conducted a population-based case–control study (529 subjects, 303 men and 226 women, period of study 2006–2009) of lifestyle factors and risk of pancreatic cancer in the Czech Republic. Newly diagnosed cases of pancreatic cancer (n = 309) were recruited from three hospitals. [The Working Group noted that no information on how the diagnosis of pancreatic cancer was established was provided.] Controls (n = 220) were a population-based sample of individuals from the same regions as cases. After adjustment for other factors, no trend was observed with respect to the amount of coffee consumption for ≥ 3 cups/day compared with 0 to ≤ 1 cup/week (OR, 0.78; 95% CI, 0.36–1.66).

(b) Hospital-based case–control studies

MacMahon et al. (1981a, b; the latter study was reported in a letter) reported on a case–control study of 367 (216 men, 151 women) subjects with cancer of the pancreas (excluding islet cell tumours) under 80 years of age identified in 11 hospitals in Boston and Rhode Island, USA, and 644 controls who had been at hospital for other diseases at the same time as the cases. Each case and control pair was interviewed personally by the same physician. Compared with non-drinkers of coffee, the relative risks for those drinking 1–2 cups/day and ≥ 3 cups/day were 1.8 (95% CI, 1.0–3.0) and 2.7 (95% CI, 1.6–4.7), respectively (P for trend, 0.001). Elevated relative risks were also reported among men and women separately, but these estimations were not adjusted for smoking. [The Working Group noted that many controls had gastrointestinal problems, meaning that subjects may have reduced their coffee intake to relieve symptoms. For this reason, the Working Group judged that the observed positive associations might have been spurious effects due to selection bias.]

A study (part of a larger study of tobacco-related cancers in six US cities) of 275 histologically verified cases (153 men, 122 women) aged 20–80 years, interviewed during 1977–1981, and of 7994 hospital controls reported null associations between risk of pancreatic cancer and coffee intake (Wynder et al., 1983). Controls were patients with diseases not related to tobacco. Personal interviews were carried out within 6 months of diagnosis. The study found no association between coffee consumption and pancreatic cancer. [The Working Group noted that the low response rate among cases and controls may have resulted in selection bias.]

Kinlen & McPherson (1984) re-evaluated data from the case–control study of Stocks (partly reported by Stocks, 1957) collected from hospitals in north-western England and north Wales during 1952–1954, including 216 cases (109 men, 107 women) aged > 40 years. These were compared with 432 controls who were patients with other cancers in the original study matched for age, sex, and area of residence; patients with cancers of the lung, bladder, mouth, pharynx, oesophagus, gastrointestinal tract, and ovary were excluded. No association between pancreatic cancer risk and coffee consumption was found either before or after adjustment for smoking.

A case–control study by Falk et al. (1988), based on 363 incident cases (203 men, 160 women) and 1234 hospital controls, was carried out in Louisiana, USA. Control subjects were matched for hospital, age, sex, and race. Patients with cancer, diabetes, circulatory disorders, and

digestive or respiratory diseases were excluded from the pool of potential controls. Direct interviews were carried out with 50% of cases and 50% were with next of kin. For controls, direct interviews were with 13%. No association was found between coffee drinking (any amount) and risk of pancreatic cancer for men or women after adjusting for age, residence, smoking, alcohol, fruit consumption, diabetes, and income. [The Working Group noted the high proportion of proxy interviews, especially among controls.]

Clavel et al. (1989) conducted a hospital-based interview study in Paris, France, with 161 cases of cancer of the pancreas (98 men, 63 women) during 1982–1985. There were 268 hospital controls, 129 of which had other cancers (excluding biliary, liver, stomach, oesophagus, respiratory, and bladder cancers) and 139 of which had non-neoplastic disease. All were matched to cases for age, sex, hospital, and interviewer. None of the cases and about 5% of controls refused to participate. After adjustment for education, alcohol, and smoking, a non-significant trend for pancreatic cancer was observed among men with a relative risk of 2.08 for ≥ 4 cups/day compared with 0 cups/day (95% CI, 0.49–8.86). In women, the respective trend was statistically significant and the corresponding relative risk was 9.56 (95% CI, 1.29–70.71). [The Working Group noted that unusually high relative risks were seen in women and in persons who had never drunk alcohol, possibly due to interview bias from publicity about the topic.]

A study of 216 cases of cancer of the pancreas (123 men, 93 women) and 279 controls was carried out in the UK during 1983–1986 (Cuzick & Babiker, 1989) based on personal interviews. The controls included 212 hospital controls without cancers or other chronic medical conditions, and the remaining 67 were population-based controls. The study reported essentially null associations between pancreatic cancer risk and coffee consumption, although a slightly elevated risk was seen in cases whose current consumption was ≥ 5 cups/day (RR, 1.4) as compared with 0 cups/day. This trend disappeared when coffee consumption approximately 10 years before the interview was examined.

Partanen et al. (1995) conducted a case–control study using pancreatic cancer deaths as cases and patients with cancers other than that of the pancreas as controls during 1984–1987 in Finland, a country with very high coffee consumption. Cases and controls were identified from the Finnish Cancer Registry: 662 endocrine pancreas cancer cases and 1770 controls (1014 stomach, 441 colon, and 315 rectum cancer). Using a mail questionnaire, data on coffee consumption 20 years before diagnosis were obtained from next of kin. There was no association between coffee consumption and pancreatic cancer mortality; the odds ratio for those drinking > 6 cups/day compared with never/occasional coffee drinkers was 0.71 (95% CI, 0.41–1.20). Odds ratios were lower (but non-significant) when rectum cancers were used as controls only, as opposed to colon cancer controls only (ORs close to 1).

Turati et al. (2011a) performed a pooled analysis of two earlier case–control studies from northern Italy, conducted between 1983 and 2008, including a total of 688 cases of cancer of the pancreas and 2204 hospital controls with acute, non-neoplastic diseases. The first study, conducted during 1983–1992 in Milan, included 362 incident cases of pancreatic cancer (229 men, 133 women) and 1552 controls and is an update of an earlier study by La Vecchia et al. (1987) and Soler et al. (1998). The second study, conducted between 1992 and 2008 in Milan and Pordenone, northern Italy, included 326 incident cases (174 men, 152 women) and 652 controls, frequency-matched with cases by age and sex (Rossi et al., 2010). In both studies, controls were admitted to the same network of hospitals as cases for a wide spectrum of acute conditions other than neoplasia or diseases of the digestive tract. Less than 5% of cases and controls refused to participate in the interview. Cases

and controls were interviewed using a structured questionnaire regarding frequency of coffee consumption. Compared with non-drinkers of coffee, the odds ratio for coffee drinkers was 1.34 (95% CI, 1.01–1.77). The odds ratio for those drinking > 3 cups/day was 1.46 (95% CI, 1.02–2.10) compared with coffee non-drinkers. However, there was no trend in risk of pancreatic cancer with respect to dose (cups/day) (*P* for trend, 0.232). The odds ratio for an increment of 1 cup/day was 1.05 (95% CI, 0.98–1.11). There was no heterogeneity in the apparent associations in strata defined by age, sex, and other covariates, including tobacco smoking. No association emerged for drinkers of decaffeinated coffee compared with non-drinkers of decaffeinated coffee (OR, 0.87; 95% CI, 0.60–1.26).

2.2.3 Meta-analyses

Meta-analyses of cohort studies on the association between coffee consumption and cancer of the pancreas were conducted by Dong et al. (2011), Yu et al. (2011), and Ran et al. (2016); these meta-analyses included studies that did not adjust for smoking, however, and also excluded several studies. Because of the shortcomings of these meta-analyses, the Working Group focused on the more rigorous meta-analysis by Turati et al. (2012).

Turati et al. (2012) conducted a meta-analysis on the association between coffee consumption and pancreatic cancer risk, using data from case–control and cohort studies that were published until March 2011. They identified 37 case–control and 17 cohort studies (10 594 cases) as eligible for meta-analysis. Random-effects models were used. When only smoking-adjusted studies were considered, 22 case–control studies and 15 cohort studies were suitable for meta-analysis. Among the smoking-adjusted studies, Turati et al. estimated pooled relative risks of pancreatic cancer for high versus low coffee consumption of 1.10 (95% CI, 0.92–1.31) for case–control studies, 1.04 (95% CI, 0.80–1.36) for cohort studies, and 1.08 (95% CI, 0.94–1.25) for all studies, with significant between-study heterogeneity ($P = 0.002$). This heterogeneity was not explained by study design, sex, or geographic location. The summary relative risk was 1.00 (95% CI, 0.83–1.19) for men and 1.15 (95% CI, 0.94–1.41) for women when combining all smoking-adjusted studies (*P* heterogeneity between sexes, 0.312). Per increment of 1 cup/day of coffee based on the smoking-adjusted studies, the summary relative risk was 1.04 (95% CI, 1.00–1.09) for case–control studies and 1.00 (95% CI, 0.95–1.05) for cohort studies. The authors estimated a weak positive association between coffee consumption and pancreatic cancer risk when combining case–control studies that were not adjusted for tobacco, which can be attributed to residual confounding by smoking.

2.3 Cancer of the liver

A total of 14 cohort and 11 case–control studies that examined the association between coffee consumption and the risk of cancer of the liver were available for review by the Working Group.

Regarding the cohort studies, seven were conducted in Japan, three in the US, three in Europe, and one in Singapore. Among these 14 cohort studies, 11 focused on incidence (Inoue et al., 2005, 2009; Shimazu et al., 2005; Hu et al., 2008; Ohishi et al., 2008; Johnson et al., 2011; Lai et al., 2013; Aleksandrova et al., 2015; Bamia et al., 2015; Petrick et al., 2015; Setiawan et al., 2015) and 3 focused on mortality (Kurozawa et al., 2004, 2005; Wakai et al., 2007). Inoue et al. (2005, 2009) reported findings from the same prospective cohort study, but the latter study (Inoue et al., 2009) reported the results from a subcohort with information on hepatitis C virus (HCV) and hepatitis B virus (HBV) status. Kurozawa et al. (2004, 2005) and Wakai et al. (2007) also reported results derived from the same study population; the latter (Wakai

et al., 2007) used a nested case–control analysis. Likewise, Bamia et al. (2015) and Aleksandrova et al. (2015) reported results derived from the same population; the latter used a nested case–control study analysis. Johnson et al. (2011) and Lai et al. (2013) reported results for both cohort and nested case–control analysis. Petrick et al. (2015) reported results from a pooled analysis of the cohort studies. One pooled analysis of US cohorts analysed the risk by histological subtypes, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma (Petrick et al., 2015).

Case–control studies were conducted in various countries: three studies in Italy, one in Greece, one in Italy and Greece, two in Japan, and one each in Serbia, the Republic of Korea, Hong Kong Special Administrative Region, and India. All studies except one (Tanaka et al., 2007) were hospital-based. Tanaka et al. (2007) included both population-based and hospital-based control groups.

The Working Group also reviewed seven meta-analyses of coffee drinking and cancer of the liver.

A cohort study (Kurozawa et al., 2004) reporting coffee consumption and risk of hepatocellular carcinoma (HCC) mortality by sex and age group has been excluded from this review; the results were derived from univariate analysis with no adjustment for other risk factors, and the results controlling for confounding factors were reported in another paper by Kurozawa et al. (2005). One case–control study (Kanazir et al., 2010) was also excluded from this review because it did not adjust for any covariates.

2.3.1 Cohort studies

See Table 2.5.

Inoue et al. (2005) investigated the association between coffee consumption and incidence of HCC among 90 452 Japanese (43 109 men and 47 343 women) aged 40–69 years at baseline in the JPHC-based prospective study, which began during 1990–1994. Information on coffee drinking was obtained by self-reported questionnaire at baseline. After adjusting for potential confounders, those who consumed coffee on a daily basis had a lower risk of HCC than non-drinkers (HR, 0.49; 95% CI, 0.36–0.66). The risk decreased with the amount of coffee consumed; compared with non-drinkers, the hazard ratio for drinking 1–2 cups/day was 0.52 (95% CI, 0.38–0.73), for 3–4 cups/day 0.48 (95% CI, 0.28–0.83), and for ≥ 5 cups/day 0.24 (95% CI, 0.08–0.77). The *P* value for trend was < 0.001. The inverse association persisted when the participants were stratified by age, smoking, alcohol intake, green vegetable intake, green tea intake, and history of chronic liver disease. Similar associations were observed when the analysis was restricted to HCV+ or HBV+ cases. [The strengths of this study were its prospective design and large scale. Limitations included the facts that consumption was self-reported, changes in coffee consumption were not considered, and the HCV/HBV status of controls was not available.]

Kurozawa et al. (2005) examined the association between coffee drinking and HCC mortality in the JACC Study. In total, 110 688 men and women aged 40–79 years were grouped by coffee intake categories. Information on habitual coffee consumption was obtained by self-reported questionnaire at baseline. On adjusting for potential confounders, including history of diabetes, liver diseases, and alcohol consumption, the hazard ratio of HCC mortality for drinkers of ≥ 1 cups/day of coffee compared with non-coffee drinkers was 0.50 (95% CI, 0.31–0.79); the hazard ratio for drinkers of < 1 cup/day was 0.83 (95% CI, 0.54–1.25). [The strengths of this study were its large scale and prospective design. Limitations included the absence of HCV and HBV markers.]

Shimazu et al. (2005) examined the association between coffee consumption and the risk of cancer of the liver in a pooled analysis of

Table 2.5 Cohort studies on cancer of the liver and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Inoue et al. (2005) Japan, 1990–1994 to 2001	90 452 (43 109 men and 47 343 women), JPHC Study subjects aged 40–69 yr, 11 public health centre-based areas, residential register Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption: men and women*			Sex, age, study area, smoking, alcohol drinking, green vegetable intake, green tea drinking	Strengths: prospective, large scale Limitations: self-report, change not considered, HCV, HBV status of controls unknown
			Almost never	161	1.00		
			1–2 days/wk	65	0.75 (0.56–1.01)		
			3–4 days/wk	36	0.79 (0.55–1.14)		
			Almost everyday	72	0.49 (0.36–0.66)		
			1–2 cups/day	54	0.52 (0.38–0.73)		
			3–4 cups/day	15	0.48 (0.28–0.83)		
			≥ 5 cups/day	3	0.24 (0.08–0.77)		
			Trend test *P* value, < 0.001				
			Coffee consumption: men				
			Almost never	116	1.00		
			1–2 days/wk	43	0.74 (0.52–1.05)		
			3–4 days/wk	27	0.76 (0.50–1.16)		
			Almost everyday	59	0.49 (0.35–0.69)		
			1–2 cups/day	45	0.55 (0.38–0.80)		
			3–4 cups/day	11	0.41 (0.21–0.77)		
			≥ 5 cups/day	3	0.27 (0.09–0.87)		
			Trend test *P* value, < 0.001				
			Coffee consumption: women				
			Almost never	45	1.00		
			1–2 days/wk	17	0.77 (0.43–1.37)		
			3–4 days/wk	9	0.89 (0.43–1.84)		
			Almost everyday	13	0.48 (0.25–0.92)		
			1–2 cups/day	9	0.43 (0.20–0.90)		
			3–4 cups/day	4	0.89 (0.31–2.59)		
			≥ 5 cups/day	0	–		
			Trend test *P* value, 0.042				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Inoue et al. (2005) (cont.)			*Coffee consumption: HCC with HCV+, men and women combined*				
			Almost never	86	1.00		
			1–2 days/wk	26	0.59 (0.38–0.91)		
			3–4 days/wk	15	0.66 (0.38–1.16)		
			Almost everyday	37	0.57 (0.37–0.86)		
			1–2 cups/day	29	0.64 (0.41–0.99)		
			3–4 cups/day	6	0.42 (0.18–0.99)		
			≥ 5 cups/day	2	0.34 (0.08–1.41)		
			Trend test *P* value, 0.005				
			Coffee consumption: HCC with HBV+, men and women combined (60 cases)				
			Almost never	24	1.00		
			1–2 days/wk	9	0.66 (0.31–1.43)		
			3–4 days/wk	9	1.14 (0.52–2.47)		
			Almost everyday	18	0.60 (0.31–1.18)		
			1–2 cups/day	12	0.56 (0.26–1.21)		
			3–4 cups/day	5	0.81 (0.30–2.22)		
			≥ 5 cups/day	1	0.39 (0.05–2.98)		
			Trend test *P* value, 0.231				
			Coffee consumption: no history of CLD				
			Almost never	NR	1.00		
			1–2 days/wk	NR	0.85 (0.59–1.24)		
			3–4 days/wk	NR	1.15 (0.76–1.74)		
			Almost everyday	NR	0.45 (0.3–0.67)		
			1–2 cups/day	NR	0.46 (0.29–0.72)		
			3–4 cups/day	NR	0.52 (0.26–1.05)		
			≥ 5 cups/day	NR	0.15 (0.02–1.05)		
			Trend test *P* value, < 0.001				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Inoue et al. (2005) (cont.)			*Coffee consumption: history of CLD*				
			Almost never	NR	1.00		
			1–2 days/wk	NR	0.79 (0.48–1.30)		
			3–4 days/wk	NR	0.44 (0.18–1.11)		
			Almost everyday	NR	0.91 (0.58–1.41)		
			1–2 cups/day	NR	0.99 (0.61–1.61)		
			3–4 cups/day	NR	0.71 (0.31–1.67)		
			≥ 5 cups/day	NR	0.76 (0.18–3.16)		
			Trend test *P* value, 0.432				
Kurozawa et al. (2005) Japan, 1988–1990, follow-up until 1999	110 688 (46 399 men, 64 289 women), JACC Study, subjects aged 40–79 yr Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day)*			Age, sex, education, history of diabetes and liver disease, smoking and alcohol habits	Strengths: large-scale, prospective design Limitations: absence of HCV and HBV markers
			All subjects				
			Non-drinkers	103	1.00		
			< 1	57	0.83 (0.54–1.25)		
			≥ 1	98	0.50 (0.31–0.79)		
			Trend test *P* value, 0.007				
			Coffee consumption (cups/day): men			Age, education, history of diabetes and liver disease, smoking and alcohol habits	
			Men				
			Non-drinkers	66	1.00		
			< 1	41	0.91 (0.57–1.45)		
			≥ 1	71	0.49 (0.28–0.85)		
			Trend test *P* value, 0.007				
			Coffee consumption (cups/day): women				
			Non-drinkers	37	1.00		
			< 1	16	0.64 (0.27–1.51)		
			≥ 1	27	0.51 (0.20–1.31)		
			Trend test *P* value, 0.141				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kurozawa et al. (2005) (cont.)			*Coffee consumption (cups/day): with history of liver diseases*			Age, sex, education, history of diabetes, smoking and alcohol habits	
			Non-drinkers	62	1.00		
			< 1	35	0.94 (0.53–1.66)		
			≥ 1	54	0.44 (0.22–0.88)		
			Trend test *P* value, 0.028				
			Coffee consumption (cups/day): without history of liver diseases				
			Non-drinkers	41	1.00		
			< 1	22	0.79 (0.44–1.41)		
			≥ 1	44	0.61 (0.32–1.16)		
			Trend test *P* value, 0.113				
Shimazu et al. (2005) Japan (Miyagi): (1) 1984–1992 and (2) 1990–1997	Cohort 1: 22 404 (10 588 men and 11 816 women), aged ≥ 40 yr Cohort 2: 38 703 (18 869 men, 19 834 women), aged 40–64 yr Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day): cohort 1*			Age, sex, history of liver disease, alcohol consumption, smoking status	Strengths: prospective, large scale Limitations: no information on HBV and HCV infection status, DCO cases possibility of misclassifying secondary metastasis to liver, former drinkers not distinguishable from non-drinkers
			Never	29	1.00		
			Occasionally	25	0.56 (0.33–0.97)		
			≥ 1	16	0.53 (0.28–1.00)		
			Trend test *P* value, 0.038				
			Coffee consumption (cups/day): cohort 2				
			Never	12	1.00		
			Occasionally	21	1.05 (0.52–2.16)		
			≥ 1	14	0.68 (0.31–1.51)		
			Trend test *P* value, 0.3				
			Coffee consumption (cups/day): pooled				
			Never	41	1.00		
			Occasionally	46	0.71 (0.46–1.09)		
			≥ 1	30	0.58 (0.36–0.96)		
			Trend test *P* value, 0.024				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wakai et al. (2007) Japan, 1988–1990	Cases: 96 of HCC mortality, identified from death certificates Controls: 420 HCV+ and 3024 HCV– controls, matched for age, sex, HCV-antibody seropositivity Exposure assessment method: questionnaire; rank correlation $r^2 = 0.79$	Liver/HCC	*Coffee consumption (cups/day): total*			Area, smoking and drinking habits, history of diabetes mellitus and liver diseases	Strengths: nested case–control design (as part of JACC) Limitations: mortality not incidence, coffee intake at baseline only
			Total				
			Non-drinkers	44	1.00		
			< 1	34	0.77 (0.45–1.32)		
			≥ 1	18	0.49 (0.25–0.96)		
			Trend test *P* value, 0.038				
			Coffee consumption (cups/day): HCV-Ab-positive				
			Non-drinkers	28	1.00		
			< 1	23	0.91 (0.41–2.04)		
			≥ 1	9	0.31 (0.11–0.85)		
			Trend test *P* value, 0.031				
			Coffee consumption (cups/day): HCV-Ab-negative				
			Non-drinkers	16	1.00		
			< 1	11	0.65 (0.29–1.46)		
			≥ 1	9	0.75 (0.29–1.92)		
			Trend test *P* value, 0.45				
Hu et al. (2008) Finland, 1972–2006	60 323; seven independent cross-sectional surveys in six geographic areas Exposure assessment method: questionnaire	Liver/HCC	*Daily coffee consumption (cups/day)*			Adjusted for age, sex, study year, alcohol consumption, education, smoking, diabetes, and CLD	Strengths: large-scale population-based, prospective, long follow-up (19.3 yr) Limitations: self-report only at baseline, impossible to assess caffeine intake, no data on HBV or HCV, residual confounding
			Total	128	–		
			0–1	20	1.00		
			2–3	30	0.66 (0.37–1.16)		
			4–5	33	0.44 (0.25–0.77)		
			6–7	28	0.38 (0.21–0.69)		
			≥ 8	17	0.32 (0.16–0.62)		
			Trend test *P* value, 0.003				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hu et al. (2008) (cont.)			*Daily coffee consumption (cups/day): men (82 cases)*				
			0–1	16	1.00		
			2–3	21	0.68 (0.35–1.31)		
			4–5	17	0.35 (0.18–0.71)		
			6–7	15	0.31 (0.15–0.63)		
			≥ 8	13	0.28 (0.13–0.61)		
			Trend test *P* value, 0.001				
			Daily coffee consumption (cups/day): women (46 cases)				
			0–1	4	1.00		
			2–3	9	0.62 (0.19–2.04)		
			4–5	16	0.60 (0.20–1.82)		
			6–7	13	0.58 (0.19–1.82)		
			≥ 8	4	0.41 (0.10–1.70)		
			Trend test *P* value, 0.82				
Ohishi et al. (2008) Japan, 1969–2002	Cases: 224 HCC identified from Hiroshima and Tissue Registry and Nagasaki Cancer Registry Controls: 644 matched from the cohort by sex, age, city, time of serum storage, method for serum storage and radiation exposure Exposure assessment method: questionnaire	Liver/HCC	*Coffee intake frequency*			Hepatitis virus infection, alcohol consumption, smoking, BMI, diabetes mellitus, radiation dose of the liver	Strengths: prospective, nested case–control, HCV and HBV infection considered Limitations: severity of liver fibrosis could not be considered
			Never	187	1.00		
			Daily	37	0.40 (0.16–1.02)		
			Trend test *P* value, 0.055				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Inoue et al. (2009) Japan, 1993–2006	18 815; JPHC Cohort II Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day): total (110 cases)*			Sex, age, area, smoking, alcohol drinking, green tea intake, BMI, history of diabetes, serum ALT, HCV and HBV infection status	Strengths: prospective analysis with blood samples Limitations: relatively small number of cases
			Almost never	67	1.00		
			< 1	35	0.67 (0.42–1.07)		
			1–2	18	0.49 (0.27–0.91)		
			≥ 3	6	0.54 (0.21–1.39)		
			Trend test *P* value, 0.025				
			Coffee consumption (cups/day): HCV+ and/or HBV+ (92 cases)				
			Almost never	43	1.00		
			< 1	28	0.55 (0.33–0.93)		
			1–2	15	0.47 (0.24–0.93)		
			≥ 3	6	0.61 (0.23–1.62)		
			Trend test *P* value, 0.036				
			Coffee intake (cups/day): HCV+ (80 cases)				
			Almost never	38	1.00		
			< 1 cup/day	24	0.56 (0.32–0.99)		
			1–2 cups/day	12	0.40 (0.18–0.88)		
			≥ 3 cups/day	6	0.78 (0.28–2.15)		
			Trend test *P* value, 0.065				
Johnson et al. (2011) Singapore, 1993–1998 to 2006	63 257 Chinese aged 45–74 yr Exposure assessment method: 165-item FFQ	Liver/HCC	*Coffee consumption (cups/day)*			Age, sex, dialect group, years of recruitment, BMI, education, consumption of alcohol beverages, cigarette smoking, black tea and green tea intake, and history of diabetes	Strengths: prospective with blood samples (in part) Limitations: lack of HBV and HCV status for all participants, participants not examined for liver damage at baseline; relatively small number of cases
			Non-drinkers	69	1.00		
			0 to < 1	38	0.94 (0.63–1.40)		
			1 to < 2	149	1.17 (0.87–1.56)		
			2 to < 3	92	0.78 (0.56–1.07)		
			≥ 3	14	0.56 (0.31–1.00)		
			Trend test *P* value, 0.05				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Johnson et al. (2011) Singapore, 1993–1998 to 2006	Cases: 92 HCC by national cancer registry Controls: 276 individually matched by sex, dialect group, age at enrolment, date of baseline interview and date of biospecimen collection (± 6 mo) Exposure assessment method: 165-item FFQ	Liver/HCC	*Coffee consumption (cups/day)* Non-drinkers 0 to < 1 1 to < 2 2 to < 3 ≥ 3 Trend test *P* value, 0.71	 17 11 34 28 2	 1.00 0.77 (0.26–2.29) 0.84 (0.38–1.85) 1.32 (0.56–3.14) 0.23 (0.05–1.21)	Age, sex, dialect group, years of recruitment, BMI, education, consumption of alcohol beverages, cigarette smoking, black tea and green tea intake, history of diabetes, and HBV/ HCV infection status	Case–control analysis of a subset of the cohort Strengths: nested case–control, prospective HBV and HCV information available Limitations: participants were not examined for liver damage at baseline, relatively small number of cases
Lai et al. (2013) Finland, 1985–1988, follow-up to December 2009	27 037; ATBC study male smokers aged 50–69 yr Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day)* Never drinker > 0 to < 1 1 to < 2 2 to < 3 3 to < 4 ≥ 4 Unit change (per cups/day) Trend test *P* value, 0.0007	 9 36 60 47 22 20 NR	 1.00 1.35 (0.65–2.82) 0.73 (0.48–1.12) 0.52 (0.33–0.82) 0.45 (0.26–0.78) 0.53 (0.30–0.95) 0.82 (0.73–0.93)	Intervention arm, age, BMI, education, marital status, history of diabetes, smoking, alcohol consumption, serum cholesterol	Strengths: prospective study, long follow-up Limitations: HCV/ HBV status available for subset only

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lai et al. (2013) (cont.)			*Coffee consumption, filtered method (cups/day)*			Type of coffee, ATBC intervention arm, age, BMI, education, marital status, history of diabetes, smoking, alcohol consumption, serum cholesterol	
			> 0 to < 1	16	1.00		
			1 to < 2	34	0.80 (0.44–1.47)		
			2 to < 3	26	0.54 (0.29–1.03)		
			3 to < 4	9	0.34 (0.15–0.78)		
			≥ 4	12	0.61 (0.28–1.34)		
			Unit increase (per cups/day)	NR	0.82 (0.69–0.98)		
			Trend test *P* value, 0.03				
			Coffee consumption, boiled method (cups/day)				
			> 0 to < 1	7	1.00		
			1 to < 2	10	0.60 (0.23–1.57)		
			2 to < 3	5	0.25 (0.08–0.80)		
			3 to < 4	7	0.60 (0.21–1.75)		
			≥ 4	4	0.40 (0.12–1.40)		
			Unit increase (per cups/day)	NR	0.85 (0.65–1.11)		
			Trend test *P* value, 0.19				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bamia et al. (2015) Europe (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, UK) 1992–2000 to 2004–2008	486 799; EPIC Study Exposure assessment method: questionnaire	Liver/HCC	*Coffee intake, quintiles (mL/day)*			Sex, diabetes, education, BMI, smoking, physical activity, alcohol intake, energy intake, tea intake	Stratified for age at recruitment and centre. Strengths: cohort design, multicentre coverage to examine variable range of intake across European countries, validated questionnaire, relatively long follow-up Limitations: modest number of HCC cases, lack of data on brewing methods
			Q1 (M: 0–83.3; F: 0–60)	47	1.00		
			Q2 (M: 83.3–200.4; F: 60–191.9)	49	0.85 (0.56–1.29)		
			Q3 (M: 200.5–476.9; F: 191.9–375)	38	0.63 (0.39–1.02)		
			Q4 (M: 477.2–830.4; F: 375–580.2)	36	0.49 (0.29–0.82)		
			Q5 (M 831.3–4500; F: 580.3–6250)	31	0.28 (0.16–0.50)		
			Trend test *P* value, < 0.001				
Petrick et al. (2015) USA, 1992–1995, 2007–2010 or variable	1 212 893; Liver Cancer Pooling Project (LCPP), USA-based NCI cohort consortium comprising NIH-AARP, AHS, USRTS, PLCO, WHS, CPS-II, IWHS, BWHS, WHI Exposure assessment method: questionnaire	Liver/HCC	*Coffee consumption (cups/day)*			Sex, age, race, cohort, BMI, smoking status, cigarette smoking intensity, alcohol, *P*-value for trend of continuous variables	Strengths: large sample size allowed stratifying by caffeine content of coffee and sex, histological subtype of liver cancer (HCC and ICC) Limitations: number of ICC limited
			Non-drinker	85	1.00		
			Ever	650	1.00 (0.79–1.27)		
			> 0 to < 1	138	1.24 (0.94–1.64)		
			1 to < 2	149	1.16 (0.88–1.52)		
			2–3	255	0.89 (0.68–1.15)		
			> 3	97	0.73 (0.53–0.99)		
			Continuous	NR	0.90 (0.85–0.94)		
			Trend test *P* value, < 0.0001				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petrick et al. (2015) (cont.)			*Coffee consumption (cups/day): men (530)*			Age, race, cohort, BMI, smoking status, cigarette smoking intensity, alcohol, *P*-value for trend of continuous variable	
			Non-drinker	40	1.00		
			Ever	490	1.21 (0.87–1.69)		
			> 0 to < 1	113	1.57 (1.09–2.25)		
			1 to < 2	103	1.35 (0.93–1.95)		
			2–3	195	1.06 (0.75–1.51)		
			> 3	79	0.93 (0.63–1.37)		
			Continuous (cups/day)	NR	0.90 (0.86–0.96)		
			Trend test *P* value, 0.0004				
			Coffee consumption (cups/day): women (205)				
			Non-drinker	45	1.00		
			Ever	160	0.78 (0.56–1.10)		
			> 0 to < 1	25	0.79 (0.47–1.33)		
			1 to < 2	46	1.01 (0.66–1.53)		
			2–3	60	0.71 (0.48–1.06)		
			> 3	18	0.46 (0.26–0.81)		
			Continuous (cups/day)	NR	0.87 (0.79–0.96)		
			Trend test *P* value, 0.004				
			Caffeinated coffee (cups/day)			Sex, age, race, cohort, BMI, smoking status, cigarette smoking intensity, alcohol, *P* value for trend of continuous variables	
			Non-drinker	85	1.00		
			Ever	379	1.00 (0.77–1.28)		
			> 0 to < 1	58	1.22 (0.87–1.73)		
			1 to < 2	85	1.19 (0.87–1.62)		
			2–3	174	0.95 (0.72–1.26)		
			> 3	62	0.71 (0.50–1.01)		
			Trend test *P* value, 0.002				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petrick et al. (2015) (cont.)			*Decaffeinated coffee (cups/day)*				
			Non-drinker	85	1.00		
			Ever	204	1.16 (0.88–1.53)		
			0	63	1.00		
			> 0 to < 1	58	1.33 (0.92–1.91)		
			1 to < 2	51	1.38 (0.95–2.02)		
			2–3	64	0.97 (0.67–1.40)		
			> 3	21	0.92 (0.55–1.54)		
			Trend test *P* value, 0.1				
		Liver and bile ducts: ICC	*Coffee consumption (cups/day)*				
			Non-drinker	33	1.00		
			Ever	199	0.93 (0.63–1.37)		
			> 0 to < 1	36	1.15 (0.70–1.89)		
			1 to < 2	33	0.79 (0.48–1.30)		
			2–3	85	0.93 (0.61–1.42)		
			> 3	40	1.00 (0.61–1.63)		
			Continuous, cups/day	NR	1.00 (0.92–1.08)		
			Trend test *P* value, 0.9				
			Caffeinated coffee (cups/day)				
			Non-drinker	33	1.00		
			Ever	119	0.91 (0.60–1.37)		
			0	33	1.00		
			> 0 to < 1	17	1.32 (0.71–2.43)		
			1 to < 2	15	0.59 (0.32–1.10)		
			2–3	57	0.91 (0.58–1.43)		
			> 3	30	1.08 (0.63–1.83)		
			Trend test *P* value, > 0.99				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Petrick et al. (2015) (cont.)			*Decaffeinated coffee (cups/day)*				
			Non-drinker	33	1.00		
			Ever	56	0.95 (0.59–1.53)		
			0	18	1.00		
			> 0 to < 1	15	1.17 (0.58–2.35)		
			1 to < 2	10	0.94 (0.43–2.07)		
			2–3	20	1.11 (0.56–2.17)		
			> 3	6	1.03 (0.39–2.70)		
			Trend test *P* value, 0.6				
Setiawan et al. (2015) USA, 1993–1996, 18 yr follow-up	162 022; multiethnic cohort (MEC) study, Hawaii and California Exposure assessment method: questionnaire	Liver/HCC	*Regular coffee (cups/day)*			Age, sex, ethnicity, education, BMI, alcohol intake, smoking status, diabetes	Strengths: prospective, long follow-up time, multiethnic and large sample size, confounder adjustment Limitations: coffee assessment by single self-report, lack of information on liver disease other than HCC, no information on HBV/HCV status
			Never	119	1.00		
			< 1	111	1.14 (0.88–1.48)		
			1	137	0.87 (0.67–1.11)		
			2–3	67	0.62 (0.46–0.84)		
			≥ 4	17	0.59 (0.35–0.99)		
			Trend test *P* value, 0.002				
			Decaffeinated coffee (cups/day)				
			Never	287	1.00		
			< 1	128	0.87 (0.70–1.08)		
			≥ 2	21	0.86 (0.55–1.34)		
			Trend test *P* value, 0.2				

Ab, antibody; AHS, Agricultural Health Study; ALT, alanine transaminase; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index; BWHS, Black Women's Health Study; CI, confidence interval; CLD, chronic liver disease; CPS-II, Cancer Prevention Study-II; DCO, death certificate only; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICC, intrahepatic cholangiocarcinoma; IWHS, Iowa Women's Health Study; JACC Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective; LCPP, Liver Cancer Pooling Project; M, male; MEC, multiethnic cohort; mo, month(s); NIH-AARP, National Institutes of Health–American Association of Retired Persons; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; USRTS, United States Radiologic Technologists Study; WHI, Women's Health Initiative; WHS, Women's Health Study; wk, week(s); yr, year(s)

data available from two cohort studies based in Miyagi, Japan. A self-administered questionnaire regarding the frequency of coffee consumption and other health habits was distributed to 22 404 women and men in Cohort 1 and 38 703 subjects in Cohort 2. After adjustment for age, sex, history of liver disease and diabetes, alcohol consumption, and smoking status, the pooled hazard ratios (95% CI) of drinking coffee occasionally and ≥ 1 cups/day compared with never were 0.71 (0.46–1.09) and 0.58 (0.36–0.96) (*P* for trend, 0.024). [The strengths of this study were its prospective design and large scale. Limitations included: the lack of information regarding HBV and HCV infection status; death certificate only (DCO) cases meant it was possible to misclassify secondary metastasis as cancer of the liver; and former drinkers were not distinguished from non-drinkers.]

Wakai et al. (2007) examined HCC mortality in relation to coffee consumption and anti-HCV antibody (Ab) seropositivity. This study was carried out in Japan as a nested case–control study as part of the JACC Study previously reported by Kurozawa et al. (2005). The analyses involved 96 HCC mortality cases with serum samples. Among 39 242 subjects donating blood samples at baseline, controls were matched for age, sex, and HCV-Ab seropositivity. Habitual coffee consumption was assessed by self-reported questionnaire at baseline. Coffee drinking was significantly associated with a decreased risk of death from HCC. After adjustment, including for history of diabetes and liver disease, odds ratios (95% CI) for daily coffee drinkers versus non-drinkers were 0.49 (0.25–0.96), 0.31 (0.11–0.85), and 0.75 (0.29–1.92) for total subjects, HCV-Ab-positive subjects and HCV-Ab-negative subjects, respectively. The increased risk observed among HCV-Ab-positive individuals with significant trend (*P* for trend, 0.031) was not observed among HCV-Ab-negative individuals. [The main strength of this study was its nested case–control design. Limitations included the consideration of mortality and not incidence, and coffee intake was only recorded at baseline.]

Hu et al. (2008) examined the single and joint associations of coffee consumption and serum gamma-glutamyltransferase (GGT) with the risk of primary cancer of the liver. The study cohort included 60 323 Finnish subjects who were aged 25–74 years and free from any cancer at baseline. Information on coffee consumption was collected using mailed self-administered questionnaires. After adjustment for risk factors including alcohol consumption, diabetes, and chronic liver disease at baseline and during follow-up, and BMI, hazard ratios (95% CI) of liver cancer in participants who drank 2–3, 4–5, 6–7, and ≥ 8 cups/day of coffee compared with none were 0.66 (0.37–1.16), 0.44 (0.25–0.77), 0.38 (0.21–0.69), and 0.32 (0.16–0.62) (*P* for trend, 0.003). Further adjustment for serum GGT in subgroup analysis did not substantially affect the results. This inverse association between coffee consumption and liver cancer risk persisted in analyses stratified by several risk factors. [The main strengths of this study were its large-scale, population-based, prospective design and long follow-up (19.3 years). Limitations included consideration of coffee consumption at baseline only, a lack of data on HBV or HCV, and residual confounding.]

Ohishi et al. (2008) conducted a nested case–control study using sera stored before HCC diagnosis in the longitudinal cohort of Japanese atomic bomb survivors, considering the joint effect (synergism) of HBV and HCV infections. The study included 224 incident HCC cases and 644 controls who were matched to cases on sex, age (± 2 years), city, and time (± 2 years) and method of serum storage, and were counter-matched on radiation dose. Information on daily coffee drinking was obtained from a survey in 1978. After adjustment for HBV and HCV infections, alcohol consumption, smoking habits, BMI, and diabetes mellitus, the odds ratio of HCC for daily coffee drinking compared with

never drinking coffee was 0.4 (95% CI, 0.16–1.02; *P* for trend, 0.055). [The strengths of this study were its prospective, nested case–control design and the fact that HCV and HBV infection status was considered. The main limitation was that severity of liver fibrosis could not be considered.]

Inoue et al. (2009) examined whether coffee consumption was associated with a reduced risk of liver cancer by hepatitis virus infection status in the JPHC Study Cohort II. This study was a subcohort analysis of Inoue et al. (2005), with HCV and HBV infections determined by analyses of blood samples. Hazard ratios of liver cancer for different levels of coffee consumption compared with almost-never drinkers were estimated after adjusting for risk factors including smoking status, ethanol intake, BMI, history of diabetes, and HCV and HBV infection status. Increased coffee consumption was associated with a reduced risk of liver cancer in all subjects; multivariate-adjusted hazard ratios (95% CI) for < 1, 1–2, and ≥ 3 cups/day were 0.67 (0.42–1.07), 0.49 (0.27–0.91), and 0.54 (0.21–1.39), respectively. A similar trend in the hazard ratios was observed in those with HCV and/or HBV infection. [The Working Group considered the strengths of this study to be its prospective analysis with blood samples as well as consideration of HCV and HBV infection status. Its main limitation was the relatively small number of cases.]

Johnson et al. (2011) examined the association between coffee consumption and the risk of developing HCC of the liver within the Singapore Chinese Health Study, a prospective cohort of 63 257 Chinese men and women aged 45–74 years (a relatively high-risk population for developing HCC). Data on coffee consumption were collected through in-person interviews at baseline during 1993–1998. A total of 362 cohort participants had developed HCC by 2006. High levels of coffee consumption were associated with reduced risk of HCC. Compared with non-drinkers, individuals who consumed coffee at a frequency of 0 to < 1, 1 to < 2, 2 to < 3, and ≥ 3 cups/day had a reduced risk of HCC with hazard ratios (95% CI) of 0.94 (0.63–1.40), 1.17 (0.87–1.56), 0.78 (0.56–1.07), and 0.56 (0.31–1.00), respectively (*P* for trend, 0.05). All results were adjusted for age at recruitment, sex, dialect group, year of recruitment, BMI, level of education, consumption of alcoholic beverages, cigarette smoking, frequency of black and green tea intake, and history of diabetes.

This study also provided results from the subset of the cohort who provided blood samples at baseline. A total of 92 cases of HCC of the liver and their controls matched for age, date of interview, and date of blood sample collection were analysed. On adjustment for HBV and HCV infection status, in addition to the factors previously indicated, the odds ratios of HCC and high consumption of coffee in the subset were similar to those based on the entire cohort, although not all odds ratios were statistically significant. Odds ratios (95% CI) of the risk of HCC for individuals who consumed coffee at a frequency of 0 to < 1, 1 to < 2, 2 to < 3, and ≥ 3 cups/day compared with non-drinkers were 0.77 (0.26–2.29), 0.84 (0.38–1.85), 1.32 (0.56–3.14), and 0.23 (0.05–1.21), respectively (*P* for trend, 0.71). [The strength of this study was its prospective nature and use of blood samples for part of the cohort. Its limitations included a lack of HBV and HCV status for all cohort participants, participants in the cohort were not measured for the amount of liver damage present at baseline, and the relatively small number of cases.]

Lai et al. (2013) evaluated the association between coffee intake and incident cancer of the liver and chronic liver disease mortality in 27 037 Finnish male smokers, aged 50–69 years, in the ATBC Study. Coffee consumption was recorded at baseline by FFQ and subjects were followed up for 24 years for incident liver cancer. Adjusted hazard ratios (95% CI) for the association between coffee intake and incident liver cancer, compared with never drinkers, were 1.35 (0.65–2.82), 0.73 (0.48–1.12), 0.52 (0.33–0.82),

0.45 (0.26–0.78), and 0.53 (0.30–0.95) for drinking coffee at a frequency of 0 to < 1, 1 to < 2, 2 to < 3, 3 to < 4, and ≥ 4 cups/day, respectively (*P* for trend, 0.0007). Inverse associations persisted in those without diabetes, among HBV- and HCV-negative subjects, and in analyses stratified by age, BMI, alcohol consumption, and smoking dose. The study observed similar associations for those drinking boiled or filtered coffee. This study also provided results among those with information on HBV and HCV using 155 cases of cancer of the liver and 770 controls. The association was not appreciably different when adjusted for HBV and HCV infection status. [The strengths of this study were its prospective nature and long follow-up. However, it was not reported whether the coffee consumed was caffeinated or decaffeinated.]

Bamia et al. (2015) investigated the association between coffee consumption and risk of HCC in the EPIC study. Information on coffee intake was obtained through centre-specific questionnaires on cups per day, week, or month. Hazard ratios for HCC incidence in relation to categories of coffee intake in mL/day were estimated, adjusting for risk factors including self-reported diabetes, ethanol intake, BMI, energy intake, and tea intake. Compared with the lowest quintile (Q1), coffee consumers in the higher quintiles had lower hazard ratios (95% CI) of 0.85 (0.56–1.29), 0.63 (0.39–1.02), 0.49 (0.29–0.82), and 0.28 (0.16–0.50) for quintiles Q2, Q3, Q4, and Q5, respectively (*P* for trend, < 0.001). There was no compelling evidence of heterogeneity of these associations across strata of important HCC risk factors, including HBV or HCV infection status, in a nested case–control analysis. The inverse, monotonic associations of coffee intake with risk of HCC were apparent for caffeinated (*P* for trend, 0.009) but not decaffeinated coffee (*P* for trend, 0.45), but this information was only available for about one third of the study subjects. [The strengths of this study included its cohort design, multicentre coverage to examine a variable range of intake across European countries, a validated questionnaire, and a relatively long follow-up. Its limitations were the modest number of HCC cases and a lack of data on brewing methods.]

Aleksandrova et al. (2015) also used the EPIC population to evaluate the potential mediating roles of inflammatory, metabolic, liver injury, and iron metabolism biomarkers on the association between coffee intake and risk of HCC using a nested case–control study design. The association between cancer of the liver and coffee consumption was similar to that reported by Bamia et al. (2015), who also provided evidence that this association was mediated by biomarkers of inflammation and hepatocellular injury.

Petrick et al. (2015) investigated whether caffeine is responsible for the inverse association between coffee and cancer of the liver. Through the Liver Cancer Pooling Project, a consortium of US-based cohort studies, data from 1 212 893 individuals (860 cases of HCC and 260 cases of intrahepatic cholangiocarcinoma (ICC)) in 9 cohorts were pooled. Hazard ratios and confidence intervals were estimated adjusting for sex, age, race, cohort, BMI, smoking status, cigarette smoking intensity, and alcohol intake. Higher coffee consumption was associated with a lower risk of HCC; the hazard ratio for consumption of > 3 cups/day of coffee compared with a non-drinker was 0.73 (95% CI, 0.53–0.99; *P* for trend, < 0.0001). When considering men and women separately, a reduced risk for consumption of > 3 cups/day of coffee compared with a non-drinker was notable among women (HR, 0.46; 95% CI, 0.26–0.81; *P* for trend, 0.004) compared with men (HR, 0.93; 95% CI, 0.63–1.37; *P* for trend, 0.0004). The associations were stronger for caffeinated coffee; the hazard ratio for consumption of > 3 cups/day of coffee compared with a non-drinker was 0.71 (95% CI, 0.50–1.01; *P* for trend, 0.002) for caffeinated coffee compared with 0.92 (95% CI, 0.55–1.54; *P* for trend, 0.1) for decaffeinated coffee. There was no association between coffee consumption and ICC. [The Working Group

noted that the large sample size allowed stratification by caffeine content of coffee and sex. An additional strength of the study was consideration of the histological subtype of liver cancer (HCC and ICC). The number of cases of ICC was however limited and no data on HBV/HCV status were provided.]

Setiawan et al. (2015) evaluated the association between coffee intake and HCC of the liver in 162 022 African-American, Native Hawaiian, Japanese-American, Latino, and white subjects in the US Multiethnic Cohort (MEC) of Hawaii and California assembled in 1993–1996. During an 18-year follow-up period, there were 451 incident cases of HCC. Compared with non-coffee drinkers, those who drank 2–3 cups/day had a 38% reduction in risk for HCC (HR, 0.62; 95% CI, 0.46–0.84); those who drank ≥ 4 cups per day had a 41% reduction in HCC risk (HR, 0.59; 95% CI, 0.35–0.99) ($P < 0.002$). The inverse associations were similar regardless of the participants' ethnicity, sex, BMI, smoking status, alcohol intake, or diabetes status. [The strengths of this study included its prospective design, the long follow-up time, its multiethnicity, and the large sample size. Limitations included coffee assessment by a single self-report, a lack of information on liver disease other than HCC, and no information on HBV and HCV infection status.]

2.3.2 Case–control studies

See Table 2.6.

(a) Population-based case–control studies

Tanaka et al. (2007) conducted a case–control study recruiting 209 incident cases of HCC and three different control sets (1308 community controls, 275 hospital controls, and 381 patients with chronic liver disease without HCC), all of whom were aged 40–79 years and residents of Saga Prefecture, Japan. A questionnaire survey obtained information on coffee use during the previous 1–2 years and 10 years before, and plasma HBV surface antigen (HBsAg) and HCV-Ab were tested for all but the community controls. After adjustment for sex, age, heavy alcohol use, smoking status, and HBV and HCV markers (except for community controls), coffee use during the previous 1–2 years was associated with a decreased HCC risk using any of the control groups. For coffee use 10 years before, comparison between HCC cases and either community controls or chronic liver disease (CLD) patients revealed a decreased risk. Against community controls, adjusted odds ratios (95% CI) for occasional use, 1–2 cups/day, and ≥ 3 cups/day compared with no use were 0.33 (0.22–0.48), 0.27 (0.15–0.48), and 0.22 (0.11–0.43), respectively (P for trend, < 0.001). Against CLD controls, the equivalent odds ratios (95% CI) were 0.86 (0.55–1.34), 0.62 (0.32–1.21), and 0.53 (0.25–1.12), respectively. No significant trend was observed using hospital patients as controls. [The strengths of this study include the multiple centres and multiple types of controls (community, hospital, and CLD). Limitations include the possible decrease of coffee use among HCC cases due to their advanced liver disease, and the fact that caffeine and unfiltered coffee intake could not be evaluated due to uncommon use.]

(b) Hospital-based case–control studies

La Vecchia et al. (1989b) investigated the association between coffee drinking and the risk of digestive tract neoplasms including cancer of the liver in a hospital-based case–control study; 151 cases of liver cancer and 1944 control subjects admitted for acute, non-digestive tract disorders in general hospitals from the Greater Milan area, Italy, during 1983–1988 were included. Information on coffee consumption was collected by interview using a standard questionnaire. There was no significant or consistent association between coffee intake and liver cancer. The multivariate odds ratio for consumption of 2 cups/day and ≥ 3 cups/day compared

Table 2.6 Case–control studies on cancer of the liver and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
La Vecchia et al. (1989b) Italy, 1983–1988	Cases: 151 (115 men, 36 women) histologically confirmed cases Controls: 1944 (1334 men, 610 women) patients admitted for acute, non-digestive tract disorders Exposure assessment method: questionnaire	Liver/ HCC	*Coffee consumption (cups/day)* 0–1 2 ≥ 3 Trend test *P* value, 0.09	 71 39 41	 1.00 0.79 (NR) 0.78 (NR)	Age, sex, social class, education, marital status, smoking, alcohol consumption	Strengths: multicentre network, well-defined catchment area Limitations: hospital-based, no virus infection status adjustment
Kuper et al. (2000a) Greece, 1995–1998	Cases: 333 (283 men, 50 women) HCC cases Controls: 360 (298 men, 62 women) hospitalized for eye, ear, nose, throat, or orthopaedic conditions (matched for sex and 5-year age band) Exposure assessment method: questionnaire	Liver/ HCC	*Coffee consumption (cups/wk)* All subjects Non-drinkers < 20 ≥ 20 *Coffee consumption for subjects with virus information (330) (cups/wk)* Non-drinkers < 20 ≥ 20 Trend test *P* value, 0.75 *Coffee consumption for subjects without both HBsHg and anti-HCV (82) (cups/wk)* Non-drinkers < 20 ≥ 20 Trend test *P* value, 0.66	 333 36 230 67 NR NR NR NR NR NR	 – 1.0 0.9 (0.5–1.5) 0.7 (0.4–1.2) 1.0 1.1 (0.5–2.6) 0.9 (0.4–2.5) 1.0 1.9 (0.6–5.9) 1.7 (0.5–5.9)	Age and sex Age, sex, year of schooling, HBsAg, and anti-HCV Age and sex	Strengths: virus infection status considered Limitations: hospital-based

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gallus et al. (2002) Italy and Greece, 1984–1997 (Italy), 1995–1998 (Greece)	Cases: 834 (661 men, 173 women) Controls: 1912 (1439 men, 473 women), Italian patients with acute non-neoplastic conditions (matched for area and hospital) and Greek patients hospitalized for eye, ear, nose, throat or orthopaedic conditions (matched for sex and 5-year age band) Exposure assessment method: questionnaire	Liver/ HCC	*Coffee consumption (cups/day): Greece and Italy combined*			Age, sex, education, tobacco smoking, alcohol drinking, BMI, history of diabetes and hepatitis	Analysis of data from La Vecchia et al. (1989b) and Gallus et al. (2002) Strengths: participation almost complete (< 5% refuse interview), confounding factors considered Limitations: hospital-based, change of exposure after hospital admission
			Non-drinkers	129	1.0		
			Drinkers	705	1.0 (0.7–1.3)		
			1	231	1.2 (0.9–1.6)		
			2	292	1.0 (0.7–1.3)		
			≥ 3	178	0.7 (0.5–1.0)		
			Trend test *P* value, 0.015				
			Duration (yr): Greece and Italy combined				
			Non-drinkers	705	1.0		
			< 30	161	1 (0.7–1.4)		
			30–39	243	1 (0.7–1.4)		
			≥ 40	294	1 (0.7–1.3)		
			Trend test *P* value, 0.864				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gelatti et al. (2005) Italy, 1994–2003	Cases: 250 (204 men, 46 women), first diagnosis of HCC admitted to two major hospitals Controls: 500 (408 men, 92 women) admitted for other than liver disease, matched with age, sex, date of hospital admission Exposure assessment method: questionnaire, interview	Liver/ HCC	*Coffee consumption (cups/day)*			Adjusted for HBV, HCV, alcohol intake, sex, age	Strengths: virus infection adjusted and stratified Limitations: hospital-based
			0	44	1.0		
			1–2	119	0.8 (0.4–1.3)		
			3–4	69	0.4 (0.2–0.8)		
			≥ 5	18	0.3 (0.1–0.7)		
			Coffee consumption (cups/day) by HBV infection				
			HBV–, 1–2	129	1.0		
			HBV–, > 2	61	0.5 (0.3–0.8)		
			HBV+, 1–2	35	16.4 (7.1–38.2)		
			HBV+, > 2	25	7.3 (3.3–16.1)		
			Coffee consumption (cups/day) by HCV infection				
			HCV–, 1–2	92	1.0		
			HCV–, > 2	53	0.6 (0.4–0.9)		
			HCV+, 1–2	70	38.2 (18.2–80.1)		
			HCV+, > 2	34	9.0 (4.5–17.8)		
Ohfuji et al. (2006) Japan, 2001–2002	Cases: 73 primary HCC diagnosis by histopathologic examination or imaging study from the hospital record Controls: 253, ratio of 1:1–5 matching for age (± 2 yr), sex, the date of first hospital visit Exposure assessment method: questionnaire	Liver/ HCC	*Frequency of consumption (cups/day) before identification of liver disease*			Duration from first identification of liver disease, BMI at first identification of liver disease, disease severity at first hospital visit, family history of liver disease, interferon therapy, smoking, alcohol drinking, other caffeine-containing beverage	Strengths: both cases and controls were HCV infection positive Limitations: hospital-based, selection bias (all subjects were HCV+), timing of HCV infection was known for 65% of subjects, imperfect memory of distant past history of coffee consumption
			Non-drinker	25	1.00		
			< 1	19	0.61 (0.18–2.03)		
			≥ 1	29	0.38 (0.13–1.12)		
			Trend test *P* value, 0.171				
			Frequency of consumption (cups/day) after identification of liver disease				
			Non-drinker	27	1.00		
			< 1	25	0.57 (0.20–1.67)		
			≥ 1	21	0.19 (0.05–0.71)		
			Trend test *P* value, 0.032				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Montella et al. (2007) Italy, 1999–2002	Cases: 185 (149 men, 36 women) incident HCC who had not yet received any cancer treatment at study entry Controls: 412 (281 men, 131 women) from same hospitals for acute, non-neoplastic diseases unrelated to diet Exposure assessment method: FFQ administered by trained interviewer	Liver/ HCC	*Coffee consumption (cups/wk)*			Age, sex, centre, education, smoking habits, maximal lifetime alcohol intake, HCV/HBV status	Strengths: virus infection status considered, minimal information bias due to same interviewer under similar setting between cases and controls Limitations: hospital-based, recall and selection bias, change of coffee consumption not considered
			Abstainers	27	2.28 (0.99–5.24)		
			< 14	67	1.00		
			14–20	50	0.54 (0.27–1.07)		
			21–27	27	0.57 (0.25–1.32)		
			≥ 28	14	0.43 (0.16–1.13)		
			Trend test *P* value, 0.02				
			Decaffeinated coffee consumption (never/ ever)				
			Never	174	1.00		
			Ever	11	0.72 (0.21–2.50)		
			Coffee consumption (cups/wk) for HCV–/HBV– (38 cases)				
			Abstainers	9	2.09 (0.72–6.07)		
			< 14	13	1.00		
			14–20	7	0.63 (0.22–1.82)		
			≥ 21	9	0.38 (0.13–1.09)		
			Trend test *P* value, < 0.01				
			Coffee consumption (cups/wk) for HCV+/HBV+ (147 cases)				
			Abstainers	18	2.64 (0.59–11.93)		
			< 14	54	1.00		
			14–20	43	0.58 (0.21–1.52)		
			≥ 21	32	0.84 (0.23–3.01)		
			Trend test *P* value, 0.15				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tanaka et al. (2007) Japan, 2001–2004	Cases: 209 from two large hospitals Controls: 1308 community control, 275 hospital control, 381 CLD control Exposure assessment method: questionnaire, interview	Liver/ HCC	*Coffee consumption (cups/day) during previous 1–2 yr: community controls*			Sex, age, heavy alcohol drinking, smoking status	Strengths: multicentre study, multiple types of controls (community, hospital, CLD) Limitations: possible decrease of coffee use among HCC cases due to their advanced liver disease
			None	135	1.00		
			Occasional	53	0.31 (0.21–0.46)		
			1–2	15	0.11 (0.06–0.21)		
			≥ 3	6	0.10 (0.04–0.24)		
			Trend test *P* value, < 0.001				
			Coffee consumption (cups/day) during previous 1–2 yr: hospital controls			Sex, age, heavy alcohol drinking, smoking status, HBsAg, anti-HCV	
			None	135	1.00		
			Occasional	53	0.42 (0.19–0.95)		
			1–2	15	0.23 (0.08–0.68)		
			≥ 3	6	1.08 (0.22–5.35)		
			Trend test *P* value, 0.03				
			Coffee consumption (cups/day) during previous 1–2 yr: CLD controls				
			None	135	1.00		
			Occasional	53	0.86 (0.55–1.35)		
			1–2	15	0.42 (0.21–0.84)		
			≥ 3	6	0.29 (0.11–0.75)		
			Trend test *P* value, 0.001				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tanaka et al. (2007) (cont.)			*Coffee consumption (cups/day) during previous 10 yr: community controls*			Sex, age, heavy alcohol drinking, smoking status	
			None	127	1.00		
			Occasional	53	0.33 (0.22–0.48)		
			1–2	17	0.27 (0.15–0.48)		
			≥ 3	12	0.22 (0.11–0.43)		
			Trend test *P* value, < 0.001				
			Coffee consumption (cups/day) during previous 10 yr: hospital controls			Sex, age, heavy alcohol drinking, smoking status, HBsAg, anti-HCV	
			None	135	1.00		
			Occasional	53	0.99 (0.42–2.32)		
			1–2	15	0.95 (0.31–2.89)		
			≥ 3	6	2.59 (0.58–11.56)		
			Trend test *P* value, 0.47				
			Coffee consumption (cups/day) during previous 10 yr: CLD controls				
			None	135	1.00		
			Occasional	53	0.86 (0.55–1.34)		
			1–2	15	0.62 (0.32–1.21)		
			≥ 3	6	0.53 (0.25–1.12)		
			Trend test *P* value, 0.05				
Leung et al. (2011) China, Hong Kong SAR, 2007–2008	Cases: 109 HCC by review of medical record Controls: 125 HBV carriers at the same hospital Exposure assessment method: questionnaire, face-to-face interview	Liver/ HCC	*Coffee consumption (times/wk)*			Age, sex, cigarette smoking, alcohol use, tea consumption, and physical activity	Strengths: HBV carriers Limitations: hospital-based
			No	81	1.00		
			Yes	28	0.54 (0.30–0.97)		
			< 1	86	1.00		
			1–3	11	0.58 (0.24–1.36)		
			≥ 4	12	0.41 (0.19–0.89)		
			Trend test *P* value, 0.02				

Table 2.6 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jang et al. (2013) Republic of Korea, 2007–2008	Cases: 258 HCC Controls: 480 health-check examinee (HCE), 626 CLD Exposure assessment method: questionnaire	Liver/ HCC	*Lifetime amount (cups): HCE (480 cases)*			Age, sex, BMI, past medical history of DM, lifetime smoking amount, lifetime alcohol consumption	Strengths: results from endemic area, multiple control (HCE and CLD), virus infection status considered Limitations: hospital-based
			≤ 20 000	54	1.00		
			> 20 000	204	0.56 (0.33–0.95)		
			Lifetime amount (cups): CLD (258 cases)			Age, sex, BMI, past medical history of DM, lifetime smoking amount, lifetime alcohol drinking amount, chronic liver disease (none, HCV, HBV, both HCV and HBV)	
			≤ 20 000	54	1.00		
			> 20 000	204	0.55 (0.36–0.85)		
			Lifetime amount (cups): patients without HBV (83 cases)			Age, sex, BMI, past medical history of DM, lifetime smoking amount, lifetime alcohol consumption	
			≤ 20 000	NR	1.00		
			> 20 000	NR	0.47 (0.23–0.94)		
			Lifetime amount (cups): patients with HBV (170 cases)			Age, sex, BMI, past medical history of DM, lifetime smoking amount, lifetime alcohol drinking amount, HBV status	
			≤ 20 000	NR	1.00		
			> 20 000	NR	0.64 (0.36–1.14)		
Patil et al. (2014) India (Mumbai), 2009–2011	Cases: 141 HCC patients, consecutive recruitment Controls: 240 patients with CLD of viral etiology, consecutive recruitment Exposure assessment method: questionnaire	Liver/ HCC	*Coffee consumption (cups/day)*			Age, alcohol consumption, ALT level, ferritin level, family income, sex, tobacco consumption	Strengths: viral infection positive only, ferritin level considered Limitations: hospital-based
			Never	105	1.00		
			Ever	36	2.00 (1.05–3.83)		
			≤ 2	20	1.00		
			> 2	3	0.37 (0.10–1.34)		

ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; CLD, chronic liver disease; DM, diabetes mellitis; FFQ, food frequency questionnaire; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCE, health-check examinee; HCV, hepatitis C virus; NR, not reported; SAR, Special Administrative Region; wk, week(s); yr, year(s)

with 0–1 cups/day were 0.79 and 0.78, respectively [confidence intervals were not reported]. The inverse exposure–response trend was not significant (*P* for trend, 0.09). [The multicentre network and well-defined catchment area were the strengths of this study, while limitations included the hospital-based design and lack of adjustment for virus infection status.]

Kuper et al. (2000a) conducted a hospital-based case–control study in Greece. Blood samples and questionnaire data were obtained from 333 incident cases of HCC of the liver during 1995–1998, as well as from 360 controls matched for sex and age (± 5 years) who were hospitalized for eye, ear, nose, throat, or orthopaedic conditions in Athens. Information on coffee consumption was collected by interview. Hepatitis B surface antigen (HBsAg) and antibodies to HCV (anti-HCV) were tested for the study participants. Coffee intake was not associated with HCC risk after controlling for age, sex, year of schooling, and HBV and HCV infection status. Compared with non-drinkers, odds ratios (95% CI) for consumption of < 20 cups/week and ≥ 20 cups/week were 1.1 (0.5–2.6) and 0.9 (0.4–2.5), respectively. [Consideration of virus infection status was a strength of this study, while its main limitation was its hospital-based design.]

Gallus et al. (2002) analysed the association between coffee consumption and HCC of the liver in the two preceding case–control studies conducted in Italy and Greece (La Vecchia et al., 1989b; Kuper et al. 2000a). Compared with non-drinkers, the multivariate odds ratio (95% CI) adjusting for age, sex, education, tobacco smoking, alcohol drinking, BMI, and history of diabetes and hepatitis was 0.7 (0.5–1.0) for drinkers of ≥ 3 cups/day (*P* for trend, 0.015). Duration (years) of coffee consumption was not associated with risk of HCC. [The strengths of this study were an almost-complete participation rate (< 5% refused interviews) and consideration of confounding factors. It was limited by its hospital-based design.]

Gelatti et al. (2005) conducted a hospital-based case–control study in an area of northern Italy. A total of 250 cases of HCC of the liver and 500 controls, hospitalized for any reason other than neoplasms and liver and alcohol-related diseases, were recruited during 1994–2003. Lifetime history of coffee consumption was assessed using a standardized questionnaire. Coffee consumption in the decade before the interview was associated with a reduced risk of HCC with a clear inverse dose–response relationship. With respect to non-drinking subjects, the odds ratio (95% CI) was 0.3 (0.1–0.7) for ≥ 5 cups/day. [The strengths of this study included adjustment and stratification for virus infection. The hospital-based study design was a limitation.]

Ohfuji et al. (2006) conducted a hospital-based case–control study in Japan to assess the association between coffee and HCC of the liver, in which both 73 cases and 253 controls were patients with chronic type C liver disease. A self-administered questionnaire was used to assess coffee consumption. The effect of coffee intake was estimated separately for before and after first identification of liver disease. Coffee drinking on a daily basis (≥ 1 cup/day) revealed lowered odds ratios as compared with non-drinkers both before first identification of liver disease (OR, 0.38; 95% CI, 0.13–1.12; *P* for trend, 0.171) as well as after disease identification (OR, 0.19; 95% CI, 0.05–0.71; *P* for trend, 0.032). Odds ratios were adjusted for time from the first identification of liver disease, BMI, smoking, alcohol drinking, consumption of other caffeine-containing beverages, and clinical characteristics. The inverse association persisted after excluding subjects who reported a reduction in the frequency of coffee intake after first identification of liver disease. [The strength of this study was that both cases and controls were HCV positive. Limitations included: hospital-based design, generalizability (all subjects were HCV-positive), missing

information on the timing of HCV infection (known for only 65% of subjects), and imperfect recall of distant past coffee consumption.]

Montella et al. (2007) conducted a hospital-based case–control study in Italy that included 185 incident, histologically confirmed cases of HCC aged 43–84 years that were identified during 1999–2002. Controls were 412 subjects admitted to the same hospital networks as the cases for acute, non-neoplastic diseases unrelated to diet. Coffee consumption was assessed using a validated FFQ. Compared with people who drank < 14 cups/week of coffee, the adjusted risk of HCC decreased for increasing levels of consumption with odds ratios (95% CI) of 0.54 (0.27–1.07) for 14–20 cups/week, 0.57 (0.25–1.32) for 21–27 cups/week, and 0.43 (0.16–1.13) for ≥ 28 cups/week (*P* for trend, 0.02). An increased risk was observed among abstainers of coffee relative to people who drank < 14 cups/week of coffee (OR, 2.28; 95% CI, 0.99–5.24). Inverse associations were observed across strata of HCV and HBV infections and alcohol drinking. A non-significant inverse association was observed with consumption of decaffeinated coffee (OR, 0.72; 95% CI, 0.21–2.50). [The strengths of this study were the consideration of hepatitis infection status, and minimal information bias due to the same interviewer being used under a similar setting between cases and controls. The hospital-based design was a limitation.]

Leung et al. (2011) examined whether coffee has a protective effect in chronic HBV carriers, a group at high risk of developing liver cancer, in a hospital-based case–control study in Hong Kong Special Administrative Region, China. A total of 234 HBV chronic carriers (109 HCC cases and 125 controls) were recruited from a core hospital during 2007–2008. Data collection included review of medical records and face-to-face interview. On adjusting for age, sex, cigarette smoking, alcohol use, tea consumption, and physical activity, coffee drinking significantly reduced the risk of HCC (OR, 0.54; 95% CI, 0.30–0.97) compared with non-drinkers. The study also observed a significant dose–response association (*P* for trend, 0.02), with a reduced risk for moderate drinkers (≥ 4 times/week) of 59% (OR, 0.41; 95% CI, 0.19–0.89) compared with those with no coffee habit (< 1 time/week). [The main strength of this study was the use of HBV carriers to control for confounding by infection status. The hospital-based design was a limitation.]

Jang et al. (2013) performed a hospital-based case–control study in the Republic of Korea to determine the association between lifetime coffee consumption and the risk of HCC development in a HBV-prevalent region. A total of 1364 subjects – 258 HCC patients, 480 health-check examinees (control group 1, HCE), and 626 patients with chronic liver disease other than HCC (control group 2, CLD) – were interviewed on smoking, alcohol consumption, and coffee drinking using a standardized questionnaire. HBV e-antigen (HBeAg) status and serum HBV DNA levels were measured in patients infected with HBV. After adjustment for risk factors, including the presence of hepatitis virus (except for HCE) and lifetime alcohol drinking/smoking, a high lifetime consumption of coffee (> 20 000 cups) compared with a low lifetime coffee consumption (≤ 20 000 cups) was associated with a reduced risk of HCC using both HCE and CLD control groups, yielding odds ratios (95% CI) of 0.56 (0.33–0.95) and 0.55 (0.36–0.85), respectively. The high coffee consumption was not associated with a significantly increased risk of HCC; among patients with HBV, the odds ratio was 0.64 (95% CI, 0.36–1.14) after adjustment for HBeAg status, serum HBV DNA level, and antiviral therapy. [The strengths of this study included the fact that results were obtained from a hepatitis endemic area with consideration of infection status, the use of multiple controls (HCE and CLD). Limitations included its hospital-based design

and the potential for selection bias with CLD controls.]

Patil et al. (2014) analysed the association between coffee consumption and HCC of the liver in an Indian population that was HCV and/or HBV positive. The study enrolled 141 patients with HCC and 240 patients with HBV or HCV infection-related CLD. After adjusting for alcohol consumption, ALT level, ferritin level, and other covariates, ever compared with never consumption of coffee was associated with an increased risk of HCC (OR, 2.00; 95% CI, 1.05–3.83) in patients with hepatitis-related CLD. [The strengths of the study included the use of HBV- and/or HCV-positive subjects and the consideration of ferritin level. Limitations included the hospital-based design, the fact that controls were patients with CLD, and the categories of coffee consumption being only never or ever.]

2.3.3 Meta-analyses

Seven meta-analyses of the association between cancer of the liver and coffee drinking have been published (Bravi et al., 2007a, 2009, 2013, 2017; Larsson & Wolk, 2007; Yu et al., 2011; Sang et al., 2013). The most recent and comprehensive meta-analyses are summarized here.

Bravi et al. (2013) conducted a meta-analysis of epidemiological studies that examined the association between liver cancer and coffee consumption. A PubMed/MEDLINE search from 1966 to September 2012 was performed to identify case–control or cohort studies that examined the association between coffee consumption and cancer or HCC of the liver. The summary relative risks for any, low, and high consumption of coffee versus no consumption were obtained from the results for eight cohort and eight case–control studies. The summary relative risk for any coffee consumption versus no consumption was 0.60 (95% CI, 0.50–0.71; I^2, 73.9%; $P < 0.001$) from 16 studies that included a total of 3153 HCC cases. The findings were similar for the case–control (RR, 0.56; 95% CI, 0.42–0.75, I^2, 74.1%; P for trend, < 0.001) and the cohort studies 0.64 (RR, 0.64; 95% CI, 0.52–0.78; I^2, 69.1%; P for trend, 0.002). Compared with no coffee consumption, the summary relative risk was 0.72 (95% CI, 0.61–0.84; I^2, 58.4%; P for trend, 0.003) for low consumption and 0.44 (95% CI, 0.39–0.50; I^2, 0.0%; P for trend, 0.495) for high consumption. The relative risk was 0.80 (95% CI, 0.77–0.84) for an increment of 1 cup/day of coffee. The inverse association between coffee and HCC risk was consistent regardless of subject sex, alcohol consumption, or history of hepatitis or liver disease. Several cohort studies reported after 2013 were not included in this meta-analysis.

Bravi et al. (2017) recently conducted an updated meta-analysis of prospective studies, including results from the recent cohort studies which were not included in the previous meta-analysis by Bravi et al. (2013), by performing a PubMed/MEDLINE and Embase search of articles published up to June 2015 on cohort studies. Twelve cohort studies (2154 cases in total) were included in this meta-analysis. Compared with no consumption, the summary relative risks for HCC by random-effect model were 0.66 (95% CI, 0.55–0.78) for regular, 0.78 (95% CI, 0.66–0.91) for low, and 0.50 (95% CI, 0.43–0.58) for high coffee consumption, with a significant heterogeneity ($P < 0.001$ for I^2-statistic). The summary relative risk for an increment of 1 cup/day was 0.85 (95% CI, 0.81–0.90). This meta-analysis supported the inverse association between coffee consumption and the risk of HCC.

2.4 Cancer of the breast in women

A total of 23 cohort and 22 case–control studies that investigated the association between coffee intake and of cancer of the breast in women were available for review by the Working Group. All but one of the cohort studies investigated

incident breast cancer; the remaining study considered breast cancer mortality. Four of the case–control studies investigated breast cancer in women with known status regarding *BRCA1/BRCA2* mutations. Four meta-analyses of the above-indicated studies, published from 2009 to 2013, are also included in this review.

Thirteen (twelve case–control and one cohort) studies were excluded for the following reasons.

The studies by Lawson et al. (1981), Lubin et al. (1981), and Franceschi et al. (1995) were excluded because coffee and tea (and decaffeinated coffee in Franceschi et al., 1995) were examined as one combined exposure; the association between coffee and risk of breast cancer could not be separated from those of the other beverages.

The study by Mansel et al. (1982) was excluded as the study design and analysis were unclear.

The studies by Lê (1985), Rohan & McMichael (1988), Smith et al. (1994), Zhang et al. (2007), and Ayari et al. (2013) were excluded as no measure of relative risk for coffee intake in relation to risk of breast cancer was reported.

The study by Pozner et al. (1986), which examined caffeine and coffee intakes in women with breast cancer to determine whether they influence cell differentiation in tumours, was excluded since, as described in the previous *IARC Monographs* evaluation (Volume 51; IARC, 1991), this study is difficult to group with other studies of etiology.

The study by Männistö et al. (1999), which used the association between coffee consumption and breast cancer risk as an illustration paradigm when investigating a methodological issue, was excluded because of the influence of recall bias in previous knowledge of health status.

The study by Shirlina et al. (2015), which investigated nutritional risk factors in association with breast cancer in the Russian Federation, was excluded as the full text (in Russian) could not be obtained.

A cohort study by Jacobsen et al. (1986), investigating the association between coffee and cancer incidence using two Norwegian cohorts, was excluded due to the small number of breast cancer cases in women (38/2891) and a lack of adjustment for reproductive factors or smoking.

2.4.1 Cohort studies

See Table 2.7.

(a) Incident cancer of the breast

Vatten et al. (1990) studied the association between coffee consumption and breast cancer incidence using a cohort of 14 593 Norwegian women (aged 35–51 years) who participated in a health screening examination for cardiovascular disease (National Health Screening Service) between 1974 and 1977. Age-adjusted incidence rate ratios (IRR) in relation to breast cancer risk indicated an overall inverse, non-statistically significant association between daily intake of coffee and risk of breast cancer. There was an indication or effect modification of the association by BMI (P-interaction = 0.02). The risk of breast cancer for coffee consumption of ≥ 5 cups/day compared with ≤ 2 cups/day yielded an incidence rate ratio of 0.5 (95% CI, 0.3–0.9; P for trend, 0.02) for BMI < 24. For BMI ≥ 24, an equivalent comparison yielded an incidence rate ratio of 2.1 (95% CI, 0.8–5.2; P for trend, 0.09). [The limitations of this study included the small number of cases and lack of information/adjustment for risk factors (apart from age) for breast cancer incidence (i.e. reproductive history, hormones, smoking).]

Høyer & Engholm (1992) studied the association between serum lipids and breast cancer risk, reporting also for coffee intake, in a cohort of 5207 Danish female participants (aged 30–80 years) recruited in the Glostrup Population Studies between 1964 and 1986. Participants were representative of urban and suburban Danes with respect to social class, housing, education, occupational conditions, and job categories (participation rate 78.5%). During the 4–26 years of

Table 2.7 Cohort studies on cancer of the breast and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Snowdon & Phillips (1984) USA, 1960–1980	23 912 (176 BC deaths) among white Seventh-day Adventists (aged ≥ 30 yr in 1960) Exposure assessment method: self-administered questionnaire	Breast	*Coffee consumption (cups/day)*			Age, sex, meat consumption, smoking	Breast cancer mortality Strengths: dietary questionnaire was used by the ACS study; record linkage for identification of cases Limitations: particular characteristics of studied population may have resulted in reporting bias, coffee consumption rare, number of events small (as cancer mortality and not incidence is the endpoint), no adjustment for important risk factors (therefore residual confounding)
			< 1	131	1.0		
			1	19	1.1 (0.7–1.8)		
			≥ 2	26	0.9 (0.6–1.3)		
			Trend test *P* value, 0.62				
Vatten et al. (1990) Norway, 1974–1977 (enrolment), 12 yr follow-up	14 593 (152 BC cases) among Norwegian women (aged 35–51 yr) who participated in National Health Screening Service Exposure assessment method: FFQ	Breast	*Coffee consumption (cups/day)*			Age	Strengths: comprehensive definition of cases, validation of questionnaire for coffee intake Limitations: small number of cases, possibility of information bias, no information/adjustment for important risk factors (e.g. reproductive or smoking), assessment of coffee at baseline only
			≤ 2	27	1.0		
			3–4	62	0.9 (0.6–1.4)		
			5–6	42	0.8 (0.5–1.3)		
			≥ 7	21	0.8 (0.5–1.4)		
			Trend test *P* value, 0.37				
Høyer & Engholm (1992) Denmark, 1964–1986 (enrolment), 1964–1986 (follow-up, 4–26 yr)	5207 (51 BC cases) among Danish women participants (aged 30–80 yr) Exposure assessment method: standardized questionnaires in all cohorts at baseline	Breast	*Coffee consumption (cups/day)*			Possibly for social class, age at menarche, menopause status, number of full-term pregnancies, height, weight, BMI, alcohol, smoking (not clear)	Minimum analysis and focus on coffee intake since main exposure was serum lipids. Strengths: random sample of the general population, linkage to cancer registry (regarded as virtually complete) Limitations: most probably RR are crude
			≤ 2	NR	1.0		
			3–6	NR	1.4 (0.6–3.4)		
			≥ 7	NR	1.7 (0.7–4.3)		
			Trend test *P* value, > 0.20				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Folsom et al. (1993) USA, 1986 (enrolment), 1990 (follow-up)	34 388 (580 BC cases) among women aged 55–69 yr in 1986 participating in the IWHS Exposure assessment method: FFQ, regular coffee and caffeine intakes over the previous year assessed	Breast	*Coffee consumption among postmenopausal women*			Age, waist/hip ratio, number of live births, age at first live birth, age at menarche, family history of BC, family history (including family waist/ hip ratio and number of live births)	Caffeine was the main exposure of interest. Strengths: use of a large cohort, the comprehensive identification of cases, and validated Harvard semi-quantitative FFQ questionnaire for assessment of exposures Limitations: short follow-up period and therefore small number of cases, caffeine and not coffee was the main exposure of interest (and therefore examined in more detail)
			Never or < 1 time/mo	183	1.00		
			1 time/mo – 4 times/wk	78	0.87 (0.66–1.14)		
			5–7 times/wk	77	0.96 (0.73–1.27)		
			2–3 times/ day	136	0.98 (0.78–1.23)		
			≥ 4 times/ day	106	1.02 (0.79–1.30)		
			Trend test *P* value, 0.6				
Stensvold & Jacobsen (1994) Norway, 1977–1982	21 238 women resident in three Norwegian counties aged 35–54 yr Exposure assessment method: validated FFQ for coffee consumption	Breast	*Coffee consumption (cups/day)*			Age, cigarettes per day, county of residence	Strengths: comprehensive definition of cases, validation of questionnaire for coffee intake Limitations: small number of cases, possibility of information bias, no information/adjustment for important risk factors for BC incidence (i.e. reproductive), assessment of coffee only at baseline, no CI reported
			≤ 2	22	1.0		
			3–4	69	1.1 (NR)		
			5–6	77	1.4 (NR)		
			≥ 7	43	1.2 (NR)		
			Per category increment	211	1.07 (0.94–1.22)		

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Key et al. (1999) Japan, 1969–1970 and 1979–1980 (enrolment), follow-up until 1993	34 759 (427 BC cases) women in Hiroshima and Nagasaki, participants of the Radiation Effects Research Foundation's Life Span Study Exposure assessment method: non-validated dietary questionnaire	Breast	*Coffee consumption (times/wk)*			Attained age, calendar period, city of residence, age at the time of the bombing, radiation dose	Strengths: comprehensive identification of cases and adequate statistical analyses Limitations: major exposure studied was soya foods so coffee intake was not examined in detail, special characteristics of the studied populations, use of a non-validated dietary questionnaire, lack of information regarding potentially important confounders
			≤ 1	151	1.00		
			2–4	71	1.03 (0.78–1.37)		
			≥ 5	122	1.19 (0.93–1.52)		
			Unknown	83	1.11 (0.84–1.46)		
			Trend test *P* value, 0.258				
Michels et al. (2002) Sweden, 1987–1990 (enrolment), follow-up for 9.5 yr	59 036 (1271 BC cases) among women aged 40–76 yr participating in the large population-based SMC cohort Exposure assessment method: self-administered semi-quantitative FFQ, assessing diet over the 6 mo before recruitment	Breast	*Coffee consumption*			Age, family history of BC, height, BMI, education, parity, age at first birth, alcohol consumption, total caloric intake	Strengths: population with high coffee intakes, high response rates, comprehensive endpoint ascertainment, FFQ validated for coffee intake Limitations: assessment of coffee only at baseline
			≤ 1 cup/wk	76	1.00		
			2–4 cups/wk	33	0.81 (0.54–1.22)		
			1 cup/day	185	0.99 (0.75–1.28)		
			2–3 cups/day	763	0.94 (0.79–1.12)		
			≥ 4 cups/day	214	0.94 (0.75–1.28)		
			Trend test *P* value, 0.91				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Suzuki et al. (2004) Japan Cohort 1: 1984 (enrolment), 9 yr follow-up (111 267 person-years) Cohort 2: 1990 (enrolment), 7 yr follow-up (151 882 person-years)	14 409 (103 BC cases) in Cohort 1 and 20 595 (119 BC cases) in Cohort 2, comprising women aged > 40 yr participating in two population-based prospective cohort studies in Japan Exposure assessment method: self-administered validated questionnaires covering recent or usual consumption	Breast	*Coffee consumption* Never Occasionally ≥ 1 cup/day Trend test *P* value, 0.44	 NR NR NR	 1.00 0.78 (0.53–1.13) 0.81 (0.55–1.18)	Age, type of health insurance, age at menarche, menopausal status, age at first birth, parity, mother's history of BC, smoking, alcohol drinking, BMI	Green tea was the main exposure. Strengths: based on two cohort studies in Japan Limitations: small number of cases, coffee not the main exposure so not examined in detail
Hirvonen et al. (2006) France, 1994 (enrolment), 6.6 yr median follow-up	4396 (95 BC cases) apparently healthy women aged 35–60 yr at recruitment, participating in a controlled, primary-prevention trial of vitamins and minerals (SU.VI.MAX) Exposure assessment method: questionnaire; computerized 24-hour dietary record every 2 mo	Breast	*Tertiles of coffee intake (mL/day)* 0–111 112–252 ≥ 253 Trend test *P* value, 0.71	 30 32 33	 1.00 1.07 (0.64–1.79) 1.10 (0.66–1.84)	Age, smoking, menopausal status, oral contraception use, family history of BC, number of children	Strengths: close monitoring and efficient detection of BC cases due to frequent examination of participants (every year) Limitations: some reproductive factors as well as HRT and randomized treatment not adjusted for limited generalizability

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ganmaa et al. (2008) USA (11 states), 1976 (enrolment), follow-up during 1980–2002	85 987 (5272 BC cases) women aged 30–55 yr, recruited in the NHS Exposure assessment method: FFQ, coffee (caffeinated or decaffeinated) assessed in 1980, 1984, 1986, 1990, 1994, 1998, through a validated (for coffee) FFQ, assessing consumption over the previous year	Breast	*All coffee consumption: cumulatively averaged and updated*			Age, smoking status, BMI, physical activity, height, history of benign breast disease, family history of BC, weight change since age 18, age at menarche, parity, age at first birth, alcohol intake, total energy intake, age at menopause, postmenopausal hormone use	Strengths: validated (for coffee) FFQ, substantial number of cases, ability to examine BC by ER/PR status, detailed assessment and repeated measures of coffee intakes, comprehensive statistical analysis, ability to extensively adjust for potential confounders Limitations: selected cohort of nurses
			< 1 cup/mo	837	1.00		
			1 cup/mo – 4.9 cups/wk	745	1.01 (0.92–1.12)		
			5 cups/wk –1.9 cups/ day	1335	0.92 (0.84–1.01)		
			2–3.9 cups/ day	1718	0.93 (0.85–1.02)		
			≥ 4 cups/day	637	0.92 (0.82–1.03)		
			Trend test *P* value, 0.14				
Ishitani et al. (2008) USA, 1992 (enrolment), average follow-up of 10 yr	38 432 (1188 BC cases) among female US health professionals, aged ≥ 45 yr when recruited to the WHS Exposure assessment method: questionnaire; coffee consumption over the year before recruitment, the validated FFQ from the Nurses' Health Study was used	Breast	*Coffee (caffeinated and decaffeinated) (cups/day)*			Age and randomized treatment, as well as, for: alcohol consumption, BMI, family history of BC, history of hysterectomy, bilateral oophorectomy, smoking status, history of benign breast disease, age at menarche, parity, age at first birth, physical activity, total energy intake, multivitamin use, age at menopause, menopausal status, and postmenopausal hormone use	Strengths: validated FFQ, the substantial number of cases, the ability to examine BC by ER/PR status, comprehensive statistical analysis, ability to extensively adjust for potential confounders, long follow-up Limitations: selected cohort of health professionals (not expected to bias the results), the lack of repeated measures of coffee intake
			Almost never	274	1.00		
			< 1	145	0.97 (0.79–1.18)		
			1	166	0.98 (0.81–1.19)		
			2–3	405	1.05 (0.89–1.22)		
			≥ 4	191	1.08 (0.89–1.3)		
			Trend test *P* value, 0.27				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Larsson et al. (2009) Sweden, 1987–1990 (enrolment), mean follow-up until 2009 (17.4 yr; 1 071 164 person-years)	61 433 (2952 BC cases) women aged 40–76 years from the SMC, study design and BC cases ascertainment described by Michels et al. (2002) Exposure assessment method: as in Michels et al. (2002), plus 1997 self-administered FFQ to assess long-term effect of diet on BC risk	Breast	*Coffee consumption (cups/day)*			Age, education, BMI, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of BC, intakes of alcohol, tea, total energy	Strengths: as for Michels et al. (2002), repeated measures for coffee intake, follow-up resulted in a substantial number of BC cases, information on ER/PR status available for majority of cases Limitations: possibility of information bias
			< 1	251	1.00		
			1	486	1.05 (0.90–1.23)		
			2–3	1723	0.97 (0.84–1.11)		
			≥ 4	492	1.02 (0.87–1.2)		
			Trend test *P* value, 0.74				
Wilson et al. (2009) USA, 1991 (enrolment), 14 yr (945 764 person-years) of follow-up	90 628 (1179 BC cases) premenopausal women aged 26–46 yr Exposure assessment method: FFQ, similar assessment as for Ganmaa et al. (2008)	Breast	*Coffee consumption: quintiles of servings/day*			Age, calendar year, BMI, height, oral contraceptive use, parity and age at first birth, age at menarche, family history of BC, history of benign breast disease, smoking, physical activity, animal fat, glycaemic load, alcohol intake, total energy intake	Premenopausal BC was the end-point of interest. Acrylamide intake was the main exposure studied. Strengths: similar to those reported for Ganmaa et al. (2008) Limitations: similar to those reported for Ganmaa et al. (2008), lack of detailed examination of coffee in relation to BC risk since acrylamide was the exposure studied
			1st quintile	270	1.00		
			2nd quintile	155	1.11 (0.91–1.36)		
			3rd quintile	230	0.97 (0.81–1.16)		
			4th quintile	266	1.01 (0.85–1.21)		
			5th quintile	258	0.92 (0.77–1.11)		
			Trend test *P* value, 0.28				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boggs et al. (2010) USA (all regions), 1995 (enrolment), follow-up until 2007 (12 yr)	52 062 (1268 BC cases) African-American women aged 21–69 yr at enrolment in the BWHS Exposure assessment method: validated FFQ, self-administered at baseline in 1995 and in 2001	Breast	*Coffee consumption* Never or < 1 cup/mo < 1 cups/day 1 cups/day 2–3 cups/day ≥ 4 cups/day Trend test *P* value, 0.9	 592 357 148 122 49	 1.00 0.98 (0.85–1.12) 0.91 (0.76–1.09) 0.94 (0.77–1.15) 1.03 (0.77–1.39)	Energy intake, age at menarche, BMI at age 18, family history of BC, education, geographic region, parity, age at first birth, oral contraceptive use, menopausal status, age at menopause, menopausal hormone use, vigorous activity, smoking status, intake of alcohol, tea, decaffeinated coffee	Strengths: population-based sample, extended follow-up, repeated measures of coffee intake, advanced statistical analysis with time-varying covariates for exposures and potential confounders, control for a large number of BC risk factors Limitations: results not generalizable to populations other than African-American women
Nilsson et al. (2010) Sweden (Västerbotten), 1992–2007 (enrolment), follow-up until 2007 (median follow-up 6.6 yr)	32 178 (587 cases) women recruited in the VIP Exposure assessment method: semi-quantitative FFQ	Breast	*Boiled coffee (occasions/day)* < 1 1–3 ≥ 4 Trend test *P* value, 0.247 *Total/boiled/brewed coffee intakes (occasions/day)* < 1 1–3 ≥ 4 *Filtered coffee intake (occasions/day)* < 1 1–3 ≥ 4	 433 141 14 58 367 163 159 328 101	 1.00 1.02 (0.84–1.23) 0.52 (0.30–0.88) 1.00 1.06 (0.80–1.40) 0.92 (0.68–1.25) 1.00 1.00 (0.83–1.21) 1.01 (0.79–1.31)	Sex, age, BMI, smoking, education, recreational physical activity	Method of coffee preparation was the main interest of the study. Discrepancies in tables and figures regarding the number of women and BC cases Strengths: country with very high consumptions of coffee, method of coffee preparation considered, case ascertainment through high-quality national cancer registry Limitations: low participation rates (57% and 67%), but minimal evidence of systematic differences in the social and demographic characteristics of participants and non-participants, age used as a proxy marker for menopausal status

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Iwasaki et al. (2010) Japan, Cohort I enrolled in 1990, Cohort II enrolled in 1993, follow-up until 31/12/2006 (average 13.6 yr)	53 793 women (581 cases) aged 40–69 yr, participants in JPHC Study Exposure assessment method: questionnaire, assessments at baseline and after 5 years (1995–1998)	Breast	*Coffee consumption*			Age, area, age at menarche, menopausal status at baseline, age at menopause for postmenopausal women, number of births, age at first birth, height, BMI, alcohol intake among regular drinkers, smoking, leisure time physical activity, exogenous hormone use, family history of BC, intakes of green tea, oolong tea, and black tea	Green tea consumption was the main exposure Strengths: population-based, comprehensive case ascertainment Limitations: relatively low consumption of coffee in this population, relatively small number of cases, unusual analysis, not particularly detailed analysis of coffee
			< 1 cup/wk	161	1.00		
			1–4 cups/wk	180	1.15 (0.91–1.46)		
			1–2 cups/day	173	1.12 (0.87–1.43)		
			≥ 3 cups/day	63	1.22 (0.87–1.71)		
			Trend test *P* value, 0.26				
Fagherazzi et al. (2011) France, 1990 (enrolment), follow-up until June 2005 (median 11 yr)	67 703 (2868 BC cases) French women aged 40–65 yr at recruitment, insured by the national health insurance system Exposure assessment method: self-administered questionnaire assessing using diet over previous year	Breast	*Coffee consumption (cups/day)*			Age, baseline variables (total energy intake, ever use of oral contraceptives, age at menarche, age at menopause, number of children, age at first pregnancy, history of BC in the family and years of schooling), time-dependent variables (current use of postmenopausal hormone therapy, postmenopausal women only), personal history of benign breast disease, menopausal status, BMI	Strengths: substantial number of cases, case ascertainment through pathology reports Limitations: selection of teachers may reduce generalizability of results, lack of repeated measures for coffee consumption
			Non-consumer	410	1.00		
			≤ 1	491	1.02 (0.91–1.15)		
			1.1–3	1133	0.98 (0.85–1.11)		
			> 3	834	1.02 (0.9–1.16)		
			Trend test *P* value, 0.79				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gierach et al. (2012) USA, 1995–1996 (enrolment), follow-up until 2006	198 404 (9915 cases) female residents of eight US states aged 50–71 yr when recruited in NIH-AARP Exposure assessment method: 124-item food FFQ assessing diet over the past year	Breast	*Coffee consumption*			Age at entry, race/ ethnicity, education, BMI, smoking status and dose, alcohol, proportion of total energy from fat, age at first live birth, menopausal HRT use, history of breast biopsy, family history of breast cancer in a first-degree relative	Results did not vary by BMI or history of benign breast biopsy, or by clinical features of the tumour. No evidence of an association between breast cancer risk and either caffeinated or decaffeinated coffee Strengths: large size, availability of extensive information on potential confounding factors, examination of associations for many clinical features of breast tumours Limitations: coffee was assessed only at baseline
			Never	1138	1.00		
			≤ 2 cups/wk	1114	1.06 (0.97–1.15)		
			3–6 cups/wk	662	1.00 (0.91–1.10)		
			1 cup/day	1833	1.02 (0.94–1.09)		
			2–3 cups/day	3951	1.02 (0.95–1.09)		
			≥ 4 cups/day	1217	0.98 (0.91–1.07)		
			Trend test *P* value, 0.38				
Oh et al. (2015) Sweden, 1991–1992 (enrolment), follow-up until 2012 (856 529 person-years)	42 099 (1395 BC cases) women aged 30–49 yr in the Swedish WLH study, a random sample of women residing in the Uppsala Health Care Region in Sweden Exposure assessment method: validated FFQ for coffee/tea intakes, diet during previous year assessed	Breast	*Coffee consumption (cups/day)*			Age, BMI, duration of breastfeeding, alcohol consumption, smoking status, education, physical activity	Similar patterns of associations were observed for pre- and postmenopausal BC Strengths: population-based sample, extended follow-up, examination of the studied association by ER/PR status Limitations: coffee assessed only at baseline
			0	99	0.86 (0.69–1.08)		
			1–2	338	1.00		
			3–4	537	0.87 (0.76–1.00)		
			≥ 5	421	0.81 (0.70–0.94)		
			Per 1 cup/day increment	1395	0.97 (0.94–0.99)		
			Trend test *P* value, 0.009				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bhoo-Pathy et al. (2015) 10 European countries, 1992–2000 (enrolment), follow-up until 2010	335 060 (10 198 BC cases) female participants aged 25–70 yr in the EPIC cohort study Exposure assessment method: self- or interviewer-administered validated country-specific questionnaires (usually FFQs)	Breast	*Coffee consumption (total, caffeinated, decaffeinated): postmenopausal*			Age at menarche, ever use of oral contraceptives, age at first delivery, ever breastfeeding, smoking status, education, physical activity, alcohol, height, weight, energy intake from fat and non-fat sources, total saturated fat and fibre intakes, tea intake, ever use of postmenopausal hormones	Strengths: substantial numbers of BC cases (even for premenopausal BC), multi-country design ensuring variation in coffee consumption, comprehensive statistical analysis Limitations: selected cohorts (volunteers in most countries), lack of repeated assessments of coffee consumption (possibly important after 10-year follow-up)
			No	732	1.02 (0.94–1.12)		
			Low	2296	1.00		
			Moderately low	1979	0.97 (0.91–1.03)		
			Moderately high	2267	0.97 (0.92–1.03)		
			High	1860	0.95 (0.89–1.01)		
			Per 100 mL/day increment	9134	0.99 (0.98–0.99)		
			Trend test *P* value, 0.055				
			Coffee consumption (total, caffeinated, decaffeinated): premenopausal			Age at menarche, ever use of oral contraceptives, age at first delivery, ever breastfeeding, smoking status, education, physical activity, alcohol, height, weight, energy intake from fat and non-fat sources, total saturated fat and fibre intakes, tea intake	
			No	81	1.08 (0.83–1.4)		
			Low	246	1.00		
			Moderately low	234	1.23 (1.02–1.48)		
			Moderately high	251	1.11 (0.93–1.34)		
			High	252	1.15 (0.96–1.39)		
			Per 100 mL/ day increment	1064	1 (0.98–1.03)		
			Trend test *P* value, 0.272				

Table 2.7 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hashibe et al. (2015) USA, 1992 and 2001 (enrolment), follow-up until 2011	50 563 (1703 BC) women in PLCO Cancer Screening Trial Exposure assessment method: validated questionnaire recording coffee consumption over the previous year	Breast	*Coffee consumption: (cups/day)* < 1 1–1.9 ≥ 2 Trend test *P* value, 0.64 Per 1 cup/day increment	 599 276 828 1703	 1.00 0.95 (0.82–1.10) 0.97 (0.87–1.08) 0.98 (0.95–1.01)	Age, sex, race, education, cigarette pack-years, alcohol drinking frequency	Strengths: prospective design, detailed tobacco smoking adjustments, large sample size Limitations: lack of longitudinal data on exposure, lack of adjustment on reproductive factors, no specific focus on BC
Lukic et al. (2016) Norway, 1991–1992, 1996–1997, 2003, and 2004 (enrolment), follow-up from 1996–2013	91 767 (3277 cases) participants of NOWAC cohort Exposure assessment method: FFQs at each follow-up visit from 1998, recording (type of) coffee consumption over the previous year	Breast	*All types of coffee consumption (cups/day)* ≤ 1 > 1 to ≤ 3 > 3 to ≤ 7 > 7 Trend test *P* value, 0.06	 626 1106 1363 182	 1.00 0.93 (0.84–1.02) 0.91 (0.82–1.00) 0.87 (0.71–1.06)	Menopausal status, smoking status, education, BMI, physical activity level, alcohol consumption, number of children age at first birth, use of HRT, maternal history of breast cancer	Strengths: prospective design, large sample size, random sample from the general population, high levels of coffee consumption, complete follow-up, validated FFQ, repeated measurements of coffee consumption and confounders, thorough analysis and use of multiple imputation Limitations: relatively low response rate

ACS, American Cancer Society; BC, breast cancer; BMI, body mass index; BWHS, Black Women's Health Study; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ER(+/–), estrogen receptor (positive/negative); FFQ, food frequency questionnaire; HRT, hormone replacement therapy; IWHS, Iowa Women's Health Study; JPHC, Japan Public Health Center-based Prospective; mo, month(s); NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health – American Association of Retired Persons; NOWAC, Norwegian Women and Cancer; NR, not reported; PR(+/–), progesterone receptor (positive/negative); RR, relative risk; SMC, Swedish Mammography Cohort; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; VIP, Västerbotten Intervention Project; WHS, Women's Health Study; WLH, Women's Lifestyle and Health; wk, week(s); yr, year(s)

follow-up, 51 incident cases of breast cancer were identified by linkage to the Danish Cancer Registry. There was a positive, albeit not statistically significant, association between highest (≥ 7 cups/day) coffee consumption and breast cancer risk (HR, 1.7; 95% CI, 0.7–4.3; *P* for trend, > 0.20) compared with lowest coffee consumption (≤ 2 cups/day). [It is not clear whether this risk estimate was adjusted for the same factors as the association between serum lipids (the main exposure) and breast cancer risk (social class, age at menarche, menopause status, number of full-term pregnancies, height, weight, BMI, alcohol consumption, and smoking). The strength of this study was its linkage to a cancer registry which is regarded as virtually complete; the subjects were therefore a representative sample. Limitations included the small number of cases and the limited interest in the association between coffee consumption and risk of breast cancer.]

Folsom et al. (1993) investigated the association between caffeine intake and the incidence of postmenopausal breast cancer in the Iowa Women's Health Study. Among 34 388 women aged 55–69 years in 1986 who were followed for 5 years (up to 1990), 580 incident breast cancer cases were identified by matching with the Iowa Health Registry, part of the National Cancer Institute's SEER Program. Hazard ratios of coffee intakes in relation to breast cancer incidence were adjusted for age, waist/hip ratio, and a large number of reproductive and family history variables. Smoking was apparently not accounted for. There was no apparent association between breast cancer occurrence and regular coffee or caffeine intake. [The limitations of this study included the short follow-up period and correspondingly low number of cases.]

Stensvold & Jacobsen (1994) analysed data from Norwegian residents in three counties who accepted an invitation to participate in a cardiovascular screening programme organized by the National Health Screening Service during 1977–1982. After an average of 10 years of follow-up, 211 breast cancer cases out of 21 238 women were identified through linkage to the Norwegian Cancer Registry and to the Norwegian Central Bureau of Statistics. Coffee intake was assessed through a validated FFQ enquiring about usual consumption in cups/day. Hazard ratios for breast cancer risk in association with coffee intakes of ≤ 2, 3–4, 5–6, and ≥ 7 cups/day were 1.0, 1.1, 1.4, and 1.2 respectively, after adjustment for age, cigarettes per day, and county of residence. [No confidence intervals were reported for these associations.] The estimated hazard ratio for an increment of 1 cup/day was 1.07 (95% CI, 0.94–1.22). No interaction by BMI was evident. [The strengths of this study included the comprehensive definition of cases and the validated FFQ for coffee intake. Limitations included the small number of cases, minimal confounding adjustment (i.e. not for reproductive history), and no confidence intervals reported for categories of exposure.]

The association between soya, as well as other foods and beverages (including coffee), and breast cancer risk was investigated in a prospective study of 34 759 women in Hiroshima and Nagasaki (Japan) by Key et al. (1999). The women were survivors of the atomic bombing in the Radiation Effects Research Foundation's Life Span Study who had completed at least one of two similar mail surveys sent out in 1969–1970 (survey 1) and 1979–1980 (survey 2). A null association between breast cancer risk and coffee intake was apparent in analyses adjusted for age, calendar time, city, and radiation dose, but not other established risk factors. [The strengths of this study were the comprehensive identification of cases and adequate statistical analyses. Limitations included: a lack of detailed analysis for coffee intake (since the major exposure was soya); a lack of generalizability of results due to the distinct population studied; the use of a non-validated dietary questionnaire; and the lack of information regarding potentially important confounders for breast cancer.]

Michels et al. (2002) studied the association between coffee, tea, and caffeine consumption and breast cancer incidence among 59 036 women (aged 40–76 years) during 1987–1990 in the population-based Swedish Mammography Cohort. Information on coffee drinking was obtained through a self-administered semiquantitative FFQ, validated for coffee/tea intakes, assessing diet over the 6 months before recruitment. During 508 267 person-years of follow-up, 1271 histologically confirmed cases of invasive breast cancer were identified by linkage with the regional cancer registries. Hazard ratios for the studied association were adjusted for several variables, but not for smoking. Coffee consumption was not associated with breast cancer incidence, overall or in subgroups by BMI and age at enrolment. [The strengths of the study included: use of a population with high coffee intake; the selection of, practically, all female residents of two cities in Sweden aged 40–76 years; validation of the FFQ for coffee consumption; and ascertainment of outcome through linkage to a cancer registry.]

In a subsequent paper based on the Swedish Mammography Cohort, Larsson et al. (2009) used data from 61 433 women to investigate the association between coffee, tea, and caffeine intake and breast cancer risk, overall as well as by estrogen/progesterone receptor (ER/PR) status. At least some of the participants included in the study by Michels et al. (2002) apparently coincide with the women included in the Larsson et al. (2009) study. Diet was assessed with a baseline FFQ (see description in study by Michels et al., 2002), but also used information gathered in 1997 in a second self-administered FFQ (to assess long-term effect of diet on breast cancer risk). Mean follow-up in 2009 was 17.4 years (1 071 164 person-years), during which 2952 incident cases of invasive breast cancer were ascertained; information on ER/PR status was also obtained for the majority of the cases. Null associations between coffee intake and breast cancer, overall as well as within ER-negative/PR-negative, ER-positive/PR-negative, and ER-positive/PR-positive breast cancer, were estimated after adjusting for various potential confounders, but not for smoking. The association did not differ by menopausal status, postmenopausal hormone use, or BMI. [A strength of this study was the repeated measures of coffee intake.]

Suzuki et al. (2004) investigated the association between risk of breast cancer and consumption of green tea and other beverages, including coffee by pooling data from two population-based prospective cohort studies of women in Japan. Women of age > 40 years were recruited in 1984 and 1990, and completed self-administered validated questionnaires covering recent or usual consumption of beverages including coffee. Hazard ratios of breast cancer risk associated with consumption of coffee in each cohort, as well as after pooling the respective data, were adjusted for potential confounders including somatometry, reproductive history, and smoking. Inverse, but not statistically significant, associations between risk of breast cancer and consumption of coffee were observed. Compared with women who never drank coffee, the pooled multivariate hazard ratios (95% CI) were 0.78 (0.53–1.13) for those drinking coffee occasionally and 0.81 (0.55–1.18) for those drinking ≥ 1 cups/day (*P* for trend, 0.44). [The limitations of this study were the small number of cases and the lack of detailed examination of coffee intake (since green tea was the exposure of interest).]

Coffee intake and risk of breast cancer was examined in a study by Hirvonen et al. (2006) in 4396 apparently healthy French women participating in the double-blind, placebo-controlled, French Supplémentation en Vitamines et Minéraux Antioxydants Study (SU.VI.MAX) of primary prevention of cardiovascular diseases with vitamin and mineral supplements. Women were aged 35–60 years at recruitment (1994) and were followed up for a median of 6.6 years. Assessment of diet (including coffee)

was performed through self-administration of a computerized 24-hour dietary record every 2 months (i.e. 6 times per year). Women who completed at least three 24-hour dietary records during the first follow-up year were included in the analysis. Hazard ratios for the studied association were adjusted for some potential confounders, but not for randomization arm. Results revealed no association between coffee consumption and breast cancer risk. [The strength of this study was the close monitoring and efficient detection of breast cancer cases due to frequent examination of participants (every year). Limitations included the fact that some reproductive factors (i.e. age at menarche/menopause), as well as hormone replacement therapy (HRT) and randomized treatment, were not adjusted for. The results may also have limited generalizability due to the eligibility criteria for participation in the clinical trial.]

Ganmaa et al. (2008) analysed data from 85 987 female participants (aged 30–55 years), recruited in 1976 in the Nurses' Health Study and followed up from 1980 to 2002 (1 715 230 person-years). Intake of coffee (and other beverages) was repeatedly assessed in 1980, 1984, 1986, 1990, 1994, and 1998 through a FFQ validated for coffee intake, assessing consumption over the previous year. Models were adjusted for an exhaustive number of potential confounders, mostly detailed for reproductive history and somatometry. Hazard ratios for breast cancer risk associated with caffeinated and decaffeinated coffee suggested inverse associations which were not statistically significant. There was no evidence for modification of the indicated associations by BMI. [The strengths of this study included: the large number of cases (long follow-up); repeated measures of coffee intakes, enabling comprehensive statistical analysis; validation of the FFQ for coffee; and extensive adjustment for potential confounders.]

In another study, Ishitani et al. (2008) studied the association between coffee/caffeine and incidence of breast cancer using data from 38 432 female US health professionals, aged ≥ 45 years in 1992 when recruited to the randomized clinical trial of the Women's Health Study (low-dose aspirin and vitamin E for the primary prevention of cancer and cardiovascular disease). Hazard ratios for breast cancer in relation to coffee and caffeine consumption were adjusted for a large number of potential confounders, as well as for randomized treatment. Intakes of coffee (and of decaffeinated coffee) were not associated with overall risk of breast cancer. Among women with a history of benign breast disease, an increased risk of breast cancer was seen for consumption of ≥ 4 cups/day of coffee (adjusted HR, 1.35; 95% CI, 1.01–1.80; *P* for trend, 0.08; *P*-interaction, 0.05). No modifications by BMI, menopausal status, or postmenopausal hormone use were evident. [The advantages of this study were the large number of cases and close monitoring. Limitations included the lack of repeated measures of coffee intake, and selective inclusion of participants fulfilling the eligibility criteria for the randomized study.]

Wilson et al. (2009) reported on coffee intake in relation to premenopausal breast cancer risk in a study focusing mainly on acrylamide intake. Data from 90 628 premenopausal women, aged 26–46 years when they participated in the US-based Nurses' Health Study (NHS) II study in 1991, were used. Questionnaires and validation methods for assessment of coffee intake were similar to those used by Ganmaa et al. (2008), as were methods for case ascertainment. Relative risks for coffee, stratified for age and calendar year, were estimated and further adjusted for many potential confounders. Null associations between coffee intake (assessed in quintiles) and risk of breast cancer were evident in this study. [The study was limited by the lack of detailed examination of coffee in relation to breast cancer risk, since the effect of exposure to acrylamide was the main focus.]

Boggs et al. (2010) prospectively examined the relation of coffee consumption to the risk of breast

cancer among 52 062 African-American women from all regions of the USA, aged 21–69 years at enrolment (1995), in the Black Women's Health Study. A validated FFQ was self-administered at baseline in 1995 and in 2001 to assess dietary intakes. Hazard ratios for the studied association were adjusted for many potential confounders. Intake of coffee was not associated with risk of breast cancer overall, or by menopausal status or hormone receptor status (assessed in a subsample of the initial cohort). [This study had many strengths, including: use of a population-based sample; the extended follow-up; repeated measures of coffee intake; advanced statistical analysis with time-varying covariates for exposures/potential confounders; and extensive adjustment for potential confounders, minimizing residual confounding. It was limited by the specific population of African-American women who were examined.]

Nilsson et al. (2010) investigated whether consumption of filtered or boiled coffee is associated with a risk of developing cancer overall via the population-based Västerbotten Intervention Project (VIP). Data on diet were collected during 1992–2007 for 32 178 women aged > 29 years through a semiquantitative FFQ. Subjects were followed up for a median of 6 years and 587 breast cancer cases were identified by linking the VIP database with the regional cancer registry. Hazard ratios for cancer risk with respect to total, brewed, or boiled coffee consumption were adjusted for sex, age, BMI, smoking, education, and recreational physical activity. For breast cancer, a decreased risk was observed overall in women drinking boiled coffee at a frequency of ≥ 4 times/day compared with < 1 time/day (HR, 0.52; 95% CI, 0.30–0.88), but with no indication of a trend (*P* for trend, 0.247). Total and filtered coffee were not associated with breast cancer risk overall, but there was evidence for effect modification with age/menopausal status. Among women < 49 years of age, both total and filtered coffee intakes were associated with increased risk; the hazard ratio (95% CI) for a consumption frequency of ≥ 4 times/day versus < 1 time/day was 1.69 (0.96–2.98; *P* for trend, 0.015) for total coffee and 1.76 (1.04–3.00; *P* for trend, 0.045) for filtered coffee. An opposite tendency was seen in women > 55 years of age; the hazard ratio (95% CI) for a consumption frequency of ≥ 4 times/day versus < 1 time/day was 0.60 (0.39–0.93; *P* for trend, 0.006) for total coffee and 0.64 (0.44–0.94; *P* for trend, 0.045) for filtered coffee. [The strengths of this study included: use of a population with very high levels of coffee consumption; investigation of the association between the method of preparing coffee and cancer risk; population-based data collection, and comprehensive case-ascertainment. It was however limited by the low participation rates for the enrolment period examined and the lack of information on menopausal status (age is used as a proxy marker) and other reproductive history variables. The Working Group also noted a discrepancy between data reported in the tables and the abstract of this paper.]

Iwasaki et al. (2010) used data from two cohorts participating in a Public Health Center-based Prospective Study, undertaken in municipalities supervised by 11 public health centres in Japan to investigate whether green tea was associated with a risk of breast cancer. Coffee intake was used as a potential confounder in the indicated association, but relative risk estimates for breast cancer were also reported for coffee consumption. Recruitment began between 1990 and 1993; 53 793 participating women (aged 40–69 years at recruitment) completed a self-administered questionnaire on beverage intakes at baseline and most (43 639) completed a second more detailed questionnaire 5 years after baseline. Analysis was conducted separately for the baseline–2006 period and for the 1995–1998 to 2006 period to account for the different questionnaires used for the assessment of exposures. Adjustment was performed for a large number of potential confounders, including family history of

breast cancer and intakes of different types of tea. Adjusted hazard ratios (95% CI) for breast cancer risk associated with coffee intakes of < 1 cup/week, 1–4 cups/week, 1–2 cups/day, and ≥ 3 cups/day were 1.00, 1.15 (0.91–1.46), 1.12 (0.87–1.43), and 1.22 (0.87–1.71) (*P* for trend, 0.26) using the baseline data analysis. The respective hazard ratios for the 5-year follow-up data analysis were apparently similar. [Particular strengths of this study included its population-based design and comprehensive case-ascertainment. It was however limited by the relatively low consumption of coffee in this population and the difficult-to-follow statistical analysis.]

Data from the Etude Epidémiologique auprès des Femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort were analysed by Fagherazzi et al. (2011). The study population was composed of 67 703 French women of age 40–65 years at recruitment (1990); the women were mainly teachers and insured by the national health insurance system. Usual diet over the previous year was assessed using a detailed validated dietary history questionnaire, self-administered in 1993. After a median follow-up of 11 years (707 137 person-years) to June 2005, 2868 cases of invasive breast cancer were diagnosed. Coffee consumption was not associated with risk of breast cancer, either overall or by menopausal or ER/PR status. [The strengths of this study included the substantial number of cases, case-ascertainment through pathology reports, and time-dependent confounding variables. Limitations included the lack of repeated measures for diet and therefore coffee consumption.]

Gierach et al. (2012) evaluated the association between coffee intake and incident breast cancer in 198 404 female residents of 8 US states aged 50–71 years when recruited in the NIH-AARP Diet and Health Study cohort. Assessment of coffee consumption was made via a validated FFQ questionnaire. By linking with a state cancer registry and mortality index, 9915 primary incident breast carcinomas were identified in 2006. Hazard ratios for breast cancer associated with coffee intake were adjusted for an exhaustive list of potential confounders, including family history of breast cancer. Effect modification by BMI, HRT use, smoking, alcohol, history of breast biopsy, family history of breast cancer, ER/PR status, stage at diagnosis, tumour grade, and histologic type was also examined. The association of coffee intake with breast cancer risk was essentially null, and results did not vary with BMI or history of benign breast biopsy. In analyses by type of tumour, no clear patterns emerged in the relationships between coffee intake and risk of any of the tumour characteristics. [The strengths of this study were its coverage of eight US states, the large number of subjects, the availability of extensive information on potential confounding factors, and the examination of associations for many clinical features of breast tumours. It was however limited by a lack of repeated assessment of coffee intake.]

Oh et al. (2015) studied the association between coffee, caffeine, and tea consumption and risk of breast cancer among 42 099 women participating in the Swedish Women's Lifestyle and Health (WLH) study during 1991–1992. Coffee consumption (cups/day) was assessed through a postal validated FFQ. Follow-up lasted until 2012 (856 529 person-years), and 1395 breast cancer cases were identified via linkage to national registries. Increased coffee intakes were associated with decreased breast cancer risk: compared with women consuming 1–2 cups/day of coffee, those consuming 3–4 cups/day or ≥ 5 cups/day had relative risks (95% CI) of 0.87 (0.76–1.00) and 0.81 (0.70–0.94), respectively. There was an indication of a dose–response pattern in breast cancer risk: relative risk was 0.97 (95% CI, 0.94–0.99) for a 1 cup/day increase in coffee consumption. Similar patterns/estimates were observed for pre- and postmenopausal breast cancer. [The strengths of this study included: use of population-based samples, extended follow-up, and examination of the studied association by

ER/PR status. The list of factors adjusted for was quite limited, but this reflects the authors' decision to adjust for only those variables which were statistically significant. Coffee intake was only assessed at baseline, although consumption may have changed during the 10 years of follow-up.]

The association between coffee (and tea) consumption and risk of pre- and postmenopausal breast cancer was examined by Bhoo-Pathy et al. (2015), undertaken in the EPIC cohort study. [Of note, this study also includes data from the EPIC-Netherlands study that was previously published by Bhoo-Pathy et al. (2010)]. A total of 335 060 women aged 25–70 years, recruited during 1992–2000 from 10 European countries, were followed up until 2010; 10 198 incident breast cancer cases were identified. Diet was assessed with self- or interviewer-administered validated (for diet) country-specific questionnaires (usually FFQs). Total coffee intake was associated with a lower risk of postmenopausal breast cancer, with no indication for modification by ER/PR status. The hazard ratio of consuming high versus low quantities of coffee was 0.95 (95% CI, 0.89–1.01; *P* for trend, 0.055), and a 100 mL/day increment yielded a hazard ratio of 0.99 (95% CI, 0.98–0.99). [This study had the advantages of: a large number of breast cancer cases, even for premenopausal breast cancer; a multicountry design, ensuring variation in coffee and types of coffee consumption; and a comprehensive and exhaustive statistical analysis. It was however limited by a lack of repeated assessments of coffee consumption, which may be important after 10 years of follow-up.]

Hashibe et al. (2015) investigated the association between coffee intake and cancer using data from the PLCO Cancer Screening Trial, aimed at evaluating the effectiveness of cancer screening tests in reducing mortality. Between 1992 and 2001, 50 563 women were recruited at 10 centres across the USA (Alabama, Michigan, Colorado, Hawaii, Wisconsin, Minnesota, Pennsylvania, Utah, Missouri, and Washington DC) and followed up until 2011; a total of 1703 breast cancer cases were identified. Coffee intake was assessed with a validated questionnaire recording coffee consumption over the 12 months preceding enrolment. For breast cancer, a null association with coffee intake was observed in women drinking 1–1.9 cups/day or ≥ 2 cups/day of coffee compared with minimal consumption (0–1 cups/day), or for 1 cup/day increment. [This study had the advantage of a prospective design and large sample size. Limitations included a lack of longitudinal data on exposure, a lack of adjustment for reproductive factors, and a lack of specific focus on breast cancer.]

Results of a study on coffee consumption and risk of cancer, with a special interest in breast cancer, was published by Lukic et al. (2016). The authors used the Norwegian Women and Cancer (NOWAC) cohort which comprises random samples of Norwegian women aged 30–70 years. Enrolment was conducted between 1991 and 2004 and subjects were followed up from 1996 to 2013. Information on coffee consumption was obtained via FFQs at each follow-up visit from 1998, recording type of coffee consumption over the previous year. To account for missing values, multiple imputation was carried out. The estimated hazard ratios (95% CI) for breast cancer risk were 1.00, 0.93 (0.84–1.02), 0.91 (0.82–1.00), and 0.87 (0.71–1.06) for consumption of ≤ 1 cup/day, > 1 to ≤ 3 cups/day, > 3 to ≤ 7 cups/day, and > 7 cups/day, respectively (*P* for trend, 0.06). After excluding cases of breast cancer diagnosed during the first 2 years of follow-up, associations among coffee consumers of low and high–moderate quantities compared with the reference group reached statistical significance with a *P* for trend of 0.01. [The strengths of this study included its prospective design, large sample size, random sample from the general population, high levels of coffee consumption, complete follow-up via linkage to the Norwegian Cancer Registry, validated FFQ, repeated measurements of coffee consumption

and of confounders, thorough analysis, and the use of multiple imputation.]

(b) Fatal cancer of the breast

In an early cohort study, Snowdon & Phillips (1984) investigated the association between coffee intake and cancer mortality (including 176 breast cancer deaths), as identified during 1960–1980 (21-year follow-up) in 23 912 white Seventh-day Adventists (aged ≥ 30 years in 1960), a religious group with very low prevalence of coffee consumption. The number of cups of coffee consumed per day was recorded by self-administered questionnaires, identical to those used by the American Cancer Society Study. Hazard ratios for coffee consumption in relation to cancer mortality, overall and by site, adjusting for age, sex, meat consumption, and smoking history, indicated null associations for fatal breast cancer. [This study was limited by: (1) the possibility of reporting bias; (2) the fact that coffee consumption is rare in this population; (3) the number of events was small, as cancer mortality and not incidence was the end-point; and (4) no adjustment for important risk factors was made, perhaps resulting in residual confounding.]

2.4.2 Case–control studies

See Table 2.8.

A potential limitation of case–control studies included in this report is, in general, the possibility of recall bias regarding the self-reported coffee consumption. Additional limitations and strengths are noted for each study.

(a) Population-based case–control studies

Schairer et al. (1987) conducted a case–control study on methylxanthine consumption and breast cancer risk in participants in the Breast Cancer Detection Demonstration Project in the USA. Breast cancer cases were women diagnosed from June 1977 to November 1980. Control subjects were women who had not been recommended for, and had not undergone, surgical evaluation during screening participation, and who were similar to breast cancer cases regarding certain characteristics including age and screening centre. Response rates were high, at 73% and 90% for cases and controls. Home interviews were obtained for the 1510 cases and 1882 controls enquiring (among other items) for both seasonal and year-round consumption of methylxanthine-containing beverages, including brewed/instant coffee with caffeine and decaffeinated coffee. Although Schairer et al. (1987) mention adjustment for potential confounders, no further information was given on the actual factors adjusted for in the analysis. Neither instant nor brewed caffeinated coffee consumption was associated with increased risk of breast cancer. Consumers of ≥ 5 cups/day of instant coffee with caffeine had an odds ratio of 0.7 (95% CI, 0.3–1.3) compared with non-drinkers (*P* for trend, 0.04), suggestive of a negative association. [The strengths of this study include the detailed assessment of coffee at multiple levels of consumption and over a long period before diagnosis (therefore eliminating misclassification and recall bias). Limitations included the lack of information on adjusting variables, although the authors mentioned that adjustment did not materially alter the reported results.]

Ewertz & Gill (1990) examined the association between dietary factors, including coffee, and breast cancer risk in a case–control study in Denmark including 1474 breast cancer cases (aged < 70 years). The cases were diagnosed during a 1-year period (March 1983 to February 1984), as identified by the Danish Cancer Registry and the nationwide clinical trial of the Danish Breast Cancer Cooperative Group. The 1322 women in the control group were an age-stratified random sample from the general population selected from the Central Population Registry. Data on diet were collected by self-administered semiquantitative FFQs, mailed to the cases 1 year after diagnosis to assess diet during the

Table 2.8 Case–control studies on cancer of the breast and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lubin et al. (1985) Israel, 1975–1979 (enrolment), 1975–1979	Cases: 807 cases from Tel Aviv metropolitan area Controls: 738 surgical and 807 neighbourhood controls matched by age, country of origin, length of residence in Israel Exposure assessment method: questionnaire; face-to-face interviews on the frequency of consumption 1 year before interview and within the previous decade	Breast	*Past coffee consumption (cups/day): surgical controls* 0 1 2–3 ≥ 4 *Past coffee consumption (cups/day): neighbourhood controls* 0 1 2–3 ≥ 4	 129 159 308 142 141 176 335 155	 1.0 0.7 (0.4–1.1) 0.7 (0.4–1.0) 0.7 (0.4–1.1) 1.0 0.5 (0.3–0.9) 0.5 (0.2–0.9) 0.6 (0.2–0.9)	Age, country of origin, length of residence in Israel	Methylxanthines daily intake was a co-exposure Strengths: inclusion of two control sets, face-to-face interview for obtaining detailed information on exposure, accounting for present and past exposure Limitations: lack of adjustment for confounders other than the matching factors
Rosenberg et al. (1985) Eastern USA, 1975–1982	Cases: 2651 first primary BC inpatients aged 30–69 yr from hospitals Controls: two control groups of patients aged 30–69 yr when admitted to the same hospitals. 1st group: 1501 women with acute non-malignant conditions (trauma or infections); 2nd group: 385 women with selected malignancies (malignant melanoma, lymphoma and leukaemia) Exposure assessment method: questionnaire; nurse-interviewers collected information on consumption of caffeinated and decaffeinated coffee during the several months before admission	Breast	*Coffee consumption (cups/day)* 0 1–2 3–4 ≥ 5 *Coffee consumption (cups/day)* 0 1–2 3–4 ≥ 5	 493 1015 721 413 493 1015 721 413	 1.0 1.0 (0.7–1.4) 0.9 (0.7–1.3) 1.1 (0.7–1.6) 1.0 1.2 (1.0–1.5) 1.2 (1.0–1.6) 1.2 (0.9–1.6)	Age, race, religion, cigarette smoking, age at menarche, age at first pregnancy, parity, type of menopause, age at menopause, history of fibrocystic breast disease, family history of BC (in the mother or sister(s)), BMI, years of education, tea, alcohol consumption, location of the hospital, year of interview, number of previous non-obstetric hospitalizations	Strengths: selection of two control groups, the exhaustive adjustment for potential confounders, additional examination of decaffeinated coffee Limitations: selection of hospital-based controls in both groups (which may have introduced selection bias), possibility of recall bias regarding coffee consumption

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Katsouyanni et al. (1986) Greece (Athens), 1983–1984	Cases: 120 patients admitted in two teaching hospitals in the greater Athens area Controls: 120 admitted for accidents and orthopaedic disorders in a third teaching hospital, chosen sequentially on the basis of sex and age Exposure assessment method: questionnaire; dietary histories concerning the consumption frequency of 120 foods and drinks obtained by interview regarding the period prior to onset of disease	Breast	*Coffee: frequency of use (tertiles)* 1st tertile 2nd tertile 3rd tertile	 29 65 24	 1.00 [0.97] [0.89]	Adjusted for age, interviewer, length of schooling, other significant food groups	Crude ORs were estimated by the numbers given in table 2 of the respective publication Strengths: detailed assessment of diet by face-to-face interviews Limitations: potential selection bias for cases and controls (not selected from the same hospitals as cases), lack of detailed information and investigation of coffee (no OR reported)
Schairer et al. (1987) USA, 1977–1980 (diagnosis)	Cases: 1510 participants in the BC Detection Demonstration Project Controls: 1882 participants of the same project Exposure assessment method: questionnaire, home interviews for both seasonal and year-round consumption of methylxanthine-containing beverages, including regular and decaffeinated coffee	Breast	*Brewed coffee consumption (cups/day)* 0 < 1 2 3 4 ≥ 5 Trend test *P* value, 0.27 *Instant coffee consumption (cups/day)* 0 < 1 2 3 4 ≥ 5 Trend test *P* value, 0.04	 171 502 311 205 127 194 766 555 106 48 19 16	 1.0 1.0 (0.8–1.3) 1.0 (0.7–1.2) 0.9 (0.7–1.2) 0.9 (0.7–1.3) 1.0 (0.8–1.3) 1.0 0.9 (0.8–1.1) 0.9 (0.7–1.2) 0.9 (0.6–1.3) 0.9 (0.5–1.7) 0.7 (0.3–1.3)	Unclear which factors were adjusted for	Crude, unmatched ORs are probably reported Strengths: detailed assessment of coffee in multiple levels of consumption Limitations: possibility of recall bias, lack of information on adjustment for potential confounders

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ewertz & Gill (1990) Denmark, 1983–1984	Cases: 1474 from Danish Cancer Registry Controls: 1322 age-stratified random samples from the general population Exposure assessment method: self-administered semi-quantitative FFQs	Breast	*Coffee consumption (cups/day)* < 3 3–5 6–9 ≥ 10	 358 643 348 82	 1.00 0.83 (0.68–1.00) 0.86 (0.69–1.07) 0.81 (0.57–1.15)	Age at diagnosis, place of residence	Strengths: use of cancer registry for identifying cases, population-based controls, FFQ, large number of cases Limitations: FFQ validated for fat and β-carotene intakes (main exposures) but not for coffee, possibility of recall bias, lack of adjustment for several important confounders
McLaughlin et al. (1992) USA (18 contiguous counties in eastern New York State), 1982 and 1984 (enrolment)	Cases: 1617 identified through hospital diagnostic index, tumour registry, pathology files, and the New York State Cancer Registry Controls: 1617 frequency-matched to cases on year of birth and county of residence from New York State Department of Motor Vehicles' files Exposure assessment method: questionnaire; telephone interviews	Breast	*All coffee: drinker vs non-drinker* Non-drinker Drinker	 154 1463	 1.00 0.98 (0.76–1.26)	Age, county of residence, race, menstrual status, age at first live birth, history of benign breast disease, family history of breast cancer, alcohol intake	Strengths: large numbers, thorough identification of BC cases, 70–80% participation rate, population-based controls Limitations: crude assessment of coffee intake (ever vs never consumed), apparent lack of adjustment for smoking, possibility of recall bias

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Levi et al. (1993a) Switzerland, 1992	Cases: 107 admitted to the University Hospital of Lausanne and linked to incidence data from Vaud Cancer Registry Controls: 318 admitted to hospital for acute, non-hormone-related, gynaecological, metabolic, or neoplastic disorders Exposure assessment method: questionnaire; interviewer assessment of weekly frequencies of coffee intake before the occurrence of symptoms	Breast	*Tertiles of coffee consumption* 1st tertile 2nd tertile 3rd tertile [Trend test *P* value, 0.93]	 32 42 33	 1.0 0.8 0.9	Age	Strengths: identification of cases confirmed with linkage to incidence data from Vaud Cancer Registry Limitations: no CI are reported, information for adjusting the reported ORs is not clear, limited adjustment is mentioned in the text
Tavani et al. (1998) Italy, 1983–1991 and 1991–1994	Cases: 5984 histologically confirmed BC, aged 22–74 yr Controls: 5504 admitted to hospital for non-traumatic orthopaedic disorders (32%), acute surgical conditions (17%), and miscellaneous other illnesses, aged 15–74 yr Exposure assessment method: questionnaire; frequency of consumption of regular coffee, cappuccino, decaffeinated coffee	Breast	*Coffee consumption (cups/day)* Non-drinkers < 2 2 > 2 to < 4 ≥ 4	 812 1430 1596 1346 784	 1.00 1.17 (1.03–1.33) 1.17 (1.04–1.33) 1.21 (1.06–1.37) 0.96 (0.83–1.11)	Study/centre, age, education, BMI, smoking status, total alcohol intake, age at menarche and menopause, parity and age at first birth, use of oral contraceptives, use of HRT, history of benign breast disease, family history of BC	Reports no trend but gives no *P* value Strengths: substantial numbers, participants from many areas, adjusted for important risk factors Limitations: hospital-based cases and controls, possibility of recall bias

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wu et al. (2003) USA (Los Angeles City), 1995–1998	Cases: 501 Chinese, Japanese and Filipino women participants of Los Angeles County Cancer Surveillance Program, and California Cancer Registry Controls: 594 selected from the same neighbourhoods as cases Exposure assessment method: FFQ, in-person interviews recording dietary intake during the year before cancer diagnosis (for cases) or during the previous year (for controls)	Breast	*Regular coffee consumption (mL/day)* None > 0–120 > 120 to ≤ 240 > 240 Trend test *P* value, 0.14 *Regular and decaffeinated coffee consumption (mL/day)* None > 0–120 > 120 to ≤ 240 > 240 Trend test *P* value, 0.14	 193 96 107 105 135 94 120 152 	 1.00 1.16 (0.78–1.72) 0.90 (0.63–1.29) 0.77 (0.53–1.12) 1.00 0.91 (0.60–1.38) 0.80 (0.55–1.19) 0.77 (0.52–1.13) 	Education, age at menarche, pregnancy, current BMI, total caloric intake, menopausal status, use of menopausal hormones, intake of soy, dark green vegetables, smoking history, alcohol intake, physical activity, family history of BC	Decaffeinated coffee examined also. Main exposure was green tea consumption. Strengths: population-based cases, adjustment for many risk factors, detailed assessment of exposure Limitations: potential of recall bias, modest sample size, low participation rate, results confined to Chinese, Japanese, and Filipino women who live in the USA
Baker et al. (2006) USA, 1982–1988	Cases: 1932 identified from the RPCI tumour registry Controls: 1895 randomly selected from a pool of 5700 eligible subjects, who received medical services at RPCI for non-neoplastic conditions Exposure assessment method: questionnaire; coffee consumption recorded collected using the PEDS questionnaire	Breast	*Regular coffee consumption (cups/day): premenopausal women* None < 1 1 2–3 ≥ 4 Trend test *P* value, 0.03 *Regular coffee consumption (cups/day): postmenopausal women* None < 1 1 2–3 ≥ 4 Trend test *P* value, 0.57	 136 45 34 126 57 462 159 180 472 261 	 1.00 1.23 (0.73–2.07) 0.95 (0.52–1.71) 0.94 (0.65–1.39) 0.62 (0.39–0.98) 1.00 0.89 (0.69–1.15) 0.93 (0.73–1.19) 1.11 (0.92–1.34) 0.99 (0.79–1.23) 	Age, residence, and age at birth of first child Adjusted for age and residence	Strengths: substantial numbers, examination of decaffeinated coffee, examination of the associations by menopausal status and histologic subtype of BC Limitations: limited adjustment for risk factors, no measures of relative risk for BC overall, potential selection bias due to selection of hospital-based controls with a suspicion of neoplastic disease

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gronwald et al. (2006) Poland, unknown	Cases: 348 Polish women with a diagnosed mutation in *BRCA1* who were seen at the International Hereditary Cancer Centre or affiliated outpatient clinics Controls: 348; details not given Exposure assessment method: questionnaire, mailed questionnaire	Breast	*Regular coffee consumption among* BRCA1 *mutation carriers* No Yes	 NR NR	 1.0 0.8 (0.5–1.1)	Year of birth, age at diagnosis, age at menarche, parity, smoking, breast-feeding, oral contraceptive use	Strengths: matched design, first study to concentrate on high-risk women with *BRCA1* mutation Limitations: unclear validation of the questionnaire, no response rate provided, no information on when the study was conducted, no detailed classification of coffee
Nkondjock et al. (2006) USA, Canada, Poland and Israel, 1970–2002 (diagnosis), 1977–2000 (questionnaire)	Cases: 845 *BRCA1* or *BRCA2* women with invasive BC Controls: 845 *BRCA1* or *BRCA2* women, matched by mutation in the same gene, year of birth and country Exposure assessment method: questionnaire administered by each of the individual centres at the time of a clinic appointment or at their home at a later date	Breast	*Average lifetime total coffee intake (cups/day)* 0 1–3 4–5 ≥ 6 Trend test *P* value, 0.03 *Average lifetime caffeinated coffee intake (cups/day)* 0 1–3 4–5 ≥ 6 Trend test *P* value, 0.02	 264 498 65 18 298 486 51 10	 1.00 0.89 (0.70–1.13) 0.73 (0.48–1.10) 0.51 (0.26–0.98) 1.00 0.90 (0.72–1.12) 0.75 (0.47–1.19) 0.31 (0.13–0.71)	Parity, smoking, oral contraceptive use, alcohol consumption, BMI at age 30	Strengths: substantial numbers, use of coffee as the main exposure, assessment of average lifetime coffee consumption as well as of decaffeinated coffee, adjustment for important risk factors Limitations: possibility of recall bias since the questionnaire assessing coffee consumption was distributed after BC diagnosis

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hirose et al. (2007) Japan, 1990–2000	Cases: 2122 Japanese women who visited the Aichi Cancer Center, whose data were obtained from the hospital-based epidemiological research programme Controls: 12 425 confirmed as free of cancer Exposure assessment method: questionnaire designed for the study, completed before diagnosis of BC for the cases	Breast	*Coffee intake (cups/day)* None Occasional 1–2 ≥ 3 Trend test *P* value, 0.85	 448 430 974 254	 1.00 1.00 (0.85–1.17) 1.00 (0.86–1.15) 1.04 (0.85–1.28)	Age, year, motivation for consultation, parity, age at first delivery, smoking, drinking, exercise, BMI, several dietary variables	Hormone-related cancer risk (breast, endometrial, and ovarian cancer) was the end-point examined. No modification with menopausal status was evident. Strengths: information on coffee intake and potential confounders was collected before diagnoses, substantial numbers of cases/controls were used Limitations: potential for selection bias due to use of non-cancer patients as controls, no apparent information with respect to the actual conditions of control subjects
Kotsopoulos et al. (2007) USA, Canada, 1970–2002	Cases: 170 cases from a registry of *BRCA1* and *BRCA2* mutation carriers at the Centre for Research in Women's Health in Toronto, Ontario Controls: 241, sourced as above Exposure assessment method: questionnaire completed at the time blood was drawn for genetic testing, or within a year of receiving the test result	Breast	*Coffee consumption (caffeinated or decaffeinated, before age 35 yr) of women with* BRCA1 *mutation* Never Ever Trend test *P* value, 0.04	 66 104	 1.00 0.61 (0.38–0.97)	Year of birth, parity, and smoking status	Shares data with Nkondjock et al. (2006). Strengths: detailed assessment of average lifetime coffee consumption and the assessment of past exposure to coffee Limitations: low power to investigate effect modifications, limited adjustment, assessment of exposure before the age of 35 yr makes comparison with other studies difficult, discrepancy in reporting ORs for coffee between table 2 and in results section

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bissonauth et al. (2009) Canada, 2004–2006	Cases: 280 early-onset BC patients who attended the breast centre of CHUM Hotel Dieu Controls: 280 women free from cancer, from the same families as cases or other families with BC Exposure assessment method: interviewer-administered validated FFQ covering the 2-year period before diagnosis (cases) or interview (controls)	Breast	*Coffee consumption (cups/day)* ≤ 2 > 2 to ≤ 8 > 8 Trend test *P* value, 0.03 *Coffee consumption (cups/day): premenopausal women* ≤ 2 > 2 to ≤ 8 > 8 Trend test *P* value, 0.1 *Coffee consumption (cups/day): postmenopausal women* ≤ 2 > 2 to ≤ 8 > 8 Trend test *P* value, 0.13	 102 90 88 56 64 48 30 40 42 	 1.00 1.79 (1.17–2.57) 1.40 (1.09–2.24) 1.00 1.12 (0.63–1.56) 1.09 (0.45–1.99) 1.00 1.23 (0.70–1.82) 1.30 (0.66–1.88) 	Age, education, physical activity, smoking, coffee consumption, total energy intake	Strengths: high quality of the FFQ which was interviewer administered Limitations: this study is described as nested case–control, but such a description is not justified by the information given in the manuscript
Rabstein et al. (2010) Germany, 2000–2004	Cases: 1020 women with histopathologically confirmed BC from the major hospitals of the region Controls: 1047 random sample from population registries, frequency-matched to cases by year of birth in 5-year classes Exposure assessment method: questionnaire, in-person interviews	Breast	*Coffee consumption (cups/day)* None 1–3 ≥ 4	 145 496 379	 1.00 1.02 (0.79–1.32) 1.19 (0.91–1.55)	Unclear	Strengths: population-based controls, high response rates Limitations: modest-to-large sample size, several different exposures, only age-adjusted ORs for coffee in relation to breast cancer risk, concerns about multiple testing

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2011) Sweden and Germany, 1993–1995 (Sweden), 2002–2005 (Germany)	Cases: 2818 (Swedish) and 2651 (German) postmenopausal women from registries Controls: 3111 (Sweden); 5395 (Germany) from population registries matched by age (Sweden) or age and region (Germany) Exposure assessment method: Swedish study: coffee consumption 1 year before interview recorded by mailed questionnaire; Germany: face-to-face interview through an FFQ recording consumption in the past year from diagnosis (cases) and FFQ completion (controls)	Breast	*Main study in Sweden: coffee consumption (cups/day) of postmenopausal women* ≤ 1 > 1 to ≤ 3 > 3 to ≤ 5 > 5 Trend test *P* value, 0.127 *Validation study in Germany: coffee consumption (cups/day) of postmenopausal women* ≤ 1 > 1 to ≤ 3 > 3 to ≤ 5 > 5 Trend test *P* value, 0.173	 298 1277 904 328 1086 1050 358 157 	 1.00 1.01 (0.84–1.23) 1.00 (0.82–1.22) 0.84 (0.66–1.06) 1.00 0.97 (0.87–1.07) 0.95 (0.82–1.10) 0.87 (0.71–1.07) 	Age at enrolment, HRT, smoking, education, daily alcohol consumption	Strengths: so-called validation of results obtained from the Swedish study by means of the German MARIE study (but no formal investigation of validation), large sample size, comprehensive design and analysis Limitations: recall bias, multiple testing concerns
Lowcock et al. (2013) Canada (Ontario), 2002 and 2003	Cases: 3062 from the Ontario Cancer Registry Controls: 3427 selected through RDD of Ontario households, frequency-matched on 5-year age groups Exposure assessment method: 178-item modified Block FFQ recording consumption within the previous 2 yr	Breast	*Caffeinated coffee (cups/day)* Never < 1 1 to < 2 2 to < 3 3 to < 5 ≥ 5	 540 581 594 772 429 71	 1.00 0.91 (0.77–1.07) 0.97 (0.82–1.15) 1.00 (0.85–1.17) 1.07 (0.89–1.29) 0.71 (0.51–0.98)	Age, smoking status, ethnicity, level of strenuous physical activity as a teenager (after model selection)	Strengths: substantial numbers of cases/controls; population-based selection of cases/controls Limitations: possibility of recall bias, lack of adjustment for reproductive factors

Table 2.8 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mizoo et al. (2013) Japan, 2010–2011	Cases: 472 consecutive patients with non-invasive or invasive BC aged > 20 yr at four hospitals Controls: 464 women who underwent BC screening at medical centres Exposure assessment method: self-administered questionnaires recording coffee consumption in the pre-diagnostic period (cases) or at recruitment (controls)	Breast	*Coffee consumption (times/wk):* ≤ 1 1 2–3 ≥ 4	 132 154 135 45	 1.00 0.77 (0.55–1.09) 0.68 (0.48–0.96) 0.91 (0.55–1.51)	Age	Limitations: modest size, lack of adjustment for factors other than age, possibility of selection bias due to controls being women who underwent BC screening (and may therefore have a family history of cancer), unclear reporting of study design

BC, breast cancer; BMI, body mass index; CHUM, Centre hospitalier de l'Université de Montréal; CI, confidence interval; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; MARIE, Mamma Carcinoma Risk Factor Investigation; NR, not recorded; OR, odds ratio; PEDS, Patient Epidemiology Data System; RDD, random-digit dialling; RPCI, Roswell Park Cancer Institute; wk, week(s); yr, year(s)

year before diagnosis and to the controls using a similar approach. Response rates for cases and controls were 88% and 79%, respectively. Results suggested a non-significant inverse association between coffee and breast cancer risk, but no test for trend was reported. [The strengths of this study included the use of a cancer registry for identifying cases, hence the inclusion of practically all breast cancer cases identified during the indicated period as well as an adequate numbers of cases. The study was however limited by the fact that the FFQ was validated for fat and β-carotene intakes (main exposures) but not coffee; there was also no adjustment for several confounders.]

McLaughlin et al. (1992) investigated breast cancer risk with methylxanthine consumption in a case–control study of 3234 women conducted in New York State, USA. A total of 1617 primary breast cancer cases (aged 20–79 years) were identified during 1982–1984 through the diagnostic index, tumour registry, and pathology files maintained by each hospital, as well as the New York State Cancer Registry. An equal number of controls were frequency-matched to the cases on year of birth and county of residence via random selection from the files of New York State Department of Motor Vehicles. Data on reproductive, contraceptive, and lifestyle histories, including frequency and quantity of consumption of coffee and decaffeinated coffee, were obtained through telephone interviews using structured questionnaires. Odds ratios adjusted for matching factors and other variables [but apparently not for smoking] revealed null association of coffee intake (assessed as ever vs never consumed) with breast cancer risk. [The advantages of this study were the large number and thorough identification of breast cancer cases. Disadvantages included the crude assessment of coffee intake (ever vs never consumed) and limited adjustment for confounders.]

Wu et al. (2003) investigated the association between consumption of green tea and the risk of breast cancer in a population-based, case–control study among Chinese, Japanese, and Filipino women (aged 25–74 years) in Los Angeles County during 1995–1998. A total of 501 out of 841 incident breast cancer cases, identified by the Los Angeles County Cancer Surveillance Program and the California Cancer Registry, were included in the study (non-participation rate was 42.5%). Control subjects (n = 594) were selected from the same neighbourhoods as cases, with replacement of controls who declined participation (68% participated at first attempt). Controls were frequency-matched to cases on specific Asian ethnicity and 5-year age group. Coffee intake during the year before cancer diagnosis for cases or during the previous year for controls was determined through a validated FFQ by in-person interviews. Odds ratios from conditional logistic regression, adjusting for several potential confounders including family history of breast cancer, revealed an inverse but non-statistically significant association between breast cancer risk and regular coffee (or regular plus decaffeinated coffee) intake, with no indication for trend. [The strengths of this study included the population-based cases, adjustment for many risk factors, and detailed assessment of beverage intake through an established FFQ. Limitations included the neighbourhood controls, low participation rate, and the fact that the results related only to Chinese, Japanese, and Filipino women living in the USA.]

Rabstein et al. (2010) explored the associations between potential sources of exposure to aromatic and heterocyclic amines (AHA) (including coffee consumption), as well as *N*-acetyltransferase 2 (NAT2) acetylation status, and the incidence of receptor-defined breast cancer. The population-based case–control study (GENICA; Gene Environmental Interaction and breast Cancer in Germany) was conducted within the greater region of Bonn, Germany during 2000–2004. Cases (1020) were recruited from the major hospitals of the region (response rate, 88%). Controls

(1047) were a random sample from the population registries, frequency-matched to cases by year of birth (response rate, 67%). Data on breast cancer risk factors (including coffee intake) were obtained from in-person interviews. Odds ratios adjusted for several potential confounders indicated that coffee intake was not associated with breast cancer overall, but a positive association with ER– (OR, 1.78; 95% CI, 1.05–3.02) and PR– (OR, 1.63; 95% CI, 1.00–2.67) breast cancer for those drinking ≥ 4 cups/day of coffee, compared with non-consumers, was apparent. Moreover, there was an indication of an interaction between both acetylation status and coffee intake with respect to breast cancer overall and by receptor status. [This was a complicated study dealing with several different exposures, creating the problem of multiple testing. The Working Group noted that the presentation and interpretation of the interaction between coffee and NAT2 acetylation status was unclear.]

Li et al. (2011) assessed coffee consumption in relation to postmenopausal breast cancer risk overall and by ER tumour subtypes in data from two studies. The main study was a population-based case–control study (2818 cases and 3111 controls) of postmenopausal women aged 50–74 years, resident in Sweden during 1993–1995 and identified through six Swedish regional cancer registries. Participation rate was 84%. Control subjects were randomly selected from a Swedish register and were frequency-matched to cases by age (participation rate, 82%). Analyses undertaken in this main study were validated using subjects drawn from the population-based case–control Mamma Carcinoma Risk Factor Investigation (MARIE) study undertaken during 2002–2005 in two study regions in Germany. MARIE subjects consisted of 2651 cases of postmenopausal breast cancer (women aged 50–74 years at diagnosis) and 5395 controls, randomly selected from the population registries and frequency-matched by year of birth and study region. In the Swedish study, data on coffee consumption 1 year before the interview were recorded in a section of an extensive mailed questionnaire. In the MARIE study, in-person FFQs recording consumption in the year before the date of diagnosis for cases and the date of questionnaire completion for controls were administered. In the Swedish study, odds ratios adjusted for covariates retained after model selection indicated a modest decrease in overall breast cancer risk in the fully adjusted model; the odds ratio for a coffee intake of > 5 cups/day versus ≤ 1 cup/day was 0.84 (95% CI, 0.66–1.06; *P* for trend, 0.127). For ER– and PR– breast cancer tumours, a statistically significant risk reduction was estimated from fully adjusted models for heavy coffee drinkers (coffee intake > 5 cups/day vs ≤ 1 cup/day) with odds ratios of 0.43 (95% CI, 0.25–0.72; *P* for trend, 0.0003) and 0.67 (95% CI, 0.44–1.01; *P* for trend, 0.034), respectively. For ER+ and PR+ cancers, the respective associations were inverse but not statistically significant. Similar findings in magnitude and direction were observed in the validation study, but did not reach statistical significance. [This study had the advantages of the validation of results by the German MARIE study, a large sample size, and a comprehensive design and analysis. The Working Group noted the multiple testing concerns in subgroups due to the estimation of the association in two studies, however.]

Lowcock et al. (2013) studied 3062 breast cancer cases (aged 25–74 years) diagnosed in 2002 or 2003, identified from the Ontario Cancer Registry, and 3427 controls (aged 25–74 years) selected through RDD and frequency-matched to cases by 5-year age groups. Cases and controls completed a 178-item modified Block FFQ, which included coffee and other caffeine-containing items as well as decaffeinated coffee, within the 2 years preceding the questionnaire completion. Odds ratios adjusted for covariates retained after model selection showed a significant reduction in breast cancer risk with the highest category of coffee consumption (OR, 0.71; 95% CI, 0.51–0.98)

for ≥ 5 cups/day versus non-consumers, but there was no evidence of a dose–response relationship. In analysis stratified for smoking, results similar to the overall data were observed for ever and never smokers. High coffee intake was also associated with reduced risk of ER– breast cancer (OR, 0.41; 95% CI, 0.19–0.92) and postmenopausal breast cancer (OR, 0.63; 95% CI, 0.43–0.94) for ≥ 5 cups/day versus non-consumers. Coffee intake was associated with a reduced, albeit not statistically significant, ER+ or premenopausal breast cancer risk. CYP1A2 genotype (variant rs762551) did not modify the indicated associations. [The Working Group noted the substantial numbers of cases/controls and the population-based design.]

Mizoo et al. (2013) reported results from a multicentre, case–control study of 472 breast cancer patients and 464 control subjects conducted in Japan during 2010–2011, examining associations between lifestyle as well as single nucleotide polymorphisms (SNPs) and breast cancer risk. [The Working Group noted that this is described as a population-based case–control study, but based on its description it was not possible to confirm this specific design.] Cases were consecutive patients with non-invasive or invasive breast cancer from four hospitals. Controls underwent breast cancer screening at certain medical centres. Questionnaires extracting details of lifestyle and dietary factors, including coffee consumption in the pre-diagnostic period (cases) or at recruitment (controls), were self-administered. Of the women who originally agreed to participate, 92.4% cases and 88% controls returned the questionnaires. [The Working Group noted the lack of information regarding the original number of identified cases and pool of controls.] Coffee intake of 2–3 cups/day (but not of ≥ 4 cups per day) versus < 1 cup/day was associated with a significantly decreased risk for breast cancer; the age-adjusted odds ratio was 0.68 (95% CI, 0.48–0.96). No modifications by SNPs were observed for the association between coffee intake and risk of breast cancer. [The Working Group noted that in table 1 of Mizoo et al. (2013), 'times/week' is used instead of 'cups/day' for coffee consumption, although 'cups/day' was used in the methods section. Further limitations of this study included: its modest size; insufficient adjustment; selection of cases/controls among consecutive patients; the possibility of selection bias due to controls being women who underwent breast cancer screening (and may therefore have had a family history of cancer); and no clear description of study design.]

(b) Hospital-based case–control studies

Lubin et al. (1985) conducted a hospital-based case–control study in Israel. Breast cancer cases were diagnosed between 1975 and 1979 [the Working Group noted that in the abstract this year is reported as 1978, but in the methods section as 1979] in the greater Tel Aviv metropolitan area. Two control series – surgical controls (SC) hospitalized primarily due to orthopaedic problems (34%) or hernia (22%), and neighbourhood controls (NC) drawn from voting lists – were used. All controls were matched individually to a case by age, country of origin, and length of residence in Israel. The analysis included 738 case-control pairs using surgical controls and 807 case-control pairs using neighbourhood controls. Information regarding the frequency of consumption of 250 food and beverage items 1 year before interview and during the 10 preceding years was sought through face-to-face interviews. Response rates among the eligible subjects were 96% for cases and surgical controls, and 72% for neighbourhood controls. Odds ratios for breast cancer risk adjusted for the matching factors indicated an inverse association with past coffee intake, an association which was similar in magnitude in breast cancer/SC and breast cancer/NC pairs. For women consuming ≥ 4 cups/day of coffee, the odds ratio was 0.7 (95% CI, 0.4–1.1) for SC and 0.6 (95% CI, 0.2–0.9) for NC. Similar results

were evident for current coffee consumption. [The strengths of this study were the inclusion of two control sets, the face-to-face interviews, and detailed information on exposure which considered both present and past exposure. Limitations were the lack of adjusting for confounders and possibility of selection bias due to the medical conditions of the selected surgical controls.]

Rosenberg et al. (1985) analysed data obtained in a case–control programme for the surveillance of drug effects in hospitals located in eastern USA. A total of 2651 cases [the Working Group noted that 2651 cases are reported most often, but 2650 are reported in the materials and methods section] of primary breast cancer inpatients were included. There were two control groups: 1501 women admitted for acute non-malignant conditions (trauma or infections); and 385 women with malignant melanoma, lymphoma, and leukaemia. About 5% of cases and controls (or their doctors) refused to participate. Information on several factors was obtained from nurse-interviewers including the usual consumption per day of caffeinated and decaffeinated coffee in the several months before admission. Odds ratios for breast cancer risk associated with coffee intake were adjusted for a large number of potential confounders including reproductive and family history, somatometry, and smoking. With either control group, odds ratios were close to 1.0 with no apparent trend and no indication of differential associations by age, reproductive history, history of fibrocystic breast disease, family history of breast cancer, or BMI. [The selection of two control groups was considered a strength of this study, as well as the exhaustive adjustment for potential confounders. The study also benefited from the additional examination of caffeinated and decaffeinated coffee in relation to breast cancer. It was limited by possible selection bias due to the recruitment of hospital-based controls with malignancies.]

La Vecchia et al. (1986) conducted a hospital-based, case–control study of breast cancer in two regions of northern Italy with 616 pairs of cases and controls selected from patients admitted to hospitals of the Greater Milan area and Porderone. Subjects were interviewed by trained personnel for the amount (cups/day) and duration (years) of coffee consumption. Eligible controls were women aged < 75 years admitted to hospitals covering the same areas for diseases unrelated to coffee or breast cancer risk factors. The 616 controls selected at random had mostly musculoskeletal conditions (65%). Refusal rate to be interviewed was about 2% for cases and controls. Adjusted odds ratios for coffee drinking were 1.1 (95% CI, 0.7–1.7) for ≥ 4 cups/day. There was no tendency for increasing breast cancer risk with increasing quantity or duration of coffee drinking. The results did not change after adjustment for several potential confounding factors, including the major risk factors for breast cancer. [The Working Group noted that this study was apparently included in the larger study by Tavani et al. (1998), which is described below. A strength of this study was the adjustment for potential confounders, but it was limited by possible selection bias due to hospital-based controls.]

Katsouyanni et al. (1986) conducted a hospital-based case–control study in Athens, Greece, to evaluate the role of diet in breast cancer risk. The study included 120 cases admitted to two teaching hospitals in the Greater Athens area. A total of 120 controls admitted for accidents and orthopaedic disorders in a third teaching hospital were chosen sequentially on the basis of sex and age. Dietary histories for the period preceding the onset of disease were obtained by interview. For coffee intakes (tertiles of frequency of consumption were low, moderate, and high) the study only reported a test for a linear trend for breast cancer risk (adjusting for age, interviewer, and years of schooling) that was not significant. [The Working Group computed crude odds ratios based on the numbers shown in table 2 of Katsouyanni et al. (1986). The strengths of this study were the detailed assessment of diet by

face-to-face interviews and inclusion of subjects from teaching hospitals. Limitations included the probability of selection bias for cases and controls, as well as minimal information on coffee consumption since vegetable intake was the main interest in this study.]

Levi et al. (1993a) examined the association between dietary factors including coffee intake and the risk of breast cancer in a case–control study in Switzerland which served as pilot for the SEARCH Programme of the International Agency for Research on Cancer. A total of 107 breast cancer cases (aged 32–75 years) admitted to the University Hospital of Lausanne, linked with the incidence data from Vaud Cancer Registry, and 318 controls admitted for traumas and other conditions were interviewed. No association between coffee intakes and breast cancer risk was evident; the odds ratio (apparently crude) for the 3rd versus 1st tertile of consumption was 0.9. [Although Levi et al. reported that the estimated association and trend were not significant, no confidence intervals or *P* value were provided. It was also not clear whether these are crude odds ratios or odds ratios adjusted for age, education, and total energy (as mentioned in the text).]

Tavani et al. (1998) examined the association between coffee (mostly espresso and mocha) as well as decaffeinated coffee and risk of breast cancer by combining data from two Italian case–control studies: during 1983–1991 in the Milan area (described previously La Vecchia et al., 1986); and during 1991–1994 in Milan, Pordenone, Genoa, and Forli in northern Italy, Latina in central Italy, and Naples in southern Italy. Less than 4% of cases/controls approached refused to participate. A total of 5984 cases (aged 11–74 years) and 5504 controls (aged 15–74 years) were included. Controls were admitted to the same hospitals as cases for non-neoplastic, non-hormone-related diseases; patients with gynaecological, hormonal, or neoplastic diseases were excluded. Odds ratios for coffee intake in relation to breast cancer risk, adjusted for several factors including family history of breast cancer, showed no overall association. No evidence for effect modification by several factors including BMI, smoking, menopausal status, or family history of breast cancer was apparent. [The strengths of this study were the substantial numbers (as a result of combining two case–control studies) and adjustment for various important risk factors; limitations were the hospital-based cases (due to the absence of a registry for the selection of cases) and controls (probability of selection bias).]

Baker et al. (2006) conducted a case–control study of patients treated at Roswell Park Cancer Institute (RPCI) who agreed to complete the Patient Epidemiology Data System (PEDS) questionnaire, which also enquired about daily regular and decaffeinated coffee consumption. About 50% of women initially contacted returned the PEDS questionnaire. Cases were 1932 women with incident breast cancer (aged 23–97 years) identified from the RPCI tumour registry. Control subjects were 1895 women (aged 21–97 years) randomly selected from a pool of 5700 eligible subjects admitted to RPCI for suspected neoplastic disease, but not subsequently diagnosed with any benign/neoplastic disease. Controls were frequency-matched to cases on 5-year age intervals and residence either inside or outside western New York. Among premenopausal women, increased consumption of regular coffee was associated with decreased breast cancer risk; the odds ratio for coffee consumption of ≥ 4 cups/day compared with non-consumers was 0.62 (95% CI, 0.39–0.98; *P* for trend, 0.03). In postmenopausal women, breast cancer risk was not associated with consumption of coffee. Results did not differ by histologic subtype of breast cancer. [The strengths of this study included the substantial number of subjects and examination of the associations by menopausal status and histologic subtype of breast cancer. Limitations included: limited adjustment; no measures of relative risk for breast cancer overall provided; and potential

for selection bias due to recruitment of hospital-based controls with a suspicion of neoplastic disease.]

Hirose et al. (2007) examined the associations between coffee intake and hormone-related cancer risk (cancer of the breast, endometrium, and ovary) among Japanese women (aged 40–79 years) attending as first-visit outpatients at the Aichi Cancer Center. A total of 2122 breast cancer cases were identified, while the control group comprised 12 425 women free from cancer. Coffee consumption was collected via a questionnaire designed for the study which was completed at the participants' first visit (i.e. before diagnosis for the cases). Odds ratios adjusted for a large number of covariates indicated null associations between coffee intake and breast cancer risk, with no apparent trend. [This study was strengthened by several factors, including: the information on exposures (including coffee intake) and potential confounders being collected before diagnoses, eliminating the possibility of recall bias; the substantial numbers of cases/controls; and the comprehensive design. Limitations included the possibility of selection bias due to the use of hospital-based, non-cancer patients as controls. No information was given with respect to the actual conditions of control subjects, although the characteristics of control subjects were not found to differ from those of the general population.]

(c) *Studies considering* BRCA1/BRCA2 *mutations*

Gronwald et al. (2006) examined the role of reproductive and lifestyle factors on risk of breast cancer among Polish women with a diagnosed mutation in *BRCA1* who had completed a baseline risk-factor mailed questionnaire which also recorded coffee consumption. A total of 348 breast cancer patients and 348 control subjects, matched by year of birth and age at diagnosis of the case, were identified. Odds ratios for coffee consumption (regular user: yes versus no) with respect to breast cancer risk, adjusting for year of birth, age at diagnosis, age at menarche, parity, smoking, breast-feeding, and oral contraceptive use, indicated no association (OR, 0.8; 95% CI, 0.5–1.1). [The study had several limitations: no information on the data or validation of the questionnaire was given; corresponding response rates were not provided; no information on when the study was conducted was reported; and no detailed classification of coffee was made. The main advantage was the investigation of high-risk *BRCA1* mutation carriers.]

Nkondjock et al. (2006) studied carriers of the *BRCA1* or *BRCA2* gene mutation identified from 40 clinical cancer genetics centres in Canada, Israel, Poland, and the USA. In the 845 case–control pairs matched by mutation, birth year, and country, lifetime coffee consumption was assessed through a detailed standardized questionnaire administered by each participating centre. Regarding cases, the average time between date of diagnosis and date of questionnaire completion was an average of 7.8 years. The date of interview of the controls was after the breast cancer diagnosis of the matching case. Odds ratios (95% CI) for breast cancer risk for drinkers of 1–3, 4–5, and ≥ 6 cups/day of caffeinated coffee compared with non-drinkers, adjusted for parity, smoking, oral contraceptive use, alcohol consumption, and BMI at age 30, were 0.90 (0.72–1.12), 0.75 (0.47–1.19), and 0.31 (0.13–0.71), respectively (*P* for trend, 0.02). These associations were also evident in country-specific analyses. The corresponding odds ratios for total coffee intake (caffeinated plus decaffeinated) were similar in magnitude and direction to the results obtained for caffeinated coffee, whereas the association was null for decaffeinated coffee consumption. When stratifying by type of mutation, inverse associations were more evident within the *BRCA1* mutation carriers than the *BRCA2* carriers (but this group was small). [The Working Group noted that part of these data were included in the study of Kotsopoulos

et al. (2007), described below. The strengths of this study were the substantial subject numbers (given that it was conducted among *BRCA1* and *BRCA2* mutation carriers) due to its multicentre design; the assessment of average lifetime coffee consumption, as well as of decaffeinated coffee; and adjustment for important risk factors.]

Kotsopoulos et al. (2007) analysed some of the data used by Nkondjock et al. (2006) (Canada and the USA) to examine whether the CYP1A2 genotype modifies the association between coffee consumption and risk of breast cancer among *BRCA1* mutation carriers. Coffee consumption (caffeinated or decaffeinated) before the age of 35 years was classified as ever or never. Breast cancer cases were 170 women with a history of invasive breast cancer; control subjects included 241 women with no history of breast cancer. Both cases and controls were carriers of a mutation in *BRCA1*. The adjusted odds ratio for breast cancer risk was 0.61 (95% CI, 0.38–0.97) for the ever versus never consumers, with a *P* for trend of 0.04. [The Working Group noted a discrepancy between odds ratios shown in table 2 of Kotsopoulos et al. (2007) and those reported in the results section of the manuscript; odds ratios listed in table 2 are reported here.] In a separate analysis by CYP1A2 genotype, an inverse association was evident among the AC or CC alleles (OR, 0.36; 95% CI, 0.18–0.73; *P* for trend, 0.005) but not among women with the AA allele (OR, 0.93; 95% CI, 0.49–1.77; *P* for trend, 0.82) with the interaction between the CYP1A2 genotype and coffee consumption in relation to breast cancer risk being significant (*P* interaction, 0.04) [The Working Group noted that this study mainly investigates whether the inverse association of coffee with breast cancer risk among *BRCA1* carriers can be further explained through a potential interaction of coffee intake with the CYP1A genotype. The study strengths included the detailed assessment of average lifetime coffee consumption and the assessment of past exposure to coffee, as well as adjustment for important risk factors. Assessing exposure before the age of 35 years makes comparison with other studies difficult, however, and the classification of coffee as ever versus never is rather crude.]

Bissonauth et al. (2009) conducted a case–control study of the association between coffee (and other dietary variables) and risk of breast cancer for non-carriers of *BRCA1/2* mutations among French-Canadian women. Cases were 280 early-onset breast cancer patients who attended the breast centre of CHUM (Centre hospitalier de l'Université de Montréal) Hotel Dieu during 2004–2006, and who were found from DNA testing not to be carriers of six specific mutations in *BRCA1* or *BRCA2*. Controls (n = 280) free from cancer, from the same families as cases or other families with breast cancer and not carriers of any of the six mutations, were matched for age and language. Dietary information was obtained by an interviewer-administered, validated, detailed FFQ covering the 2-year period before diagnosis (cases) or date of interview (controls). Adjustment was performed only for statistically significantly potential confounders associated with breast cancer risk in univariate analyses. A positive association was noted between coffee consumption and breast cancer risk: for drinkers of ≤ 2, > 2 to ≤ 8, and > 8 cups/day compared with non-drinkers, odds ratios (95% CI) were 1.00, 1.79 (1.17–2.57), and 1.40 (1.09–2.24), respectively (*P* for trend, 0.03). When analyses were repeated by menopausal status the associations were effectively null, especially among premenopausal women. [This study benefited from the high-quality FFQ which was interviewer administered, but was limited by the retrospective measures of exposure which may have resulted in recall bias.]

2.4.3 Meta-analyses

Tang et al. (2009), Yu et al. (2011), and Li et al. (2013a) (updating the 2009 meta-analysis conducted by Tang et al.) reported results for the

association of coffee intake with breast cancer incidence, based on meta-analyses of published studies.

The most recent meta-analysis was conducted by Jiang et al. (2013) who analysed 37 cohort and case–control studies identified by a search of PubMed, and by reviewing the reference lists of retrieved articles, with a total of 59 018 breast cancer cases among 966 263 participants. Pooled relative risks with 95% confidence intervals were calculated using fixed- and random-effects models, and the dose–response association was assessed by restricted cubic spline models and multivariate random-effect meta-regression. The overall meta-relative risk of breast cancer (fixed-effects model) was 0.97 (95% CI, 0.93–1.00) for the highest compared with lowest coffee consumption, whereas the meta-relative risk for an increment of 2 cups/day was 0.98 (95% CI, 0.96–1.00). The corresponding meta-relative risks for caffeine intakes were 0.99 (95% CI, 0.94–1.04) and 0.99 (95% CI, 0.98–1.01) for an increase in caffeine of 200 mg/day. No significant association was found between risk of breast cancer and consumption of decaffeinated coffee. A statistically significant inverse association between coffee/caffeine and risk of breast cancer was observed for postmenopausal women (meta-RR, 0.94; 95% CI, 0.8–0.99) and *BRCA1* mutation carriers (meta-RR, 0.69; 95% CI, 0.53–0.89). Sensitivity analysis showed that no individual study had excessive influence on the pooled association between breast cancer risk and intakes of coffee and caffeine. The Egger test showed no evidence of significant publication bias for the analysis of breast cancer risk and coffee (*P* for trend, 0.23) and caffeine (*P* for trend, 0.35). Statistical heterogeneity was moderate to low in all analyses. [The Working Group noted this was the largest meta-analysis estimating the association between coffee consumption with risk of breast cancer. A major strength was the large number of participants included, allowing for finer conclusions and exhaustive subgroup analysis. A dose–response analysis was also performed with advanced statistical methodology to better describe the association between risk of breast cancer and coffee and caffeine intake. However, it should be noted that the pooled relative risk among the *BRCA1* mutation carriers should be interpreted with caution since only three studies were included.]

2.5 Cancer of the endometrium

Fourteen cohort and eleven case–control studies investigated the association between coffee intake and risk of cancer of the endometrium. As BMI and smoking are important confounders, studies not adjusting for these factors (Jacobsen et al. 1986; Levi et al., 1993b; Stensvold & Jacobsen 1994; Goodman et al., 1997; Bravi et al., 2009b) were considered uninformative and were excluded from further review. A case–control study (Petridou et al., 2002a) considering all risk factors for endometrial cancer was also excluded because it was updated by Petridou et al. (2002b).

Among cohort studies, eight were focused on the relation between coffee consumption and endometrial cancer. One study considered the relation between coffee and endometrial cancer type I and type II separately (Uccella et al., 2013), and two studies focused on the association between coffee consumption and selected cancers (both considering mortality as the end-point) (Nilsson et al., 2010; Hashibe et al., 2015). Among the published case–control studies, four focused on the association between coffee consumption and endometrial cancer, and four on the relation to diet or various risk factors. The Working Group also reviewed five meta-analyses of the above-indicated studies, published from 2009 to 2015.

2.5.1 Cohort studies

See Table 2.9.

Shimazu et al. (2008) investigated the association between coffee intake and risk of cancer of the endometrium in the JPHC Prospective Study. Among 53 724 women, enrolled in 1990 for Cohort I (aged 40–59 years) and during 1993–1994 for Cohort II (aged 40–69 years), 117 incident endometrial cancer cases were identified by the major hospitals of the areas and population-based cancer registries. Coffee intake was assessed at baseline using a self-administered FFQ tested for reproducibility. There was a statistically significant inverse association between risk of endometrial cancer and daily coffee intake, with an adjusted hazard ratio of 0.38 (95% CI, 0.16–0.91) for an intake of ≥ 3 cups/day and an inverse trend in risk (*P* for trend, 0.007). The relation was not heterogeneous in strata of exogenous hormone use, BMI, menopausal status, and parity. [The strengths of this study included: linkage with registries; FFQ tested for reproducibility (correlation coefficient, 0.38); high response rate (83%); low loss to follow-up; exclusion of women with previous malignancy; and full adjustment for confounding. It was however limited by the lack of information on hysterectomy and number of cups/day for occasional consumption.]

Friberg et al. (2009) studied the association between coffee consumption and endometrial cancer incidence using a cohort of 60 634 Swedish women who participated in a health mammography screening (the Swedish Mammograpy Cohort) during 1987–1990. After a mean follow-up of 17.6 years, 677 incident cases of endometrial cancer were identified through linkage to the National Swedish Cancer Register and the National Cancer Register. Information on coffee consumption (cups/day) was obtained from two validated FFQs self-administered at an interval of approximately 8 years. Incidence relative risks adjusted for age, BMI, and smoking indicated an overall statistically significant inverse association between daily intake of coffee and risk of endometrial cancer for an intake of ≥ 4 cups/day (RR, 0.75; 95% CI, 0.58–0.97) and for an increment of 1 cup/day (RR, 0.90; 95% CI, 0.83–0.97) (*P* for trend, 0.02). Analysis of long-term coffee consumption revealed a significant inverse association only in the 2–3 cups/day category compared with the reference group (RR, 0.82; 95% CI, 0.68–0.98). The inverse association was found only in obese women; a relative risk of 0.80 (95% CI, 0.69–0.93) for an increment of 1 cup/day for BMI > 30 versus a relative risk of 1.00 (95% CI, 0.88–1.15) for a BMI of of 20–25 was reported, and was not significantly stronger in more inactive or diabetic women. No differences were found in strata of postmenopausal hormone use and smoking. [The strengths of this study were: linkage with Cancer Registries; FFQ tested for validity (correlation coefficient, 0.6); and high response rate (74%). Limitations included the lack of information on previous malignancy and on eventual hysterectomy.]

Nilsson et al. (2010) investigated whether consumption of filtered or boiled coffee is associated with a risk of developing cancer overall. Data on diet were collected through a semiquantitative FFQ for 30 639 women ≥ 30 years of age, recruited within the population-based health survey VIP with a participation rate of 57–67%. Subjects were followed up for a median of 6 years (range 0–15 years) and 108 cases of endometrial cancer were identified by linking the VIP database with the regional cancer registry. Cox regression was used to estimate hazard ratios for cancer risk overall and by site with respect to total, brewed, or boiled coffee consumption, adjusting for age, BMI, smoking, education, and recreational physical activity. For endometrial cancer, no association with coffee consumption was found with a relative risk of 0.88 (95% CI, 0.44–1.78) for an intake of ≥ 4 cups/day. [The main strength of this study was its linkage with the cancer registry. Limitations included: no mention of FFQ testing;

Table 2.9 Cohort studies on cancer of the endometrium and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shimazu et al. (2008) Japan, 1990–1994	53 724; two cohorts of JPHC Study Exposure assessment method: FFQ	Endometrium	*Coffee consumption* ≤ 2 cups/wk 3–4 cups/wk 1–2 cups/day ≥ 3 cups/day Trend test *P* value, 0.007	 66 16 29 6	 1.00 0.97 (0.56–1.68) 0.61 (0.39–0.97) 0.38 (0.16–0.91)	Age, BMI, menopausal status, age at menopause, parity, exogenous hormone use, smoking, green vegetables, beef, pork, green tea, geographic area	Strengths: FFQ tested for reproducibility, high response rate, low loss to follow-up, fully adjusted for confounding Limitations: no information on eventual hysterectomy
Friberg et al. (2009) Sweden, 1987–1990, follow-up until 1997	60 634 participants of SMC aged 40–76 yr Exposure assessment method: FFQ, average consumption from two questionnaires (about 8 yr apart)	Endometrium	*Coffee consumption at baseline (cups/day)* ≤ 1 2–3 ≥ 4 Increment of 1 cup/day Trend test *P* value, 0.02 *Coffee consumption over long term (cups/day)* ≤ 1 2–3 ≥ 4 Increment of 1 cup/day Trend test *P* value, 0.03	 271 312 94 677 224 304 149 677	 1.00 0.78 (0.64–0.95) 0.75 (0.58–0.97) 0.90 (0.83–0.97) 1.00 0.82 (0.68–0.98) 0.85 (0.69–1.05) 0.93 (0.86–1.00)	Age, BMI, smoking	Strengths: linkage with cancer registries, FFQ tested for validity, high response rate, the assessment of long-term coffee consumption effect by using updated information Limitations: no information on eventual hysterectomy, no adjustment for menstrual and reproductive factors
Nilsson et al. (2010) Sweden, 1992–2007	30 639 women (aged > 30 yr) Exposure assessment method: FFQ	Endometrium	*Coffee consumption (occasions/day)* < 1 1–3 ≥ 4	 11 67 30	 1.00 0.92 (0.48–1.76) 0.88 (0.44–1.78)	Age, BMI, education, physical activity, smoking	Strengths: linkage with cancer registry Limitations: no mention of FFQ testing, no adjustment for menstrual and reproductive factors, exposure reported as occasions/day rather than cups/day, very short follow-up for some subjects, small number of cases in some of the categories

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Giri et al. (2011) USA, 1993–1998	45 696 post-menopausal women (aged 50–79 yr) recruited at 40 clinical centres Exposure assessment method: FFQ	Endometrium	*Coffee consumption (cups/day)*			Age, ethnicity, BMI, smoking, estrogen use, estrogen plus progestin use	Strengths: women with previous cancer and hysterectomy were excluded Limitations: no detailed information on validation/reproducibility, no information on loss to follow-up and on participation rate, no adjustment for menstrual and reproductive factors
			< 1	126	1.00		
			1	71	1.12 (0.84–1.50)		
			2–3	168	0.91 (0.72–1.16)		
			≥ 4	62	0.86 (0.63–1.18)		
			Trend test *P* value, 0.23				
Je et al. (2011) USA, 1980	67 470 women aged 34–59 yr Exposure assessment method: FFQ, average intake from information collected every 4 yr	Endometrium	*Coffee consumption (cups/day)*			Age, BMI, age at menarche, age at menopause, parity, age last birth, HRT, smoking pack-years, total energy intake, calendar year of the current FFQ, alcohol intake, duration of OC use	Strengths: women with previous cancer and hysterectomy excluded, repeated measures of coffee intake, fully adjusted
			< 1	168	1.00		
			1	140	0.94 (0.73–1.19)		
			2–3	275	0.94 (0.77–1.16)		
			≥ 4	89	0.68 (0.52–0.90)		
			Trend test *P* value, 0.01				
Gunter et al. (2012) USA, 1995–1996	111 429 women aged 50–71 yr Exposure assessment method: FFQ	Endometrium	*Coffee consumption (cups/day)*			Age, BMI, smoking, age at menarche, age at first birth, parity, age at menopause, HRT use, OC use, diabetes, physical activity, ethnicity	Strengths: women with previous cancer and hysterectomy were excluded, linkage with cancer registries, fully adjusted, information on validation/reproducibility of FFQ available Limitations: no information on participation rate
			0	231	1.00		
			< 1	276	0.87 (0.73–1.05)		
			1	273	0.82 (0.68–0.98)		
			2–3	573	0.83 (0.71–0.97)		
			> 3	133	0.64 (0.51–0.80)		
			Increment of 1 cup/day	1486	0.94 (0.90–0.97)		
			Trend test *P* value, 0.004				

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Uccella et al. (2013) USA, 1986	23 356 post-menopausal women (aged 55–69 yr) Exposure assessment method: FFQ	Endometrium	*Coffee consumption: type I endometrial cancer*			Age, diabetes, hypertension, age at menarche, age at menopause, BMI, waist to hip ratio, smoking pack-years, total energy intake, alcohol consumption, smoking status, duration of HRT use	Strengths: exclusion of women with previous cancer and hysterectomy , information on validity/ reproducibility, linkage with cancer registries, fully adjusted Limitations: no information on participation rate
			≤ 1 cup/mo	64	1.00		
			< 1 cup/wk	64	0.95 (0.66–1.36)		
			1 cup/day	55	0.75 (0.52–1.09)		
			2–3 cups/ day	188	0.95 (0.71–1.28)		
			≥ 4 cups/day	100	0.71 (0.51–0.99)		
			Trend test *P* value, 0.11				
			Coffee consumption: type II endometrial cancer				
			≤ 1 cup/mo	7	1.00		
			< 1 cup/wk	8	0.98 (0.36–2.72)		
			1 cup/day	13	1.31 (0.51–3.35)		
			2–3 cups/ day	26	1.01 (0.43–2.36)		
			≥ 4 cups/day	17	0.84 (0.33–2.12)		
			Trend test *P* value, 0.64				
Gavrilyuk et al. (2014) Norway, 1991–1997, 2003–2007	97 926 women aged 30–70 yr, only post-menopausal included Exposure assessment method: FFQ	Endometrium	*Coffee (cups/day)*			Age, parity, smoking, BMI, duration of OC use, HRT	Strengths: population-based cohort; women with previous cancer, previous hysterectomy, and incident uterine sarcoma during follow-up excluded; linkage with cancer registries; fully adjusted; FFQ tested for validity and reproducibility Limitations: Lack of information on decaffeinated coffee
			≤ 1	82	1.00		
			2–3	171	0.91 (0.70–1.19)		
			4–7	177	0.84 (0.65–1.10)		
			≥ 8	32	0.52 (0.34–0.79)		
			Trend test *P* value, 0.003				

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Weiderpass et al. (2014) Sweden, 1991–1992	42 270 women aged 30–49 yr Exposure assessment method: FFQ, coffee intake only at baseline; second FFQ in 2002–2003 in a subgroup	Endometrium	*Coffee (cups/day)*			Age, education, parity, BMI, diabetes, smoking status, number of cigarettes/ day, menopausal status, duration of OC use, duration of breastfeeding	Similar results in the analyses stratified according to BMI and smoking status Strengths: women with previous breast cancer and hysterectomy excluded, FFQ tested for reproducibility (correlation coefficient, 0.61), linkage with cancer registries, full adjustment, information on response rate (51.3%) Limitations: no information on validity, caffeine assessed only through caffeinated coffee, no separate information for coffee/ decaffeinated coffee
			< 2	23	1.00		
			2–3	47	0.65 (0.39–1.10)		
			> 3	74	0.64 (0.39–1.06)		
			Trend test *P* value, 0.1743				
Hashibe et al. (2015) USA, 1992–2001	32 392 postmenopausal women (age 55–74 yr) Exposure assessment method: FFQ	Endometrium	*All coffee (cups/day)*			Age, BMI, race, education, alcohol consumption, years on birth control, parity, OC, HRT, age at menopause, smoking status, smoking frequency, smoking duration, time since smoking cessation	Strengths: women with previous cancers excluded, linkage with registries, fully adjusted Limitations: no information on reproducibility/validity of FFQ, no information on hysterectomy, no information on participation rates, no clear information on follow-up length
			< 1	106	1.00		
			1–1.9	36	0.67 (0.45–0.99)		
			≥ 2	112	0.72 (0.55–0.95)		
			Increment of 1 cup/day	254	0.92 (0.85–1.00)		
			Trend test *P* value, 0.0205				

Table 2.9 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Merritt et al. (2015) USA, 1976–1980 (NHS), 1989–1991 (NHS-II)	155 406 women in NHS (age 30–55 yr) and in NHS-II (age 25–42 yr) Exposure assessment method: FFQ, average intake from information collected every 4 yr	Endometrium	*Coffee consumption (g/day)*			Age, cohort, time period, BMI, total energy intake, smoking, age at menarche, OC, menopause, HRT, parity	Strengths: women with previous cancer and hysterectomy excluded, FFQ tested for reproducibility/ validity, repeated measures of coffee intake (every 4 yr), fully adjusted
			0	365	1.00		
			16.6–270.2	286	0.88 (0.76–1.03)		
			289.1–592.5	439	0.92 (0.80–1.06)		
			≥ 609.1	314	0.82 (0.70–0.96)		
			Trend test *P* value, 0.04				
			Quartiles (cumulative average intake)				
			1	263	1.00		
			2	378	1.08 (0.92–1.27)		
			3	363	0.98 (0.83–1.16)		
			4	370	0.89 (0.75–1.05)		
			Trend test *P* value, 0.03				
Merritt et al. (2015) European countries, EPIC, 1992–2000	301 107 women aged 25–70 years Exposure assessment method: FFQ	Endometrium	*Quartiles (baseline intake, g/day)*			BMI, total energy intake, smoking, age at menarche, OC, HRT, parity, age, study centre, menopausal status	Strengths: women with previous cancer and hysterectomy excluded, FFQ tested for validity, fully adjusted, very low loss at follow-up (0.8%) Limitations: no information on reproducibility, no information on participation rate
			1	329	1.00		
			2	275	0.77 (0.66–0.91)		
			3	369	0.88 (0.74–1.04)		
			4	330	0.81 (0.68–0.97)		
			Trend test *P* value, 0.09				
Yang et al. (2015) UK, 1996–2001	560 356 middle-aged women Exposure assessment method: FFQ, average consumption (information at baseline and 4 yr later)	Endometrium	*Coffee (cups/day)*			Age, region, socioeconomic level, age at menarche, OC, BMI, smoking, alcohol consumption, physical activity, tea, non-alcoholic fluid intake, height, duration of OC use, duration of HRT use, menopausal status	Strengths: large number of cases; women with previous breast cancer and hysterectomy excluded, linkage with registries, fully adjusted, FFQ tested for reproducibility Limitations: no information on validation of FFQ
			< 1	1009	0.99 (0.92–1.06)		
			1–2	1839	1.00 (0.95–1.05)		
			3–4	842	0.94 (0.88–1.01)		
			≥ 5	377	0.92 (0.82–1.03)		
			Increment of 1 cup/day	4067	0.98 (0.96–1.01)		
			Daily consumers	3058	0.97 (0.94–1.01)		

BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; JPHC, Japan Public Health Center-based Prospective; mo, month(s); NHS, Nurses' Health Study; OC, oral contraceptive; SMC, Swedish Mammography Cohort; wk, week(s); yr, year(s)

no adjustment for main confounders, except for female hormones (menstrual/reproductive factors and exogenous hormone use); very short follow-up for some subjects; no information on loss to eventual hysterectomy; exposure mentioned as occasions/day rather than cups/day (occasion may be different from cup); and the small number of cases in some of the categories.]

Giri et al. (2011) studied the association between coffee consumption and incidence of endometrial cancer among 45 696 postmenopausal women recruited in 40 clinical centres in the USA using the WHI Observational Study research material obtained from a National Heart, Lung, and Blood Institute biological specimen repository. During the mean follow-up period of 7.5 years, there were 427 incident cases of endometrial cancer. Information on consumption of coffee (caffeinated and decaffeinated) was obtained through a self-administered FFQ. Coffee, both caffeinated and decaffeinated, was not associated with endometrial cancer incidence with an adjusted hazard ratio of 0.86 (95% CI, 0.63–1.18) for an intake of ≥ 4 cups/day (*P* for trend, 0.23), although a tendency for a lower risk for such consumption emerged mainly for decaffeinated coffee (HR, 0.51; 95% CI, 0.25–1.03). A significant inverse association was found for caffeinated coffee in obese women (HR, 0.66; 95% CI, 0.45–0.97) for an intake of ≥ 2 cups/day (*P* for trend, 0.05). [A strength of this study was that women with previous cancer and hysterectomy were excluded from the cohort. Limitations included: no information on loss to follow-up (defined as low) and on participation rate; no information on FFQ validation/reproducibility, although the same questionnaire was administered 3 years after baseline; and no adjustment for main confounders, except for menstrual and reproductive factors.]

Je et al. (2011) assessed total coffee consumption (either caffeinated or decaffeinated) in relation to risk of endometrial cancer in the Nurses' Health Study (NHS) using 67 470 women. The first validated FFQ (Pearson correlation coefficient, 0.78) was self-administered in 1980 and repeated in 1984, 1986, 1990, 1994, 1998, and 2002, and coffee intake considered in the analyses was the cumulative average intake from all previous FFQs. During 26 years of follow-up, a total of 672 cases of endometrial cancer were ascertained. Coffee intake was inversely related to endometrial cancer incidence, with a relative risk of 0.68 (95% CI, 0.52–0.90) for an intake of ≥ 4 cups/day and a linear trend in risk (*P* for trend, 0.01). The inverse association was weaker and not significant for decaffeinated coffee (RR, 0.72; 95% CI, 0.52–1.01). Stratification for selected covariates showed that the inverse association was: statistically significant in ever smokers (RR, 0.65; 95% CI, 0.44–0.95) and in postmenopausal women with a BMI of ≥ 25 (RR, 0.67; 95% CI, 0.46–0.98); stronger but not significant in women with a BMI of ≥ 30 (RR, 0.62; 95% CI, 0.38–1.01); and similar in strata of HRT use. [This study had several strengths, including repeated measures of coffee intake, validation of FFQ, exclusion of women with previous cancer and hysterectomy, and full adjustment. No information on participation rate was provided, however.]

Gunter et al. (2012) analysed data from the US-based cohort NIH-AARP Diet and Health Study, including 111 429 women followed up for a mean of 9.3 years; 1486 cases of endometrial cancer were ascertained during this period. Intake of coffee (caffeinated and decaffeinated) was assessed in cups/day at baseline through a FFQ. A significant inverse association with incidence of endometrial cancer was found for total coffee and either regular or decaffeinated, with a significant trend. The hazard ratios for an increment of 1 cup/day were 0.94 (95% CI, 0.90–0.97), 0.90 (95% CI, 0.86–0.95), and 0.93 (95% CI, 0.87–0.99) for total, decaffeinated, and regular coffee, respectively. Stratified analyses by smoking status yielded similar hazard ratios, while there was no significant association in HRT users or in women with a BMI < 25. [The main

strengths of this study included the substantial number of cases, exclusion of women with previous cancer and hysterectomy, linkage with cancer registries, validation/reproducibility of FFQ, and full adjustment. However, no information on participation rate was included.]

Uccella et al. (2013) investigated the association between coffee/tea consumption and the risk of endometrial cancer among 23 356 women in the IWHS. During the 20-year period of follow-up, 542 cases of endometrial cancer (471 type I and 71 type II) were identified. Coffee consumption was measured by a FFQ tested for reproducibility and validity, and was classified as ≤ 1 cup/month (reference group), < 1 cup/week, and 1, 2–3, and ≥ 4 cups/day [the Working Group noted a mistake in the reported classification]. Compared with never intake or intake of ≤ 1 cup/month, a significant inverse association for endometrial cancer type I was found for consumption of ≥ 4 cups/day of total coffee with a relative risk of 0.71 (95% CI, 0.51–0.99) with no trend in risk. For caffeinated coffee the corresponding relative risk was 0.65 (95% CI, 0.47–0.89; *P* for trend, 0.033); no significant association was found for decaffeinated coffee with a relative risk of 0.76 (95% CI, 0.50–1.15). There was no relation between coffee intake and endometrial cancer type II. The relative risks for ≥ 4 cups/day were 0.84 (95% CI, 0.33–2.12) for total, 0.85 (95% CI, 0.37–1.93) for caffeinated, and 1.08 (95% CI, 0.41–2.80) for decaffeinated coffee. The inverse association with total and caffeinated coffee was statistically significant for type I endometrial cancer in obese women, with a relative risk of 0.53 (95% CI, 0.34–0.84) for an intake of ≥ 4 cups/day and inverse trend in risk. No consistent heterogeneity was found in data stratified for smoking and HRT use. [This study had several strengths: exclusion of women with previous cancer and hysterectomy; FFQ tested for validity/reproducibility; linkage with cancer registries; and full adjustment. However, no information was provided on participation rate.]

Gavrilyuk et al. (2014) examined the association between coffee consumption and risk of endometrial cancer among 97 926 Norwegian women; the subjects, selected from the Central Population Registry of Norway, accepted an invitation to participate in the Norwegian Women and Cancer (NOWAC) Study (response rate was 54.2%). By the end of follow-up (mean 10.9 years), 462 cases of endometrial cancer were identified by linkage of cancer registries. A FFQ tested for validity (Spearman correlation coefficient, 0.82) and reproducibility was self-administered at baseline. For women enrolled during 2003–2007 it also included information on the most common methods of coffee preparation in Norway (filtered, boiled, and instant coffee). Intake of coffee (either filtered or boiled) was inversely associated with incidence of endometrial cancer with a relative risk of 0.52 (95% CI, 0.34–0.79) for an intake of ≥ 8 cups/day and a significant trend in risk (*P* for trend, 0.003). The relative risks were 0.45 (95% CI, 0.21–1.01) for only boiled coffee and 0.55 (95% CI, 0.32–0.94) for only filtered coffee. For an intake of ≥ 8 cups/day, stratified analyses showed that the inverse association was statistically significant only in overweight women with a BMI ≥ 25 kg/m^2 (RR, 0.39; 95% CI, 0.21–0.73) and in current smokers (RR, 0.37; 95% CI, 0.17–0.81). [The strengths of this study included: population-based cohort; exclusion of women with previous cancer and hysterectomy; linkage with cancer registries; full adjustment; and a FFQ tested for validity and reproducibility.]

Weiderpass et al. (2014) evaluated the effect of coffee intake on incidence of endometrial cancer in 42 270 women residing in Sweden as part of the Swedish Women's Lifestyle and Health cohort study (response rate 51.3%). After a follow-up of about 18 years, 144 cases of type I endometrial cancer were ascertained. The information on coffee intake was obtained using an open-ended questionnaire that asked how many cups/day or cups/week women

consumed, while also considering portion sizes (small, 0.75 g; medium, 150 g; large, 225 g). To test reproducibility, similar questions were used in a comparable population giving a Spearman correlation coefficient (r_S) of 0.61. Coffee intake of > 3 cups/day tended to have a favourable effect on risk of endometrial cancer, but this effect did not reach statistical significance (RR, 0.64; 95% CI, 0.39–1.06). There was no heterogeneity in strata of BMI or smoking status. [The strengths of this study included: population-based cohort; exclusion of women with previous breast cancer and hysterectomy; linkage with cancer registries; full adjustment; and information on reproducibility. No information was provided on questionnaire validity, however.]

Hashibe et al. (2015) investigated the association between cancer and consumption of coffee and tea in the PLCO prospective study. At entry, participants were randomized to receive routine health care or screening for prostate, lung, colorectal, and ovarian cancer. A self-administered FFQ was compiled in 1998–2001 at baseline; follow-up started at FFQ administration and stopped in May 2011. Among 32 392 at baseline, 254 incident cases of endometrial cancer were reported. Coffee intake was inversely associated with endometrial cancer incidence, with an adjusted relative risk of 0.72 (95% CI, 0.55–0.95) for ≥ 2 cups/day (*P* for trend, 0.0205). The inverse relation for a consumption increment of 1 cup/day was not statistically significant (RR, 0.92; 95% CI, 0.85–1.00). There was a non-significant inverse relation in never smokers. [The strengths of this study included a linkage with cancer registry, an adjustment for main confounders, and the exclusion of women with previous cancer. Limitations included a lack of information on FFQ testing, participation rate, eventual hysterectomy, or follow-up length. Although this study included never smokers, there was no analysis of coffee intake and cancer risk within this group.]

Merritt et al. (2015) evaluated the effect of diet, including coffee, on risk of cancer of the endometrium using data from three cohort studies: NHS, NHS-II, and EPIC. The analysis included 68 063 women from NHS, which was established in 1976–1980 among female nurses aged 30–55 years, and 87 343 women from the NHS-II, comprising female nurses aged 25–42 years during 1989–1991 and 301 107 women from the EPIC cohort who were aged 25–70 years in 1992–2000 with no previous cancer or hysterectomy. In the NHS, the first validated FFQ (Pearson correlation coefficient, 0.78) was self-administered in 1980 and repeated in 1984, 1986, 1990, 1994, 1998, and 2002, and coffee intake considered in the analyses was the cumulative average intake from all previous FFQs. The EPIC FFQ was validated and self-administered or interviewer-administered (depending on the study centre) only at baseline. During follow-up, 1531 and 1303 cases of endometrial cancer were identified in the NHS cohorts and the EPIC cohort, respectively. For all cohorts combined, a significant inverse association was found: the pooled HR for the highest compared to the lowest level of consumption was 0.82 (95% CI 0.73-0.92). For the NHS cohorts the corresponding HR was 0.82; 95% CI, 0.70–0.96, *P* for trend, 0.04) and for the EPIC cohort, the HR was 0.81 (95% CI, 0.68–0.97, *P* for trend, 0.09). [The strengths of this study included: the linkage to registries; the exclusion of women with previous cancer and hysterectomy; the repeated measures of coffee intake for the NHS cohorts; the validation of FFQs; and full adjustment. No information on reproducibility was provided in the EPIC study, and no information on participation rate was included for any of the cohorts. The Working Group noted an overlap with the populations studied by Je et al. (2011).]

Yang et al. (2015) considered the effect of coffee intake on the incidence of endometrial cancer in the Million Women Study, a population-based cohort of 560 356 women residing in England and Scotland, selected from those invited to attend routine screening for breast cancer (response rate

65%). After a mean follow-up period of 9.3 years, 4067 cases of endometrial cancer were identified. Women were asked to report consumption of coffee in cups/day at baseline and, on average, 4 years after baseline. A total of 57% of women provided the same information, giving a Spearman correlation coefficient ranging over 0.67–0.78 depending on the time between the two reports; the mean consumption from repeated responses was used when available. No association between coffee intake and incidence of endometrial cancer was found, with relative risks of 0.92 (95% CI, 0.82–1.03) for an intake of ≥ 5 cups/day and 0.98 (95% CI, 0.96–1.01) for an increment of 1 cup/day. There was no heterogeneity in strata of BMI, smoking status, or the addition of milk to coffee. [This study benefited from being a population-based cohort, the high number of cases of endometrial cancer, the exclusion of women with previous cancer and hysterectomy, the linkage with cancer registries, full adjustment, and including information on reproducibility. No information on validity was provided, however.]

2.5.2 Case–control studies

See Table 2.10.

Kalandidi et al. (1996) analysed various risk factors for cancer of the endometrium using data obtained in a study which considered women admitted to two Athens hospitals during 1992–1994. Cases were 145 women with incident, invasive cancer of the endometrium. Controls were 298 women admitted to Athens hospitals for orthopaedic disorders. Information was obtained from physician-administered interviews and odds ratios were adjusted for multiple risk factors. There was no significant association between coffee consumption and risk of endometrial cancer, with an odds ratio of 1.04 (95% CI, 0.86–1.27) for an increment of consumption of 1 cup/day. [The physician-administered FFQs, full adjustment, and high participation rate among cases (83%) and controls (88%) were the strengths of this study. A limitation was the use of hospital controls including only orthopaedic disorders. Further, no information was provided on mean or range of age of subjects, previous cancer incidence among cases and controls, hysterectomy among controls, FFQ validity/reproducibility, or intake of caffeinated/decaffeinated coffee.]

Jain et al. (2000) analysed the relation between nutritional factors and cancer of the endometrium in a study conducted in Canada. A total of 552 cases were included, and controls were 562 women with an intact uterus, matched to cases for age and geographic area. Information was obtained from an interviewer-administered validated FFQ. There was no observed association between coffee drinking and risk of endometrial cancer, with an adjusted odds ratio of 0.68 (95% CI, 0.45–1.04) for > 500 g/day of coffee with no trend in risk (*P* for trend, 0.3). [The strengths of this study included: the identification of cases through the cancer registry, population controls, exclusion of women with hysterectomies among controls, validated interviewer-administered FFQ, and full adjustment. No information was provided on the intake of caffeinated/decaffeinated coffee, however.]

Petridou et al. (2002b) analysed various risk factors for cancer of the endometrium in a study conducted in an Athens hospital in 1999. Cases were 84 women with a diagnosis of endometrial cancer identified through medical records, and controls were 84 women with an intact uterus who had been admitted to the same hospital for minor gynaecological conditions. Full participation rate was reported for cases and controls, and subjects with previous cancer were eliminated. Information was obtained from an interviewer-administered FFQ, tested for validity. There was a favourable effect of coffee drinking on the risk of endometrial cancer with an odds ratio of 0.39 (95% CI, 0.17–0.93) for ≥ 4 cups/week. [The strengths of this study were: the exclusion of

Table 2.10 Case–control studies on cancer of the endometrium and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kalandidi et al. (1996) Greece, 1992–1994	Cases: 145 hospital-based Controls: 298 hospital-based (orthopaedic) Exposure assessment method: FFQ	Endometrium	*All types of coffee consumption (cups/day)* Increment of 1 cup/day	145	1.04 (0.86–1.27)	Age, education, occupation, age at menarche, age at menopause, parity, OC, HRT, smoking, alcohol consumption, height, BMI, total energy intake, induced abortions, miscarriages	Strengths: high participation rate among cases and controls, FFQ tested for validity, physician-administered FFQ, fully adjusted Limitations: hospital controls (only orthopaedic diseases), no information on hysterectomy, no information on age
Jain et al. (2000) Canada, 1994–1998	Cases: 552 identified through Ontario Cancer Registry Controls: 562 population controls with intact uterus from Ontario Ministry of Finance, matched by age and geographic areas Exposure assessment method: FFQ, home interviews	Endometrium	*Coffee consumption (g/day), quartiles* 0 ≤ 250 > 250–500 > 500 Trend test *P* value, 0.3	87 197 140 128	1.00 0.80 (0.54–1.18) 1.18 (0.78–1.79) 0.68 (0.45–1.04)	Age, total energy intake, smoking, diabetes, OC, HRT, education, parity, age at menarche, body weight, geographic region	Response rate among cases (70%) and controls (41%) Strengths: population-based study, validated and interviewer-administered FFQ, excluded women who have undergone hysterectomy, fully adjusted
Petridou et al. (2002b) Greece, 1999	Cases: 84 hospital-based Controls: 84 hospital-based (small gynaecological operations) Exposure assessment method: FFQ	Endometrium	*Coffee consumption (cups/wk)* No ≥ 4	29 55	1.00 0.39 (0.17–0.93)	Age, education, height, BMI, age at menarche, menopause, parity, alcohol consumption, smoking, cholecystectomy, pregnancies, abortions	Strengths: exclusion of controls with previous cancer or hysterectomy, interviewer-administered FFQ, high participation rate, fully adjusted Limitations: small numbers, hospital controls with mild gynaecological conditions

Table 2.10 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Terry et al. (2002) Sweden, 1994–1995	Cases: 709 cases identified through six regional cancer registries Controls: 2870 population-based Exposure assessment method: FFQ	Endometrium	*Coffee consumption (quartiles, median cups/wk)* 1 (4) 2 (11) 3 (22) 4 (30) Trend test *P* value, 0.19	 250 167 137 155	 1.00 0.9 (0.6–1.3) 0.8 (0.6–1.1) 0.7 (0.5–1.0)	Age, BMI, smoking, physical activity, diabetes, fatty fish, quintiles of total food, various dietary items	Postmenopausal women aged 50–74 years Strengths: identification of cases through cancer registries, population controls, exclusion of previous endometrial/breast cancer, exclusion of controls having undergone hysterectomy, FFQ tested for validity and reproducibility Limitations: self-administered FFQ, no adjustment for menstrual and reproductive factors, no adjustment for hormone use
Hirose et al. (2007) Japan, 1990–2000	Cases: 229 cases identified through medical records and cancer registries Controls: 12 425 first-visit outpatients Exposure assessment method: self-administered FFQ, which was then checked by an interviewer	Endometrium	*All coffee (cups/day)* 0 < 1 1–2 ≥ 3 Trend test *P* value, < 0.01	 72 50 90 13	 1.00 0.70 (0.45–1.08) 0.64 (0.43–0.94) 0.41 (0.19–0.87)	Age, year of interview, motivation for consultation, parity, age at first delivery, smoking, alcohol consumption, type of breakfast, physical activity, BMI, various dietary items	Strengths: cases identified through medical records and cancer registries, checking of FFQ, exclusion of previous cancer among controls Limitations: hospital controls, no exclusion of controls having undergone hysterectomy, no information on FFQ validity/ reproducibility and other characteristics, no adjustment for menstrual factors and exogenous hormones

Table 2.10 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Koizumi et al. (2008) Japan, 2002–2005	Cases: 107 hospital-based Controls: 214 women attending cancer screening programme Exposure assessment method: FFQ	Endometrium	*All coffee consumption* < 4 times/wk 5 times/wk – 1 cup/day ≥ 2 cups/day Trend test *P* value, 0.014	 48 25 34	 1.0 0.6 (0.3–1.2) 0.4 (0.2–0.9)	Age, geographic area, education, BMI, smoking, age at menarche, OC, diabetes, energy intake, number of pregnancies, menopausal status	Inverse association only in postmenopausal women, similar inverse association in strata of BMI and education Strengths: population controls, previous cancer excluded, exclusion of controls having undergone hysterectomy, high participation rate, FFQ tested for validity/reproducibility, fully adjusted Limitations: self-administered FFQ
McCann et al. (2009) USA, 1982–1998	Cases: 513 hospital-based (tumour registry and diagnostic index) Controls: 512 hospital-based Exposure assessment method: FFQ, referred to few years before the administration	Endometrium	*All coffee consumption (cups/day)* 0 0.5 1–2 > 2 Trend test *P* value, 0.5	 170 68 165 110	 1.00 0.77 (0.50–1.18) 0.89 (0.63–1.24) 0.71 (0.49–1.03)	Age, HRT, OC, education, smoking, BMI, decaffeinated coffee, tea	Strengths: cases identified by cancer registries, information for caffeinated/decaffeinated coffee, exclusion of controls with previous hysterectomy and cancer, fully adjusted Limitations: hospital controls, self-administered FFQ, no clear information on participation rate among controls, no information on validity/ reproducibility of FFQ
Bandera et al. (2010) USA, 2001–2005	Cases: 417 population-based Controls: 395 population-based Exposure assessment method: FFQ	Endometrium	*All coffee consumption (cups/day)* 0 ≤ 1 1–2 > 2 Trend test *P* value, 0.11	 70 181 110 52	 1.00 1.05 (0.58–1.89) 1.02 (0.56–1.88) 0.69 (0.36–1.33)	Age, education, race, age at menarche, parity, OC, HRT, BMI, menopause, smoking (pack-years), smoking status, age at menopause, addition of sugar/honey/milk/cream/ non-dairy cream	Strengths: cases identified through cancer registries, population controls, exclusion of controls having undergone hysterectomy, FFQ tested for validity and reproducibility, fully adjusted Limitations: low participation rate, self-administered FFQ

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; OC, oral contraceptive; wk, week(s)

women with previous cancer among cases and controls, and of women with hysterectomies among controls; the validated interviewer-administered FFQ; the high participation rate; and full adjustment. The study was however limited by: the low number of participants; hospital controls with mild gynaecological conditions; and a lack of information on age of participants and intake of caffeinated/decaffeinated coffee.]

Terry et al. (2002) analysed the relation of dietary factors to cancer of the endometrium in a study conducted in Sweden. The 709 cases of endometrial cancer were identified through six regional cancer registries. Controls were 2870 women with an intact uterus selected from a national population registry. Cases and controls with previous endometrial or breast cancer were excluded, and information was obtained from a self-administered questionnaire. A non-significant inverse association between coffee drinking and risk of endometrial cancer was observed, with an adjusted odds ratio of 0.7 (95% CI, 0.5–1.0) for the highest quartile of coffee intake (corresponding to a median intake of 30 cups/week), with no trend in risk (*P* for trend, 0.19). [This study benefited from the identification of cases through cancer registries, population-based controls, the exclusion of cases with previous endometrial/breast cancer and of controls with hysterectomies, the high participation rate, and that fact that FFQs were tested for validity/reproducibility (correlation coefficient, 0.3–0.6). It was however limited by the self-administered FFQ (except for a few telephone interviews), the lack of information on intake of caffeinated/decaffeinated coffee, and the lack of adjustment for menstrual/reproductive factors and HRT use.]

Hirose et al. (2007) examined the associations between coffee intake and the risk of cancer of the breast, endometrium, and ovary among Japanese women (described in Section 2.4.2 (b) on breast cancer). A total of 229 cases of endometrial cancer were reported. Coffee intake decreased the risk of endometrial cancer with an odds ratio of 0.41 (95% CI, 0.19–0.87) for consumption of ≥ 3 cups/day compared with non–drinkers, with a significant trend in risk (*P* for trend, < 0.01). The inverse association was statistically significant in women aged < 55 years but not in older women, with odds ratios for ≥ 3 cups/day versus non-drinkers of 0.40 (95% CI, 0.16–0.99; *P* for trend, 0.03) and 0.33 (95% CI, 0.08–1.45), respectively. The inverse association was also statistically significant in women with a BMI ≤ 22 kg/m^2 but not for women with a BMI of > 22, with odds ratios for ≥ 3 cups/day versus non-drinkers of 0.08 (95% CI, 0.01–0.60; *P* for trend, 0.001) and 0.78 (95% CI, 0.34–1.81), respectively. The inverse association was consistent in data stratified for smoking, alcohol drinking, and fruit consumption. [This study had several strengths, including the facts that cases were identified through medical records and cancer registries, the self-administered FFQs were checked by an interviewer, and controls with previous cancer were excluded. It was however limited by: the hospital-based controls; the lack of information on exclusion of hysterectomized women from controls, FFQ validity/reproducibility, and other characteristics; the lack of adjustment for menstrual factors and exogenous hormones; and no separate information for coffee/decaffeinated coffee.]

Koizumi et al. (2008) analysed the association between coffee consumption and risk of cancer of the endometrium in a study conducted at two centres in Japan. Cases were 107 women aged < 80 years with endometrial endometrioid adenocarcinoma (endometrial cancer type I) identified from the histopathological records. Controls were 214 women matched with cases for age and geographical region, identified among women attending a cancer screening programme. Cases and controls were excluded if they had had any cancer, and controls were excluded if they had hysterectomies. Coffee consumption was collected through a self-administered questionnaire before surgery for cases and by mail

for controls. Coffee was inversely related to the risk of endometrial cancer type I, with an intake of ≥ 2 cups/day compared with < 4 times/week [not specified whether 'time' is equal to 'cup'] yielding an adjusted odds ratio of 0.4 (95% CI, 0.2–0.9) with a trend in risk (*P* for trend, 0.014). No heterogeneity was found in strata of BMI and education, but the inverse association was found only in postmenopausal women with an intake of ≥ 2 cups/day compared with ≤ 4 times/week yielding an odds ratio of 0.3 (95% CI, 0.1–0.8) with a trend in risk (*P* for trend, 0.016); the corresponding odds ratio in premenopausal women was 1.2 (95% CI, 0.3–4.3). [The strengths of this study included: the use of population-based controls; the exclusion of previous cancer among cases and controls, and of hysterectomies among controls; the high participation rate; the fact that the FFQ was tested for validity/reproducibility; and full adjustment of data. It was however limited by the self-administered FFQ and lack of separate information for caffeinated and decaffeinated coffee intake.]

McCann et al. (2009) analysed the association between consumption of coffee and tea and risk of cancer of the endometrium in a study conducted at the RPCI in USA during 1982–1998. Cases were 513 women newly diagnosed with endometrial cancer, identified from the tumor registry. Controls were 512 subjects matched to cases by age, identified among women who had received medical services at the same institute with a suspicion of neoplastic disease but were not diagnosed with malignant conditions. There was no information provided on participation rate, but about 50% of patients returned the mailed questionnaire. Coffee consumption was collected through a self-administered FFQ questionnaire. Regular coffee consumption was associated with a decreased risk of endometrial cancer, with an odds ratio of 0.71 (95% CI, 0.49–1.03; *P* for trend, 0.50) for > 2 cups/day versus non-drinkers. The results were similar in data stratified for BMI. Decaffeinated coffee was not related to overall risk of endometrial cancer (OR, 1.17; 95% CI, 0.74–1.84) for an intake of > 2 cups/day or in strata of BMI. [The strengths of this study were identification of cases by cancer registries, exclusion of controls with cancer diagnosis or hysterectomy, consideration of caffeinated and decaffeinated coffee intake, and full adjustment. It was however limited by the use of hospital-based controls, the self-administered FFQ, and lack of information about FFQ validity/reproducibility.]

Bandera et al. (2010) considered the association between the consumption of coffee and tea and the risk of cancer of the endometrium using data from the Estrogen, Diet, Genetics, and Endometrial Cancer (EDGE) study conducted in six New Jersey counties (USA). The 417 cases (aged > 21 years) were identified through the New Jersey State Cancer Registry (participation rate 42%). The 395 controls were identified from various sources: RDD for women aged < 65 years (participation rate 49%); lists for Medicare/Medicaid services for those aged ≥ 65 years (participation rate 22%); and households in randomly selected neighbourhoods for those aged ≥ 55 years (participation rate 43%). Women with hysterectomies were excluded from controls. Coffee consumption was collected through a self-administered FFQ tested for validity (Block version 98.2). Coffee consumption was not related to incidence of endometrial cancer, with an odds ratio of 0.69 (95% CI, 0.36–1.33) for > 2 cups/day compared with non-drinkers (*P* for trend, 0.11). [The study benefited from identification of cases through cancer registries, the use of population-based controls, the exclusion of hysterectomized women from controls, the testing of the FFQ for validity/reproducibility, and full adjustment. Limitations noted included a low participation rate, no information on previous cancer among cases and controls, the self-administered FFQ, and a lack of information regarding consumption of caffeinated and decaffeinated coffee separately.]

2.5.3 Meta-analyses

Bravi et al. (2009a) conducted the first meta-analysis of the association of endometrial cancer and coffee consumption by performing a MEDLINE search of the literature spanning 1966 to July 2008; the nine observational studies identified (two cohort and seven case–control) included a total of 2610 cases. A meta-relative risk for an increment of 1 cup/day of 0.93 (95% CI, 0.89–0.97) was estimated, with substantial heterogeneity between the studies. Yu et al. (2011) studied coffee intake in association with cancer incidence based on cohort studies, but the Working Group found the meta-analysis had important methodological limitations. Je & Giovannucci (2012) searched the electronic databases MEDLINE and Embase for epidemiologic studies published between 1966 and October 2011, and reviewed the reference lists of retrieved articles. The analyses were based on 16 observational studies for a total of 6628 cases, including 6 cohort (3144 cases) and 10 case–control studies (3484 cases). There was no indication of publication bias based on funnel plots and the Egger test. The summary relative risks with 95% confidence interval were calculated using random-effects models because of the heterogeneity among studies. The pooled relative risks (95% CI) for the study-specific highest versus the study-specific lowest consumption were: 0.71 (0.62–0.81) based on all studies; 0.70 (0.61–0.80) for the 6 cohort studies; and 0.69 (0.55–0.87) for the 10 case–control studies. Sensitivity analysis showed that excluding the study of Levi et al. (1993b) (which did not adjust for BMI) increased the strength of the inverse association. The inverse association was similar in the 12 studies after adjusting for smoking and BMI, and apparently stronger in the 3 studies conducted in Japan (RR, 0.40; 95% CI, 0.25–0.63) than in the 8 studies conducted in Europe (RR, 0.79; 95% CI, 0.63–0.99) or 5 in North America (RR, 0.69; 95% CI, 0.60–0.79). The pooled relative risks for an increment of 1 cup/day were 0.92 (95% CI, 0.90–0.95) based on 14 studies, 0.94 (95% CI, 0.90–0.97) for the cohort studies, and 0.90 (95% CI, 0.86–0.95) for the case–control studies. The inverse association was again apparently stronger in studies conducted in Japan (RR, 0.76; 95% CI, 0.68–0.86) than in Europe (RR, 0.93; 95% CI, 0.90–0.97) or North America (RR, 0.94; 95% CI, 0.91–0.97). Coffee intake therefore appeared consistently inversely associated with risk of endometrial cancer. [This meta-analysis benefited from searching also within the Embase database; the inclusion of 'dietary factors' among keywords, resulting in the inclusion of all published studies; checking for publication bias; deep analysis that allowed information on dose–response relationship, and in strata of study design and geographical area; appropriate statistical analysis; clear information on number of studies included in subgroup analyses; analyses for a subgroup of papers adjusting for smoking and BMI; and a sensitivity analysis with the exclusion of each paper in turn. No subgroup analyses based on BMI and menopausal status was performed, however.]

In a report of the association between intake of coffee and tea and risk of cancer of the endometrium, part of the UK-based Million Women Study, Yang et al. (2015) included a meta-analysis from searching in PubMed and Embase [there was no indication of the date of the reference search, which appears to have been around the end of 2012] and looking at the reference lists of retrieved articles. Analyses were based on eight cohort and eight case–control studies. Compared with the previous meta-analysis of Je & Giovannucci (2012), this meta-analysis included two further cohorts but excluded two case–control studies. [The strengths of this analysis were the stratification by study design and geographical region, and investigation of dose–response relationship. It was however limited by: the unspecificied date of the literature search; no inclusion of the keyword 'diet', which led to the exclusion of two papers; no check for

publication bias; and no sensitivity analysis with the exclusion of each paper in turn.]

Zhou et al. (2015) reported the results of a meta-analysis of prospective cohort studies updated to May 2015, based on 13 studies. The relative risks (95% CI) were 0.80 (0.74–0.86) for the highest versus the lowest coffee intake and 0.95 (0.93–0.97) for an increment of 1 cup/day. The inverse association for the highest versus the lowest coffee intake was similar for regular (RR, 0.66; 95% CI, 0.52–0.85) and decaffeinated coffee (RR, 0.77; 95% CI, 0.63–0.94), and was apparently stronger in women with a BMI > 25 kg/m^2 and in those who never used HRT. [The Working Group noted that the analyses in strata of BMI excluded several relevant studies.] The only cohort study published after this meta-analysis had similar results (Hashibe et al., 2015). [The strengths of this analysis were the investigation of a dose–response relationship, stratification by many covariates, and sensitivity analysis with the exclusion of each paper in turn. It was however limited by the fact that the stratified analyses did not include all papers.]

2.6 Cancer of the prostate

More than for any other cancer, the incidence of cancer of the prostate must be interpreted in the context of diagnostic intensity and screening behaviour. Latent prostate cancer is quite common, and screening by prostate-specific antigen (PSA) has allowed for the detection of many of these lesions. Consequently, incidence rates in some countries, the USA being a prime example, reflect the sum of clinical disease and latent disease. There is therefore a focus on identifying risk factors for clinically important prostate cancer, or disease that is most likely to progress, both for biological relevance and to deal with confounding by screening. As a result, the Working Group considered associations for risk of total prostate cancer, but also for risk of fatal, advanced (based on stage), and high-grade (based on Gleason grade, a histological assessment of differentiation) disease. In studies that combined stage and grade-based definitions, we refer to this as 'aggressive' disease.

Studies that did not control for smoking behaviour were judged to be non-informative. Smoking is not associated with total prostate cancer incidence, but is associated with prostate cancer mortality (US Department of Health and Human Services, 2014). Because smoking is also strongly associated with coffee intake in many populations, and because many high-quality studies of coffee and prostate cancer with adjustment for smoking are available, those without adjustment for smoking were excluded.

2.6.1 Cohort studies

See Table 2.11.

Four cohort studies, three of prostate cancer incidence (Severson et al., 1989; Le Marchand et al., 1994, an updated report from the cohort in Nomura et al., 1986; Ellison, 2000) and one of fatal prostate cancer (Hsing et al., 1990), that did not control for smoking were reviewed but excluded from evaluation due to the potential for confounding.

Jacobsen et al. (1986) studied the association between coffee drinking and risk of multiple cancers in a cohort of Norwegian men. Smoking information was only provided for part of the study population, so only those results were considered here. Among those 10 517 men, there were 205 cases of cancer of the prostate. Coffee consumption in the population was very high, so the comparison group was ≤ 2 cups/day. Men consuming ≥ 7 cups/day had an odds ratio of 0.89 (*P* for trend, 0.14). Results were adjusted only for age in 10-year groups, area of residence, and cigarette smoking, and confidence intervals were not provided. [Strengths included the prospective design and high-quality cancer registry. There was no consideration of stage or grade; however, the study was conducted before the introduction

Table 2.11 Cohort studies on cancer of the prostate and drinking coffee

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jacobsen et al. (1986) Norway, 1964–1967/1978	10 517 Norwegian men who completed a questionnaire in 1964 followed by one in 1967 on coffee habits Exposure assessment method: FFQ	Prostate	*Baseline coffee intake (cups/day)*			Age (10-year groups), residence, smoking	Only included analyses from the subgroup of men who also provided information on smoking habits for adjustment Strengths: prospective design, high-quality cancer registry, conducted before introduction of PSA screening Limitations: high coffee intake in the target population made a wide reference group (non-drinkers up to 2 cups/day), analysis adjusted for age in 10-yr groups
			≤ 2	62	1.17		
			3–4	79	0.97		
			5–6	43	0.91		
			≥ 7	21	0.89		
			Trend test *P* value, 0.14				
Stensvold & Jacobsen (1994) Norway, 1977/1982–1990	21 735 men aged 35–54 yr from three counties in Norway identified via cardiovascular screening programme Exposure assessment method: FFQ	Prostate: all combined	*All coffee (cups/day)*			Age, residence, smoking	Strengths: prospective design, high-quality cancer registry, before PSA screening Limitations: see Jacobsen et al. (1986)
			≤ 2	8	1.0		
			3–4	6	0.3		
			5–6	13	0.6		
			≥ 7	11	0.4		
			Trend test *P* value, > 0.05				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nilsson et al. (2010) Sweden, 1992–2007	32 425 residents in Västerbotten county, Sweden Exposure assessment method: FFQ, nine frequency options for both filtered and boiled coffee	Prostate: ICD7:177 malignant neoplasm of prostate Prostate	*Total coffee (boiled + filtered) from baseline questionnaire (occasions/day)*			Age, BMI, smoking, education, physical activity	Strengths: long follow-up, high-quality cancer registry Limitations: no information on cancer grade, stage, or PSA testing
			< 1	60	1.00		
			1–3	384	0.92 (0.70–1.21)		
			≥ 4	209	1.03 (0.77–1.38)		
			Filtered coffee from baseline questionnaire (occasions/day)				
			< 1	196	1.00		
			1–3	343	0.98 (0.82–1.16)		
			≥ 4	114	1.07 (0.85–1.36)		
			Boiled coffee from baseline questionnaire (occasions/day)				
			< 1	452	1.00		
			1–3	161	0.99 (0.82–1.18)		
			≥ 4	40	1.13 (0.81–1.56)		
Wilson et al. (2011) USA, 1986–2006	47 911 men, health professionals in the USA aged 40–75 in 1986 Exposure assessment method: validated FFQ in 1986 and every 4 yr thereafter	Prostate: all combined	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*			Age and calendar period, race, BMI at age 21, current BMI, vigorous physical activity, smoking, diabetes, family history of prostate cancer, multivitamin use, processed meat intake, tomato sauce intake, calcium intake, α-linolenic acid, supplemental vitamin E, alcohol consumption, energy intake, history of PSA testing, height	Strengths: validated FFQ with repeated diet measurements, long follow-up (20 yr), prostate cancer risk analysed by grade/ stage/lethality, adjusted for PSA screening Limitations: sample size for very high intakes of coffee (> 5 cups/day) was small
			None	587	1.00		
			< 1	1139	0.94 (0.85–1.05)		
			1–3	2438	0.94 (0.86–1.04)		
			4–5	719	0.93 (0.83–1.04)		
			≥ 6	152	0.82 (0.68–0.98)		
			Trend test *P* value, 0.1				
		Prostate: lethal	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	89	1.00		
			< 1	150	0.76 (0.58–1.00)		
			1–3	298	0.71 (0.55–0.92)		
			4–5	93	0.76 (0.56–1.04)		
			≥ 6	12	0.40 (0.22–0.75)		
			Trend test *P* value, 0.03				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wilson et al. (2011) (cont.)		Prostate: advanced stage	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	122	1.00		
			< 1	211	0.81 (0.64–1.02)		
			1–3	422	0.75 (0.60–0.93)		
			4–5	122	0.73 (0.56–0.95)		
			≥ 6	19	0.47 (0.28–0.77)		
			Trend test *P* value, 0.004				
		Prostate: non-advanced stage	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	353	1.00		
			< 1	729	1.01 (0.88–1.15)		
			1–3	1554	0.99 (0.87–1.12)		
			4–5	483	1.02 (0.88–1.18)		
			≥ 6	102	0.93 (0.74–1.16)		
			Trend test *P* value, 0.77				
		Prostate: grade 8–10	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	61	1.00		
			< 1	111	0.84 (0.61–1.16)		
			1–3	255	0.87 (0.65–1.18)		
			4–5	78	0.88 (0.61–1.26)		
			≥ 6	11	0.53 (0.27–1.02)		
			Trend test *P* value, 0.29				
		Prostate: grade 7	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	174	1.00		
			< 1	295	0.85 (0.70–1.04)		
			1–3	641	0.85 (0.71–1.02)		
			4–5	226	0.94 (0.76–1.16)		
			≥ 6	41	0.69 (0.49–0.99)		
			Trend test *P* value, 0.50				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wilson et al. (2011) (cont.)		Prostate: grade 2–6	*Cumulative average total coffee intake, updated every 4 yr (cups/day)*				
			None	232	1.00		
			< 1	489	1.02 (0.87–1.20)		
			1–3	1045	1.01 (0.87–1.18)		
			4–5	298	0.96 (0.80–1.15)		
			≥ 6	70	1.00 (0.75–1.31)		
			Trend test *P* value, 0.53				
Shafique et al. (2012) Scotland, 1970/1973–2007	6017 men aged 21–75 yr Exposure assessment method: questionnaire; details of how coffee assessed were not provided; full diet unknown, appears that only coffee and alcohol were assessed	Prostate: all combined	*Baseline coffee intake (cups/day)*			Age, cholesterol levels, systolic blood pressure, BMI, alcohol intake, tea intake, smoking status, social class	Strengths: long-term follow-up (28 yr median), analysis by cancer grade as well as by total prostate cancer, clean reference group of never drinkers Limitations: smaller cohort, baseline coffee intake with very long follow-up, lack of information on PSA screening
			0	139	1.00		
			1–2	114	0.95 (0.72–1.24)		
			≥ 3	65	0.93 (0.66–1.31)		
			Trend test *P* value, 0.64				
		Prostate	*Cups of coffee continuous*				
			Per 1 cup/ day	318	0.96 (0.81–1.13)		
		Prostate: all combined	*Baseline coffee intake (survivor) (cups/day)*				
			0	81	1.00		
			1–2	67	0.84 (0.60–1.21)		
			≥ 3	38	0.74 (0.47–1.16)		
			Trend test *P* value, 0.23				
		Prostate: aggressive/ advanced (Gleason 8–10)	*Baseline coffee intake (survivor) (cups/day)*				
			0	39	1.00		
			1–2	20	0.51 (0.28–0.92)		
			≥ 3	11	0.47 (0.22–1.01)		
			Trend test *P* value, 0.03				
		Prostate: aggressive/ advanced (Gleason 7)	*Baseline coffee intake (survivor) (cups/day)*				
			0	12	1.00		
			1–2	14	1.23 (0.53–2.84)		
			≥ 3	12	1.79 (0.69–4.62)		
			Trend test *P* value, 0.17				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shafique et al. (2012) (cont.)		Prostate: aggressive/ advanced (Gleason < 7)	*Baseline coffee intake (survivor) (cups/day)*				
			0	17	1.00		
			1–2	17	1.04 (0.51–2.17)		
			≥ 3	7	0.54 (0.19–1.57)		
			Trend test *P* value, 0.48				
		Prostate: aggressive/ advanced (unknown Gleason)	*Baseline coffee intake (survivor) (cups/day)*				
			0	13	1.00		
			1–2	16	1.17 (0.52–2.64)		
			≥ 3	8	0.88 (0.31–2.48)		
			Trend test *P* value, 0.89				
Discacciati et al. (2013) Sweden, 1997–2010	44 613 men aged 45–79 yr residing in two central Sweden counties during 1997–1998 Exposure assessment method: FFQ	Prostate: aggressive/ advanced (fatal)	*Baseline coffee intake (cups/day)*			Age, tea, alcohol consumption, BMI, diabetes, family history of prostate cancer, smoking status, physical activity, education, energy intake	Strengths: analysis of risk performed by stage, grade, and fatal disease; validated FFQ Limitations: subhazard ratios are not comparable to other studies, lack of information on PSA screening, use of 1–3 cups/ day as reference group, coffee consumption was self-reported
			None	28	1.24 (0.83–1.97)		
			< 1	63	1.19 (0.90–1.56)		
			1–3	316	1.00		
			4–5	82	1.01 (0.79–1.30)		
			≥ 6	26	0.88 (0.58–1.31)		
			Trend test *P* value, 0.18				
		Prostate: aggressive/ advanced (advanced–stage)	*Baseline coffee intake (cups/day)*				
			None	37	0.96 (0.68–1.35)		
			< 1	93	0.97 (0.78–1.21)		
			1–3	582	1.00		
			4–5	153	0.95 (0.79–1.14)		
			≥ 6	53	0.87 (0.66–1.16)		
			Trend test *P* value, 0.49				
		Prostate: localized	*Baseline coffee intake (cups/day)*				
			None	129	1.13 (0.93–1.37)		
			< 1	212	1.00 (0.86–1.16)		
			1–3	1397	1.00		
			4–5	457	0.93 (0.83–1.03)		
			≥ 6	173	0.81 (0.69–0.96)		
			Trend test *P* value, 0.005				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2013b) Japan (Ohsaki), 1994–2005	18 853 National Health Insurance beneficiaries aged 40–79 resident in the Ohsaki Public Health Center administrative region Exposure assessment method: validated FFQ with five response categories for coffee	Prostate: all combined	*Baseline coffee intake (cups/day)*			Age, education, BMI, physical activity, marital status, walking, smoking status, family history of cancer, tea intake, job status, energy intake, passive smoking, alcohol consumption, miso soup consumption	Strengths: validated FFQ, reference group of non-drinkers of coffee, population with relatively stable dietary habits Limitations: small number of cases, low coffee consumption in this study population, lack of PSA testing information (PSA testing is not as common in Japan as it is in Europe/ USA), coffee intake assessed once at baseline
			Never	84	1.00		
			Occasionally	124	0.81 (0.61–1.07)		
			1–2	86	0.73 (0.53–1.00)		
			≥ 3	24	0.63 (0.39–1.00)		
			Trend test *P* value, 0.02				
		Prostate: aggressive/ advanced (advanced-stage or high-grade)	*Baseline coffee intake (cups/day)*			Age, education, BMI, physical activity, marital status, walking, smoking status, family history of cancer, tea intake, job status, energy intake, passive smoking, alcohol consumption, miso soup consumption, time period of diagnosis	
			Never	24	1.00		
			Occasionally	50	1.26 (0.73–2.16)		
			1–2	27	0.73 (0.38–1.39)		
			≥ 3	8	0.90 (0.38–2.12)		
			Trend test *P* value, 0.33				
		Prostate: localized	*Baseline coffee intake (cups/day)*				
			Never	18	1.00		
			Occasionally	29	0.89 (0.48–1.65)		
			1–2	27	1.16 (0.61–2.20)		
			≥ 3	4	0.54 (0.18–1.66)		
			Trend test *P* value, 0.77				
		Prostate: missing stage (cases)	*Baseline coffee intake (cups/day)*				
			Never	42	1.00		
			Occasionally	45	0.55 (0.35–0.85)		
			1–2	32	0.50 (0.30–0.81)		
			≥ 3	12	0.61 (0.31–1.20)		
			Trend test *P* value, 0.03				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bosire et al. (2013) USA, 1995–2006	288 391 members of the AARP from six US states and two US cities, aged 50–71 yr during 1995–96 Exposure assessment method: FFQ	Prostate: all combined	*Baseline coffee intake (cups/day)*			Age, race, height, BMI, physical activity, smoking status, diabetes, family history of prostate cancer, history of PSA testing, tomato sauce, α-linolenic acid, energy intake	Strengths: very large cohort, PSA screening information for 69% of cohort, clean reference group of non-drinkers of coffee, long follow-up period Limitations: US state cancer registries are of varying quality, coffee intake only assessed at baseline
			None	2136	1.00		
			< 1	3894	1.03 (0.98–1.08)		
			1	3781	1.00 (0.95–1.06)		
			2–3	9835	1.00 (0.96–1.05)		
			4–5	2902	1.00 (0.94–1.06)		
			≥ 6	787	0.94 (0.87–1.02)		
			Trend test *P* value, 0.08				
		Prostate: aggressive/ advanced (fatal)	*Baseline coffee intake (cups/day)*				
			None	87	1.00		
			< 1	144	0.89 (0.68–1.16)		
			1	139	0.81 (0.62–1.06)		
			2–3	400	0.87 (0.69–1.11)		
			4–5	110	0.77 (0.58–1.03)		
			≥ 6	37	0.80 (0.53–1.18)		
			Trend test *P* value, 0.2				
		Prostate: aggressive/ advanced (advanced-stage)	*Baseline coffee intake (cups/day)*				
			None	264	1.00		
			< 1	510	1.10 (0.95–1.28)		
			1	440	0.97 (0.83–1.14)		
			2–3	1185	0.98 (0.86–1.12)		
			4–5	401	1.08 (0.92–1.27)		
			≥ 6	127	1.15 (0.92–1.43)		
			Trend test *P* value, 0.62				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bosire et al. (2013) (cont.)		Prostate: aggressive/ advanced (non-advanced-stage)	*Baseline coffee intake (cups/day)*				
			None	1744	1.00		
			< 1	3168	1.03 (0.97–1.09)		
			1	3097	1.01 (0.95–1.07)		
			2–3	8048	1.01 (0.96–1.07)		
			4–5	2325	0.99 (0.93–1.06)		
			≥ 6	611	0.92 (0.84–1.01)		
			Trend test *P* value, 0.07				
		Prostate: aggressive/ advanced (all combined)	*Baseline coffee intake (cups/day): non-smokers only*				
			None	1901	1.00		
			< 1	3272	1.01 (0.95–1.07)		
			1	3084	0.98 (0.92–1.04)		
			2–3	7459	0.97 (0.92–1.02)		
			≥ 4	2366	0.98 (0.92–1.04)		
			Trend test *P* value, 0.16				
		Prostate: aggressive/ advanced (fatal)	*Baseline coffee intake (cups/day): non-smokers only*				
			None	68	1.00		
			< 1	112	0.94 (0.70–1.27)		
			1	107	0.87 (0.64–1.19)		
			2–3	252	0.86 (0.66–1.13)		
			≥ 4	72	0.81 (0.58–1.14)		
			Trend test *P* value, 0.19				
		Prostate: aggressive/ advanced (advanced-stage)	*Baseline coffee intake (cups/day): non-smokers only*				
			None	230	1.00		
			< 1	419	1.09 (0.93–1.28)		
			1	352	0.97 (0.82–1.14)		
			2–3	875	0.96 (0.83–1.11)		
			≥ 4	311	1.07 (0.90–1.27)		
			Trend test *P* value, 0.82				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bosire et al. (2013) (cont.)		Prostate: aggressive/ advanced (non-advanced-stage)	*Baseline coffee intake (cups/day): non-smokers only*				
			None	1557	1.00		
			< 1	2674	1.00 (0.94–1.07)		
			1	2553	0.99 (0.93–1.05)		
			2–3	6171	0.98 (0.93–1.03)		
			≥ 4	1933	0.98 (0.92–1.05)		
			Trend test *P* value, 0.28				
Tverdal (2015) Norway, 1985/1999 – 2010	224 234 men aged 40–42 yr and samples of men of age 20–39 and 43–69 yr invited to participate in Norwegian cardiovascular screening programme during 1985–1999 Exposure assessment method: questionnaire, recording coffee (boiled, filtered, instant, decaffeinated) consumption during 1985–1994 and coffee (boiled, other) consumption from 1994 onwards	Prostate: all combined	*Baseline intake, type of coffee*			Age, smoking status, BMI, height, physical activity, total cholesterol, triglycerides, systolic blood pressure, diabetes, cups/day, year of examination	Strengths: large study with long follow-up period (up to 25 yr), wide range of coffee intakes all cases verified by histological examination Limitations: no analysis shown for fatal prostate cancer, inadequate breakdown by cancer type and severity as seen in other studies, lack of information on PSA screening, coffee consumption habits only assessed once
			None	389	1.00		
			Not boiled	3503	0.94 (0.83–1.06)		
			Boiled and not boiled	500	0.94 (0.81–1.09)		
			Boiled only	1348	0.82 (0.72–0.94)		
			Baseline intake, all types of coffee (cups/day)				
			None	389	1.00		
			< 1 to 4	2404	0.88 (0.79–0.98)		
			5–8	2305	0.88 (0.79–0.98)		
			≥ 9	642	0.78 (0.69–0.89)		
			Trend test *P* value, < 0.01				

Table 2.11 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tverdal (2015) (cont.)			*Baseline intake, non-boiled coffee (cups/day)*				
			None	389	1.00		
			< 1 to 4	1669	0.89 (0.80–0.99)		
			5–8	1467	0.91 (0.81–1.02)		
			≥ 9	367	0.86 (0.74–1.00)		
			Trend test *P* value, 0.22				
			Baseline intake, boiled and non-boiled coffee (cups/day)				
			None	389	1.00		
			< 1 to 4	176	0.83 (0.69–0.99)		
			5–8	248	0.88 (0.75–1.04)		
			≥ 9	76	0.74 (0.57–0.96)		
			Trend test *P* value, 0.02				
			Baseline intake, boiled coffee only (cups/day)				
			None	389	1.00		
			< 1 to 4	559	0.84 (0.73–0.96)		
			5–8	590	0.80 (0.70–0.92)		
			≥ 9	199	0.66 (0.55–0.80)		
			Trend test *P* value, 0.00				
Hashibe et al. (2015) USA, 1992–2001 (enrolment), 2011	46 667 men in PLCO cancer screening trial enrolled from 10 centres across USA, FFQ began in 1998 and screening ended in late 2006 Exposure assessment method: FFQ	Prostate: all combined	*Baseline coffee intake (cups/day)*			Age, race, education	Strengths: validated FFQ, long follow-up time, prospective design, large sample size Limitations: unclear whether smoking was adjusted for in the prostate cancer models, no analysis by stage or grade, no in-depth analysis of low or high coffee intakes, coffee intake measured once at baseline
			< 1	889	1.00		
			1–1.9	417	1.02 (0.91–1.15)		
			≥ 2	1731	1.02 (0.94–1.10)		
			Trend test *P* value, 0.7				

AARP, American Association of Retired Persons; BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen; yr, year(s)

of PSA testing, so cases will represent fairly advanced cancers relative to those diagnosed in more recent studies. The limitations of the study were the crude adjustment for confounders and a very wide and somewhat high coffee intake (up to 2 cups/day) in the reference group.]

In another Norwegian cohort, Stensvold & Jacobsen (1994) studied the risk of various cancers among 21 735 younger men (aged 35–54 years at baseline) followed for an average of 10 years. With 38 cases of cancer of the prostate, there was no association between coffee intake and risk. Coffee consumption was again high so those consuming ≥ 7 cups/day were compared with those consuming ≤ 2 cups/day; an adjusted hazard ratio of 0.4 was observed, with a non-significant trend. Confidence intervals were not provided. [Strengths include the prospective study design and high-quality cancer registry. There was no consideration of stage or grade; however, the study was conducted before the introduction of PSA testing, so cases will represent fairly advanced cancers relative to those diagnosed in more recent studies. Limitations were the same as for the previous study with the addition of the small number (n = 38) of cases, likely due to the younger age of the cohort.]

In the VIP cohort (Nilsson et al., 2010) described in Sections 2.2.1, 2.4.1, and 2.5.1, 653 prostate cancer cases were ascertained. There was no suggestion of an association between total, filtered, or boiled coffee intake and risk of prostate cancer after adjustment for age, BMI, smoking, education, and recreational physical activity. Rates of coffee consumption in the population were high so the lowest/reference category was < 1 occasion/day, which is somewhat high compared with other studies. The analysis of filtered coffee intake was not adjusted for boiled coffee intake, making interpretation difficult. [Strengths included the prospective design, long follow-up period, and high-quality cancer registry. Limitations included a lack of information on stage or grade of disease. In addition, there was no information provided on PSA testing although the study took place well into the PSA era.]

The HPFS (Wilson et al., 2011) enrolled US male health professionals aged 40–75 years in 1986 and followed them through until 2006; questionnaires were issued every 2 years and FFQs every 4 years. With 5035 cases of prostate cancer, there was an inverse association between higher total coffee intake and overall risk of prostate cancer risk (HR, 0.82; 95% CI, 0.68–0.98) for ≥ 6 cups/day compared with non-drinkers of coffee (P for trend, 0.10). The association was significantly inverse for lethal (n = 642, defined as distant metastasis or fatal prostate cancer) and advanced (n = 896, defined as lethal or stage T3b or above at diagnosis) disease; hazard ratios (95% CI) were 0.40 (0.22–0.75; P for trend, 0.03) and 0.47 (0.28–0.77; P for trend, 0.004), respectively, for ≥ 6 cups/day compared with non-drinkers. There was an inverse association for high-grade (n = 516, Gleason 8–10) disease, but no association for non-advanced or low-grade (Gleason 2–6) disease. Similar inverse associations were seen for lethal and advanced disease for both regular and decaffeinated coffee. In all analyses, coffee intake was updated over time and PSA testing was adjusted for as a time-varying covariate. Two other analyses from this cohort, one of antioxidant intake (Russnes et al., 2014) and one of acrylamide intake (Wilson et al., 2012), also reported similar associations between total coffee intake and total prostate cancer risk, but with less detailed analysis. [Strengths included: the prospective design; long follow-up; repeated measures of diet to update coffee intake every 4 years; and analysis by stage, grade, and lethality. In addition, PSA testing was included in multivariable models. Coffee intake in the population allowed for a clean reference group of never drinkers. Limitations included a lower sample size for very high intakes of coffee compared with some of the European study populations.]

Shafique et al. (2012) used data from a Scottish cohort of 6017 men enrolled between 1970 and 1973, median follow-up 28 years, to investigate the association between coffee consumption and risk of prostate cancer. Coffee intake was assessed via self-administered questionnaire, although a full dietary questionnaire was not administered. With 318 cases of prostate cancer, there was no association between coffee intake and risk; a hazard ratio of 0.93 (95% CI, 0.66–1.31) was observed for ≥ 3 cups/day versus no coffee. There was a suggestion of an inverse association between coffee intake and risk of high-grade disease (Gleason score 8–10), with a hazard ratio of 0.47 (95% CI, 0.22–1.01; *P* for trend, 0.03) for ≥ 3 cups/day versus none. [Strengths included the prospective design, long-term follow-up, analysis by grade of disease, and the clean reference group of non-drinkers. Limitations included the smaller cohort size, lack of food intake data for adjustment for other dietary factors, and lack of information on PSA screening (although the follow-up period extended well into the PSA era). Although the follow-up period was long, there was a concern about misclassification of coffee intake over such a long time period with a single baseline measure.]

In the cohort of Swedish men, Discacciati et al. (2013) examined coffee intake and risk of fatal, aggressive, and non-aggressive disease among 44 613 men. There were 3601 cases, including 515 cases of fatal cancer. Fine and Gray competing risks models were used to calculate subhazard ratios. Coffee intake was inversely associated with non-aggressive disease (defined by stage, grade, and PSA at diagnosis), but not with aggressive or fatal disease. The subhazard ratio (SHR) for fatal prostate cancer was 0.88 (95% CI, 0.58–1.31) for ≥ 6 cups/day compared with 1–3 cups/day, while the subhazard ratio was 1.24 (95% CI, 0.83–1.97) for no coffee compared with 1–3 cups/day. The *P* value for linear trend was 0.18, and the subhazard ratio per 1 cup/day increment was 0.98 (95% CI, 0.93–1.03). For the analysis of fatal prostate cancer, deaths from causes other than prostate cancer were treated as competing events. The possibility of reverse causation, that is, lower urinary tract symptoms (LUTS) from preclinical disease causing men to reduce coffee intake before diagnosis, was also assessed. LUTS symptoms at baseline, assessed from a standard battery of questions, were not significantly associated with coffee intake after adjusting for age. [Strengths included the prospective design and analysis by stage, grade, and fatal disease. There was also a validated FFQ and high coffee intake in the population, allowing for robust analysis of ≥ 6 cups/day. Limitations included the use of only Fine and Gray competing risk models, resulting in subhazard ratio estimates rather than hazard ratios; these results are difficult to compare with those from other cohorts. The study was also limited by a lack of information on PSA testing, although the follow-up extended well into the PSA era, as well as a high-intake reference group (1–3 cups/day).]

Li et al. (2013b) studied the association between coffee consumption and risk of prostate cancer in the Ohsaki cohort, which included 18 853 men aged 40–79 years at enrolment in 1994; follow-up continued until 2005. A validated FFQ assessed coffee intake with five response options. With 318 total cases, coffee intake was inversely associated with risk of prostate cancer with a hazard ratio of 0.63 (95% CI, 0.39–1.00; *P* for trend, 0.02) for ≥ 3 cups/day compared with non-drinkers. Coffee intake was not associated with aggressive disease (n = 109), although stage and grade information was only available for 59% of cases. In addition, aggressive disease was defined as extra-prostatic, regional, or distant spread, or by a Gleason grade of 8–10 only among cases missing stage information. Information on PSA testing was not available. [Strengths included the prospective design, validated FFQ, and clean reference group of non-drinkers. Limitations included the low number of cases and low coffee consumption in the population,

limiting the upper intake categories that could be assessed. There was a lack of PSA testing information; however, rates in Japan are lower than in the USA and Europe, so this is possibly less of a concern.]

In the very large NIH-AARP cohort, Bosire et al. (2013) examined coffee intake among 288 391 men who completed a validated FFQ in 1995–1996, with follow-up until 2006. A total of 23 335 cases of cancer of the prostate were diagnosed, 917 of which were fatal. Coffee intake was not significantly associated with risk of total, fatal, or advanced prostate cancer. The hazard ratio (95% CI) for ≥ 6 cups/day compared with no coffee was 0.94 (0.87–1.02; *P* for trend, 0.08) for total, 0.80 (0.53–1.18; *P* for trend, 0.20) for fatal, and 1.15 (0.92–1.43; *P* for trend, 0.62) for advanced prostate cancer (n = 2927; defined as stage T3 and above or fatal prostate cancer). Analyses among never smokers only and among men who reported a PSA test yielded similar results. [Strengths included the prospective design and very large cohort size, with almost 3000 advanced cases of prostate cancer. PSA testing information was available from 69% of cohort members from a second questionnaire 1–2 years after baseline, and there was also a clean reference group of non-drinkers. Limitations included possible misclassification of prostate cancer, particularly by stage and grade, as US state cancer registries are of varying quality.]

Another large study in Norway (Tverdal, 2015) used data from 224 234 men aged 20–69 years who participated in a cardiovascular screening programme. Men were asked about consumption of boiled, filtered, instant, and decaffeinated coffee, or about boiled and non-boiled coffee depending on the time period. Total coffee intake was associated with a significantly lower risk of total prostate cancer, with a hazard ratio of 0.78 (95% CI, 0.69–0.89; *P* for trend, < 0.01) for those consuming ≥ 9 cups/day versus non-drinkers. Consumption of boiled coffee only or of boiled and non-boiled coffee was associated with a lower risk. Consumption of only non-boiled coffee was only suggestively associated with lower risk. Among a subset of cases with stage information available, there were no significant associations with regionally advanced or distantly spread disease; however, results were not shown. There were 622 cases of fatal prostate cancer, but risk of fatal disease was not analysed. [Strengths included its prospective design, very large size, and long follow-up period. There was a wide range of coffee intakes, allowing for a clean reference group and a high consumption category of ≥ 9 cups/day. Limitations included the lack of analysis for fatal prostate cancer and a lack of results for regionally or distantly advanced cases. There was also a lack of PSA screening information, although the follow-up period extended well into the PSA era.]

The PLCO Cancer Screening Trial (Hashibe et al., 2015) assessed the association between coffee consumption and risk of multiple cancers among men and women in either the screening or control groups who completed a baseline validated FFQ. There were 46 667 men and 3037 incident cases of prostate cancer. Coffee intake was not associated with prostate cancer risk, with a hazard ratio of 1.02 (95% CI, 0.94–1.10; *P* for trend, 0.70) for ≥ 2 cups/day compared with < 1 cup/day. No analysis was conducted by stage or grade. Due to the high rates of PSA screening in both the intervention and control arms of the study, there were very few advanced cancers diagnosed. [The Working Group noted that it was not clear from the paper whether smoking was adjusted for in the prostate cancer analysis. Strengths included the large study population, long follow-up time, and validated FFQ. Limitations included the lack of analysis by stage and grade, lack of adjustment for PSA testing, and unclear reporting of adjustment for smoking status. In addition, because many cancer sites were included in the analysis, the coffee categories are fairly large to accommodate less-common cancers. As a result, there was little

analysis of very high or low intakes despite the large number of cases.]

2.6.2 Case–control studies

See Table 2.12.

Case–control studies that did not control for smoking were reviewed but excluded from evaluation due to the potential for confounding (Slattery & West, 1993; Grönberg et al., 1996; Jain et al., 1998; Hsieh et al., 1999; Chen et al., 2005; Gallus et al., 2007; Ganesh et al., 2011b; Deneo-Pellegrini et al., 2012). Of these, three population-based case–control studies found no association between coffee consumption and risk of cancer of the prostate (Slattery & West, 1993; Grönberg et al., 1996; Jain et al., 1998). Three of the five hospital-based studies (Hsieh et al., 1999; Ganesh et al., 2011b; Deneo-Pellegrini et al., 2012) found no association, while two found positive associations (Chen et al., 2005; Gallus et al., 2007). One case-only study of prostate cancer aggressiveness (defined by stage, grade, and PSA at diagnosis) was not considered for evaluation as there was no comparison to cancer-free controls (Arab et al., 2012).

This left only four case–control studies under consideration (Villeneuve et al., 1999; Sharpe & Siemiatycki, 2002; Geybels et al., 2013; Wilson et al., 2013). All four were population-based studies, and two (Geybels et al., 2013; Wilson et al., 2013) assessed the association between coffee consumption and advanced-stage and high-grade disease in addition to total prostate cancer risk. Wilson et al. (2013) also assessed the association for fatal prostate cancer.

Villeneuve et al. (1999) conducted a population-based case–control study in Canada, with 1623 cases aged 50–74 years and 1623 controls selected through several methods depending on the province. Coffee intake was not associated with prostate cancer risk in multivariable models. [Strengths included the population-based design, large sample size, and use of a clean reference group of non-drinkers. Limitations included a lack of information on PSA testing, although the study period was at the very beginning of the PSA testing era. In addition, the time between diagnosis and questionnaire for cases was 6 months to 1 year on average, raising concerns about accuracy of diet recall. Finally, participants with missing data for any covariates were excluded from multivariable models, so the age-adjusted and fully adjusted models were not comparable.]

Sharpe & Siemiatycki (2002) conducted a population-based case–control study in Montreal, Canada, that included cases with 15 different types of cancer. The analysis included 399 histologically confirmed cases of cancer of the prostate who completed in-person interviews, 476 prostate cancer controls, and 621 other cancers as controls. Compared with never drinking coffee at least weekly, weekly or daily coffee drinking was not associated with prostate cancer risk. A more detailed categorization of daily coffee drinking, including age when daily drinking began, duration of daily drinking, cups/day, or cumulative daily consumption (based on drink-years), were also not associated with risk. However, confidence intervals were wide as the number of cases and controls in the reference group of 'never drank coffee at least weekly' was low. [Strengths included the population-based design. Limitations included a lack of information on the dietary assessment instrument and its validity. Further, there was no analysis by stage or grade, and no information on PSA screening although the study was conducted within the PSA screening era.]

Wilson et al. (2013) conducted a population-based case–control study in Sweden including incident cases of cancer of the prostate from regional cancer registries. Coffee was assessed as an open-ended question, asking men to provide the number of cups they drank per week or day. Stage and grade were available for 95% of cases. There was no association between coffee intake and risk of total prostate cancer

Table 2.12 Case–control studies on cancer of the prostate and coffee consumption

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Villeneuve et al. (1999) Canada, 1994–1997	1623 cases and 1623 controls aged 50–74 yr identified from province cancer registries; population-based controls sampled from health insurance plan lists, other government lists or RDD Exposure assessment method: FFQ		*Coffee intake 2 yr previous (cups/day)*			Age, province of residence, race, years since quitting smoking, smoking pack-years, BMI, rice and pasta intake, grains and cereals intake, alcohol, fruit and juice intake, tofu intake, meat intake, income, family history of cancer	Strengths: population-based study, large number of cases, clean reference group of non-drinkers Limitations: lack of information on PSA testing, long time between diagnosis and interview (concerns about accuracy of recall), participants with missing data excluded from multivariable models
			None	134	1.0		
			< 1	358	0.8 (0.6–1.1)		
			1 to < 4	551	1.0 (0.7–1.3)		
			≥ 4	367	1.1 (0.8–1.5)		
			Trend test *P* value, 0.06				

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sharpe & Siemiatycki (2002) Canada (Montreal), 1979–1985	Cases: 399 aged 47–70 yr diagnosed at any hospital in Montreal Controls: 476 selected from electoral lists or RDD, 621 other cancer controls Exposure assessment method: questionnaire recording weekly and daily coffee drinking and age started, allowing calculation of cumulative intake	Prostate	*Duration of daily drinking (yr)*			Age, ethnicity, respondent (direct/proxy), family income, BMI, cumulative cigarette smoking, cumulative alcohol consumption	Strengths: population-based study Limitations: diet assessment instrument and its validity not specified, only participants who did face-to-face interviews are included (response rate for this subset is not given), no information on stage or grade available, no analysis of advanced or aggressive prostate cancer
			Never drank weekly	29	1.0		
			< 20	28	1.0 (0.5–2.1)		
			20–39	89	0.8 (0.4–1.4)		
			> 39	209	1.2 (0.7–2.1)		
			Age at start of daily drinking (yr)				
			Never drank weekly	29	1.0		
			< 15	50	1.4 (0.7–2.7)		
			15–19	124	1.3 (0.7–2.3)		
			20–24	69	1.0 (0.5–1.8)		
			≥ 25	83	0.7 (0.4–1.4)		
			Never drank weekly	29	1		
			Drank weekly, never daily	23	0.9 (0.4–2.0)		
			Drank daily	347	1.1 (0.6–1.8)		
			Cumulative consumption (drink-years)				
			Never drank weekly	29	1.0		
			< 57	108	1.0 (0.6–1.9)		
			57–119	93	1.0 (0.6–1.8)		
			> 119	125	1.1 (0.6–2.0)		

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wilson et al. (2013) Sweden, 2001–2002	Cases: 1489 incident pathologically confirmed prostate cancer identified from four of six regional cancer registries in Sweden Controls: 1112 randomly selected from Swedish population register, frequency matched to cases by 5-yr age group and region of residence Exposure assessment method: 261-item FFQ recording intake over previous 12 mo, open-ended question on cups of coffee per week or day	All prostate	*Coffee intake in year before questionnaire (cups/day)*			Age, region, smoking (never/ former/current), BMI, education, calcium intake, zinc intake, total energy intake	Strengths: population-based study, assessed risk of fatal and non-fatal and by stage and grade in addition to total prostate cancer, validated FFQ Limitations: response rate lower in controls than cases, lowest (reference) group is < 1 cup/day, no information on PSA screening
			< 1	139	1.0		
			1 to < 2	150	0.97 (0.62–1.52)		
			2 to < 4	644	0.98 (0.65–1.49)		
			4–5	413	1.06 (0.69–1.62)		
			> 5	143	0.97 (0.60–1.57)		
			Trend test *P* value, 0.84				
		Fatal prostate cancer	*Coffee intake in year before questionnaire (cups/day)*				
			< 1	31	1.0		
			1 to < 2	24	0.59 (0.32–1.09)		
			2 to < 4	133	0.79 (0.49–1.26)		
			4–5	94	0.93 (0.57–1.51)		
			> 5	25	0.64 (0.34–1.19)		
			Trend test *P* value, 0.81				

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wilson et al. (2013) (cont.)		Advanced-stage prostate cancer	*Coffee intake in year before questionnaire (cups/day)*				
			< 1	35	1.0		
			1 to < 2	32	0.70 (0.40–1.23)		
			2 to < 4	159	0.83 (0.53–1.29)		
			4–5	119	1.02 (0.64–1.62)		
			> 5	32	0.73 (0.41–1.30)		
			Trend test *P* value, 0.98				
		High-grade prostate cancer	*Coffee intake in year before questionnaire (cups/day)*				
			< 1	30	1.0		
			1 – < 2	22	0.54 (0.29–1.01)		
			2 to < 4	98	0.59 (0.36–1.95)		
			4–5	62	0.61 (0.36–1.03)		
			> 5	19	0.50 (0.26–0.98)		
			Trend test *P* value, 0.13				

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Geybels et al. (2013) USA (Washington State), 2002–2005	Cases: 894 men aged 35–74 yr identified through Seattle–Puget Sound SEER Program cancer registry Controls: 860 identified by RDD, frequency matched in 5-yr age groups and recruited evenly through study period Exposure assessment method: FFQ recording intake in 2 yr before diagnosis for cases or reference date for controls	All prostate	*Coffee intake 2 yr prior*			Age, race, family history of prostate cancer, smoking (never/former/current), PSA screening	Strengths: population-based study, information on stage/ grade/PSA at diagnosis available from cancer registry, information on PSA testing in the prior 5 yr was assessed and included as potential confounder Limitations: response rate lower in controls than in cases
			≤ 1 cup/wk	246	1.0		
			2–6 cups/wk	113	1.22 (0.88–1.69)		
			1 cup/day	154	1.13 (0.84–1.51)		
			2–3 cups/day	273	1.16 (0.90–1.50)		
			≥ 4 cups/day	108	1.16 (0.82–1.63)		
			Trend test *P* value, 0.32				
		High-grade prostate cancer	*Coffee intake 2 yr prior*				
			≤ 1 cup/wk	39	1.00		
			2–6 cups/wk	28	1.72 (1.00–2.97)		
			1 cup/day	30	1.30 (0.77–2.19)		
			2–3 cups/day	51	1.25 (0.78–1.99)		
			≥ 4 cups/day	18	1.04 (0.55–1.96)		
			Trend test *P* value, 0.81				
		Advanced-stage prostate cancer	*Coffee intake 2 yr prior*				
			≤ 1 cup/wk	46	1.00		
			2–6 cups/wk	18	1.01 (0.55–1.83)		
			1 cup/day	31	1.27 (0.77–2.11)		
			2–3 cups/day	51	1.23 (0.78–1.93)		
			≥ 4 cups/day	23	1.33 (0.74–2.38)		
			Trend test *P* value, 0.24				

Table 2.12 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Villeneuve et al. (1999) Canada, 1994–1997	Cases: 1623 aged 50–74 yr identified from 8 of 10 province cancer registries in Canada Controls: 1623 population-based sampled from health insurance plan lists, other government lists, or RDD Exposure assessment method: FFQ, recording diet 2 yr previously	Prostate	*Coffee intake 2 yr prior (cups/day)*			Age, province of residence, race, yrs since quitting smoking, smoking pack-years, BMI, rice and pasta intake, grains and cereals intake, alcohol, fruit and juice intake, tofu intake, meat intake, income, family history of cancer	69% response rate in both cases and controls Strengths: population-based study, large number of cases, clean reference group of non-drinkers Limitations: lack of information on PSA testing, time between diagnosis and questionnaire 1 yr on average in Ontario and 6 mo in other provinces, concerns about accuracy of recall, participants with missing data were excluded from multivariable models
			None	134	1.0		
			< 1	358	0.8 (0.6–1.1)		
			1 to < 4	551	1.0 (0.7–1.3)		
			≥ 4	367	1.1 (0.8–1.5)		
			Trend test *P* value, 0.06				

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; mo, month(s); PSA, prostate-specific antigen; RDD, random-digit dialling; SEER, Surveillance, Epidemiology and End Results; wk, week(s); yr, year(s)

(OR, 0.97; 95% CI, 0.6–1.57) for > 5 cups/day. There was a suggestion of an inverse association for fatal disease and for advanced disease (stage T4, N1, or M1 at diagnosis, or fatal disease); odds ratios of 0.64 (95% CI, 0.34–1.19) and 0.73 (95% CI, 0.41–1.30), respectively, were reported for those consuming > 5 cups/day compared with < 1 cup/day. For high-grade disease, defined as Gleason grade 8–10, there was a statistically significant lower risk in the highest category with an odds ratio of 0.50 (95% CI, 0.26–0.98), although the *P* value for a linear trend across intakes was not significant (*P* for trend, 0.13). As coffee consumption in this population was high, the lowest and reference intake category was < 1 cup/day rather than non-drinkers of coffee. [The strengths of this study included: the population-based design; use of a validated FFQ; and the analysis of stage, grade, and fatal disease. Limitations included the lower response rate in controls compared with cases, raising concern about selection bias. In addition, the high coffee intake in the population did not allow for a clean reference group of non-drinkers. Finally, there was no information on PSA screening, despite being conducted during the PSA screening era.]

Geybels et al. (2013) conducted a population-based case–control study in Washington State, USA, with 894 cases and 860 controls. Diet was assessed through a validated 120-item FFQ, and stage and grade information were available from the cancer registry through which cases were identified. Coffee intake was not significantly associated with risk of total prostate cancer, with an odds ratio of 1.16 (95% CI, 0.82–1.63) for men consuming ≥ 4 cups/day compared with those consuming ≤ 1 cups/week. Coffee intake was not associated with high-grade disease, defined as Gleason grade 4+3 or above (OR, 1.04; 95% CI, 0.55–1.96), or advanced-stage disease, defined as having regional or distant spread (OR, 1.33; 95% CI, 0.74–2.38). Results were adjusted for PSA testing within the 5-year period before date of diagnosis for cases, or before some reference date assigned to controls to match the distribution of diagnosis dates, helping to eliminate concern about confounding due to differences in screening practices associated with coffee intake. [The strengths of this study included the population-based design, and the analysis by stage and grade. In addition, PSA testing in the 5 years prior was assessed and included as a potential confounder. The limitations of this study included the lower response rate in controls than cases, raising a concern about selection bias.]

2.6.3 Meta-analyses

Seven meta-analyses of coffee consumption and risk of prostate cancer have been conducted recently, six of which focus on prostate cancer and one of which assesses multiple cancer sites. Of these, two (Discacciati et al., 2014; Lu et al., 2014) are recent enough to include the recent cohort studies reviewed above, provide a detailed analysis of results for fatal disease as well as disease by stage and grade, and do not include studies without an adjustment for smoking. To be included in the meta-analysis by Discacciati et al. (2014), studies had to report results by prostate cancer aggressiveness, report the number of cases and person-years by coffee category, and adjust for smoking. There were five cohort studies, two population-based case–control studies, and one hospital-based case–control study of benign prostatic hypertrophy (BPH). Six studies assessed high-grade prostate cancer (*n* = 1965, Gleason 8–10 in four studies, Gleason 4+3 and up in one study, and Gleason 7–10 in one study) and estimated a meta-relative risk for a 3 cups/day increase of 0.89 (95% CI, 0.78–1.00). For six studies of advanced prostate cancer (*n* = 5724, T3 or above in two studies, T3b or above in one study, T4 or above in one study, and unspecified TNM stage 'extraprostatic extension' or above in two studies), the relative risk was 0.95 (95% CI, 0.85–1.06). For four studies of fatal prostate cancer (*n* = 2381), the relative risk was

0.89 (95% CI, 0.82–0.97). All studies but one in the meta-analysis were reviewed above.

The meta-analysis of high-grade disease included data from a non-peer-reviewed letter to the editor of the *Journal of the National Cancer Institute* (Polesel et al., 2012), which used data from a hospital-based Italian case–control study. This analysis included Gleason 7 tumours in its definition of high-grade disease. The pooled relative risk for high-grade prostate cancer would be more inverse with elimination of this study. There was no indication of between-study heterogeneity or publication bias. Cohort studies found stronger inverse associations for all three outcomes than case–control studies; however, there were only two case–control studies of advanced prostate cancer and one case–control study of fatal prostate cancer.

The Lu et al. (2014) meta-analysis of fatal and advanced disease included the same four fatal and six advanced prostate cancer studies as Discacciati et al. (2014), but calculated a meta-relative risk for the highest versus lowest categories as reported in the original reports. Using a random-effects model, the meta-relative risk was 0.66 (95% CI, 0.43–0.90) for fatal disease and 0.85 (95% CI, 0.58–1.12) for advanced disease.

Another recent meta-analysis of only cohort studies included studies that did not adjust for smoking and considered only total prostate cancer risk (Cao et al., 2014). The meta-analysis of Yu et al. (2011), which covered multiple cancer sites, preceded the most recent cohort studies of coffee and prostate cancer. Similarly, the Park et al. (2010) meta-analysis preceded the most recent cohort studies and included studies that did not adjust for smoking. The Zhong et al. (2014) meta-analysis included studies that did not adjust for smoking, and the risk of prostate cancer was not examined by stage or grade in detail. The Liu et al. (2015a) meta-analysis also included studies that did not adjust for smoking, and mixed stage- and grade-based outcomes in defining advanced and non-advanced disease.

2.7 Cancer of the lung

2.7.1 Cohort studies

Table 2.13 (web only; available at: http://publications.iarc.fr/566)

Of the eight cohort studies that examined the association between coffee consumption and risk of lung cancer, seven focused on incidence (Jacobsen et al., 1986; Nomura et al., 1986; Stensvold & Jacobsen, 1994; Bae et al., 2013; Hashibe et al., 2015; Guertin et al., 2016; Lukic et al., 2016) and one study focused on mortality (Khan et al., 2004).

One cohort study from the Republic of Korea (Bae et al., 2013) was excluded from this review due to a lack of adjustment for any lung cancer risk factors, including tobacco smoking.

Among the cohort studies that observed a positive association between coffee consumption and lung cancer risk, results were attenuated after adjusting for tobacco smoking. The Working Group concluded that this could be an indication that increases in lung cancer risk could be due to residual confounding by tobacco smoking.

Nomura et al. (1986) observed a non-significant positive association for consumption of ≥ 5 cups/day coffee (OR, 1.44) after adjusting for smoking status, duration, and number of cigarettes consumed, but there was no evidence of an exposure–response trend (*P* for trend, 0.19) among 7355 Japanese men in Hawaii (born during 1900–1919). There was no evidence of an exposure–response trend among non-smokers, although this analysis was based on only 9 cases. [The main strength of this study was its prospective design. It was however limited by being based on only a single-day history of coffee intake. The lung cancer results may be due to residual confounding by smoking, as supported by the negative findings among non-smokers. Confidence intervals were not provided.]

Jacobsen et al. (1986) reported significant positive associations in a Norwegian study of

13 664 men and 2891 women; compared with drinking ≤ 2 cups/day, consuming ≥ 7 cups/day of coffee significantly increased the risk of lung cancer (OR, 1.82; *P* for trend, 0.02). [The strengths of this study included the prospective design and the relatively short follow-up. Limitations included the single measurement of coffee intake, and lack of confidence intervals which could not be calculated.]

Stensvold & Jacobsen (1994) found a positive association between coffee drinking and risk of lung cancer after adjustment for cigarettes smoked per day in the highest exposure group of > 7 cups/day (RR, 2.4; $P < 0.01$; 95% CI, not reported), and a significant trend among 42 973 men and women participating in a cardiovascular screening in three counties of Norway. [Strengths included the complete follow-up by linkage of national data by national personal identification number. Residual confounding by smoking was however possible, as this study did not control for duration of smoking or smoking status.]

In a cohort of 1524 men and 1634 women aged over 40 years from 45 health-centre areas of Hokkaido, Japan, Khan et al. (2004) observed no association between coffee intake and lung cancer mortality in both men and women after adjusting for smoking. [Strengths included the population-based and prospective design. The study was limited by the small number of cases, however.]

In the NIH-AARP Diet and Health Study of 457 366 subjects, Guertin et al. (2016) observed a strong positive association between coffee intake and lung cancer (HR, 4.56; 95% CI, 4.08–5.10) for consumption of ≥ 6 cups/day adjusted for age and sex; the association was substantially attenuated after adjusting for smoking, however (HR, 1.27; 95% CI, 1.14–1.42). Similar findings were observed for each different histological type and for participants drinking predominantly caffeinated or decaffeinated coffee. There was little evidence for an association either for never smokers or within most categories of tobacco use. [The Working Group noted that the association observed could be due to residual confounding by tobacco smoking, imperfect adjustment by lifetime tobacco use, or other risk factors. Strengths included the large scale, prospective design, large numbers of outcomes, and ability to categorize decaffeinated or caffeinated. Limitations included the self-reporting of coffee consumption, the recording of typical coffee consumption over the past year, the lack of data on cumulative exposure (coffee consumption is considered relatively stable over time), and the fact that one third of the cancer cases were histologically unknown.]

Hashibe et al. (2015) reported that coffee intake was not associated with lung cancer after adjusting for smoking status, frequency, duration, and time since cessation in the PLCO cohort, which included nearly 100 000 persons. Compared with drinking < 1 cup/day, hazard ratios (95% CI) for 1–1.9 cups/day and ≥ 2 cups/day were 1.03 (0.83–1.27) and 1.10 (0.94–1.28), respectively (*P* for trend, 0.196). [Strengths included the prospective design and large sample size. Limitations included the lack of data on age when coffee consumption began, duration of coffee drinking, and any change in coffee drinking habits.]

Lukic et al. (2016) observed positive associations between coffee consumption and risk of lung cancer among 91 767 Norwegian women in the Norwegian Women and Cancer (NOWAC) Study. Compared with consumers of low quantities of coffee (≤ 1 cup/day), large-quantity consumers (> 7 cups/day) had a significantly higher risk of lung cancer in age-adjusted analysis (HR, 5.65; 95% CI, 4.20–7.60). This association was substantially attenuated after further adjusting for smoking status, age at smoking initiation, number of pack-years smoked, and exposure to smoking during childhood, as well as education, BMI, and physical activity level; an increase in risk was still observed in the

highest coffee consumption group (> 7 cups/day) however, with a hazard ratio of 2.01 (95% CI, 1.47–2.75). No statistically significant association was observed in never smokers (HR, 1.42; 95% CI, 0.44–4.57) for consumption of > 5 cups/day (*P* for trend, 0.30). [Strengths included the population-based design, the large scale, validation of questionnaire, repeated measurements of coffee consumption and smoking exposure, use of updated information, and high validity of coffee consumption. Limitations included possible residual confounding from smoking.]

2.7.2 Case–control studies

See Tables 2.14 and 2.15 (web only; available at: http://publications.iarc.fr/566).

Among the 17 case–control studies that examined the association between coffee consumption and the risk of lung cancer; 12 studies (Mettlin, 1989; Restrepo et al., 1989; Chen et al., 1990; Mendilaharsu et al., 1998; Kubík et al., 2001, 2004a,b, 2008; Takezaki et al., 2001; Baker et al., 2005; Ganesh et al., 2011a; Luqman et al., 2014) were hospital-based and five were population-based (Axelsson et al., 1996; Nyberg et al., 1998; Hu et al., 2002; Chiu et al., 2010; Sanikini et al., 2015a).

There were four reports (Kubík et al., 2001, 2004a, b, 2008) and two case–control studies (Mettlin, 1989; Baker et al., 2005) from the same study population. Five case–control studies analysed the risk by histological subtypes (Takezaki et al., 2001; Kubík et al., 2001, 2008; Baker et al., 2005; Sanikini et al., 2015a). Two USA-based case–control studies (Mettlin, 1989; Baker et al., 2005) also analysed the risk for caffeinated and decaffeinated coffee separately.

The Working Group considered studies to be informative only if they controlled for smoking. Consequently, one case–control study from Pakistan (Luqman et al., 2014) was excluded from this review due to a lack of adjustment for any lung cancer risk factors, including tobacco smoking.

(a) Population-based case–control studies

Axelsson et al. (1996) reported that coffee drinking was not associated with lung cancer in a population-based case–control study (308 male cases, 504 controls) in west Sweden, after adjusting for number of cigarettes/day, number of years smoked, and other covariates. [Strengths included the population-based controls, and in-person direct interviews of cases and controls.]

In Stockholm, Sweden, Nyberg et al. (1998) reported that coffee drinking was non-significantly associated with a decreased risk of lung cancer (OR, 0.5; 95% CI, 0.24–1.06) for consumption of ≥ 3 cups/day, after adjusting for passive smoking status (ever-exposure status, years since last exposure, and hour-years of exposure to environmental tobacco smoke) and other covariates. A total of 124 cases of lung cancer (35 men and 89 women) of age > 30 years from major county hospitals were frequency-matched with 235 controls (72 men and 163 women) derived from a population register. [Strengths included the fact that 96% of cases had a histological or cytological confirmation for diagnosis, and the use of only never smokers.]

Hu et al. (2002) reported no association between coffee intake and risk of lung cancer in never-smoking women in Canada after controlling for 10-year age groups, province, education, and social class. [Strengths included the population-based design and restriction to never-smoking women. Limitations included the misclassification of exposure variables and covariates, the low response rate (61.6%) of cases, and the small sample size.]

In Hong Kong Special Administrative Region, China, Chiu et al. (2010) observed a significantly decreased risk in the middle category of coffee consumption (OR, 0.41; 95% CI, 0.21–0.78) for 1–10 coffee–years, compared with never drinkers, after adjusting

for smoking and other potential confounders. [Strengths included the population-based design. Limitations included use of data from a single centre, and the fact that coffee consumption is low in this population.]

In the ICARE (Investigation of occupational and environmental causes of respiratory cancers) study, Sanikini et al. (2015a) reported that coffee consumption was positively associated with lung cancer (OR, 1.65; 95% CI, 1.28–2.12) without adjustment for smoking by cumulative smoking index (CSI). After adjustment for CSI, however, coffee consumption was not associated with lung cancer (OR, 1.09; 95% CI, 0.80–1.49). No association was detected in analyses stratified by sex, histological subtype, and smoking status. [Strengths included: the large-scale, multicentre, and population-based design; the large sample size; provision of comprehensive information on coffee consumption and potential confounders; careful adjustment for smoking; and analysis by histological type, sex, and smoking status. Limitations included the potential for recall bias and the non-differential misclassification of exposure.]

(b) Hospital-based case–control studies

In a hospital-based case–control study among patients admitted to Roswell Park Memorial Institute (RPMI) in Buffalo, New York, Mettlin (1989) reported odds ratios (95% CI) for < 1 cup/day, 2–3 cups/day, and ≥ 4 cups/day compared with never drinkers of coffee of 1.01 (0.67–1.51), 0.94 (0.65–1.37), and 1.26 (0.86–1.84), respectively, in multivariable models adjusted for smoking and other potential confounders. An association was not evident for either total or decaffeinated coffee intake. [Strengths included the relatively accurate matching and use of control variables. Limitations included the hospital-based, single-centre design and the possibility of residual confounding.]

Baker et al. (2005) reported findings regarding the association between coffee consumption and lung cancer among current and former smokers using the same case–control study in Buffalo, New York, as for Mettlin (1989), but with a more restricted set of cases and controls. While the previous report by Mettlin (1989) included subjects with all types of smoking status, never smokers were excluded from the analysis by Baker et al. (2005). Compared with non-drinkers of coffee, elevated lung cancer risk was observed for those who consumed 2–3 cups/day (OR, 1.34; 95% CI, 0.99–1.82) or ≥ 4 cups/day (OR, 1.51; 95% CI, 1.11–2.05) of regular coffee, although a reduced risk was observed for decaffeinated coffee. Compared with non-drinkers, odds ratios (95% CI) for consumption of ≤ 1 cup/day and ≥ 2 cups/day were 0.67 (0.54–0.84) and 0.64 (0.51–0.80) of decaffeinated coffee, respectively. Similar results were observed by histological subtype. [Strengths included matching of smoking status; the use of current and former smokers only; analysis by histology; and a separate analysis for regular and decaffeinated coffee. Limitations included the single-centre, hospital-based design.]

In Colombia, Restrepo et al. (1989) observed no association between coffee consumption and risk of lung cancer; an odds ratio of 1.1 (95% CI not reported) was observed for drinking > 7 cups/day (*P* for trend, 0.67) after adjusting for number of cigarettes smoked per day and alcohol consumption. [Strengths included coverage of a well-defined population and adjustment by socioeconomic level. Limitations included the hospital-based study design.]

In Taiwan, China, Chen et al. (1990) reported that coffee drinking was found to be significantly associated with epidermoid carcinoma (OR, 2.10) after adjusting only for sex and age, but coffee drinking was not significantly associated with any pathological type of lung cancer after cigarette smoking was adjusted for. [Strengths included analysis by pathological subtype. Limitations

included the hospital-based study design and lack of provision of confidence intervals.]

In Uruguay, Mendilaharsu et al. (1998) observed coffee intake had no effect on the risk of all lung cancer, or for squamous and small-cell lung cancer. [Limitations included the hospital-based design and the possibility of differential misclassification of exposure due to preclinical disease.]

In Nagoya, Japan, Takezaki et al. (2001) reported that an association between coffee consumption and lung adenocarcinoma in both men and women and lung squamous cell carcinoma in women was not evident, while in men a positive association of coffee intake was observed with lung squamous cell carcinoma (OR, 1.61; 95% CI, 1.09–2.39) was seen for consumption of ≥ 3 cups/day of coffee. [The main strength of this study was its large scale. Limitations included the potential for selection bias since controls were recruited from non-cancer hospital outpatients. The duration of smoking was not controlled for in the analysis and the amount smoked was only crudely controlled for (< or > 20 cigarettes/day); residual confounding by smoking was therefore possible in this study.]

Kubík et al. reported the findings from a hospital-based case–control study in the Czech Republic that examined the association between coffee consumption and the risk of lung cancer (Kubík et al., 2001, 2004a, b, 2008). In the most recent report, recruitment of cases and controls was extended to 2006 (Kubík et al., 2008). Stratified analysis by smoking status showed no association for both non-smokers and smokers, and in both men and women; for daily or several times per week versus less, odds ratios (95% CI) were 0.86 (0.59–1.26) and 0.76 (0.48–1.20) for female non-smokers and smokers, respectively, and 0.91 (0.43–1.92) and 1.07 (0.61–1.86) for male non-smokers and smokers, respectively. Null associations were consistently observed in any histological subtype of cancer. Similar associations were reported in earlier publications fom this study (Kubík et al., 2001, 2004a, b). [Strengths included the large number of subjectss, and stratified analysis by histology and smoking status. Limitations included the hospital-based case–control design and the self-reporting of coffee consumption.]

In Mumbai, India, Ganesh et al. (2011a) reported that coffee drinkers had a significantly increased risk of lung cancer (OR, 1.9; 95% CI, 1.3–2.7) after adjusting for age, literacy status, cigarette smoking, bidi smoking, tobacco chewing, and alcohol drinking, as well as consumption of milk, chicken, red meat, fish, and chilli, and exposure to pesticide. The definition of coffee drinker was unclear, however. Cigarette smoking (yes/no) was only crudely controlled for, and there was a strong possibility that the increased risk observed for coffee drinking was due to residual confounding by smoking. [Limitations included the hospital-based design; the poor-quality, inadequate adjustment for confounding, and the unclear definition of exposure.]

2.7.3 Meta-analyses

Four meta-analyses of the association between coffee drinking and risk of lung cancer have been published (Tang et al., 2010; Wang et al., 2012; Galarraga & Boffetta, 2016; Xie et al., 2016). The most recent meta-analysis (Galarraga & Boffetta, 2016), assessing the effect of coffee consumption on risk of lung cancer independently of tobacco use, addressed the potential role of tobacco as a confounder. Using PubMed and Embase databases, and the references from the retrieved articles up to 2015, 8 cohort and 13 case–control studies involving 19 892 cases and 623 645 non-cases were included in the meta-analysis. The summary relative risk (95% CI) of lung cancer for coffee drinking compared with never drinkers, without controlling for tobacco smoking, was 1.09 (95% CI, 1.00–1.19). Coffee drinking was not associated with lung

cancer risk among non-smokers (summary RR 0.92; 95% CI, 0.75–1.10). The summary relative risk for 1 cup/day increase, unadjusted for smoking, was 1.04 (95% CI, 1.03–1.05); the corresponding relative risk for non-smokers was 0.95 (95% CI, 0.83–1.09). The results stratified by different geographic regions (Asia, Europe, North and South America) were not heterogeneous. The study indicated that when the potential confounding effect from smoking is controlled for, coffee drinking does not appear to be a risk factor for lung cancer.

2.8 Cancer of the larynx

The association between coffee consumption and cancer of the larynx has been examined in seven case–control studies and one large prospective cohort study (Ren et al., 2010); the latter reported no association. A significantly increased risk was observed in four (Restrepo et al., 1989; Pintos et al., 1994; Zvrko et al., 2008; Vassileiou et al., 2012) of the seven case–control studies. However, all of the studies that reported evidence of an association had inadequately controlled for smoking and alcohol use; no association was observed in the three other studies that tightly controlled for smoking and alcohol drinking (La Vecchia et al., 1990; Bosetti et al., 2002; Galeone et al., 2010a). Two meta-analyses of the association of cancer of the larynx and coffee drinking have also been conducted. These studies are discussed in Sections 2.8.1–2.8.3 below.

2.8.1 Cohort studies

See Table 2.16 (web only; available at: http://publications.iarc.fr/566).

One cohort study with 481 563 subjects, members of the NIH-AARP Diet and Health Study, assessed the association between cancer of the larynx and coffee consumption (Ren et al., 2010); no association was found. The hazard ratio for the highest category of exposure was 1.01 (95% CI, 0.71–1.44) and the *P* value for the test of the exposure–response trend was 0.95. [The Working Group regarded this study as the most informative because of its prospective design, large size, and extensive control for smoking, alcohol, diet, and other risk factors.]

2.8.2 Case–control studies

See Table 2.17 (web only; available at: http://publications.iarc.fr/566).

The earliest case–control study to report findings on the association between coffee consumption and cancer of the larynx was that by Restrepo et al. (1989) in Medellin, Columbia. An association between laryngeal cancer and the highest category of exposure (OR, 2.87 for > 7 cups/day) and a statistically significant (*P* for trend, 0.01) exposure–response relationship was observed in a logistic regression analysis. The logistic model included variables that controlled for current smoking (packs/day), but did not include information on former smoking or duration of smoking. [The Working Group believed there was potential for residual confounding by tobacco smoking in this study.]

La Vecchia et al. (1990) did not find evidence of an exposure–response relationship (*P* for trend, 0.65) between coffee consumption and the risk of laryngeal cancer in the Greater Milan area. Although the study provided detailed information on smoking and alcohol consumption, the results from analyses controlling for these risk factors was not presented; however, La Vecchia et al. (1990) reported that none of the results were materially changed when smoking and alcohol consumption were controlled for.

Pintos et al. (1994) reported a statistically significant ($P < 0.009$) exposure–response relationship between coffee consumption and laryngeal cancer in southern Brazil. A significant increased risk was observed among those who drank 2 cups/day and ≥ 3 cups/day with odds

ratios of 4.29 (95% CI, 1.40–12.90) and 2.87 (95% CI, 1.00–1.83), respectively. This study controlled for cigarette smoking (pack-years) and lifetime alcohol consumption. It did not control for smoking status, however (i.e. former versus current). [The study may have been biased by the use of other diseases as controls if these other sites were associated with coffee consumption (e.g. gastritis or prostatic diseases).]

Bosetti et al. (2002) reported that consumption of coffee was not associated with an increased risk of laryngeal cancer in a study in northern Italy and the Swiss canton of Vaud, which tightly controlled for smoking (smoking status and cigarettes/day) and alcohol consumption (drinks/week).

Zvrko et al. (2008) reported that drinking > 5 cups/day of coffee was found to be associated with a significant increased risk of laryngeal cancer (OR, 4.52; 95% CI, 1.01–20.12) in Montenegro. Cigarette smoking and alcohol consumption were only crudely controlled for with yes/no responses to smoking duration of > 40 years, > 30 cigarettes per day, hard liquor consumption, and > 2 alcoholic drinks/day. [The Working Group judged that there was a strong possibility of residual confounding by tobacco and alcohol consumption in this study.]

Galeone et al. (2010a) conducted a pooled analysis of seven case–control studies of cancer of the larynx from France, Italy, Switzerland, and the USA. Data from the Bosetti et al. (2002) and the La Vecchia et al. (1990) studies (described earlier in this section) were a part of this study. The study included 1224 incident cases of laryngeal cancer and 7239 controls. Five of the included studies were hospital-based and two used population-based controls. The analysis controlled for tobacco smoking as cigarette pack years and duration of cigar and pipe smoking, alcohol consumption, age, study centre, education, intake of fruit or vegetables, race/ethnicity, sex, and body weight. Exposures to caffeinated and decaffeinated coffee were considered separately. For caffeinated coffee, the odds ratio in the highest exposure group (> 4 cups/day) was 0.96 (95% CI, 0.64–1.45) and there was no evidence of an exposure–response relationship (*P* for trend, 0.82). The data were sparse for decaffeinated coffee, and there was no indication of an increased risk in the highest exposure group of ≥ 1 cup/day (OR, 0.84; 95% CI, 0.34–2.06) or evidence of an exposure–response relationship (*P* for trend, 0.75).

Vassileiou et al. (2012) reported that coffee consumption (yes/no) was significantly associated with an increased risk of cancer of the larynx in Greece. The association was primarily attributable to consumption of "Turkish" coffee (OR, 1.77; 95% CI, 1.24–2.52), and a significant exposure–response relationship between consumption of Turkish coffee and laryngeal cancer was observed (*P* for trend, 0.002) in a logistic model. [It is unclear from the paper which other covariates were controlled for in the logistic analysis but it appears that smoking and alcohol drinking were represented by yes/no variables. The Working Group judged that there was a strong possibility of residual confounding by tobacco and alcohol consumption in this study.]

2.8.3 Meta-analyses

A recent meta-analysis (Chen & Long, 2014) reported a summary risk estimate of 1.47 (95% CI, 1.03–2.11) and evidence of an exposure–response relationship between coffee consumption and cancer of the larynx (*P* for trend, 0.001). The results were unchanged when the meta-analysis was restricted to studies considered to be of high quality (i.e. > 6 on a scale of 1–9) based on the Newcastle–Ottawa scale. However, there was significant evidence of heterogeneity in the analysis (I^2, 72.8%; *P* for trend, 0.002). Several of the studies that were considered to be of high quality (i.e. Pintos et al., 1994; Zvrko et al., 2008; Vassileiou et al., 2012) did not (as discussed in Section 2.8.2 above) adequately control for

confounding by tobacco smoking and alcohol drinking. It is also noteworthy that the two studies with the highest scores for quality (8) (Ren et al., 2010; Galeone et al., 2010a) both had null findings. [The Working Group did not agree with the conclusions of the analysis by Chen & Long that "The results from this meta-analysis of observational studies demonstrate that coffee consumption would increase the laryngeal cancer risk" because of the lack of adequate control for confounding by smoking and alcohol in several of the included case–control studies, the lack of an association in the single cohort study which the group considered the most informative study, and the very large heterogeneity.]

An earlier meta-analysis by Turati et al. (2011b) did not demonstrate a significant association between coffee consumption and cancer of the larynx (RR, 1.56; 95% CI, 0.60–4.02). However, it was based on fewer studies then the analysis by Chen & Long (2014) and only included three of the eight published case-control studies (Pintos et al., 1994; Bosetti et al., 2002; Zvrko et al., 2008). There was also significant evidence of heterogeneity of the findings across the three studies (P for heterogeneity, 0.036; I^2, 70.0%).

2.9 Cancer of the ovary

See Table 2.18 and Table 2.19 (web only; available at: http://publications.iarc.fr/566).

The evidence for the association between coffee consumption and incidence and mortality of cancer of the ovary is based on 13 reports from cohort studies (including a nested case–control study, and a pooled analysis of that nested case–control study with another case–control study) and 21 case–control studies. The lack of adjustment for female endogenous and exogenous hormones has been considered a limitation, but not an exclusion criterion. Tobacco smoking is an important potential confounder.

2.9.1 Cohort studies

Table 2.18 (web only; available at: http://publications.iarc.fr/566).

The Working Group reviewed 11 cohort studies that reported on the association between coffee consumption and risk of cancer of the ovary. All studies presented multivariable analyses adjusted for important potential confounders including age; all but two studies adjusted for smoking (Tavani et al., 2001; Larsson & Wolk, 2005).

Three cohort studies were not reviewed further due to methodological limitations. Snowdon & Phillips (1984) assessed cancer mortality for selected sites among Seventh-day Adventists; however, there is no information on the cohort size for women separately, it is based on 51 cases of ovarian cancer, and it is adjusted only for age. Jacobsen et al. (1986) considered cancer mortality at selected sites, included 12 cases of ovarian cancer, and adjusted the relative risk only for age. Both studies found no association between coffee consumption and ovarian cancer. The study by Stensvold & Jacobsen (1994) considered cancer incidence at selected sites (93 cases of ovarian cancer) but adjusted only for age, area of residence, and smoking; this study found an increased risk of ovarian cancer with coffee drinking, but no trend in risk.

Larsson & Wolk (2005) reported no association between coffee intake either at baseline (RR, 0.99; 95% CI, 0.88–1.11 for an increment of 1 cup/day) or long-term (RR, 0.98; 95% CI, 0.88–1.01 for an increment of 1 cup/day) with risk of cancer of the ovary in the Swedish Mammography Cohort. Further, no association was found for risk of serous carcinoma of the ovary. [The strengths of this study included: population-based cohort; linkage with population registers; exclusion of previous malignancies and oophorectomy; FFQ tested for validity; and full adjustment for confounding. No information on type of coffee (regular/decaffeinated) was provided, however.]

Silvera et al. (2007) reported a hazard ratio of 1.62 (95% CI, 0.95–2.75; *P* for trend, 0.06) for the association between risk of ovarian cancer and coffee intake in the Canadian National Breast Screening Study (NBSS), adjusted for several potential confounders including smoking and endogenous and exogenous hormones. [The strengths of this study included linkage with registries; FFQ tested for validity/reliability; exclusion of women with previous ovarian cancer and oophorectomy; and full adjustment for confounding. No information on type of coffee (regular/decaffeinated) was provided, however.]

Steevens et al. (2007) reported that coffee was not associated with incidence of cancer of the ovary, with a relative risk of 1.04 (95% CI, 0.97–1.12; *P* for trend, 0.35) for an increment in consumption of 1 cup/day in the Netherlands Cohort Study on Diet and Cancer; data were adjusted for age, smoking, oral contraceptives, parity, and tea. [The strengths of this study included linkage to cancer registry; no loss to follow-up; exclusion of women with previous cancer and oophorectomy from the cohort; and FFQ tested for validity/reproducibility. However, the results were not adjusted for menstrual factors.]

In the IWHS, Lueth et al. (2008) found no association for total coffee (*P* for trend, 0.51), decaffeinated coffee (*P* for trend, 0.36), or total caffeine (*P* for trend, 0.53). A significant increased risk was found for ≥ 5 cups/day of caffeinated coffee compared with non-drinkers (HR, 1.81; 95% CI, 1.11–2.95), with no trend in risk (*P* for trend, 0.15), after adjusting for multiple risk factors. [The strengths of this study included: linkage with cancer registries; exclusion of women with previous cancer and oophorectomy; FFQ tested for validity/reproducibility; and fully adjusted results (further adjustment did not modify the hazard ratio).]

In the NHS cohort Tworoger et al. (2008) reported that caffeinated coffee intake was not statistically related to incidence of cancer of the ovary, although a weak inverse relation emerged (RR, 0.75; 95% CI, 0.55–1.02) for ≥ 3 cups/day versus non-drinkers (*P* for trend, 0.03) after adjusting for risk factors. Decaffeinated coffee (follow-up starting in 1984) was not associated with risk of ovarian cancer (*P* for trend, 0.97). Coffee consumption was inversely associated with risk of ovarian cancer in oral contraceptive users (RR, 0.64; 95% CI, 0.44–0.93). [The strengths of this study included minimal loss to follow-up; repeated measures of coffee intake; validation of FFQ; exclusion of women with previous cancer and oophorectomy; and full adjustment.]

Kotsopoulos et al. (2009) pooled the results of the New England Case–Control Study (NECC) with a case–control study nested within the NHS and NHS-II cohorts. Kuper et al. (2000b) previously assessed the association between coffee consumption and risk of ovarian cancer in this study population. There was no association between coffee consumption and risk of ovarian cancer for all women or postmenopausal women in the NECC and NHS/NHS-II studies, with pooled estimates adjusted for multiple risk factors of 0.99 (95% CI, 0.77–1.28; *P* for trend, 0.34) and 0.83 (95% CI, 0.66–1.04; *P* for trend, 0.51), respectively. For premenopausal women, the odds ratio was 1.35 (95% CI, 1.03–1.78; *P* for trend, 0.003) for the NECC study and 0.60 (95% CI, 0.26–1.41; *P* for trend, 0.20) for the NHS/NHS-II study, with a pooled odds ratio of 1.00. There were no clear gene–environment interactions between caffeine-metabolizing genes and ovarian cancer. [The strengths of this study included: the population-based controls; interviewer-administered FFQ for most participants; fully adjusted; and strata of selected covariates. However, no clear information on the general methods for the participants of the nested case–control study from the NHS-II cohort was provided.]

Within the VIP, Nilsson et al. (2010) reported an adjusted hazard ratio of 1.41 (95% CI, 0.53–3.74) for ≥ 4 occasions/day total coffee consumption (*P* for trend, 0.490) for the risk of ovarian cancer;

similar hazard ratios were reported for filtered coffee. [The strengths of this study included the linkage with cancer registry and a high participation rate. Limitations included: no mention of validity/reproducibility of FFQ; no adjustment for menstrual/reproductive factors and exogenous hormone use; very short follow-up for some subjects; and no information on eventual oophorectomy.]

In the EPIC cohort study, Braem et al. (2012) reported an adjusted hazard ratio of 1.05 (95% CI, 0.75–1.46) for the highest quintile of intake compared with the lowest with no trend in risk (*P* for trend, 0.43); results were adjusted for several potential confounders, including smoking and endogenous and exogenous hormones. [The strengths of this study included: its large size; linkage to registries; exclusion of women with previous cancer and oophorectomy; very low loss to follow-up (although not clearly reported); validation of FFQ; and full adjustment. Limitations included: self-administered or interviewer-administered FFQ, depending on the study centre; categorization into country-specific quintiles in millilitres, rather than in absolute amount of coffee intake in cups/day.]

In the PLCO prospective study, Hashibe et al. (2015) reported an adjusted relative risk of 1.17 (95% CI, 0.82–1.67) for the highest compared with the lowest coffee intake (*P* for trend, 0.3982), and of 1.04 (95% CI, 0.95–1.14) for an increment of 1 cup/day. [This study benefited from linkage with the cancer registry and adjustment for main confounders. Limitations included no mention of FFQ testing, no information provided on eventual oophorectomy, and no clear information provided on follow-up length.]

Within the NOWAC study, Lukic et al. (2016) reported an adjusted hazard ratio of 0.87 (95% CI, 0.50–1.51) for > 7 cups/day total coffee consumption (*P* for trend, 0.89). The hazard ratios were similar for non-smokers. [Strengths included: linkage with cancer registry, exclusion of women with previous cancer, adjustment for main confounders, and FFQ tested for validity/reproducibility. Limitations included a lack of information on eventual oophorectomy; further, no information was provided on coffee drinking and smoking status for approximately 27% of subjects at follow-up.]

2.9.2 Case–control studies

In the USA, Hartge et al. (1982) reported an odds ratio of 1.4 (95% CI, 0.6–3.0) for risk of ovarian cancer in coffee drinkers. The results were similar when the analyses were restricted to non-smokers. [Strengths included an interviewer-administered FFQ and the elimination of controls admitted for diet-modifying diseases. Limitations included: the use of hospital controls; the lack of information on the length of the study (years), age of subjects, participation rate, oophorectomy among controls, FFQ validity/reproducibility, and no adjustment for menstrual factors and exogenous hormone use.]

In a case–control study conducted in the USA in the RPMI, Byers et al. (1983) reported no association between coffee intake and risk of cancer of the ovary in any of the three strata of age considered (OR, 0.97, non-significant for ≥ 3 cups/day). [Strengths included: the interviewer-administered FFQ; elimination of controls admitted for diet-modifying diseases; and a 100% participation rate of cases and controls. Limitations included: the use of hospital controls; no information on oophorectomy among controls, FFQ validity/reproducibility, and no adjustment for menstrual factors and exogenous hormone use.]

In Boston, USA, Cramer et al. (1984) reported an odds ratio of 2.0 ($P > 0.05$) in drinkers of ≥ 5 cups/day coffee who also smoked ≥ 50 pack-years of cigarettes. For coffee drinkers who also smoked and drank alcohol, the relative risk was 1.79 (95% CI, 0.69–4.62 for coffee consumption at least once a week). [The strengths of this study included: population controls; exclusion of bilateral oophorectomized women from

controls; interviewer-administered FFQ; and a high participation rate of cases and controls. Limitations included: a lack of information on FFQ validity/reproducibility and no adjustment for smoking, menstrual factors, and exogenous hormone use.]

In a hospital-based case–control study in Italy, La Vecchia et al. (1984) reported an adjusted odds ratio of 2.2 (95% CI, 1.2–3.9) for ≥ 4 cups/day of coffee, with a significant trend in risk of ovarian cancer (*P* for trend, < 0.003). The risk of ovarian cancer increased with the duration of coffee drinking (*P* for trend, 0.02). [The strengths of this study included: high participation rates; exclusion of previous cancer and gastrointestinal diseases among cases and controls and of oophorectomized controls; interviewer-administered FFQ; and fully adjusted results. Limitations included the use of hospital controls, and a lack of information about FFQ validity/reproducibility.]

In a study from 10 Athens hospitals (Greece), Tzonou et al. (1984) observed no significant association between coffee consumption and risk of ovarian cancer, and no trend in risk with the amount consumed (adjusted non-significant RR, 1.5; *P* for trend, 0.14). [This study includes the same cases as for that of Trichopoulos et al. (1981). Strengths included: the interviewer-administered FFQ; no refusal to participate (percent not reported); and adjustment for major covariates. Limitations included: the use of hospital controls including only orthopaedic disorders; very little information on methods; no information on oophorectomy among controls, FFQ validity/reproducibility, no adjustment for potential confounders; and no confidence interval reported.]

In a US hospital-based study, Miller et al. (1987) reported no association between coffee consumption of ≥ 5 cups/day and risk of ovarian cancer using either cancer (RR, 1.0; 95% CI, 0.5–1.8) or non-cancer (RR, 1.1; 95% CI, 0.6–2.0) controls. No association was also reported for decaffeinated coffee after adjusting for many covariates. [The strengths of this study included: high participation rates, exclusion of previous cancer among cases and controls, nurse-administered FFQ, and fully adjusted results. Limitations included: the use of hospital controls, no exclusion of oophorectomized women from controls, and a lack of information about FFQ validity/reproducibility.]

From a study based in Hokkaido, Japan, Mori et al. (1988) reported no significant association between daily coffee consumption and risk of ovarian cancer (RR, 1.4; 95% CI, 0.8–2.5), although the amount consumed in cups/day was not specified. [The strengths of this study included the interviewer-administered FFQ and no refusal to participate. Limitations included: the use of hospital controls including gynaecological disorders; no information on oophorectomy among controls, FFQ validity/reproducibility, or cups/day of coffee; and no specification of variables used for adjustment for potential confounders.]

In California, USA, Whittemore et al. (1988) reported odds ratios for ovarian cancer risk adjusted for smoking that were consistently above unity for any amount of coffee consumption, but with no trend in risk. The odds ratio was 2.07 (95% CI, 0.97–4.38) for ≥ 4 cups/day and 1.01 (95% CI, 0.93–1.08) for an increment in consumption of 1 cup/day. The direct relation increased with the duration of coffee drinking, with an odds ratio of 3.41 (95% CI, 1.46–7.96) in drinkers of at least 40 years compared with non-drinkers; the odds ratio for an increase of 10 years in duration of coffee drinking was 1.11 (95% CI, 0.89–1.38), however. Lifelong consumption of coffee (cup-years) was also directly associated, but the odds ratio for the overall trend per 10 cup-years among coffee drinkers was 1.01 (95% CI, 0.99–1.03). The association was consistently stronger for hospital-based compared with population-based controls. [The strengths of this study included: interviewer-administered FFQ;

a high response rate; exclusion of oophorectomized women from controls; and the provision of information on duration of and lifetime coffee drinking. Limitations included: no information on ascertainment of cases, FFQ validity/reproducibility, and no adjustment for many potential confounders.]

In a study conducted in two major cancer hospitals in Athens, Polychronopoulou et al. (1993) reported no association between coffee drinking and risk of ovarian cancer after a multivariate analysis. The odds ratio for an increment of 1 cup/day was 1.04 (95% CI, 0.82–1.30). [The strengths of this study included: population-based controls, exclusion of women with previous cancer or oophorectomy from controls, interviewer-administered FFQ, a high participation rate, and fully adjusted results. Limitations included a lack of information on FFQ validity/reproducibility]

In a population-based case–control study conducted in the USA, Kuper et al. (2000b) reported a relative risk of 1.88 (95% CI, 1.14–3.09) for ≥ 4 cups/day coffee, with no trend in risk with dose (*P* for trend, 0.17) after adjusting for risk factors. Stratified analyses showed that the increased risk was evident in premenopausal women; an odds ratio of 2.78 (95% CI, 1.44–5.37) for drinkers of ≥ 4 cups/day, with a significant trend in risk (*P* for trend, 0.0004), was reported. No relation was found in postmenopausal women (OR, 1.26; 95% CI, 0.57–2.81) for ≥ 4 cups/day. There were no differences in strata of histological subtypes of ovarian cancer. [The strengths of this study included: population-based design; cases identified by medical records and cancer registries; FFQ tested for validity/reproducibility, although the validity was not specific for coffee intake; interviewer-administered FFQ; and adjustment for major confounders. Limitations included the failure to exclude oophorectomized women from controls.]

In Italy, Tavani et al. (2001) reported no association between coffee or cappuccino consumption and risk of ovarian cancer (OR, 0.93; 95% CI, 0.69–1.27) for ≥ 4 cups/day, adjusting for covariates. Decaffeinated coffee had an inverse association, with an odds ratio of 0.64 (95% CI, 0.42–0.96) for drinkers compared with non-drinkers. Stratified analyses showed no heterogeneity in strata of age, education, parity, oral contraceptive use, BMI, total energy intake, and family history of ovarian/breast cancer. [Strengths of this study included: very large size; exclusion of previous cancer from cases and controls and oophorectomized women from controls; FFQ tested for validity/reproducibility; interviewer-administered FFQ; fully adjusted; and separate information for caffeinated/decaffeinated coffee and cappuccino. The study was however limited by the use of hospital-based controls.]

In a population-based study in Hawaii, USA, Goodman et al. (2003) reported an odds ratio of 1.5 (95% CI, 0.8–2.7) for ≥ 7 cups/day total coffee, with a non-significant trend in risk with dose (*P* for trend, 0.27) on adjusting for age, race, use of oral contraceptives, and tubal ligation. Regular coffee or caffeine were positively related to risk of ovarian cancer, with an odds ratio of 1.7 (95% CI, 1.0–3.1) for ≥ 7 cups/week of caffeinated coffee compared with non-drinkers (*P* for trend, 0.07) and 2.3 (95% CI, 1.3–4.0) for > 1.24 g/week of caffeine; a significant trend in risk was only observed for caffeinated coffee (*P* for trend, 0.02). Decaffeinated coffee drinking was not associated with an increased risk of ovarian cancer. For consumption of regular coffee, the odds ratios were consistent across strata of menopausal status and for mucinous histological type. Similar results were found in a larger group of women for which blood samples were not available. [The strengths of this study included use of population-based controls, interviewer-administered FFQ for most participants, fully adjusted results, separate information for coffee/decaffeinated coffee/caffeine, and in strata of selected covariates. Limitations included

failure to exclude oophorectomized women from controls, and a lack of information about FFQ validity/reproducibility.]

In an Australian study, Jordan et al. (2004) observed that coffee was inversely associated with risk of ovarian cancer (OR, 0.62; 95% CI, 0.41–0.95) for ≥ 4 cups/day, with a significant trend in risk (*P* for trend, 0.05) after adjustingfor multiple risk factors. The inverse association was found for invasive serous tumours (*P* for trend, 0.01), invasive endometrioid/clear-cell tumours (*P* for trend, 0.01), and overall for invasive tumours (*P* for trend, 0.009), while there was no association for invasive mucinous and all borderline tumours. The inverse association was evident only in postmenopausal women (*P* for trend, 0.005). No heterogeneity was found in strata of smoking, alcohol, BMI, parity, and in women with invasive stage I or advanced disease. [The strengths of this study included the use of population-based controls, the exclusion of oophorectomized women from controls, FFQ tested for validity/reproducibility (not for the coffee question), and fully adjusted results. Limitations included the fact that FFQs were interviewer-administered among cases and self-administered among controls.]

In Sweden, Riman et al. (2004) reported a non-significant inverse association between coffee drinking and risk of ovarian cancer, with an odds ratio of 0.68 (95% CI, 0.42–1.10) for ≥ 6 cups/day of coffee with no trend in risk (*P* for trend, 0.18). The results were similar for all histological subtypes (serous, mucinous, and clear-cell tumours) while there was no association for endometrioid subtype. [The strengths of this study included the use of population-based controls, its large size, the exclusion of oophorectomized women among controls, high participation rate, and fully adjusted data. Limitations included the self-administered FFQ or telephone interview for more controls than cases, and a lack of information regarding FFQ validity/reproducibility and intake of caffeinated/decaffeinated coffee.]

In a study conducted within the RPCI, USA, Baker et al. (2007) reported that regular coffee was not related to risk of ovarian cancer (OR, 1.05; 95% CI, 0.73–1.52) for ≥ 4 cups/day, and no heterogeneity was found in strata of borderline tumours or serous, mucinous, endometrioid, and clear-cell histological subtypes. Decaffeinated coffee was inversely associated with overall risk of ovarian cancer; an odds ratio of 0.71 (95% CI, 0.51–0.99) for ≥ 2 cups/day compared with non–drinkers, with an inverse statistically significant trend in risk (*P* for trend, 0.002), was reported. Stratified analyses showed that the decreased risk did not reach statistical significance for serous, mucinous, and borderline tumours, and that there was no association for endometrioid and clear-cell tumours. [The strengths of this study were the identifiication of cases through cancer registries and the provision of information on caffeinated/decaffeinated coffee. Limitations included: the use of hospital-based controls, self-administered FFQ, no exclusion of oophorectomized women from controls, no information on FFQ validity/reproducibility, and no adjustment for confounders.]

Using data from the Hospital-based Epidemiological Research Program at Aichi Cancer Centre (HERPACC) in Japan, Hirose et al. (2007) observed a non-significant positive association between coffee intake and risk of ovarian cancer (OR, 1.33; 95% CI, 0.68–2.60) for ≥ 3 cups/day versus non-drinkers (*P* for trend, 0.88). [This study benefited from cases being identified through medical records and cancer registries, and the checking of the self-administered FFQ by an interviewer. Limitations included the hospital-based controls, no exclusion of oophorectomized women from controls, no information on FFQ validity/reproducibility, and no adjustment for menstrual factors and exogenous hormones.]

In a study conducted in a 13-county area of Washington State, USA, Song et al. (2008) reported an odds ratio for regular coffee of 0.87 (95% CI, 0.64–1.19) for ≥ 3 cups/day. The intake of decaffeinated coffee or caffeine equivalent to the content of ≥ 3 cups/day of regular coffee were not related to the risk of ovarian cancer (*P* for trend, 0.54 and 0.38, respectively). [The strengths of this study were its large size, identification of cases through cancer registries as part of the SEER Program; population-based controls, exclusion of oophorectomized women from controls, and the provision of information on caffeinated/decaffeinated coffee and caffeine consumption. Limitations included the self-administered FFQ, no information on FFQ validity/reproducibility, and no adjustment for menstrual factors.]

In the Danish MALignant OVArian cancer (MALOVA) study, Gosvig et al. (2015) reported that coffee was inversely related to invasive ovarian cancer (although not always statistically significant); odds ratios (95% CI) for an increment of 1 cup/day of coffee were 0.90 (0.84–0.97) for overall, 0.89 (0.83–0.97) for serous, 0.90 (0.77–1.06) for endometrioid, and 0.88 (0.74–1.05) for other types of ovarian cancer. No association was evident for mucinous ovarian cancer (OR, 1.07; 95% CI, 0.90–1.28). Coffee consumption was not related to overall, serous, or mucinous borderline risk of ovarian cancer. [The strengths of this study included cases identified by cancer registries, use of population-based controls, exclusion of oophorectomized women from controls, and fully adjusted results. Limitations included the self-administered FFQ as part of a larger questionnaire on other variables, and no information was provided on on FFQ validity/reproducibility.]

2.9.3 Meta-analyses

Braem et al. (2012) added a meta-analysis to their analysis within the EPIC cohort study. The literature was searched up to April 2011 using PubMed and Embase, and manually in reference lists of retrieved articles. Studies were included if they met the following criteria: cohort studies; frequency of coffee consumption was reported; the exposure was total and/or caffeinated and/or decaffeinated coffee; the number of cases and person-years were provided; the outcome was ovarian cancer. Seven articles were included in the meta-analyses (three studies were not included as they did not report 95% CI), with a total of 3236 cases of ovarian cancer. There was some heterogeneity across studies, and no evidence of publication bias. The summary hazard ratio for the study-specific highest versus the lowest coffee intake was 1.13 (95% CI, 0.89–1.43); the results did not change on exclusion of the study of Nilsson et al. (2010), which did not adjust for parity and oral contraceptive use. The hazard ratio for an increment of 1 cup/day was 1.02 (95% CI, 0.99–1.05), showing no association between coffee intake and risk of ovarian cancer. [The strengths of this meta-analysis were the comprehensive selection of studies and the detailed extraction information, allowing the computation of a dose–response association between coffee intake and risk of ovarian cancer.]

2.10 Childhood cancer

2.10.1 Childhood leukaemia

See Table 2.20 (web only; available at: http://publications.iarc.fr/566).

In general, childhood leukaemia refers to diagnoses in children less than 15 years of age. Almost all are acute leukaemias (AL), including acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), and a few other rare or unspecified types. Together, AML and other

non-ALL leukaemias are sometimes referred to as acute non-lymphoblastic leukaemia (ANLL).

Seven case–control studies reporting results of the association between maternal coffee consumption during pregnancy and risk of childhood leukaemia in the offspring are described below. Six of the seven studies included all acute leukaemias, and four of these studies presented results separately for ALL and AML (or ANLL). One study (Milne et al., 2011) included ALL cases only. Unless otherwise stated, the studies included children younger than 15 years. There were no cohort studies.

The child's sex and age were used as matching variables in all studies. The following variables were also identified as confounders, and considered in the analysis of the association between maternal coffee consumption and risk of childhood leukaemia in one or more studies: socioeconomic status (e.g. maternal education, socioprofessional category, and income); mother's ethnicity/country of birth; mother's age at the child's birth; birth order; and breastfeeding. There is little or no evidence that maternal smoking is associated with risk of childhood leukaemia. Maternal alcohol consumption is not considered a confounder of this association, and studies that did examine it as a potential confounder reported that it did not alter the findings. Maternal recall of coffee consumption during pregnancy up to 15 years in the past may have led to error in exposure assessment, although most childhood leukaemias are diagnosed within the first 6 years of life. Further, there is evidence that diet during a past pregnancy (3–7 years previously) is generally recalled with similar accuracy as adult diet; this may partly reflect the influence of current diet on recall of past diet (Bunin et al., 2001). However, it cannot be excluded that mothers of children with leukaemia overestimate exposure.

(a) Case–control studies

An early case–control study of childhood leukaemia reported that "there was no apparent risk associated with coffee consumption" but did not present data (Peters et al., 1994).

Ross et al. (1996) analysed data on infant leukaemia (diagnosed at ≤ 1 year of age) from three North American case–control studies of childhood leukaemia. In total, there were 303 cases in the original studies. Ross et al. recontacted women up to 10 years after the original studies, and 84 matched sets of infant cases and controls were available for analysis. Controls (n = 97) had been recruited through RDD and matched to cases on year of birth, geographical area, and, in two of the three studies, race. Maternal intake of coffee was assessed as part of a dietary questionnaire completed by telephone interview. Regular coffee intake was associated with an increased risk of infant leukaemia, with an adjusted odds ratio of 2.5 (95% CI, 1.0–6.2) for ≥ 4 cups/week (P for trend, 0.04). Odds ratios for ALL and AML individually were similarly elevated, but estimates were imprecise. [Strengths included presentation of results for infant AL, ALL, and AML separately, and inclusion of exposure–response analysis. Limitations included the small sample size and potential for selection bias, given the low participation rate.]

Petridou et al. (1997) conducted a hospital-based case–control study of childhood leukaemia in Greece. The investigators recruited 153 cases confirmed by bone marrow analysis and 300 hospital-based controls admitted with "acute conditions", matched on age, sex, and town or region. Maternal coffee intake was assessed by interview and categorized as < 3 and ≥ 3 cups/week. No association was observed, with an adjusted odds ratio of 0.89 (95% CI, 0.55–1.46). [Strengths included control for confounding by multiple factors. Limitations included: a lack of detail about control diagnosis/reason for hospitalization; analysis of all

types of childhood leukaemia together; exposure was categorized as only binary, so an exposure–response analysis was not possible; and the modest sample size.]

Milne et al. (2011) conducted a population-based case–control study in Australia that included 337 incident cases of childhood ALL and 697 controls recruited by nationwide RDD. Controls were frequency-matched to the cases on age, sex, and state of residence. Maternal coffee intake during the last 6 months of the index pregnancy was assessed by FFQ, and reported in cups/day. No overall association between maternal coffee consumption and risk of ALL was observed; the adjusted odds ratio for any coffee consumption was 0.89 (95% CI, 0.61–1.30), and there was no evidence of an exposure–response association (*P* for trend, 0.50). [Strengths included the use of population-based cases and controls, standardized questionnaires, adjustment for a range of confounders, and assessment of exposure–response relationship. The study was however limited by the low participation rate.]

Several independent case–control studies of childhood leukaemia were conducted in France, described in the following paragraphs.

Menegaux et al. (2005) conducted a study including 280 incident cases of childhood acute leukaemia from hospitals in Paris, Lille, Lyon, and Nancy. Controls comprised 288 children admitted to the same hospitals as the cases, mainly with orthopaedic conditions. Recruitment was stratified by age, sex, hospital, and ethnic origin. Maternal coffee intake during pregnancy was assessed by face-to-face interview using a standardized questionnaire. The adjusted odds ratios (95% CI) for AL were 1.0 (0.7–1.5), 2.1 (1.2–3.8), and 2.8 (0.9–8.1) for ≤ 3 cups/day, 4–8 cups/day, and > 8 cups/day, respectively, compared with non-drinkers (*P* value for trend, < 0.05). Positive associations were also seen for both ALL and ANLL, although results for the latter were imprecise. For ALL, the corresponding odds ratios (95% CI) were 1.1 (0.7–1.8), 2.4 (1.3–4.7), and 3.1 (1.0–9.5), respectively, while for ANLL they were 1.6 (0.6–4.3), 2.8 (0.7–10.4), and 3.0 (0.3–35.1). [Strengths included standardized interviews, adjustment for a range of confounders, presentation of results for ALL and ANLL separately, and assessment of exposure–response relationship. The study was however limited by the use of hospital-based controls and the modest sample size for ANLL.]

Menegaux et al. (2007) conducted a second study including 470 incident cases of childhood acute leukaemia (407 ALL and 62 AML) and 567 controls. Cases were diagnosed between 1995 and 1998 in 14 regions of France, and identified through the National Registry of Childhood Blood Malignancies (NRCL). The four regions that provided cases in Menegaux et al. (2005) were excluded from this study. Controls were recruited by RDD and frequency-matched to cases on age, sex, and region. Mothers completed a standardized self-administered questionnaire that asked about a range of exposures, including coffee consumption, during pregnancy. Overall, maternal coffee intake was not significantly associated with risk of AL, ALL, or AML; odds ratios (95% CI) for > 3 cups/day versus none were 1.5 (0.9–2.4), 1.4 (0.9–2.4), and 1.4 (0.5–4.4), respectively. [Strengths included use of population-based controls, standardized questionnaires, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of the exposure–response relationship. The modest sample size for AML was a limitation.]

Bonaventure et al. (2013) reported results from the Etude Sur les Cancers et les Leucémies de l'Enfant (ESCALE) study, a population-based case–control study conducted in France. The cases comprised 764 children diagnosed with AL (including 648 ALL and 101 AML), identified through the National Registry of Childhood Haematopoietic Malignancies (NRCH) during 2003–2004. Controls were selected contemporaneously from French households with landline telephones using RDD, with quotas applied

to ensure their age and sex distributions were comparable to the case group and the French population. Data were collected by telephone interview. The adjusted odds ratios (95% CI) for > 2 cups/day for AL, ALL, and AML were 1.6 (1.2–2.1), 1.5 (1.1–2.0), and 2.4 (1.3–4.3), respectively, with *P* values for trend of < 0.001, 0.0027, and 0.002, respectively. [Strengths included the use of population-based controls, standardized questionnaires, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of an exposure–response relationship.]

Orsi et al. (2015) reported results from the ESTELLE study, a nation-wide French population-based case–control study of childhood malignancies. In this study, 747 children newly diagnosed with leukaemia in 2010 and 2011 (including 636 ALL, 100 AML, and 11 unspecified) were identified by the investigators of the NRCH. Controls (n = 1421) were children free from cancer selected using RDD and a quota sampling method; the latter was applied to ensure their age and sex distributions were comparable to the case group and the French population. Data on maternal coffee intake during the index pregnancy were collected during a standardized telephone interview. Maternal coffee consumption was not found to be associated with AL overall (adjusted OR for > 2 cups/day 1.1, 95% CI: 0.9–1.5) or with AML (OR for > 2 cups/day 0.5, 95% CI: 0.2–1.1), while for ALL, the OR for > 2 cups/day was 1.3 (95% CI: 1.0–1.7). [Strengths included the use of population-based controls, a standardized CATI interview, adjustment for a range of confounders, presentation of results for ALL and AML separately, and assessment of the exposure–response relationship. *P* values for trend were not provided, however.]

(b) Meta-analyses

Three meta-analyses of the association between maternal coffee consumption and childhood leukaemia have been conducted, and all reported elevated risks with higher levels of maternal coffee intake (Milne et al., 2011; Cheng et al., 2014; Thomopoulos et al., 2015). The results are presented only for the most recent meta-analysis of Thomopoulos et al. (2015), which included all studies published to date. High maternal coffee intake during pregnancy was positively associated with AL overall, ALL, and AML with summary odds ratios (95% CI) of 1.57 (1.16–2.11), 1.43 (1.22–1.68), and 1.81 (0.93–3.53), respectively. [A limitation of this meta-analysis was that "high level" coffee intake was not defined consistently in the included studies, varying from ≥ 4 times/week (Ross et al., 1996) to ≥ 8 cups/day (Menegaux et al., 2007).]

Another meta-analysis (Yan et al., 2015) lacked methodological detail and excluded some relevant studies. Ross et al. (1996) was a study of only infants (of age ≤ 1 year). The authors also included unpublished data from one of their own studies.

2.10.2 Wilms tumour

Bunin et al. (1987) reported that there was no association with maternal coffee drinking in a case-control study of risk factors for Wilms tumour, but did not present an effect estimate. Three other case–control studies (e.g., Schüz et al., 2001) reported findings for the association of Wilms tumour and maternal coffee or tea consumption combined; these studies were excluded from further consideration because of the ambiguous exposure definition.

2.10.3 Childhood cancer of the brain

Three population-based case–control studies have reported findings for prenatal exposure to coffee and risk of childhood brain tumours. All reported non-significant positive associations, with odds ratios (95% CI) of 1.9 (0.9–3.9) for any coffee (Cordier et al., 1994), 1.4 (0.8–2.4) for > 3 cups/day (Plichart et al., 2008), and

1.35 (0.90–2.04) for ≥ 2 cups/day (Greenop et al., 2014). None of the studies reported a significant exposure–response trend overall. However, in a subgroup analysis of cases of age < 5 years at diagnosis, Greenop et al. observed significantly elevated odds ratios (95% CI) of 1.76 (1.09–2.84) for any maternal coffee intake, 1.55 (0.92–2.63) for > 0–2 cups/day, and 2.52 (1.26–5.04) for ≥ 2 cups/day (Greenop et al., 2014). A significant trend (P = 0.007) was also observed in this age group. Two earlier population-based case–control studies reported no significant association between maternal consumption of caffeinated beverages (including coffee, tea, and cola drinks) and risk of astrocytoma (Bunin et al., 1994) or primitive neuroectodermal tumours (Bunin et al., 1993) in children aged < 6 years.

[The strengths of these studies included their population-based controls, appropriate assessment of and adjustment for confounders, and examination of the exposure–response trend in the three most recent studies. The main limitation was suboptimal response rates, leading to the potential for selection bias.]

2.11 Cancer of the oral cavity and pharynx

Twenty-six studies that evaluated associations between coffee consumption and cancers of the oral cavity and pharynx were reviewed by the Working Group: seven were prospective cohort studies, eighteen were case–control studies, and one (Galeone et al., 2010a) was a pooled analysis of nine case–control studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. However, several were not considered for evaluation; two studies did not present risk estimates for the association between coffee consumption and oral or pharyngeal cancer (McLaughlin et al. 1988; Lagiou et al. 2009); two did not specifically analyse coffee consumption as an exposure (Franceschi et al., 1999; Escribano Uzcudun et al., 2002); and one (Hashibe et al. 2015) did not have oral or pharyngeal cancers as outcomes. Four meta-analyses of the indicated studies were also identified and reviewed (Turati et al., 2011b; Yu et al., 2011; Zhang et al., 2015; Li et al., 2016).

2.11.1 Cohort studies

Table 2.21 (web only; available at: http://publications.iarc.fr/566)

The six informative cohort studies were conducted in Japan (Naganuma et al., 2008), Norway (Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Tverdal et al., 2011), and the USA (Ren et al., 2010; Hildebrand et al., 2013). Four studies provided data for incident (Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Naganuma et al., 2008; Tverdal et al., 2011) or fatal (Hildebrand et al., 2013) oral and pharyngeal cancers combined, and one study reported separate associations for each cancer site (Ren et al., 2010). All studies controlled for tobacco smoking and alcohol drinking. All of the studies that treated oropharyngeal cancer as a single entity reported null or inverse associations with coffee consumption (Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Naganuma et al., 2008; Tverdal et al., 2011; Hildebrand et al., 2013). Ren et al. (2010) reported no association with oral cancer and a positive, non-significant association with pharyngeal cancer.

2.11.2 Case–control studies

The 14 informative case–control studies were undertaken in Brazil (Franco et al., 1989; Pintos et al., 1994; Biazevic et al., 2011), Colombia (Restrepo et al., 1989), Denmark (Bundgaard et al., 1995), France (Radoï et al., 2013), India (Heck et al., 2008), Italy (La Vecchia et al., 1989b; Franceschi et al., 1992), Italy and Switzerland (Tavani et al., 2003; Rodriguez et al., 2004), Japan (Takezaki et al., 1996a; Oze et al., 2014), and the

USA (Mashberg et al., 1993). [The Working Group noted that the studies by Tavani et al. (2003) and Rodriguez et al. (2004) may partly overlap.] All but two of these studies (Bundgaard et al., 1995; Radoï et al., 2013) were hospital-based.

Most studies investigated cancers of the oral cavity and pharynx combined. Aggregated data were also reported for oral, pharyngeal, and laryngeal cancer (Oze et al. 2014) and for cancers of the mouth and hypopharynx (Restrepo et al., 1989). Data for cancer of the oral cavity alone were reported in five studies (Franco et al., 1989; Franceschi et al. 1992; Pintos et al., 1994; Bundgaard et al. 1995; Radoï et al. 2013); data for cancer of the pharynx and hypopharynx alone were reported by Pintos et al. (1994) and Heck et al. (2008), respectively. Adjustment for at least age, sex, smoking status, and alcohol intake was performed in all studies.

The estimated association between coffee consumption and oral and/or pharyngeal cancer incidence was null or inverse in all but three studies: Franco et al. (1989) reported a non-statistically significant increased risk of cancer of the oral cavity for coffee consumption of ≥ 6 cups/day versus < 1 cup/day (OR, 1.5; 95% CI, 0.9–2.6; *P* for trend, 0.14), and Bundgaard et al. (1995) estimated a similarly increased odds ratio of 1.4 (95% CI, 0.4–4.5) for oral squamous cell cancer among drinkers versus non-drinkers of coffee. Restrepo et al. (1989) reported a statistically significant sex- and age-adjusted odds ratio for the association between coffee (≥ 7 cups/day vs 0 cups/day) and cancers of the oral cavity and hypopharynx, reduced after additional adjustment for socioeconomic level, smoking, and alcohol intake, of 5.12 (*P* for trend, 0.002) [95% CI not reported].

Heck et al. (2008) reported odds ratios (95% CI) for hypopharyngeal cancer for highest versus lowest coffee consumption of 1.07 (0.41–2.81; *P* for trend, 0.7) for never smokers and 0.81 (0.39–1.66; *P* for trend, 0.4) for ever smokers. In the remaining studies, the estimated odds ratios for the highest versus lowest coffee consumption ranged over 0.25–0.90 and were statistically significant in six studies (Franceschi et al., 1992; Tavani et al., 2003; Rodriguez et al., 2004; Biazevic et al., 2011; Radoï et al. 2013; Oze et al., 2014). In the pooled analyses of data from the INHANCE consortium, Galeone et al. (2010a) used individual-level data from five hospital-based case–control studies and four population-based case–control studies of head and neck cancers conducted in Europe and North and Central America. Caffeinated coffee intake was inversely related to the risk of cancer of the oral cavity and pharynx combined; odds ratios (95% CI) of 0.96 (0.94–0.98) for an increment of 1 cup/day and 0.61 (0.47–0.80) in drinkers of > 4 cups/day versus non-drinkers were reported (*P* for trend, < 0.01). In a separate analysis by anatomical site, the respective estimates were 0.46 (0.30–0.71; *P* for trend, < 0.01) for oral cavity and 0.58 (0.41–0.82; *P* for trend, 0.02) for oropharynx/hypopharynx. [The Working Group noted that this paper reported that results on coffee drinking had been published by four out of nine of the studies before the pooled analysis undertaken in their paper, but it is not clear from the indicated references which studies are meant. There may therefore be some overlap between this pooled analysis and some of the case–control studies reviewed individually.]

2.11.3 Meta-analyses

Meta-analyses of the association between coffee intake and risk of cancer of the upper aerodigestive tract (Turati et al., 2011b) and cancer risk overall (Yu et al., 2011) were published in 2011. Summary relative risks (95% CI) for oral cavity/pharyngeal cancer were 0.64 (0.51–0.80) and 0.40 (0.12–0.68) for the highest versus lowest level of coffee drinking in the two studies, respectively. [The Working Group noted that the meta-relative risk for highest versus lowest consumption in Yu et al. (2011) was taken from Supplementary Table S2 of the publication.]

Zhang et al. (2015) undertook a meta-analysis of 12 studies focusing on the association between oral cancer and coffee intake, comprising 4037 cases and 1 872 231 participants. The summary relative risk of oral cancer for the highest versus lowest level of coffee consumption was 0.69 (95% CI, 0.54–0.89).

The most recent meta-analysis of 11 case–control and 4 cohort studies through 2015 that reported on cancer of the oral cavity alone or in combination with cancer of the pharynx was undertaken by Li et al. (2016). The summary relative risk of oral cancer for the highest versus the lowest consumption of coffee was 0.63 (95% CI, 0.52–0.75; I^2, 53.1%). Results were consistent in subgroup analysis by study design, with 0.60 (95% CI, 0.49–0.74) for case–control and 0.66 (95% CI, 0.45–0.98) for cohort studies), by country (Americas, Asia, and Europe), by number of cases and study quality score, as well as in analysis by trim and fill undertaken to examine potential publication bias. Heterogeneity, however, remained medium–high even in subgroup analyses. The pooled analysis by Galeone et al. (2010a) is not included in this meta-analysis.

2.12 Cancer of the oesophagus

In reviewing data on the association between coffee consumption and cancer of the oesophagus, the Working Group considered only studies that adjusted for the important potential confounders of tobacco smoking and alcohol drinking. One cohort study that presented results for oral and oesophageal cancers combined was excluded from the Working Group evaluation (Tverdal et al., 2011).

2.12.1 Cohort studies

Four pertinent cohort studies (Jacobsen et al., 1986; Naganuma et al., 2008; Ren et al., 2010; Zamora-Ros et al., 2014) were identified; three of these studies observed no association. A study based in Japan (Naganuma et al., 2008) observed an inverse association. The earliest cohort study from Norway (Jacobsen et al., 1986) analysed a very small number of cases (n = 15). The other cohort studies were sufficiently large and adequately designed. Two studies conducted stratified analyses by histological type (Ren et al., 2010; Zamora-Ros et al., 2014), but did not observe notable differences in the association by histological type.

2.12.2 Case–control studies

Eight case–control studies in the Americas, Asia, and Europe (La Vecchia et al., 1989b; Brown et al., 1995; Garidou et al., 1996; Inoue et al., 1998; Castellsagué et al., 2000; Terry et al., 2000; Tavani et al., 2003; Chen et al., 2009) were identified. All studies were hospital-based with the exception of one study from Sweden that applied population-based controls from a National Register. (Terry et al., 2000). Six studies (La Vecchia et al., 1989b; Brown et al., 1995; Garidou et al., 1996; Inoue et al., 1998; Castellsagué et al., 2000; Terry et al., 2000) among the eight found no notable association between coffee intake and risk of cancer of the oesophagus. Among the two more recent studies, one observed significantly decreased risk (Tavani et al., 2003) and one observed a decreased risk of cancer, particularly in the middle third part of the oesophagus (Chen et al., 2009).

2.12.3 Meta-analyses

Two meta-analyses of coffee consumption and the risk of cancer of the oesophagus have been published (Turati et al., 2011b; Zheng et al., 2013). The summary relative risk reported by the most recent meta-analysis (Zheng et al., 2013) was 0.88 (95% CI, 0.76–1.01) for highest versus lowest coffee consumption. The other meta-analysis (Turati et al., 2011b) reported summary relative risks for the same comparison category of 0.87

(95% CI, 0.65–1.17) for squamous cell carcinoma and 1.18 (95% CI, 0.81–1.71) for adenocarcinoma of the oesophagus.

2.13 Cancer of the stomach, small intestine, gall bladder, and biliary tract

2.13.1 Cancer of the stomach

(a) Cohort studies

Twelve cohort studies that reported on the association between coffee consumption and cancer of the stomach were identified (Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Galanis et al., 1998; Tsubono et al., 2001; Khan et al., 2004; Larsson et al., 2006a; Nilsson et al., 2010; Ren et al., 2010; Bidel et al., 2013; Ainslie-Waldman et al., 2014; Hashibe et al., 2015; Sanikini et al., 2015b).

Nine studies observed no association (Jacobsen et al., 1986; Galanis et al., 1998; Tsubono et al., 2001; Khan et al., 2004; Nilsson et al., 2010; Bidel et al., 2013; Ainslie-Waldman et al., 2014; Hashibe et al., 2015; Sanikini et al., 2015b). One early study from Norway reported risk estimates of < 1 that were not statistically significant (Stensvold & Jacobsen, 1994). One study from Sweden (Larsson et al., 2006a) showed positive associations for both baseline and cumulative consumption of coffee. One study from the USA showed an increased risk for gastric cardia cancer but not for non-cardia cancer (Ren et al., 2010). A nested case–control study within a cohort from Singapore observed a significant inverse association in analyses adjusted for *Helicobacter pylori* (Ainslie-Waldman et al., 2014). In general, the data were inconclusive on the association between coffee intake and cancer of the stomach.

(b) Case–control studies

Fourteen case–control studies that reported on the association between coffee consumption and cancer of the stomach were identified (Correa et al., 1985; La Vecchia et al., 1989b; Agudo et al., 1992; Hoshiyama & Sasaba, 1992; Hansson et al., 1993; Inoue et al., 1998; Komoto et al., 1998; Chow et al., 1999; Terry et al., 2000; Muñoz et al., 2001; Rao et al., 2002; De Stefani et al., 2004; Gallus et al., 2009; Icli et al., 2011). The majority of the studies were hospital-based (Correa et al., 1985; La Vecchia et al., 1989b; Agudo et al., 1992; Inoue et al., 1998; Komoto et al., 1998; Muñoz et al., 2001; Rao et al., 2002; De Stefani et al., 2004; Gallus et al., 2009; Icli et al., 2011) and the remainder were population-based (Hoshiyama & Sasaba, 1992; Hansson et al., 1993; Chow et al., 1999; Terry et al., 2000). All studies but two, conducted in Uruguay (De Stefani et al., 2004) and Turkey (Icli et al., 2011), found no association between coffee intake and risk of cancer of the stomach. The remaining studies (De Stefani et al., 2004; Icli et al., 2011) observed significant inverse associations. However, results from the study by Icli et al. (2011) were only adjusted for age, so potential confounding could not be ruled out.

(c) Meta-analyses

Eight meta-analyses of the association of cancer of the stomach and coffee consumption were available for review (Botelho et al., 2006; Xie et al., 2014; Fang et al., 2015; Li et al., 2015; Liu et al., 2015b; Shen et al., 2015; Zeng et al., 2015; Deng et al., 2016). The latter seven meta-analyses focused on prospective studies only. These were published around the same time and employed slightly different methods, but yielded similar results. Summary relative risks (95% CI) for highest versus lowest consumption of the most recent meta-analysis (Deng et al., 2016) was 1.36 (1.06–1.74) for the USA, 0.96 (0.72–1.27) for Asia, and 1.12 (0.86–1.46) for Europe.

2.13.2 Cancer of the small intestine, gall bladder, and biliary tract

One case–control study of adenocarcinoma of the small intestine cancer (Negri et al., 1999), one case–control study for extrahepatic bile duct cancer (Yen et al., 1987), and one case–control study for cancer of the gallbladder (Poland) (Zatonski et al., 1992) have been published, all of which reported null associations with coffee intake. One case–control study in Canada found a decreased risk of cancer of the bile duct with coffee intake (Ghadirian et al., 1993).

In one cohort study from Japan (Makiuchi et al., 2016), there was no clear association between coffee consumption and cancer of the biliary tract, gallbladder, or extrahepatic bile duct.

2.14 Cancer of the colorectum

Several cohort and case–control studies, pooled analyses, and meta-analyses have been conducted to evaluate the association between coffee drinking and cancer of the colorectum. The Working Group's review gave the greatest weight to data from well-conducted prospective cohort studies. Case–control studies were seen as less informative because they necessarily assess diet after the onset of disease; reported dietary intakes of people with colorectal cancers can therefore be influenced by the disease.

2.14.1 Cohort studies

Table 2.22 (web only; available at: http://publications.iarc.fr/566)

The Working Group evaluated 18 cohort studies of coffee drinking and colorectal cancers (Phillips & Snowdon, 1985; Hartman et al., 1998; Terry et al., 2001; Mucci et al., 2003; Michels et al., 2005; Larsson et al., 2006b; Oba et al., 2006; Lee et al., 2007a; Naganuma et al., 2007; Bidel et al., 2010; Nilsson et al., 2010; Peterson et al., 2010; Simons et al., 2010; Sinha et al., 2012; Dominianni et al., 2013; Dik et al., 2014; Yamada et al., 2014; Lukic et al., 2016) and a large pooled analysis (Zhang et al., 2010).

Phillips & Snowdon (1985) investigated the association of coffee intake with colorectal cancer mortality in a large cohort of California Seventh-day Adventists. After 21 years of follow-up, the relative risk of colorectal cancer mortality in men and women combined was 1.5 (95% CI, 1.0–2.2) for an intake of ≥ 2 cups/day with a trend in risk (*P* for trend, 0.02).

Among participants of the ATBC Cancer Prevention trial of 29 133 male smokers in Finland (Hartman et al., 1998), the relative risks (95% CI) of drinking 4–5 cups/day or > 6 cups/day compared with ≤ 4 cups/day were 0.73 (0.47–1.16) and 0.69 (0.42–1.13), respectively. The corresponding odds ratios (95% CIs) for rectal cancer were 1.05 (0.63–1.75) and 0.77 (0.43–1.40).

Among 61 463 Swedish women followed for an average of 9.6 years (Terry et al., 2001), the adjusted relative risks (95% CI) for consumption of 1, 2–3, and ≥ 4 cups/day compared with drinking < 1 cup/day were 0.96 (0.66–1.40), 0.93 (0.67–1.29), and 1.04 (0.70–1.54), with a *P* for trend of 0.95. Results were similar for colon and rectal cancers separately, and for subsites within the colon.

In the follow-up period of the NHS and HPFS cohorts until 1998 (Michels et al., 2005), there was no association between higher caffeinated coffee intake and risk of colorectal cancer (HR, 0.98; 95% CI, 0.69–1.38) for > 5 cups/day compared with non-drinkers of coffee (*P* for trend, 0.60). For colon cancer alone, the association was similar. For rectal cancer, the hazard ratio was 1.55 (95% CI, 0.97–2.45) for ≥ 4 cups/day (the highest category) compared with non-drinkers (*P* for trend, 0.31). There was an inverse association between decaffeinated coffee and colorectal cancer risk (HR, 0.82; 95% CI, 0.67–0.99) for ≥ 2 cups/day compared with non-drinkers (*P* for trend, 0.08). Results among non-smokers were

similar to those in the full study population for both caffeinated and decaffeinated coffee.

A large Japanese cohort study of more than 50 000 men and women (Oba et al., 2006) found that coffee consumption was inversely associated with colon cancer risk in women, but not in men. The relative risks (95% CI) for ≥ 1 cup/day versus never and < 1 cup/day were 0.43 (0.22–0.85) and 0.81 (0.46–1.42), respectively, with an inverse trend observed for women (*P* for trend, < 0.01).

Larsson et al. (2006b) studied the association between coffee drinking and risk of colorectal cancer among participants from two population-based cohort studies of women and men in Sweden. Coffee consumption was not associated with risk of colorectal cancer, colon cancer, or rectal cancer in women or men. The multivariate rate ratio for colorectal cancer in both cohorts combined was 1.00 (95% CI, 0.97–1.04) for an increment of 1 cup/day of coffee.

Naganuma et al. (2007) examined coffee consumption and colorectal cancer risk in the Miyagi Cohort Study of approximately 48 000 men and women in Japan. For a consumption frequency of ≥ 3 cups/day versus none, there was no association between coffee intake and risk of colorectal cancer (HR, 0.95; 95% CI, 0.65–1.39; *P* for trend, 0.55) for women or men; results were similar for both colon and rectal cancer.

Bidel et al. (2010) examined the association between coffee consumption and risk of colorectal cancer in a randomly selected cohort of Finnish men and women making up 6.6% of the population. After a mean follow-up period of 18 years, the multivariate-adjusted hazard ratio of colorectal cancer incidence for ≥ 10 cups/day of coffee compared with non-drinkers was 0.98 (95% CI, 0.47–2.03) for men (*P* for trend, 0.86), 1.24 (95% CI, 0.49–3.14) for women (*P* for trend, 0.83), and 1.03 (95% CI, 0.58–1.83) for men and women combined (*P* for trend, 0.61).

In the JPHC Study of > 96 000 men and women (Lee et al., 2007a), the multivariate hazard ratio for ≥ 3 cups/day of coffee compared with never drinkers was 0.44 (95% CI, 0.19–1.04; *P* for trend, 0.04). No significant association was found for rectal cancer in women or for colorectal cancer in men.

Simons et al. (2010) evaluated coffee intake in the context of total fluid intake with colorectal cancer within the Netherlands Cohort Study. After 13.3 years of observation, no association was observed between coffee consumption and colorectal cancer, colon cancer overall, or cancer in the proximal or distal colon in women or men. However, a significant positive trend with coffee intake was observed for rectal cancer in men (HR, 1.60; 95% CI, 0.96–2.66) for > 6 cups/day versus ≤ 2 cups/day (*P* for trend, 0.05).

Nilsson et al. (2010) evaluated filtered and boiled coffee consumption and colorectal cancer in a 15-year follow-up of over 60 000 participants in the VIP in Sweden. For subjects consuming ≥ 4 cups/day compared with < 1 cup/per day of coffee, a hazard ratio of 1.43 (95% CI, 0.86–2.38; *P* for trend, 0.168) was reported. The risk was similar for boiled coffee, while for ≥ 4 cups/day of filtered coffee compared with < 1 cup/day the hazard ratio was 0.73 (95% CI, 0.50–1.08; *P* for trend, 0.116).

After 12 years of observation during the Singapore Chinese Health Study (Peterson et al., 2010) of over 60 000 men and women, there was no association or exposure–response relationship between coffee consumption and the risk of colorectal cancer for the entire cohort; multivariate hazard ratio for ≥ 2 cups/day versus < 1 cup/day was reported as 0.90 (95% CI, 0.73–1.11; *P* for trend, 0.31). There was also no association between coffee consumption and cancer of the rectum. However, there was a statistically significant decreased risk for consumption of ≥ 2 cups/day versus < 1 cup/day (HR, 0.56; 95% CI, 0.35–0.90; *P* for trend, 0.01) for ever smokers with advanced colon cancer, and no association among never smokers (*P* for interaction, 0.009).

Sinha et al. (2012) evaluated coffee intakes in relation to colon and rectal cancer in the NIH-AARP Diet and Health Study of 489 706 men and women. Participants who reported drinking ≥ 6 cups/day of coffee (HR, 0.74; 95% CI, 0.61–0.89; *P* for trend, < 0.001) had a lower risk of colon cancer than non-coffee drinkers, particularly of proximal tumours (HR, 0.62; 95% CI, 0.49–0.81; *P* for trend, < 0.0001). Results were similar for drinkers of predominantly caffeinated coffee. There were significant trends for both colon and rectal cancers for decaffeinated coffee drinking, but individual hazard ratios were not significant.

Dominianni et al. (2013) investigated the association between coffee intake and colorectal cancer risk among women and men participating in the PLCO Cancer Screening Trial in the USA. Increasing coffee intake was not associated with a higher risk of colorectal cancer; for consumption of ≥ 4 cups/day versus none, a hazard ratio of 1.08 (95% CI, 0.79–1.48) was reported (*P* for trend, 0.229). Associations were similar for caffeinated and decaffeinated coffee, and were consistently null by cancer site and stage.

In the JACC Study with 58 221 participants (Yamada et al. 2014), drinking > 4 cups/day of coffee versus < 1 cup/day yielded a hazard ratio of 1.79 (95% CI, 1.01–3.18) for men (*P* for trend, 0.03). However, coffee consumption was not associated with an increased risk of colon cancer among women, or with an increased risk of rectal cancer in women or men.

In the EPIC study of more than 500 000 participants in 10 European countries (Dik et al., 2014), median follow-up 11.6 years, the hazard ratio for the association between high coffee consumption (> 625 mL/day) versus none or low consumption and colorectal cancer risk was 1.06 (95% CI, 0.95–1.18; *P* for trend, 0.58) after adjustment for multiple risk factors. Associations were similar for caffeinated and decaffeinated coffee, for colon and rectal cancer, and for subsites within the colon.

Lukic et al. (2016) investigated whether consumption of boiled, filtered, or instant coffee is associated with the risk of developing cancer overall or at four specific sites within the population-based Norwegian Women and Cancer Study. No association between coffee consumption and the risk of colorectal cancer was found, with a hazard ratio of 0.98 (95% CI, 0.72–1.32) for > 7 cups/day (*P* for trend, 0.10).

A pooled analysis (Zhang et al., 2010) of primary data from 13 cohort studies evaluated the relationships between consumption of coffee, tea, and sugar-sweetened carbonated soft drinks and risk of colon cancer. Among 731 441 participants, 5604 incident cases of colon cancer were identified. Compared with non-drinkers of coffee, the pooled multivariable relative risk was 1.07 (95% CI, 0.89–1.30) for coffee consumption of > 1400 g/day (*P* for trend, 0.68). No statistically significant between-studies heterogeneity was observed for the highest category of coffee consumed (*P* for trend, > 0.20), and the associations were not modified by risk factors including sex, BMI, or physical activity (*P* for trend, > 0.05).

2.14.2 Case–control studies

Twenty-eight hospital- and population-based case–control studies in the Americas, Asia, Australia, and Europe were identified. The number of cases varied substantially from < 100 cases to > 3500 cases. Fifteen of these studies found inverse associations between coffee consumption and colorectal cancer (La Vecchia et al., 1988; Lee et al., 1989; Rosenberg et al., 1989; Benito et al., 1990; Kato et al., 1990; Baron et al., 1994; Centonze et al., 1994; Franceschi et al., 1997; Tavani et al., 1997a; Favero et al., 1998; Inoue et al., 1998; Levi et al., 1999; Woolcott et al., 2002; Wang et al., 2013b; Theodoratou et al., 2014). Three studies found null associations between coffee consumption and colorectal cancer overall (Hunter et al., 1980; Fredrikson et al., 1995; Muñoz et al., 1998). Other studies reported null associations only for

colon cancer (Kotake et al., 1995; Slattery et al., 2000) or rectal cancer (Jarebinski et al., 1989). Six studies found evidence of increased risk (Vlajinac et al., 1987; Slattery et al., 1990; Boutron-Ruault et al., 1999; Yeh et al., 2003; Kontou et al., 2013; Green et al., 2014), but in one study this was seen primarily in men (Boutron-Ruault et al., 1999). In two other studies, an increase in odds of coffee consumption was observed for for overall cancer of the large bowel (Jarebinski et al., 1988) and for rectal cancer only (Kotake et al., 1995). However, these positive studies were small in terms of the number of subjects.

2.14.3 Meta-analyses

Seven meta-analyses were available for review (Giovannucci, 1998; Je et al., 2009; Galeone et al., 2010b; Yu et al., 2011; Li et al., 2013c; Tian et al., 2013; Gan et al., 2017). In the most recent meta-analysis including both case–control studies (n = 25) and cohort studies (n = 16) published up until 2012 (Li et al., 2013c), inverse associations with coffee consumption were estimated for colorectal and colon cancer but not rectal cancer. The inverse associations were stronger in case–control studies (e.g. meta-OR, 0.85; 95% CI, 0.75–0.97 for colorectal cancer for the highest levels of consumption versus the lowest) than in cohort studies (e.g. meta-OR, 0.94; 95% CI, 0.88–1.01). Testing and graphical analysis gave no indication of publication bias. A subsequent analysis of the same studies using flexible dose–response models suggested inverse relationships for consumption of > 2 cups/day for both types of study design, although more pronounced for case–control studies (Tian et al., 2013). A later meta-analysis of only cohort studies (n = 19) reported similar results (e.g. meta-RR, 0.98; 95% CI, 0.90–1.06) for highest versus lowest consumption (Gan et al., 2017).

2.15 Cancer of the kidney

Cancer of the kidney comprises different histologic subtypes, with renal cell carcinoma accounting for 90% of cases and transitional cell carcinoma of the renal pelvis accounting for the remainder. The two subtypes likely have different etiologies; renal pelvis cancer has features in common with bladder cancer. Despite this, some studies (particularly older studies) have grouped renal cell carcinoma and renal pelvis cancer together in examining risk factors. Smoking is an established risk factor for both types of kidney cancer, which is significant as a potential confounder given the positive association between smoking and coffee consumption in many populations. Type 2 diabetes, obesity, and hypertension are also risk factors for renal cell carcinoma; this risk is significant given coffee's consistent inverse association with type 2 diabetes risk, and its positive effects on insulin levels and glucose metabolism. Ideally, studies assessing the association between coffee consumption and renal cell carcinoma should adjust for smoking and all of these metabolic factors.

2.15.1 Combined cancer of the kidney

Three cohort studies of total kidney cancer (renal cell carcinoma and renal pelvis combined) have reported data for coffee intake. A Norwegian cohort study (Jacobsen et al., 1986) of 10 517 men (which also recorded information on smoking) found a fairly strong inverse association between coffee intake and total kidney cancer; a relative risk of 0.15 for ≥ 7 cups/day versus ≤ 2 cups/day (P for trend, 0.008) was reported, but was only based on 31 cases. [Results were adjusted only for age in 10-year groups, residence, and smoking status.] Another Norwegian cohort (Stensvold & Jacobsen, 1994) of 43 000 men and women found a suggestive inverse association for total kidney cancer among men; for consumption of ≥ 7 cups/day versus ≤ 2 cups/day, a relative risk

of 0.7 [confidence intervals and *P* values were not presented] and a non-significant trend were reported, based on 30 cases. Only 13 cases were diagnosed in women in this study, and the relative risk for ≥ 5 cups/day versus < 5 cups/day was 1.2 with a non-significant trend. [These results for men and women were adjusted only for age, county of residence, and cigarettes smoked per day.] Finally, the more recent study by Hashibe et al. (2015) in the PLCO Cancer Screening Trial cohort found a non-significant hazard ratio of 0.84 (95% CI, 0.65–1.09) comparing high levels (≥ 2 cups/day) versus low levels (< 1 cup/day) of consumption. For consumption levels of ≥ 4 cups/day, the hazard ratio was 0.43 (95% CI, 0.20–0.93; *P* for trend, 0.10). This analysis included 318 cases and adjusted for sex, race, and smoking. Smoking was adjusted for in considerable detail, but BMI, type 2 diabetes, and hypertension were not considered. [The Hashibe et al. (2015) study was notable for adequate case numbers and adjusting for confounders; however, some key confounders (BMI and hypertension) were not considered. The Norway-based studies of Jacobsen et al. (1986) and Stensvold & Jacobsen (1994) were very limited by low case numbers and a lack of adjustment for risk factors other than age or smoking. All studies were limited by the study of total kidney cancer rather than separating renal cell carcinoma and renal pelvis cancer.]

A meta-analysis of coffee and urologic cancer risk (Huang et al., 2014) included results from Jacobsen et al. (1986), Stensvold & Jacobsen (1994), Washio et al. (2005) [a cohort study of fatal renal cell carcinoma, considered non-informative by the Working Group due to lack of control for smoking], and Lee et al. (2006), a study of renal cell carcinoma risk (discussed in Section 2.15.3 below). Coffee consumption was not associated with risk of cancer of the kidney in this meta-analysis, with a meta-relative risk of 0.95 (95% CI, 0.56–1.59) per increment of 2 cups/day. [The strengths of this meta-analysis included the dose–response meta-analysis. It was however limited by combining studies of total kidney cancer and renal cell carcinoma only, and combining studies of incidence and mortality.]

2.15.2 Renal pelvis cancer

Five case–control studies of coffee drinking and renal pelvis cancer (or renal pelvis plus ureter cancer) were identified. Two were considered non-informative due to a lack of control for smoking (Schmauz & Cole, 1974; Armstrong et al., 1976). Another study by Wakai et al. (2004) was considered non-informative for renal pelvis cancer as it included mainly bladder cancer cases and only 5 cases of renal pelvis cancer.

The remaining two studies were US population-based case–control studies; one was based in Minneapolis–St Paul (McLaughlin et al., 1983) and the other in Los Angeles County (Ross et al., 1989). With 74 cases, McLaughlin et al. found no association between coffee intake and renal pelvis cancer risk in either men or women, adjusting for smoking, with an odds ratio for ≥ 7 cups/day versus none of 1.1 for men (95% CI, 0.2–8.7) and 0.4 for women (95% CI, 0.03–4.0). With 187 cases, Ross et al. found a suggestion of a positive association between coffee intake and renal pelvis cancer risk when smoking and several other risk factors were adjusted for, with an odds ratio of 1.8 for ≥ 7 cups/day compared with none and a *P* value for trend of 0.11 [confidence intervals for the relative risk were not presented]. [Both studies benefited from the use of population-based controls. They were however disadvantaged by limited precision and limited adjustment for confounders.]

2.15.3 Renal cell carcinoma

Twelve case–control studies of the association between coffee consumption and renal cell carcinoma were identified. Four were considered non-informative due to a lack of control

for smoking (Armstrong et al., 1976; Goodman et al., 1986; Yu et al., 1986; Talamini et al., 1990), and one (Bravi et al., 2007b) was not considered as a more detailed report (Montella et al., 2009) from the same case–control study was available. An additional study (McCredie et al., 1988) was considered non-informative as no analytical results were presented for coffee, only a statement that there was no association.

Of the remaining case–control studies, two were hospital-based and three were population-based. The hospital-based case-control studies (Benhamou et al., 1993; Montella et al., 2009) found no associations between coffee intake and risk of renal cell carcinoma. Of the population-based case–control studies, one in Denmark (Mellemgaard et al., 1994) found a significant inverse association with renal cell carcinoma risk in men, but not in women; for > 8 cups/day versus < 2 cups/day, the odds ratio was 0.4 (95% CI, 0.2–1.0; *P* for trend, 0.02) for men and 1.5 (95% CI, 0.5–4.8; *P* for trend, 0.07) for women. A study in Sweden (Mucci et al., 2004) found association for the highest versus lowest quartile with an odds ratio of 0.7 (95% CI, 0.4–1.1). A large study in Canada (Hu et al., 2009) with 1138 cases and 5039 controls found a significant positive association with an odds ratio of 1.33 (95% CI, 1.07–1.66) for those consuming > 2.5 cups/day compared with < 0.5 cups/day, and a significant trend across categories; for an increment of 1 cup/day, an odds ratio of 1.06 (95% CI, 1.02–1.10; *P* for trend, 0.006) was reported. All three studies adjusted for smoking and BMI along with other covariates. [These studies benefited from adjustment for both smoking and BMI; however, all except for Hu et al. had low case numbers and wide confidence intervals.]

There were four cohort studies of the association between coffee drinking and risk of renal cell carcinoma. One cohort study on the risk of fatal renal cell carcinoma was considered non-informative due to a lack of control for smoking (Washio et al., 2005). Another of these was a pooled analysis of individual-level data from 13 prospective studies (Lee et al., 2007b). This analysis included 1478 incident renal cell cancer cases, and yielded a hazard ratio of 0.84 (95% CI, 0.67–1.05; *P* for trend, 0.22) among individuals consuming ≥ 3 cups/day of coffee compared with < 1 cup/day (Lee et al., 2007b). The inverse association for coffee was statistically significant among women (HR, 0.71; 95% CI, 0.53–0.97; *P* for trend, 0.07) but was not observed among men (RR, 1.00; 95% CI, 0.73–1.37; *P* for trend, 0.83), although the test for interaction was not significant. Smoking, BMI, hypertension, and alcohol intake, among other possible confounders, were adjusted for across studies. In an analysis stratified by smoking status, there was a significant inverse association among never smokers for an increment of 1 cup/day (RR, 0.91; 95% CI, 0.84–0.98) and no association among former (RR, 0.98; 95% CI, 0.90–1.06) and current (RR, 0.98; 95% CI, 0.90–1.08) smokers. [The strengths of this study were the large number of cases and adequate adjustment for covariates including smoking, BMI, and hypertension.]

A separate publication (Lee et al., 2006) from the NHS and HPFS studies, both of which were included in the pooled analysis, was also considered informative as it was based on updated coffee intake information collected every 4 years rather than simply baseline information. Follow-up was 20 years for NHS and 14 years for HPFS. The pooled hazard ratio across the two cohorts, based on 248 cases, was 0.84 (95% CI, 0.54–1.30; *P* for trend, 0.41) for ≥ 3 cups/day compared with < 1 cup/month. [This study benefited from its prospective design, multiple assessments of coffee intake over time, and complete adjustment for confounders. The number of cases was only 248 however, even with two large cohorts combined.]

Two other cohort studies were not included in the pooled analysis (Nilsson et al., 2010; Allen et al., 2011). A Norwegian cohort (Nilsson et al., 2010) of 64 604 men and women with median

follow-up of 6 years and 56 cases of renal cell carcinoma found a strong inverse association between total coffee consumption (filtered and boiled coffee combined); a hazard ratio for drinking coffee ≥ 4 occasions/day compared with < 1 occasion/per day of 0.30 (95% CI, 0.11–0.79; *P* for trend, 0.009) was reported. Results were adjusted for age, sex, BMI, smoking, education, and physical activity. [The strengths of this study included its prospective design. It was however limited by the low number of cases and lack of clarity regarding occasions/day versus cups/day.]

A cohort of 779 369 women in the UK (Allen et al., 2011) including 588 cases of renal cell carcinoma (average follow-up 5.2 years) found no association between coffee intake and risk, adjusting for region, socioeconomic status, BMI, and smoking. The relative risk per drink per day was 0.98 (95% CI, 0.94–1.02; *P* for trend, 0.4). [This study benefited from being a very large prospective cohort with a large number of cases. The results were not adjusted for hypertension, however. The Working Group also noted that results as presented were difficult to interpret.]

2.16 Malignant melanoma

Thirteen pertinent studies – seven cohort studies and six case–control studies – reporting results for an association between coffee consumption and risk of cutaneous malignant melanoma were available for review. Most of the studies presented relative risks for consumption of coffee overall, others for caffeinated and decaffeinated coffee separately, and a few presented results for caffeinated coffee only. Where available, the results for total coffee are provided in the following.

Of the cohort studies, one early small study (19 cases) reported a non-significantly elevated relative risk (2.63) [95% CI not given] for ≥ 7 cups/day versus ≤ 2 cups/day after adjustment for age, sex, and residence (*P* for trend, 0.16) (Jacobsen et al., 1986). Three others presented largely null associations (Paffenbarger et al., 1978; Nilsson et al., 2010; Wu et al., 2015a). Another three cohort studies reported inverse associations in part or overall with coffee intake. In a 12-year follow-up of over 50 000 Norwegians enrolled in a cardiovascular screening programme (Veierød et al., 1997), the adjusted incidence rate ratio (IRR) among women was 0.4 (95% CI, 0.2–0.9) for ≥ 7 cups/day versus ≤ 2 cups/day (*P* for trend, < 0.01), while the corresponding incidence rate ratio for men was 1.5 (95% CI, 0.5–4.6). Another cohort study included women from the NHS and NHS-II and men from the HPFS after 20–32 years of follow-up (Wu et al., 2015b). The adjusted pooled hazard ratio for women and men in all three studies for > 2 cups/day caffeinated coffee vs never was 0.85 (95% CI, 0.66–1.11; *P* for trend, 0.18). The corresponding hazard ratio in the two women's cohorts combined was 0.76 (95% CI, 0.64–0.89; *P* for trend, 0.001), and a hazard ratio of 1.1 (95% CI, 0.86–1.3) was reported for men (*P* for trend, 0.55). The other cohort study reported a hazard ratio of 0.80 (95% CI, 0.68–0.93) for ≥ 4 cups/day versus no coffee (*P* for trend, 0.01) in a large cohort of non-Hispanic white men and women in the US (Loftfield et al., 2015). Wu et al. (2015a, b) and Loftfield et al. (2015) examined associations between risk of cutaneous malignant melanoma and caffeinated and decaffeinated coffee separately, and reported null associations.

Of the six case–control studies, four reported no association (Gallagher et al., 1986; Green et al., 1986; Holman et al., 1986; Naldi et al., 2004). Two reported reduced risks of cutaneous malignant melanoma with increased coffee consumption. In the first of these, the adjusted odds ratio for high coffee intake (not defined) was 0.7 (95% CI, 0.5–1.0; *P* for trend, 0.02) (Osterlind et al., 1988), while the second reported an odds ratio of 0.46 (95% CI, 0.31–0.68) for ≥ 7 cups/week versus < 7 cups/week (Fortes et al., 2013).

Three meta-analyses of this association were available (Wang et al., 2016; Liu et al., 2016;

Yew et al., 2016). The most comprehensive meta-analysis, judged to be highest in quality by the Working Group, included 12 studies with a total of 832 956 participants and 7140 cases of cutaneous malignant melanoma (Wang et al., 2016). The summary relative risk for the highest versus lowest category of total coffee consumption was 0.80 (95% CI, 0.69–0.93); a linear inverse dose–response relationship was evident, where the meta-relative risk decreased by 3% with each additional 1 cup/day. Sex-specific summary relative risks for the highest versus lowest category of total coffee consumption were 0.75 (95% CI, 0.63–0.89) for women and 1.11 (95% CI, 0.91–1.36) for men.

[The strengths of the studies on cutaneous malignant melanoma included large size, long follow-up periods, pathological confirmation of cases, adjustment for relevant confounders (including sun-related variables in the three most recent cohort studies and all case–control studies), updated data on coffee intake in most cohort studies, sex-specific analyses, and investigation of exposure–response associations. However, the metric of coffee intake varied among studies, and the reference category in some studies included people who drank 2 cups/day of coffee, which could lead to an underestimation of an association. The four earliest cohort studies did not adjust for sun-related variables.]

One case–control study of the association between coffee consumption and incidence of uveal melanoma was identified (Holly et al., 1990). After adjustment for host factors and sun exposure, an increased risk of this cancer was observed among coffee drinkers: the odds ratio for ≥ 6 cups/day was 2.32 (95% CI, 1.53–3.53; *P* for trend, < 0.001). However, while increased odds ratios were seen for both sexes separately, a significant increase was seen only in women. There was a higher than usual proportion of non-coffee drinkers among women in the control group.

2.17 Non-melanoma cancer of the skin

Three cohort studies and three case–control studies have reported on the association between coffee consumption and risk of non-melanoma skin cancer.

Two cohort studies found evidence of inverse associations. The first reported a relative risk for non-melanoma skin cancer overall of 0.56 [95% CI not given] for ≥ 7 cups/day versus ≤ 2 cups/day (*P* for trend, 0.01) (Jacobsen et al., 1986). The second reported a reduction in risk of basal cell carcinoma only, with adjusted relative risks of 0.79 (95% CI, 0.74–0.85; *P* for trend, < 0.0001) in women and 0.90 (95% CI, 0.80–1.01; *P* for trend, 0.003) in men for > 3 cups/day caffeinated coffee versus < 1 cup/month (Song et al., 2012). A third cohort study found no association between intake of caffeinated or decaffeinated coffee and the incidence of basal or squamous cell carcinoma (Miura et al., 2014).

The three case–control studies (Corona et al., 2001; Milán et al., 2003; Ferrucci et al., 2014) investigated basal cell carcinoma only, and did not report any significant positive or inverse association with coffee drinking.

[The strengths of the studies of non-melanoma skin cancer included large sample size, long cohort follow-up, pathological confirmation of cases, adjustment for relevant confounders (including sun-related variables in cohort studies published since 2010 and all case–control studies), and investigation of exposure–response associations. However, the methods of exposure assessment differed among studies and two hospital-based case–control studies used patients with other dermatological conditions as controls.]

2.18 Adult cancer of the brain

Four prospective cohort studies and two hospital-based case–control studies reported findings for adult brain or central nervous system

tumours in relation to coffee consumption. One cohort study (Efird et al., 2004) reported a positive association of glioma with consumption of ≥ 7 cups/day of coffee (OR, 1.7; 95% CI, 0.8–3.6; *P* for trend, 0.17). A second study (Holick et al., 2010) reported a reduced odds ratio for glioma among consumers of ≥ 4 cups/day, (OR 0.80, 95% CI, 0.54–1.17; *P* for trend, 0.51) with no evidence of a dose–response relationship. The two other cohort studies reported no association of glioma or meningioma with coffee intake (Michaud et al., 2010; Dubrow et al., 2012). Neither of the case–control studies found any association (Burch et al., 1987; Hochberg et al., 1990). A meta-analysis of these six studies concluded there was no association between coffee intake and brain tumour (glioma) risk, with a summary odds ratio of 1.01 (95% CI, 0.83–1.22) for the highest versus lowest levels of intake (Malerba et al., 2013b).

2.19 Adult haematopoietic cancers

The association between coffee consumption and several adult haematopoietic cancers has been assessed in a single cohort study (Ma et al., 2010) and eight reports from five case–control studies (Oleske et al., 1985; Franceschi et al., 1989; Tavani et al., 1994, 1997b; Chiu et al., 2008; Balasubramaniam et al., 2013a, b; Parodi et al., 2016).

Ma et al. (2010) assessed the etiological role of coffee drinking in acute myeloid leukaemia in the US-based NIH-AARP Diet and Health Study during 1995–2003. Significant inverse associations were observed between AML and and tertile of coffee intake, with risk estimates of approximately 0.6 in in each tertile and no evidence of dose-response (*P* for trend, 0.24).

Of the five case–control studies that assessed adult leukaemia or non-Hodgkin lymphoma (NHL), including hairy cell leukaemia (HCL), multiple myeloma (MM), and chronic lymphocytic leukaemia (CLL), odds ratios were < 1 in a hospital-based study of leukaemia and NHL in India (Balasubramaniam et al., 2013a, b), in population-based studies of NHL and HCL in the USA (Oleske et al., 1985; Chiu et al., 2008), and in an investigation of lymphoid and myeloid cancers in Italy (Parodi et al., 2016). A hospital-based case–control study in a different region of Italy reported non-significantly increased risk of multiple myeloma, but not other NHL or Hodgkin lymphoma, among higher coffee consumers (Franceschi et al., 1989; Tavani et al., 1994, 1997b). [In general, the assessment of coffee consumption in these studies was crude, that is, via an unvalidated questionnaire.]

2.20 Other cancers

Systematic searches for epidemiological studies that reported associations between coffee drinking and cancer outcomes identified studies of several other cancer sites. Most were case–control studies that reported associations for a wide range of exposures and risk factors, and were not specifically focused on coffee consumption. The number of studies available for each of these cancers was small.

2.20.1 Cancer of the thyroid

For thyroid cancer, case–control studies on potential risk factors in Germany, Greece, and Japan reported inverse associations with coffee drinking (Linos et al., 1989; Takezaki et al., 1996b; Frentzel-Beyme & Helmert, 2000), while a similar study in the USA reported no association (Mack et al., 2002). A pooled analysis of nine thyroid cancer case–control studies from several countries (Mack et al., 2003), most of which did not report data for coffee consumption in the original publications, found no association with coffee drinking (RR, 0.9; 95% CI, 0.8–1.1). A cohort study of the relationship between thyroid cancer and coffee consumption in Japan reported no association in women and a non-statistically

significant positive association (RR, 1.18) among men drinking ≥ 1 cup/day (Michikawa et al., 2011).

2.20.2 Cancer of the vulva

Three hospital-based case–control studies on risk factors for cancer of the vulva reported on associations with coffee consumption. Two studies in the USA reported statistically significant increased risks (OR, 1.72–2.42) for women drinking > 4–5 cups/day of coffee (Mabuchi et al.,1985a; Sturgeon et al., 1991), while a study in Italy reported no association with regular coffee drinking (Parazzini et al., 1995).

2.20.3 Cancer of the breast in men

The association between coffee drinking and breast cancer in men was examined in three studies of dietary and lifestyle risk factors in the USA and Canada. Two studies reported inverse associations between the amount of coffee consumed and the risk of breast cancer in men; these associations were statistically significant for coffee consumption overall in a Canadian study (Johnson et al., 2002) and for total caffeinated coffee consumption in a study in the USA (Rosenblatt et al., 1999). In another study in the USA, Mabuchi et al. (1985b) reported no difference in the proportions of coffee drinkers among cases and controls, but measures of relative risk were not reported.

2.20.4 Soft tissue sarcoma

A hospital-based case–control study of risk factors for soft tissue sarcoma in Italy reported no association with frequency of coffee consumption (Tavani et al., 1997b).

2.20.5 Cancer of the testes

A prospective study of pregnant women in the USA found an inverse, non-statistically significant association between mothers' coffee drinking during pregnancy and development of testicular cancer in their sons (Mongraw-Chaffin et al., 2009).

2.21 All cancers combined

The association between coffee consumption and the occurrence of all cancers combined has been investigated in a number of prospective cohort studies from Europe, Japan, and North America. Most studies found no association between coffee consumption and incidence (e.g. Jacobsen et al., 1986; Stensvold & Jacobsen, 1994; Nilsson et al., 2010; Floegel et al., 2012; von Ruesten et al., 2013; Hashibe et al., 2015) or mortality (e.g. Andersen et al., 2006; Happonen et al., 2008; Sugiyama et al., 2010; Tamakoshi et al., 2011; Gardener at al., 2013; Löf et al., 2015; Saito et al., 2015) of all cancers combined, with no exposure–response trends and no statistically significant overall increase or decrease in risk among the heaviest consumers. One study reported non-significantly increased mortality from all cancers among men who drank ≥ 6 cups/day of coffee with a significant trend (HR, 1.08; 95% CI, 0.98–1.19; *P* for trend, 0.02), but no association among women (Freedman et al., 2012). Another study that found no association with cancer mortality in the full cohort reported increased mortality in a subgroup of women aged > 50 years consuming > 5 cups/day of coffee (RR, 1.40; 95% CI, 1.05–1.89) (Löf et al., 2015). A statistically significant inverse exposure–response trend (*P* for trend, 0.01) was reported for cancer mortality among women, but not men, in a study by Tamakoshi et al. (2011).

Two meta-analyses of prospective studies estimated null associations between coffee consumption and mortality from all cancers combined (Malerba et al., 2013a; Crippa et al., 2014).

References

Agudo A, González CA, Marcos G, Sanz M, Saigi E, Verge J, et al. (1992). Consumption of alcohol, coffee, and tobacco, and gastric cancer in Spain. *Cancer Causes Control*, 3(2):137–43. doi:10.1007/BF00051653 PMID:1562703

Ainslie-Waldman CE, Koh WP, Jin A, Yeoh KG, Zhu F, Wang R, et al. (2014). Coffee intake and gastric cancer risk: the Singapore Chinese health study. *Cancer Epidemiol Biomarkers Prev*, 23(4):638–47. doi:10.1158/1055-9965.EPI-13-0886 PMID:24608187

Akdaş A, Kirkali Z, Bilir N (1990). Epidemiological case-control study on the etiology of bladder cancer in Turkey. *Eur Urol*, 17(1):23–6. doi:10.1159/000463993 PMID:2318234

Aleksandrova K, Bamia C, Drogan D, Lagiou P, Trichopoulou A, Jenab M, et al. (2015). The association of coffee intake with liver cancer risk is mediated by biomarkers of inflammation and hepatocellular injury: data from the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*, 102(6):1498–508. doi:10.3945/ajcn.115.116095 PMID:26561631

Allen NE, Balkwill A, Beral V, Green J, Reeves G; Million Women Study Collaborators (2011). Fluid intake and incidence of renal cell carcinoma in UK women. *Br J Cancer*, 104(9):1487–92. doi:10.1038/bjc.2011.90 PMID:21407222

Andersen LF, Jacobs DR Jr, Carlsen MH, Blomhoff R (2006). Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. *Am J Clin Nutr*, 83(5):1039–46. doi:10.1093/ajcn/83.5.1039 PMID:16685044

Arab L, Su LJ, Steck SE, Ang A, Fontham ET, Bensen JT, et al. (2012). Coffee consumption and prostate cancer aggressiveness among African and Caucasian Americans in a population-based study. *Nutr Cancer*, 64(5):637–42. doi:10.1080/01635581.2012.676144 PMID:22564042

Armstrong B, Garrod A, Doll R (1976). A retrospective study of renal cancer with special reference to coffee and animal protein consumption. *Br J Cancer*, 33(2):127–36. doi:10.1038/bjc.1976.17 PMID:944046

Axelsson G, Liljeqvist T, Andersson L, Bergman B, Rylander R (1996). Dietary factors and lung cancer among men in west Sweden. *Int J Epidemiol*, 25(1):32–9. doi:10.1093/ije/25.1.32 PMID:8666501

Ayari I, Fedeli U, Saguem S, Hidar S, Khlifi S, Pavanello S (2013). Role of CYP1A2 polymorphisms in breast cancer risk in women. *Mol Med Rep*, 7(1):280–6. doi:10.3892/mmr.2012.1164 PMID:23128882

Azeem K, Sevčíková J, Tomášková H, Horáková D, Procházka V, Martínek A, et al. (2013). [Pancreatic cancer and lifestyle factors] *Klin Onkol*, 26(4):257–62. [Czech] doi:10.14735/amko2013257 PMID:23961856

Bae JM, Li ZM, Shin MH, Kim DH, Lee MS, Ahn YO (2013). Pulmonary tuberculosis and lung cancer risk in current smokers: the Seoul Male Cancer Cohort Study. *J Korean Med Sci*, 28(6):896–900. doi:10.3346/jkms.2013.28.6.896 PMID:23772155

Baghurst PA, McMichael AJ, Slavotinek AH, Baghurst KI, Boyle P, Walker AM (1991). A case-control study of diet and cancer of the pancreas. *Am J Epidemiol*, 134(2):167–79. doi:10.1093/oxfordjournals.aje.a116069 PMID:1862800

Baker JA, Beehler GP, Sawant AC, Jayaprakash V, McCann SE, Moysich KB (2006). Consumption of coffee, but not black tea, is associated with decreased risk of premenopausal breast cancer. *J Nutr*, 136(1):166–71. doi:10.1093/jn/136.1.166 PMID:16365077

Baker JA, Boakye K, McCann SE, Beehler GP, Rodabaugh KJ, Villella JA, et al. (2007). Consumption of black tea or coffee and risk of ovarian cancer. *Int J Gynecol Cancer*, 17(1):50–4. doi:10.1111/j.1525-1438.2006.00773.x PMID:17291231

Baker JA, McCann SE, Reid ME, Nowell S, Beehler GP, Moysich KB (2005). Associations between black tea and coffee consumption and risk of lung cancer among current and former smokers. *Nutr Cancer*, 52(1):15–21. doi:10.1207/s15327914nc5201_2 PMID:16090999

Balasubramaniam G, Saoba S, Sarade M, Pinjare S (2013a). Case-control study of risk factors for non-Hodgkin lymphoma in Mumbai, India. *Asian Pac J Cancer Prev*, 14(2):775–80. doi:10.7314/APJCP.2013.14.2.775 PMID:23621236

Balasubramaniam G, Saoba SL, Sarhade MN, Kolekar SA (2013b). Lifestyle factors including diet and leukemia development: a case-control study from Mumbai, India. *Asian Pac J Cancer Prev*, 14(10):5657–61. doi:10.7314/APJCP.2013.14.10.5657 PMID:24289558

Balbi JC, Larrinaga MT, De Stefani E, Mendilaharsu M, Ronco AL, Boffetta P, et al. (2001). Foods and risk of bladder cancer: a case-control study in Uruguay. *Eur J Cancer Prev*, 10(5):453–8. doi:10.1097/00008469-200110000-00009 PMID:11711760

Bamia C, Lagiou P, Jenab M, Trichopoulou A, Fedirko V, Aleksandrova K, et al. (2015). Coffee, tea and decaffeinated coffee in relation to hepatocellular carcinoma in a European population: multicentre, prospective cohort study. *Int J Cancer*, 136(8):1899–908. doi:10.1002/ijc.29214 PMID:25219573

Bandera EV, Williams-King MG, Sima C, Bayuga-Miller S, Pulick K, Wilcox H, et al. (2010). Coffee and tea consumption and endometrial cancer risk in a population-based study in New Jersey. *Cancer Causes Control*, 21(9):1467–73. doi:10.1007/s10552-010-9575-9 PMID:20467800

Baron JA, Gerhardsson de Verdier M, Ekbom A (1994). Coffee, tea, tobacco, and cancer of the large bowel. *Cancer Epidemiol Biomarkers Prev*, 3(7):565–70. PMID:7827586

Benhamou S, Lenfant MH, Ory-Paoletti C, Flamant R (1993). Risk factors for renal-cell carcinoma in a French case-control study. *Int J Cancer*, 55(1):32–6. doi:10.1002/ijc.2910550107 PMID:8344750

Benito E, Obrador A, Stiggelbout A, Bosch FX, Mulet M, Muñoz N, et al. (1990). A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer*, 45(1):69–76. doi:10.1002/ijc.2910450114 PMID:2298506

Bento MJ, Barros H (1997). [Life style and occupational risk factors in bladder carcinoma]. *Acta Med Port*, 10(1):39–45. [Portuguese] PMID:9245175

Bhoo-Pathy N, Peeters P, van Gils C, Beulens JW, van der Graaf Y, Bueno-de-Mesquita B, et al. (2010). Coffee and tea intake and risk of breast cancer. *Breast Cancer Res Treat*, 121(2):461–7. doi:10.1007/s10549-009-0583-y PMID:19847643

Bhoo-Pathy N, Peeters PH, Uiterwaal CS, Bueno-de-Mesquita HB, Bulgiba AM, Bech BH, et al. (2015). Coffee and tea consumption and risk of pre- and post-menopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Breast Cancer Res*, 17(1):15. doi:10.1186/s13058-015-0521-3 PMID:25637171

Bhoo-Pathy N, Uiterwaal CS, Dik VK, Jeurnink SM, Bech BH, Overvad K, et al. (2013). Intake of coffee, decaffeinated coffee, or tea does not affect risk for pancreatic cancer: results from the European Prospective Investigation into Nutrition and Cancer Study. *Clin Gastroenterol Hepatol*, 11(11):1486–92. doi:10.1016/j.cgh.2013.05.029 PMID:23756220

Biazevic MG, Toporcov TN, Antunes JL, Rotundo LD, Brasileiro RS, de Carvalho MB, et al. (2011). Cumulative coffee consumption and reduced risk of oral and oropharyngeal cancer. *Nutr Cancer*, 63(3):350–6. doi:10.1080/01635581.2011.536065 PMID:21462087

Bidel S, Hu G, Jousilahti P, Antikainen R, Pukkala E, Hakulinen T, et al. (2010). Coffee consumption and risk of colorectal cancer. *Eur J Clin Nutr*, 64(9):917–23. doi:10.1038/ejcn.2010.103 PMID:20571499

Bidel S, Hu G, Jousilahti P, Pukkala E, Hakulinen T, Tuomilehto J (2013). Coffee consumption and risk of gastric and pancreatic cancer–a prospective cohort study. *Int J Cancer*, 132(7):1651–9. doi:10.1002/ijc.27773 PMID:22886387

Bissonauth V, Shatenstein B, Fafard E, Maugard C, Robidoux A, Narod S, et al. (2009). Risk of breast cancer among French-Canadian women, noncarriers of more frequent BRCA1/2 mutations and consumption of total energy, coffee, and alcohol. *Breast J*, 15(Suppl 1):S63–71. doi:10.1111/j.1524-4741.2009.00806.x PMID:19775332

Boada LD, Henríquez-Hernández LA, Navarro P, Zumbado M, Almeida-González M, Camacho M, et al. (2015). Exposure to polycyclic aromatic hydrocarbons (PAHs) and bladder cancer: evaluation from a gene-environment perspective in a hospital-based case-control study in the Canary Islands (Spain). *Int J Occup Environ Health*, 21(1):23–30. doi:10.1179/2049396714Y.0000000085 PMID:25291984

Boggs DA, Palmer JR, Stampfer MJ, Spiegelman D, Adams-Campbell LL, Rosenberg L (2010). Tea and coffee intake in relation to risk of breast cancer in the Black Women's Health Study. *Cancer Causes Control*, 21(11):1941–8. doi:10.1007/s10552-010-9622-6 PMID:20680436

Bonaventure A, Rudant J, Goujon-Bellec S, Orsi L, Leverger G, Baruchel A, et al. (2013). Childhood acute leukemia, maternal beverage intake during pregnancy, and metabolic polymorphisms. *Cancer Causes Control*, 24(4):783–93. doi:10.1007/s10552-013-0161-9 PMID:23404349

Bosetti C, La Vecchia C, Talamini R, Negri E, Levi F, Dal Maso L, et al. (2002). Food groups and laryngeal cancer risk: a case-control study from Italy and Switzerland. *Int J Cancer*, 100(3):355–60. doi:10.1002/ijc.10485 PMID:12115553

Bosire C, Stampfer MJ, Subar AF, Wilson KM, Park Y, Sinha R (2013). Coffee consumption and the risk of overall and fatal prostate cancer in the NIH-AARP Diet and Health Study. *Cancer Causes Control*, 24(8):1527–34. doi:10.1007/s10552-013-0229-6 PMID:23681472

Botelho F, Lunet N, Barros H (2006). Coffee and gastric cancer: systematic review and meta-analysis. *Cad Saude Publica*, 22(5):889–900. doi:10.1590/S0102-311X2006000500002 PMID:16680342

Boutron-Ruault MC, Senesse P, Faivre J, Chatelain N, Belghiti C, Méance S (1999). Foods as risk factors for colorectal cancer: a case-control study in Burgundy (France). *Eur J Cancer Prev*, 8(3):229–35. doi:10.1097/00008469-199906000-00011 PMID:10443952

Braem MG, Onland-Moret NC, Schouten LJ, Tjønneland A, Hansen L, Dahm CC, et al. (2012). Coffee and tea consumption and the risk of ovarian cancer: a prospective cohort study and updated meta-analysis. *Am J Clin Nutr*, 95(5):1172–81. doi:10.3945/ajcn.111.026393 PMID:22440851

Bravi F, Bosetti C, Scotti L, Talamini R, Montella M, Ramazzotti V, et al. (2007b). Food groups and renal cell carcinoma: a case-control study from Italy. *Int J Cancer*, 120(3):681–5. doi:10.1002/ijc.22225 PMID:17058282

Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, et al. (2007a). Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. *Hepatology*, 46(2):430–5. doi:10.1002/hep.21708 PMID:17580359

Bravi F, Bosetti C, Tavani A, Gallus S, La Vecchia C (2013). Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. *Clin Gastroenterol Hepatol*,

11(11):1413–1421.e1, e1. doi:10.1016/j.cgh.2013.04.039 PMID:23660416

Bravi F, Bosetti C, Tavani A, La Vecchia C (2009). Coffee drinking and hepatocellular carcinoma: an update. *Hepatology*, 50(4):1317–8. doi:10.1002/hep.23272 PMID:19790082

Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, et al. (2009a). Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies. *Am J Obstet Gynecol*, 200(2):130–5. doi:10.1016/j.ajog.2008.10.032 PMID:19110217

Bravi F, Scotti L, Bosetti C, Zucchetto A, Talamini R, Montella M, et al. (2009b). Food groups and endometrial cancer risk: a case-control study from Italy. *Am J Obstet Gynecol*, 200(3):293.e1–7. doi:10.1016/j.ajog.2008.09.015 PMID:19091304

Bravi F, Tavani A, Bosetti C, Boffetta P, La Vecchia C (2017). Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. *Eur J Cancer Prev*, 26(5):368–77. doi:10.1097/CEJ.0000000000000252 PMID:27111112

Bravo P, del Rey J, Sánchez J, Conde M (1986). [Coffee and analgesics as risk factors for cancer of the bladder]. *Arch Esp Urol*, 39(5):337–41. [Spanish] PMID:3753045

Bross ID, Tidings J (1973). Another look at coffee drinking and cancer of the urinary bladder. *Prev Med*, 2(3):445–51. doi:10.1016/0091-7435(73)90040-6 PMID:4774263

Brown LM, Swanson CA, Gridley G, Swanson GM, Schoenberg JB, Greenberg RS, et al. (1995). Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst*, 87(2):104–9. doi:10.1093/jnci/87.2.104 PMID:7707381

Bruemmer B, White E, Vaughan TL, Cheney CL (1997). Fluid intake and the incidence of bladder cancer among middle-aged men and women in a three-county area of western Washington. *Nutr Cancer*, 29(2):163–8. doi:10.1080/01635589709514619 PMID:9427981

Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, Runia S, Boyle P (1992). Lifetime consumption of alcoholic beverages, tea and coffee and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. *Int J Cancer*, 50(4):514–22. doi:10.1002/ijc.2910500403 PMID:1537615

Bundgaard T, Wildt J, Frydenberg M, Elbrønd O, Nielsen JE (1995). Case-control study of squamous cell cancer of the oral cavity in Denmark. *Cancer Causes Control*, 6(1):57–67. doi:10.1007/BF00051681 PMID:7718736

Bunin GR, Gyllstrom ME, Brown JE, Kahn EB, Kushi LH (2001). Recall of diet during a past pregnancy. *Am J Epidemiol*, 154(12):1136–42. doi:10.1093/aje/154.12.1136 PMID:11744519

Bunin GR, Kramer S, Marrero O, Meadows AT (1987). Gestational risk factors for Wilms' tumor: results of a case-control study. *Cancer Res*, 47(11):2972–7. PMID:3032418

Bunin GR, Kuijten RR, Boesel CP, Buckley JD, Meadows AT (1994). Maternal diet and risk of astrocytic glioma in children: a report from the Childrens Cancer Group (United States and Canada) *Cancer Causes Control*, 5(2):177–87. doi:10.1007/BF01830264 PMID:8167265

Bunin GR, Kuijten RR, Buckley JD, Rorke LB, Meadows AT (1993). Relation between maternal diet and subsequent primitive neuroectodermal brain tumors in young children. *N Engl J Med*, 329(8):536–41. doi:10.1056/NEJM199308193290804 PMID:8336753

Burch JD, Craib KJ, Choi BC, Miller AB, Risch HA, Howe GR (1987). An exploratory case-control study of brain tumors in adults. *J Natl Cancer Inst*, 78(4):601–9. PMID:3104645

Byers T, Marshall J, Graham S, Mettlin C, Swanson M (1983). A case-control study of dietary and nondietary factors in ovarian cancer. *J Natl Cancer Inst*, 71(4):681–6. PMID:6578362

Cao S, Liu L, Yin X, Wang Y, Liu J, Lu Z (2014). Coffee consumption and risk of prostate cancer: a meta-analysis of prospective cohort studies. *Carcinogenesis*, 35(2):256–61. doi:10.1093/carcin/bgt482 PMID:24343360

Castellsagué X, Muñoz N, De Stefani E, Victora CG, Castelletto R, Rolón PA (2000). Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. *Int J Cancer*, 88(4):658–64. doi:10.1002/1097-0215(20001115)88:4<658::AID-IJC22>3.0.CO;2-T PMID:11058886

Centonze S, Boeing H, Leoci C, Guerra V, Misciagna G (1994). Dietary habits and colorectal cancer in a low-risk area. Results from a population-based case-control study in southern Italy. *Nutr Cancer*, 21(3):233–46. doi:10.1080/01635589409514322 PMID:8072877

Chan JM, Wang F, Holly EA (2009). Sweets, sweetened beverages, and risk of pancreatic cancer in a large population-based case-control study. *Cancer Causes Control*, 20(6):835–46. doi:10.1007/s10552-009-9323-1 PMID:19277880

Chen CJ, Wu HY, Chuang YC, Chang AS, Luh KT, Chao HH, et al. (1990). Epidemiologic characteristics and multiple risk factors of lung cancer in Taiwan. *Anticancer Res*, 10(4):971–6. PMID:2382996

Chen J, Long S (2014). Tea and coffee consumption and risk of laryngeal cancer: a systematic review meta-analysis. *PLoS One*, 9(12):e112006. doi:10.1371/journal.pone.0112006 PMID:25502726

Chen YC, Chiang CI, Lin RS, Pu YS, Lai MK, Sung FC (2005). Diet, vegetarian food and prostate carcinoma among men in Taiwan. *Br J Cancer*, 93(9):1057–61. doi:10.1038/sj.bjc.6602809 PMID:16205693

Chen YK, Lee CH, Wu IC, Liu JS, Wu DC, Lee JM, et al. (2009). Food intake and the occurrence of squamous cell carcinoma in different sections of the esophagus in Taiwanese men. *Nutrition*, 25(7-8):753–61. doi:10.1016/j.nut.2009.02.002 PMID:19394796

Cheng J, Su H, Zhu R, Wang X, Peng M, Song J, et al. (2014). Maternal coffee consumption during pregnancy and risk of childhood acute leukemia: a metaanalysis. *Am J Obstet Gynecol*, 210(2):151.e1–10. doi:10.1016/j.ajog.2013.09.026 PMID:24060443

Chiu BC, Dave BJ, Ward MH, Fought AJ, Hou L, Jain S, et al. (2008). Dietary factors and risk of t(14;18)-defined subgroups of non-Hodgkin lymphoma. *Cancer Causes Control*, 19(8):859–67. doi:10.1007/s10552-008-9148-3 PMID:18386141

Chiu YL, Wang XR, Qiu H, Yu IT (2010). Risk factors for lung cancer: a case-control study in Hong Kong women. *Cancer Causes Control*, 21(5):777–85. doi:10.1007/s10552-010-9506-9 PMID:20084541

Chow WH, Swanson CA, Lissowska J, Groves FD, Sobin LH, Nasierowska-Guttmejer A, et al. (1999). Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland. *Int J Cancer*, 81(6):871–6. doi:10.1002/(SICI)1097-0215(19990611)81:6<871::AID-IJC6>3.0.CO;2-# PMID:10362132

Chyou PH, Nomura AM, Stemmermann GN (1993). A prospective study of diet, smoking, and lower urinary tract cancer. *Ann Epidemiol*, 3(3):211–6. doi:10.1016/1047-2797(93)90021-U PMID:8275191

Ciccone G, Vineis P (1988). Coffee drinking and bladder cancer. *Cancer Lett*, 41(1):45–52. doi:10.1016/0304-3835(88)90053-5 PMID:3390802

Claude J, Kunze E, Frentzel-Beyme R, Paczkowski K, Schneider J, Schubert H (1986). Life-style and occupational risk factors in cancer of the lower urinary tract. *Am J Epidemiol*, 124(4):578–89. doi:10.1093/oxfordjournals.aje.a114430 PMID:3752052

Clavel F, Benhamou E, Auquier A, Tarayre M, Flamant R (1989). Coffee, alcohol, smoking and cancer of the pancreas: a case-control study. *Int J Cancer*, 43(1):17–21. doi:10.1002/ijc.2910430105 PMID:2910828

Clavel J, Cordier S (1991). Coffee consumption and bladder cancer risk. *Int J Cancer*, 47(2):207–12. doi:10.1002/ijc.2910470208 PMID:1988365

Cole P (1971). Coffee-drinking and cancer of the lower urinary tract. *Lancet*, 1(7713):1335–7. doi:10.1016/S0140-6736(71)91890-3 PMID:4103399

Cordier S, Iglesias MJ, Le Goaster C, Guyot MM, Mandereau L, Hemon D (1994). Incidence and risk factors for childhood brain tumors in the Ile de France. *Int J Cancer*, 59(6):776–82. doi:10.1002/ijc.2910590612 PMID:7989118

Corona R, Dogliotti E, D'Errico M, Sera F, Iavarone I, Baliva G, et al. (2001). Risk factors for basal cell carcinoma in a Mediterranean population: role of recreational sun exposure early in life. *Arch Dermatol*, 137(9):1162–8. doi:10.1001/archderm.137.9.1162 PMID:11559211

Correa P, Fontham E, Pickle LW, Chen V, Lin YP, Haenszel W (1985). Dietary determinants of gastric cancer in south Louisiana inhabitants. *J Natl Cancer Inst*, 75(4):645–54. PMID:3862897

Covolo L, Placidi D, Gelatti U, Carta A, Scotto Di Carlo A, Lodetti P, et al. (2008). Bladder cancer, GSTs, NAT1, NAT2, SULT1A1, XRCC1, XRCC3, XPD genetic polymorphisms and coffee consumption: a case-control study. *Eur J Epidemiol*, 23(5):355–62. doi:10.1007/s10654-008-9238-2 PMID:18365755

Cramer DW, Welch WR, Hutchison GB, Willett W, Scully RE (1984). Dietary animal fat in relation to ovarian cancer risk. *Obstet Gynecol*, 63(6):833–8. PMID:6728366

Crippa A, Discacciati A, Larsson SC, Wolk A, Orsini N (2014). Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: a dose-response meta-analysis. *Am J Epidemiol*, 180(8):763–75. doi:10.1093/aje/kwu194 PMID:25156996

Cuzick J, Babiker AG (1989). Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. *Int J Cancer*, 43(3):415–21. doi:10.1002/ijc.2910430312 PMID:2925272

D'Avanzo B, La Vecchia C, Franceschi S, Negri E, Talamini R, Buttino I (1992). Coffee consumption and bladder cancer risk. *Eur J Cancer*, 28A(8-9):1480–4. doi:10.1016/0959-8049(92)90548-G PMID:1515271

De Stefani E, Boffetta P, Deneo-Pellegrini H, Correa P, Ronco AL, Brennan P, et al. (2007). Non-alcoholic beverages and risk of bladder cancer in Uruguay. *BMC Cancer*, 7(1):57. doi:10.1186/1471-2407-7-57 PMID:17394632

De Stefani E, Correa P, Boffetta P, Deneo-Pellegrini H, Ronco AL, Mendilaharsu M (2004). Dietary patterns and risk of gastric cancer: a case-control study in Uruguay. *Gastric Cancer*, 7(4):211–20. doi:10.1007/s10120-004-0295-2 PMID:15616769

Demirel F, Cakan M, Yalçinkaya F, Topcuoglu M, Altug U (2008). The association between personal habits and bladder cancer in Turkey. *Int Urol Nephrol*, 40(3):643–7. doi:10.1007/s11255-008-9331-1 PMID:18247151

Deneo-Pellegrini H, Ronco AL, De Stefani E, Boffetta P, Correa P, Mendilaharsu M, et al. (2012). Food groups and risk of prostate cancer: a case-control study in Uruguay. *Cancer Causes Control*, 23(7):1031–8. doi:10.1007/s10552-012-9968-z PMID:22544454

Deng W, Yang H, Wang J, Cai J, Bai Z, Song J, et al. (2016). Coffee consumption and the risk of incident gastric cancer–A meta-analysis of prospective cohort studies. *Nutr Cancer*, 68(1):40–7. doi:10.1080/01635581.2016.1115093 PMID:26710312

Dik VK, Bueno-de-Mesquita HB, Van Oijen MG, Siersema PD, Uiterwaal CS, Van Gils CH, et al. (2014). Coffee and tea consumption, genotype-based CYP1A2 and NAT2 activity and colorectal cancer risk-results from

the EPIC cohort study. *Int J Cancer*, 135(2):401–12. doi:10.1002/ijc.28655 PMID:24318358

Discacciati A, Orsini N, Andersson SO, Andrén O, Johansson JE, Mantzoros CS, et al. (2013). Coffee consumption and risk of localized, advanced and fatal prostate cancer: a population-based prospective study. *Ann Oncol*, 24(7):1912–8. doi:10.1093/annonc/mdt105 PMID:23508823

Discacciati A, Orsini N, Wolk A (2014). Coffee consumption and risk of nonaggressive, aggressive and fatal prostate cancer–a dose-response meta-analysis. *Ann Oncol*, 25(3):584–91. doi:10.1093/annonc/mdt420 PMID:24276028

Dominianni C, Huang WY, Berndt S, Hayes RB, Ahn J (2013). Prospective study of the relationship between coffee and tea with colorectal cancer risk: the PLCO Cancer Screening Trial. *Br J Cancer*, 109(5):1352–9. doi:10.1038/bjc.2013.434 PMID:23907431

Donato F, Boffetta P, Fazioli R, Aulenti V, Gelatti U, Porru S (1997). Bladder cancer, tobacco smoking, coffee and alcohol drinking in Brescia, northern Italy. *Eur J Epidemiol*, 13(7):795–800. doi:10.1023/A:1007453322899 PMID:9384269

Dong J, Zou J, Yu XF (2011). Coffee drinking and pancreatic cancer risk: a meta-analysis of cohort studies. *World J Gastroenterol*, 17(9):1204–10. doi:10.3748/wjg.v17.i9.1204 PMID:21448427

Dubrow R, Darefsky AS, Freedman ND, Hollenbeck AR, Sinha R (2012). Coffee, tea, soda, and caffeine intake in relation to risk of adult glioma in the NIH-AARP Diet and Health Study. *Cancer Causes Control*, 23(5):757–68. doi:10.1007/s10552-012-9945-6 PMID:22457000

Dunham LJ, Rabson AS, Stewart HL, Frank AS, Young JL (1968). Rates, interview, and pathology study of cancer of the urinary bladder in New Orleans, Louisiana. *J Natl Cancer Inst*, 41(3):683–709. PMID:5677316

Efird JT, Friedman GD, Sidney S, Klatsky A, Habel LA, Udaltsova NV, et al. (2004). The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors. *J Neurooncol*, 68(1):57–69. doi:10.1023/B:NEON.0000024746.87666.ed PMID:15174522

Ellison LF (2000). Tea and other beverage consumption and prostate cancer risk: a Canadian retrospective cohort study. *Eur J Cancer Prev*, 9(2):125–30. doi:10.1097/00008469-200004000-00009 PMID:10830580

Escolar Pujolar A, González CA, López-Abente G, Errezola M, Izarzugaza I, Nebot M, et al. (1993). Bladder cancer and coffee consumption in smokers and non-smokers in Spain. *Int J Epidemiol*, 22(1):38–44. doi:10.1093/ije/22.1.38 PMID:8449645

Escribano Uzcudun A, Rabanal Retolaza I, García Grande A, Miralles Olivar L, García García A, González Barón M, et al. (2002). Pharyngeal cancer prevention: evidence from a case–control study involving 232 consecutive patients. *J Laryngol Otol*, 116(7):523–31. PMID:12238672

Ewertz M, Gill C (1990). Dietary factors and breast-cancer risk in Denmark. *Int J Cancer*, 46(5):779–84. doi:10.1002/ijc.2910460505 PMID:2228305

Fagherazzi G, Touillaud MS, Boutron-Ruault MC, Clavel-Chapelon F, Romieu I (2011). No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study. *Public Health Nutr*, 14(7):1315–20. doi:10.1017/S1368980011000371 PMID:21466740

Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF Jr (1988). Life-style risk factors for pancreatic cancer in Louisiana: a case-control study. *Am J Epidemiol*, 128(2):324–36. doi:10.1093/oxfordjournals.aje.a114972 PMID:3394699

Fang X, Wei J, He X, An P, Wang H, Jiang L, et al. (2015). Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. *Eur J Cancer*, 51(18):2820–32. doi:10.1016/j.ejca.2015.09.010 PMID:26589974

Farrow DC, Davis S (1990). Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *Int J Cancer*, 45(5):816–20. doi:10.1002/ijc.2910450504 PMID:2335385

Favero A, Franceschi S, La Vecchia C, Negri E, Conti E, Montella M (1998). Meal frequency and coffee intake in colon cancer. *Nutr Cancer*, 30(3):182–5. doi:10.1080/01635589809514661 PMID:9631488

Ferrucci LM, Cartmel B, Molinaro AM, Leffell DJ, Bale AE, Mayne ST (2014). Tea, coffee, and caffeine and early-onset basal cell carcinoma in a case-control study. *Eur J Cancer Prev*, 23(4):296–302. doi:10.1097/CEJ.0000000000000037 PMID:24841641

Floegel A, Pischon T, Bergmann MM, Teucher B, Kaaks R, Boeing H (2012). Coffee consumption and risk of chronic disease in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Germany study. *Am J Clin Nutr*, 95(4):901–8. doi:10.3945/ajcn.111.023648 PMID:22338038

Folsom AR, McKenzie DR, Bisgard KM, Kushi LH, Sellers TA (1993). No association between caffeine intake and postmenopausal breast cancer incidence in the Iowa Women's Health Study. *Am J Epidemiol*, 138(6):380–3. doi:10.1093/oxfordjournals.aje.a116870 PMID:8213743

Fortes C, Mastroeni S, Boffetta P, Antonelli G, Pilla MA, Bottà G, et al. (2013). The protective effect of coffee consumption on cutaneous melanoma risk and the role of GSTM1 and GSTT1 polymorphisms. *Cancer Causes Control*, 24(10):1779–87. doi:10.1007/s10552-013-0255-4 PMID:23860951

Franceschi S, Barra S, La Vecchia C, Bidoli E, Negri E, Talamini R (1992). Risk factors for cancer of the tongue and the mouth. A case-control study

from northern Italy. *Cancer*, 70(9):2227–33. doi:10.1002/1097-0142(19921101)70:9<2227::AID-CNCR2820700902>3.0.CO;2-Z PMID:1394055

Franceschi S, Favero A, Conti E, Talamini R, Volpe R, Negri E, et al. (1999). Food groups, oils and butter, and cancer of the oral cavity and pharynx. *Br J Cancer*, 80(3-4):614–20. doi:10.1038/sj.bjc.6690400 PMID:10408875

Franceschi S, Favero A, La Vecchia C, Negri E, Conti E, Montella M, et al. (1997). Food groups and risk of colorectal cancer in Italy. *Int J Cancer*, 72(1):56–61. doi:10.1002/(SICI)1097-0215(19970703)72:1<56::AID-IJC8>3.0.CO;2-3 PMID:9212223

Franceschi S, Favero A, La Vecchia C, Negri E, Dal Maso L, Salvini S, et al. (1995). Influence of food groups and food diversity on breast cancer risk in Italy. *Int J Cancer*, 63(6):785–9. doi:10.1002/ijc.2910630606 PMID:8847134

Franceschi S, Serraino D, Carbone A, Talamini R, La Vecchia C (1989). Dietary factors and non-Hodgkin's lymphoma: a case-control study in the northeastern part of Italy. *Nutr Cancer*, 12(4):333–41. doi:10.1080/01635588909514034 PMID:2608538

Franco EL, Kowalski LP, Oliveira BV, Curado MP, Pereira RN, Silva ME, et al. (1989). Risk factors for oral cancer in Brazil: a case-control study. *Int J Cancer*, 43(6):992–1000. doi:10.1002/ijc.2910430607 PMID:2732011

Fraumeni JF Jr, Scotto J, Dunham LJ (1971). Coffee-drinking and bladder cancer. *Lancet*, 2(7735):1204 doi:10.1016/S0140-6736(71)90523-X PMID:4108010

Fredrikson M, Hardell L, Bengtsson N, Axelson O (1995). Colon-cancer and dietary habits - a case-control study. *Int J Oncol*, 7(1):133–41. PMID:21552818

Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R (2012). Association of coffee drinking with total and cause-specific mortality. *N Engl J Med*, 366(20):1891–904. doi:10.1056/NEJMoa1112010 PMID:22591295

Frentzel-Beyme R, Helmert U (2000). Association between malignant tumors of the thyroid gland and exposure to environmental protective and risk factors. *Rev Environ Health*, 15(3):337–58. doi:10.1515/REVEH.2000.15.3.337 PMID:11048335

Friberg E, Orsini N, Mantzoros CS, Wolk A (2009). Coffee drinking and risk of endometrial cancer–a population-based cohort study. *Int J Cancer*, 125(10):2413–7. doi:10.1002/ijc.24543 PMID:19585497

Friedman GD, van den Eeden SK (1993). Risk factors for pancreatic cancer: an exploratory study. *Int J Epidemiol*, 22(1):30–7. doi:10.1093/ije/22.1.30 PMID:8449644

Galanis DJ, Kolonel LN, Lee J, Nomura A (1998). Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. *Int J Epidemiol*, 27(2):173–80. doi:10.1093/ije/27.2.173 PMID:9602395

Galarraga V, Boffetta P (2016). Coffee drinking and risk of lung cancer – a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 25(6):951–7. doi:10.1158/1055-9965.EPI-15-0727 PMID:27021045

Galeone C, Tavani A, Pelucchi C, Turati F, Winn DM, Levi F, et al. (2010a). Coffee and tea intake and risk of head and neck cancer: pooled analysis in the international head and neck cancer epidemiology consortium. *Cancer Epidemiol Biomarkers Prev*, 19(7):1723–36. doi:10.1158/1055-9965.EPI-10-0191 PMID:20570908

Galeone C, Turati F, La Vecchia C, Tavani A (2010b). Coffee consumption and risk of colorectal cancer: a meta-analysis of case-control studies. *Cancer Causes Control*, 21(11):1949–59. doi:10.1007/s10552-010-9623-5 PMID:20680435

Gallagher RP, Elwood JM, Hill GB (1986). Risk factors for cutaneous malignant melanoma: the Western Canada Melanoma Study. *Recent Results Cancer Res*, 102:38–55. doi:10.1007/978-3-642-82641-2_4 PMID:3738186

Gallus S, Bertuzzi M, Tavani A, Bosetti C, Negri E, La Vecchia C, et al. (2002). Does coffee protect against hepatocellular carcinoma? *Br J Cancer*, 87(9):956–9. doi:10.1038/sj.bjc.6600582 PMID:12434283

Gallus S, Foschi R, Talamini R, Altieri A, Negri E, Franceschi S, et al. (2007). Risk factors for prostate cancer in men aged less than 60 years: a case-control study from Italy. *Urology*, 70(6):1121–6. doi:10.1016/j.urology.2007.07.020 PMID:18158031

Gallus S, Tramacere I, Tavani A, Bosetti C, Bertuccio P, Negri E, et al. (2009). Coffee, black tea and risk of gastric cancer. *Cancer Causes Control*, 20(8):1303–8. doi:10.1007/s10552-009-9350-y PMID:19430969

Gan Y, Wu J, Zhang S, Li L, Cao S, Mkandawire N, et al. (2017). Association of coffee consumption with risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Oncotarget*, 8(12):18699–711. doi:10.18632/oncotarget.8627 PMID:27078843

Ganesh B, Saoba SL, Sarade MN, Pinjari SV (2011b). Risk factors for prostate cancer: An hospital-based case-control study from Mumbai, India. *Indian J Urol*, 27(3):345–50. doi:10.4103/0970-1591.85438 PMID:22022057

Ganesh B, Sushama S, Monika S, Suvarna P (2011a). A case-control study of risk factors for lung cancer in Mumbai, India. *Asian Pac J Cancer Prev*, 12(2):357–62. PMID:21545194

Ganmaa D, Willett WC, Li TY, Feskanich D, van Dam RM, Lopez-Garcia E, et al. (2008). Coffee, tea, caffeine and risk of breast cancer: a 22-year follow-up. *Int J Cancer*, 122(9):2071–6. doi:10.1002/ijc.23336 PMID:18183588

Gardener H, Rundek T, Wright CB, Elkind MS, Sacco RL (2013). Coffee and tea consumption are inversely associated with mortality in a multiethnic urban population. *J Nutr*, 143(8):1299–308. doi:10.3945/jn.112.173807 PMID:23784068

Garidou A, Tzonou A, Lipworth L, Signorello LB, Kalapothaki V, Trichopoulos D (1996). Life-style factors and medical conditions in relation to esophageal cancer by histologic type in a low-risk population. *Int J Cancer*, 68(3):295–9. doi:10.1002/(SICI)1097-0215(19961104)68:3<295::AID-IJC5>3.0.CO;2-X PMID:8903469

Gavrilyuk O, Braaten T, Skeie G, Weiderpass E, Dumeaux V, Lund E (2014). High coffee consumption and different brewing methods in relation to postmenopausal endometrial cancer risk in the Norwegian women and cancer study: a population-based prospective study. *BMC Womens Health*, 14(1):48. doi:10.1186/1472-6874-14-48 PMID:24666820

Gelatti U, Covolo L, Franceschini M, Pirali F, Tagger A, Ribero ML, et al.; Brescia HCC Study Group (2005). Coffee consumption reduces the risk of hepatocellular carcinoma independently of its aetiology: a case-control study. *J Hepatol*, 42(4):528–34. doi:10.1016/j.jhep.2004.11.039 PMID:15868652

Genkinger JM, Li R, Spiegelman D, Anderson KE, Albanes D, Bergkvist L, et al. (2012). Coffee, tea, and sugar-sweetened carbonated soft drink intake and pancreatic cancer risk: a pooled analysis of 14 cohort studies. *Cancer Epidemiol Biomarkers Prev*, 21(2):305–18. doi:10.1158/1055-9965.EPI-11-0945-T PMID:22194529

Geoffroy-Perez B, Cordier S (2001). Fluid consumption and the risk of bladder cancer: results of a multicenter case-control study. *Int J Cancer*, 93(6):880–7. doi:10.1002/ijc.1411 PMID:11519052

Geybels MS, Neuhouser ML, Stanford JL (2013). Associations of tea and coffee consumption with prostate cancer risk. *Cancer Causes Control*, 24(5):941–8. doi:10.1007/s10552-013-0170-8 PMID:23412806

Ghadirian P, Simard A, Baillargeon J (1991). Tobacco, alcohol, and coffee and cancer of the pancreas. A population-based, case-control study in Quebec, Canada. *Cancer*, 67(10):2664–70. doi:10.1002/1097-0142(19910515)67:10<2664::AID-CNCR2820671043>3.0.CO;2-K PMID:2015568

Ghadirian P, Simard A, Baillargeon J (1993). A population-based case-control study of cancer of the bile ducts and gallbladder in Quebec, Canada. *Rev Epidemiol Sante Publique*, 41(2):107–12. PMID:8493388

Gierach GL, Freedman ND, Andaya A, Hollenbeck AR, Park Y, Schatzkin A, et al. (2012). Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort. *Int J Cancer*, 131(2):452–60. doi:10.1002/ijc.26372 PMID:22020403

Giovannucci E (1998). Meta-analysis of coffee consumption and risk of colorectal cancer. *Am J Epidemiol*, 147(11):1043–52. doi:10.1093/oxfordjournals.aje.a009398 PMID:9620048

Giri A, Sturgeon SR, Luisi N, Bertone-Johnson E, Balasubramanian R, Reeves KW (2011). Caffeinated coffee, decaffeinated coffee and endometrial cancer risk: a prospective cohort study among US postmenopausal women. *Nutrients*, 3(11):937–50. doi:10.3390/nu3110937 PMID:22254087

Gold EB, Gordis L, Diener MD, Seltser R, Boitnott JK, Bynum TE, et al. (1985). Diet and other risk factors for cancer of the pancreas. *Cancer*, 55(2):460–7. doi:10.1002/1097-0142(19850115)55:2<460::AID-CNCR2820550229>3.0.CO;2-V PMID:3965101

Goldstein HR (1982). No association found between coffee and cancer of the pancreas. *N Engl J Med*, 306(16):997. doi:10.1056/NEJM198204223061624 PMID:7062988

González CA, López-Abente G, Errezola M, Castejón J, Estrada A, Garcia-Milá M, et al. (1985). Occupation, tobacco use, coffee, and bladder cancer in the county of Mataro (Spain). *Cancer*, 55(9):2031–4. doi:10.1002/1097-0142(19850501)55:9<2031::AID-CNCR2820550934>3.0.CO;2-I PMID:3978583

Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ, et al. (1997). Diet, body size, physical activity, and the risk of endometrial cancer. *Cancer Res*, 57(22):5077–85. PMID:9371506

Goodman MT, Morgenstern H, Wynder EL (1986). A case-control study of factors affecting the development of renal cell cancer. *Am J Epidemiol*, 124(6):926–41. doi:10.1093/oxfordjournals.aje.a114482 PMID:3776975

Goodman MT, Tung KH, McDuffie K, Wilkens LR, Donlon TA (2003). Association of caffeine intake and CYP1A2 genotype with ovarian cancer. *Nutr Cancer*, 46(1):23–9. doi:10.1207/S15327914NC4601_03 PMID:12925300

Gorham ED, Garland CF, Garland FC, Benenson AS, Cottrell L (1988). Coffee and pancreatic cancer in a rural California county. *West J Med*, 148(1):48–53. PMID:3277336

Gosvig CF, Kjaer SK, Blaakær J, Høgdall E, Høgdall C, Jensen A (2015). Coffee, tea, and caffeine consumption and risk of epithelial ovarian cancer and borderline ovarian tumors: results from a Danish case-control study. *Acta Oncol*, 54(8):1144–51. doi:10.3109/0284186X.2014.1001035 PMID:25629440

Goto R, Masuoka H, Yoshida K, Mori M, Miyake H (1990). [A case control study of cancer of the pancreas]. *Gan No Rinsho*, (Spec No):344–50. [Japanese] PMID:2313889

Green A, Bain C, McLennan R, Siskind V (1986). Risk factors for cutaneous melanoma in Queensland. *Recent Results Cancer Res*, 102:76–97. doi:10.1007/978-3-642-82641-2_6 PMID:3738188

Green CJ, de Dauwe P, Boyle T, Tabatabaei SM, Fritschi L, Heyworth JS (2014). Tea, coffee, and milk consumption and colorectal cancer risk. *J Epidemiol*, 24(2):146–53. doi:10.2188/jea.JE20130063 PMID:24531002

Greenop KR, Miller M, Attia J, Ashton LJ, Cohn R, Armstrong BK, et al. (2014). Maternal consumption of coffee and tea during pregnancy and risk of childhood

brain tumors: results from an Australian case-control study. *Cancer Causes Control*, 25(10):1321–7. doi:10.1007/s10552-014-0437-8 PMID:25030503

Grönberg H, Damber L, Damber JE (1996). Total food consumption and body mass index in relation to prostate cancer risk: a case-control study in Sweden with prospectively collected exposure data. *J Urol*, 155(3):969–74. doi:10.1016/S0022-5347(01)66360-2 PMID:8583620

Gronwald J, Byrski T, Huzarski T, Cybulski C, Sun P, Tulman A, et al. (2006). Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. *Breast Cancer Res Treat*, 95(2):105–9. doi:10.1007/s10549-005-9051-5 PMID:16261399

Guertin KA, Freedman ND, Loftfield E, Graubard BI, Caporaso NE, Sinha R (2016). Coffee consumption and incidence of lung cancer in the NIH-AARP Diet and Health Study. *Int J Epidemiol*, 45(3):929–39. doi:10.1093/ije/dyv104 PMID:26082405

Gullo L, Pezzilli R, Morselli-Labate AM; Italian Pancreatic Cancer Study Group (1995). Coffee and cancer of the pancreas: an Italian multicenter study. *Pancreas*, 11(3):223–9. doi:10.1097/00006676-199510000-00002 PMID:8577674

Gunter MJ, Schaub JA, Xue X, Freedman ND, Gaudet MM, Rohan TE, et al. (2012). A prospective investigation of coffee drinking and endometrial cancer incidence. *Int J Cancer*, 131(4):E530–6. doi:10.1002/ijc.26482 PMID:22021096

Hansson LE, Nyrén O, Bergström R, Wolk A, Lindgren A, Baron J, et al. (1993). Diet and risk of gastric cancer. A population-based case-control study in Sweden. *Int J Cancer*, 55(2):181–9. doi:10.1002/ijc.2910550203 PMID:8370614

Happonen P, Läärä E, Hiltunen L, Luukinen H (2008). Coffee consumption and mortality in a 14-year follow-up of an elderly northern Finnish population. *Br J Nutr*, 99(6):1354–61. doi:10.1017/S0007114507871650 PMID:18062826

Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH (1997). Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev*, 6(12):1081–6. PMID:9419407

Hartge P, Hoover R, West DW, Lyon JL (1983). Coffee drinking and risk of bladder cancer. *J Natl Cancer Inst*, 70(6):1021–6. PMID:6574270

Hartge P, Lesher LP, McGowan L, Hoover R (1982). Coffee and ovarian cancer. *Int J Cancer*, 30(4):531–2. doi:10.1002/ijc.2910300422 PMID:7141746

Hartman TJ, Tangrea JA, Pietinen P, Malila N, Virtanen M, Taylor PR, et al. (1998). Tea and coffee consumption and risk of colon and rectal cancer in middle-aged Finnish men. *Nutr Cancer*, 31(1):41–8. doi:10.1080/01635589809514676 PMID:9682247

Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, et al. (2015). Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. *Br J Cancer*, 113(5):809–16. doi:10.1038/bjc.2015.276 PMID:26291054

Heck JE, Sapkota A, Vendhan G, Roychowdhury S, Dikshit RP, Jetly DH, et al. (2008). Dietary risk factors for hypopharyngeal cancer in India. *Cancer Causes Control*, 19(10):1329–37. doi:10.1007/s10552-008-9204-z PMID:18704720

Heuch I, Kvåle G, Jacobsen BK, Bjelke E (1983). Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. *Br J Cancer*, 48(5):637–43. doi:10.1038/bjc.1983.245 PMID:6685527

Hiatt RA, Klatsky AL, Armstrong MA (1988). Pancreatic cancer, blood glucose and beverage consumption. *Int J Cancer*, 41(6):794–7. doi:10.1002/ijc.2910410603 PMID:3372055

Hildebrand JS, Patel AV, McCullough ML, Gaudet MM, Chen AY, Hayes RB, et al. (2013). Coffee, tea, and fatal oral/pharyngeal cancer in a large prospective US cohort. *Am J Epidemiol*, 177(1):50–8. doi:10.1093/aje/kws222 PMID:23230042

Hirose K, Niwa Y, Wakai K, Matsuo K, Nakanishi T, Tajima K (2007). Coffee consumption and the risk of endometrial cancer: Evidence from a case-control study of female hormone-related cancers in Japan. *Cancer Sci*, 98(3):411–5. doi:10.1111/j.1349-7006.2007.00391.x PMID:17270030

Hirvonen T, Mennen LI, de Bree A, Castetbon K, Galan P, Bertrais S, et al. (2006). Consumption of antioxidant-rich beverages and risk for breast cancer in French women. *Ann Epidemiol*, 16(7):503–8. doi:10.1016/j.annepidem.2005.09.011 PMID:16406814

Hochberg F, Toniolo P, Cole P, Salcman M (1990). Nonoccupational risk indicators of glioblastoma in adults. *J Neurooncol*, 8(1):55–60. doi:10.1007/BF00182087 PMID:2319291

Holick CN, Smith SG, Giovannucci E, Michaud DS (2010). Coffee, tea, caffeine intake, and risk of adult glioma in three prospective cohort studies. *Cancer Epidemiol Biomarkers Prev*, 19(1):39–47. doi:10.1158/1055-9965.EPI-09-0732 PMID:20056621

Holly EA, Aston DA, Char DH, Kristiansen JJ, Ahn DK (1990). Uveal melanoma in relation to ultraviolet light exposure and host factors. *Cancer Res*, 50(18):5773–7. PMID:2393851

Holman CD, Armstrong BK, Heenan PJ, Blackwell JB, Cumming FJ, English DR, et al. (1986). The causes of malignant melanoma: results from the West Australian Lions Melanoma Research Project. *Recent Results Cancer Res*, 102:18–37. doi:10.1007/978-3-642-82641-2_3 PMID:3738185

Hoshiyama Y, Sasaba T (1992). A case-control study of single and multiple stomach cancers in Saitama Prefecture, Japan. *Jpn J Cancer Res*, 83(9):937–43. doi:10.1111/j.1349-7006.1992.tb02004.x PMID:1429203

Howe GR, Burch JD, Miller AB, Cook GM, Estève J, Morrison B, et al. (1980). Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *J Natl Cancer Inst*, 64(4):701–13. PMID:6928984

Høyer AP, Engholm G (1992). Serum lipids and breast cancer risk: a cohort study of 5,207 Danish women. *Cancer Causes Control*, 3(5):403–8. doi:10.1007/BF00051352 PMID:1525320

Hsieh CC, MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G (1986). Coffee and pancreatic cancer (Chapter 2) *N Engl J Med*, 315(9):587–9. doi:10.1056/NEJM198608283150918 PMID:3736647

Hsieh CC, Thanos A, Mitropoulos D, Deliveliotis C, Mantzoros CS, Trichopoulos D (1999). Risk factors for prostate cancer: a case-control study in Greece. *Int J Cancer*, 80(5):699–703. doi:10.1002/(SICI)1097-0215(19990301)80:5<699::AID-IJC12>3.0.CO;2-7 PMID:10048970

Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, et al. (1990). Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. *Cancer Res*, 50(21):6836–40. PMID:2208150

Hu G, Tuomilehto J, Pukkala E, Hakulinen T, Antikainen R, Vartiainen E, et al. (2008). Joint effects of coffee consumption and serum gamma-glutamyltransferase on the risk of liver cancer. *Hepatology*, 48(1):129–36. doi:10.1002/hep.22320 PMID:18537182

Hu J, Mao Y, DesMeules M, Csizmadi I, Friedenreich C, Mery L; Canadian Cancer Registries Epidemiology Research Group (2009). Total fluid and specific beverage intake and risk of renal cell carcinoma in Canada. *Cancer Epidemiol*, 33(5):355–62. doi:10.1016/j.canep.2009.10.004 PMID:19896918

Hu J, Mao Y, Dryer D, White K; Canadian Cancer Registries Epidemiology Research Group (2002). Risk factors for lung cancer among Canadian women who have never smoked. *Cancer Detect Prev*, 26(2):129–38. doi:10.1016/S0361-090X(02)00038-7 PMID:12102147

Huang TB, Guo ZF, Zhang XL, Zhang XP, Liu H, Geng J, et al. (2014). Coffee consumption and urologic cancer risk: a meta-analysis of cohort studies. *Int Urol Nephrol*, 46(8):1481–93. doi:10.1007/s11255-014-0699-9 PMID:24677003

Hunter K, Linn MW, Harris R (1980). Dietary patterns and cancer of the digestive tract in older patients. *J Am Geriatr Soc*, 28(9):405–9. doi:10.1111/j.1532-5415.1980.tb01107.x PMID:7410764

IARC (1991). Coffee, tea, mate, methylxanthines and methylglyoxal. *IARC Monogr Eval Carcinog Risks Hum*, 51:41–199. Available from: http://publications.iarc.fr/69 PMID:1674554

Icli F, Akbulut H, Yalcin B, Ozdemir F, Isıkdogan A, Hayran M, et al. (2011). Education, economic status and other risk factors in gastric cancer: "a case-control study of Turkish Oncology Group". *Med Oncol*, 28(1):112–20. doi:10.1007/s12032-009-9406-6 PMID:20054718

Inoue M, Kurahashi N, Iwasaki M, Shimazu T, Tanaka Y, Mizokami M, et al.; Japan Public Health Center-Based Prospective Study Group (2009). Effect of coffee and green tea consumption on the risk of liver cancer: cohort analysis by hepatitis virus infection status. *Cancer Epidemiol Biomarkers Prev*, 18(6):1746–53. doi:10.1158/1055-9965.EPI-08-0923 PMID:19505908

Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, et al. (1998). Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. *Cancer Causes Control*, 9(2):209–16. doi:10.1023/A:1008890529261 PMID:9578298

Inoue M, Yoshimi I, Sobue T, Tsugane S; JPHC Study Group (2005). Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan. *J Natl Cancer Inst*, 97(4):293–300. doi:10.1093/jnci/dji040 PMID:15713964

Isaksson B, Jonsson F, Pedersen NL, Larsson J, Feychting M, Permert J (2002). Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer*, 98(3):480–2. doi:10.1002/ijc.10256 PMID:11920604

Iscovich J, Castelletto R, Estève J, Muñoz N, Colanzi R, Coronel A, et al. (1987). Tobacco smoking, occupational exposure and bladder cancer in Argentina. *Int J Cancer*, 40(6):734–40. doi:10.1002/ijc.2910400604 PMID:3692621

Ishitani K, Lin J, Manson JE, Buring JE, Zhang SM (2008). Caffeine consumption and the risk of breast cancer in a large prospective cohort of women. *Arch Intern Med*, 168(18):2022–31. doi:10.1001/archinte.168.18.2022 PMID:18852405

Iwasaki M, Inoue M, Sasazuki S, Sawada N, Yamaji T, Shimazu T, et al. ; Japan Public Health Center-Based Prospective Study Group (2010). Green tea drinking and subsequent risk of breast cancer in a population-based cohort of Japanese women. *Breast Cancer Res*, 12(5):R88. doi:10.1186/bcr2756 PMID:22889409

Jacobsen BK, Bjelke E, Kvåle G, Heuch I (1986). Coffee drinking, mortality, and cancer incidence: results from a Norwegian prospective study. *J Natl Cancer Inst*, 76(5):823–31. PMID:3457969

Jain M, Howe GR, St Louis P, Miller AB (1991). Coffee and alcohol as determinants of risk of pancreas cancer: a case-control study from Toronto. *Int J Cancer*, 47(3):384–9. doi:10.1002/ijc.2910470313 PMID:1993545

Jain MG, Hislop GT, Howe GR, Burch JD, Ghadirian P (1998). Alcohol and other beverage use and prostate cancer risk among Canadian men. *Int J Cancer*, 78(6):707–11. doi:10.1002/(SICI)1097-0215(19981209)78:6<707::AID-IJC7>3.0.CO;2-2 PMID:9833763

Jain MG, Howe GR, Rohan TE (2000). Nutritional factors and endometrial cancer in Ontario, Canada. *Cancer Contr*, 7(3):288–96. doi:10.1177/107327480000700312 PMID:10832115

Jang ES, Jeong SH, Lee SH, Hwang SH, Ahn SY, Lee J, et al. (2013). The effect of coffee consumption on the development of hepatocellular carcinoma in hepatitis B virus endemic area. *Liver Int*, 33(7):1092–9. doi:10.1111/liv.12186 PMID:23651110

Jarebinski M, Adanja B, Vlajinac H (1989). Case-control study of relationship of some biosocial correlates to rectal cancer patients in Belgrade, Yugoslavia. *Neoplasma*, 36(3):369–74. PMID:2739817

Jarebinski M, Vlajinac H, Adanja B (1988). Biosocial and other characteristics of the large bowel cancer patients in Belgrade (Yugoslavia). *Arch Geschwulstforsch*, 58(6):411–7. PMID:3223792

Je Y, Giovannucci E (2012). Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. *Int J Cancer*, 131(7):1700–10. doi:10.1002/ijc.27408 PMID:22190017

Je Y, Hankinson SE, Tworoger SS, De Vivo I, Giovannucci E (2011). A prospective cohort study of coffee consumption and risk of endometrial cancer over a 26-year follow-up. *Cancer Epidemiol Biomarkers Prev*, 20(12):2487–95. doi:10.1158/1055-9965.EPI-11-0766 PMID:22109346

Je Y, Liu W, Giovannucci E (2009). Coffee consumption and risk of colorectal cancer: a systematic review and meta-analysis of prospective cohort studies. *Int J Cancer*, 124(7):1662–8. doi:10.1002/ijc.24124 PMID:19115212

Jensen OM, Wahrendorf J, Knudsen JB, Sørensen BL (1986). The Copenhagen case-control study of bladder cancer. II. Effect of coffee and other beverages. *Int J Cancer*, 37(5):651–7. doi:10.1002/ijc.2910370503 PMID:3699928

Jiang W, Wu Y, Jiang X (2013). Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies. *Gynecol Oncol*, 129(3):620–9. doi:10.1016/j.ygyno.2013.03.014 PMID:23535278

Jiang X, Castelao JE, Groshen S, Cortessis VK, Shibata DK, Conti DV, et al. (2008). Water intake and bladder cancer risk in Los Angeles County. *Int J Cancer*, 123(7):1649–56. doi:10.1002/ijc.23711 PMID:18623082

Jick H, Dinan BJ (1981). Coffee and pancreatic cancer. *Lancet*, 2(8237):92. doi:10.1016/S0140-6736(81)90442-6 PMID:6113465

Johnson KC, Pan S, Mao Y; Canadian Cancer Registries Epidemiology Research Group (2002). Risk factors for male breast cancer in Canada, 1994-1998. *Eur J Cancer Prev*, 11(3):253–63. doi:10.1097/00008469-200206000-00009 PMID:12131659

Johnson S, Koh WP, Wang R, Govindarajan S, Yu MC, Yuan JM (2011). Coffee consumption and reduced risk of hepatocellular carcinoma: findings from the Singapore Chinese Health Study. *Cancer Causes Control*, 22(3):503–10. doi:10.1007/s10552-010-9725-0 PMID:21258859

Jordan SJ, Purdie DM, Green AC, Webb PM (2004). Coffee, tea and caffeine and risk of epithelial ovarian cancer. *Cancer Causes Control*, 15(4):359–65. doi:10.1023/B:-CACO.0000027482.00077.8b PMID:15141137

Kabat GC, Dieck GS, Wynder EL (1986). Bladder cancer in nonsmokers. *Cancer*, 57(2):362–7. doi:10.1002/1097-0142(19860115)57:2<362::AID-CN-CR2820570229>3.0.CO;2-F PMID:3942969

Kalandidi A, Tzonou A, Lipworth L, Gamatsi I, Filippa D, Trichopoulos D (1996). A case-control study of endometrial cancer in relation to reproductive, somatometric, and life-style variables. *Oncology*, 53(5):354–9. doi:10.1159/000227587 PMID:8784467

Kalapothaki V, Tzonou A, Hsieh CC, Toupadaki N, Karakatsani A, Trichopoulos D (1993). Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. *Cancer Causes Control*, 4(4):375–82. doi:10.1007/BF00051341 PMID:8347787

Kanazir M, Boricic I, Delic D, Tepavcevic DK, Knezevic A, Jovanovic T, et al. (2010). Risk factors for hepatocellular carcinoma: a case-control study in Belgrade (Serbia). *Tumori*, 96(6):911–7. doi:10.1177/548.6508 PMID:21388051

Kantor AF, Hartge P, Hoover RN, Fraumeni JF Jr (1988). Epidemiological characteristics of squamous cell carcinoma and adenocarcinoma of the bladder. *Cancer Res*, 48(13):3853–5. PMID:3378221

Kato I, Tominaga S, Matsuura A, Yoshii Y, Shirai M, Kobayashi S (1990). A comparative case-control study of colorectal cancer and adenoma. *Jpn J Cancer Res*, 81(11):1101–8. doi:10.1111/j.1349-7006.1990.tb02520.x PMID:2125036

Katsouyanni K, Trichopoulos D, Boyle P, Xirouchaki E, Trichopoulou A, Lisseos B, et al. (1986). Diet and breast cancer: a case-control study in Greece. *Int J Cancer*, 38(6):815–20. doi:10.1002/ijc.2910380606 PMID:3793261

Kessler II (1981). Coffee and cancer of the pancreas (Letter to the Editor). *N Engl J Med*, 304:1605.

Key TJ, Sharp GB, Appleby PN, Beral V, Goodman MT, Soda M, et al. (1999). Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. *Br J Cancer*, 81(7):1248–56. doi:10.1038/sj.bjc.6690837 PMID:10584890

Khan MM, Goto R, Kobayashi K, Suzumura S, Nagata Y, Sonoda T, et al. (2004). Dietary habits and cancer mortality among middle aged and older Japanese living in Hokkaido, Japan by cancer site and sex. *Asian Pac J Cancer Prev*, 5(1):58–65. PMID:15075007

Kinlen LJ, McPherson K (1984). Pancreas cancer and coffee and tea consumption: a case-control study. *Br J Cancer*, 49(1):93–6. doi:10.1038/bjc.1984.14 PMID:6691902

Kobeissi LH, Yassine IA, Jabbour ME, Moussa MA, Dhaini HR (2013). Urinary bladder cancer risk factors: a Lebanese case- control study. *Asian Pac J Cancer Prev*, 14(5):3205–11. doi:10.7314/APJCP.2013.14.5.3205 PMID:23803105

Koizumi T, Nakaya N, Okamura C, Sato Y, Shimazu T, Nagase S, et al. (2008). Case-control study of coffee consumption and the risk of endometrial endometrioid adenocarcinoma. *Eur J Cancer Prev*, 17(4):358–63. doi:10.1097/CEJ.0b013e3282f0c02c PMID:18562962

Kokic NZ, Adanja JB, Vlajinac DH, Marinkovic PJ, Colovic BR, Jarebinski SM (1996). Case-control study of pancreatic cancer in Serbia, Yugoslavia. *Neoplasma*, 43(5):353–6. PMID:8996557

Komoto K, Haruma K, Kamada T, Tanaka S, Yoshihara M, Sumii K, et al. (1998). Helicobacter pylori infection and gastric neoplasia: correlations with histological gastritis and tumor histology. *Am J Gastroenterol*, 93(8):1271–6. doi:10.1111/j.1572-0241.1998.00408.x PMID:9707050

Kontou N, Psaltopoulou T, Soupos N, Polychronopoulos E, Linos A, Xinopoulos D, et al. (2013). The role of number of meals, coffee intake, salt and type of cookware on colorectal cancer development in the context of the Mediterranean diet. *Public Health Nutr*, 16(5):928–35. doi:10.1017/S1368980012003369 PMID:22874008

Kotake K, Koyama Y, Nasu J, Fukutomi T, Yamaguchi N (1995). Relation of family history of cancer and environmental factors to the risk of colorectal cancer: a case-control study. *Jpn J Clin Oncol*, 25(5):195–202. PMID:7474407

Kotsopoulos J, Ghadirian P, El-Sohemy A, Lynch HT, Snyder C, Daly M, et al. (2007). The CYP1A2 genotype modifies the association between coffee consumption and breast cancer risk among BRCA1 mutation carriers. *Cancer Epidemiol Biomarkers Prev*, 16(5):912–6. doi:10.1158/1055-9965.EPI-06-1074 PMID:17507615

Kotsopoulos J, Vitonis AF, Terry KL, De Vivo I, Cramer DW, Hankinson SE, et al. (2009). Coffee intake, variants in genes involved in caffeine metabolism, and the risk of epithelial ovarian cancer. *Cancer Causes Control*, 20(3):335–44. doi:10.1007/s10552-008-9247-1 PMID:18941913

Kubík A, Zatloukal P, Tomásek L, Dolezal J, Syllabova L, Kara J, et al. (2008). A case-control study of lifestyle and lung cancer associations by histological types. *Neoplasma*, 55(3):192–9. PMID:18348651

Kubík A, Zatloukal P, Tomásek L, Kríz J, Petruzelka L, Plesko I (2001). Diet and the risk of lung cancer among women. A hospital-based case-control study. *Neoplasma*, 48(4):262–6. PMID:11712676

Kubík A, Zatloukal P, Tomásek L, Pauk N, Petruzelka L, Plesko I (2004a). Lung cancer risk among nonsmoking women in relation to diet and physical activity. *Neoplasma*, 51(2):136–43. PMID:15190423

Kubík AK, Zatloukal P, Tomásek L, Pauk N, Havel L, Krepela E, et al. (2004b). Dietary habits and lung cancer risk among non-smoking women. *Eur J Cancer Prev*, 13(6):471–80. doi:10.1097/00008469-200412000-00002 PMID:15548939

Kunze E, Chang-Claude J, Frentzel-Beyme R (1992). Life style and occupational risk factors for bladder cancer in Germany. A case-control study. *Cancer*, 69(7):1776–90. doi:10.1002/1097-0142(19920401)69:7<1776::AID-CNCR2820690721>3.0.CO;2-P PMID:1551063

Kuper H, Titus-Ernstoff L, Harlow BL, Cramer DW (2000b). Population based study of coffee, alcohol and tobacco use and risk of ovarian cancer. *Int J Cancer*, 88(2):313–8. doi:10.1002/1097-0215(20001015)88:2<313::AID-IJC26>3.0.CO;2-5 PMID:11004686

Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, et al. (2000a). Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer*, 85(4):498–502. doi:10.1002/(SICI)1097-0215(20000215)85:4<498::AID-IJC9>3.0.CO;2-F PMID:10699921

Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane S; Japan Public Health Center (JPHC) Study Group (2009). Coffee, green tea, and caffeine consumption and subsequent risk of bladder cancer in relation to smoking status: a prospective study in Japan. *Cancer Sci*, 100(2):294–91. doi:10.1111/j.1349-7006.2008.01027.x PMID:19068095

Kurozawa Y, Ogimoto I, Shibata A, Nose T, Yoshimura T, Suzuki H, et al.; JACC Study Group (2005). Coffee and risk of death from hepatocellular carcinoma in a large cohort study in Japan. *Br J Cancer*, 93(5):607–10. doi:10.1038/sj.bjc.6602737 PMID:16091758

Kurozawa Y, Ogimoto I, Shibata A, Nose T, Yoshimura T, Suzuki H, et al.; Univariate Analysis of JACC Study Data (2004). Dietary habits and risk of death due to hepatocellular carcinoma in a large scale cohort study in Japan. Univariate analysis of JACC study data. *Kurume Med J*, 51(2):141–9. doi:10.2739/kurumemedj.51.141 PMID:15373231

La Vecchia C, Ferraroni M, Negri E, D'Avanzo B, Decarli A, Levi F, et al. (1989b). Coffee consumption and digestive tract cancers. *Cancer Res*, 49(4):1049–51. PMID:2912550

La Vecchia C, Franceschi S, Decarli A, Gentile A, Liati P, Regallo M, et al. (1984). Coffee drinking and the risk of epithelial ovarian cancer. *Int J Cancer*, 33(5):559–62. doi:10.1002/ijc.2910330502 PMID:6724734

La Vecchia C, Liati P, Decarli A, Negri E, Franceschi S (1987). Coffee consumption and risk of pancreatic cancer. *Int J Cancer*, 40(3):309–13. doi:10.1002/ijc.2910400305 PMID:3623714

La Vecchia C, Negri E, D'Avanzo B, Franceschi S, Decarli A, Boyle P (1990). Dietary indicators of laryngeal cancer risk. *Cancer Res*, 50(15):4497–500. PMID:2369728

La Vecchia C, Negri E, Decarli A, D'Avanzo B, Gallotti L, Gentile A, et al. (1988). A case-control study of diet and colo-rectal cancer in northern Italy. *Int J Cancer*, 41(4):492–8. doi:10.1002/ijc.2910410404 PMID:3356484

La Vecchia C, Negri E, Decarli A, D'Avanzo B, Liberati C, Franceschi S (1989a). Dietary factors in the risk of bladder cancer. *Nutr Cancer*, 12(1):93–101. doi:10.1080/01635588909514006 PMID:2710651

La Vecchia C, Talamini R, Decarli A, Franceschi S, Parazzini F, Tognoni G (1986). Coffee consumption and the risk of breast cancer. *Surgery*, 100(3):477–81. PMID:3738766

Lagiou P, Talamini R, Samoli E, Lagiou A, Ahrens W, Pohlabeln H, et al. (2009). Diet and upper-aerodigestive tract cancer in Europe: the ARCAGE study. *Int J Cancer*, 124(11):2671–6. doi:10.1002/ijc.24246 PMID:19230023

Lai GY, Weinstein SJ, Albanes D, Taylor PR, McGlynn KA, Virtamo J, et al. (2013). The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers. *Br J Cancer*, 109(5):1344–51. doi:10.1038/bjc.2013.405 PMID:23880821

Larsson SC, Bergkvist L, Giovannucci E, Wolk A (2006b). Coffee consumption and incidence of colorectal cancer in two prospective cohort studies of Swedish women and men. *Am J Epidemiol*, 163(7):638–44. doi:10.1093/aje/kwj067 PMID:16443798

Larsson SC, Bergkvist L, Wolk A (2009). Coffee and black tea consumption and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort. *Cancer Causes Control*, 20(10):2039–44. doi:10.1007/s10552-009-9396-x PMID:19597749

Larsson SC, Giovannucci E, Wolk A (2006a). Coffee consumption and stomach cancer risk in a cohort of Swedish women. *Int J Cancer*, 119(9):2186–9. doi:10.1002/ijc.22105 PMID:16841331

Larsson SC, Wolk A (2005). Coffee consumption is not associated with ovarian cancer incidence. *Cancer Epidemiol Biomarkers Prev*, 14(9):2273–4. doi:10.1158/1055-9965.EPI-05-0280 PMID:16172244

Larsson SC, Wolk A (2007). Coffee consumption and risk of liver cancer: a meta-analysis. *Gastroenterology*, 132(5):1740–5. doi:10.1053/j.gastro.2007.03.044 PMID:17484871

Lawson DH, Jick H, Rothman KJ (1981). Coffee and tea consumption and breast disease. *Surgery*, 90(5):801–3. PMID:7302833

Lê MG (1985). Coffee consumption, benign breast disease, and breast cancer. *Am J Epidemiol*, 122(4):721. doi:10.1093/oxfordjournals.aje.a114152 PMID:4025311

Le Marchand L, Kolonel LN, Wilkens LR, Myers BC, Hirohata T (1994). Animal fat consumption and prostate cancer: a prospective study in Hawaii. *Epidemiology*, 5(3):276–82. doi:10.1097/00001648-199405000-00004 PMID:8038241

Lee HP, Gourley L, Duffy SW, Estève J, Lee J, Day NE (1989). Colorectal cancer and diet in an Asian population–a case-control study among Singapore Chinese. *Int J Cancer*, 43(6):1007–16. doi:10.1002/ijc.2910430609 PMID:2731998

Lee JE, Giovannucci E, Smith-Warner SA, Spiegelman D, Willett WC, Curhan GC (2006). Total fluid intake and use of individual beverages and risk of renal cell cancer in two large cohorts. *Cancer Epidemiol Biomarkers Prev*, 15(6):1204–11. doi:10.1158/1055-9965.EPI-05-0889 PMID:16775182

Lee JE, Hunter DJ, Spiegelman D, Adami HO, Bernstein L, van den Brandt PA, et al. (2007b). Intakes of coffee, tea, milk, soda and juice and renal cell cancer in a pooled analysis of 13 prospective studies. *Int J Cancer*, 121(10):2246–53. doi:10.1002/ijc.22909 PMID:17583573

Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S; JPHC Study Group (2007a). Coffee consumption and risk of colorectal cancer in a population-based prospective cohort of Japanese men and women. *Int J Cancer*, 121(6):1312–8. doi:10.1002/ijc.22778 PMID:17450527

Leung WW, Ho SC, Chan HL, Wong V, Yeo W, Mok TS (2011). Moderate coffee consumption reduces the risk of hepatocellular carcinoma in hepatitis B chronic carriers: a case-control study. *J Epidemiol Community Health*, 65(6):556–8. doi:10.1136/jech.2009.104125 PMID:20693491

Levi F, Franceschi S, Negri E, La Vecchia C (1993b). Dietary factors and the risk of endometrial cancer. *Cancer*, 71(11):3575–81. doi:10.1002/1097-0142(19930601)71:11<3575::AID-CNCR2820711119>3.0.CO;2-0 PMID:8490907

Levi F, La Vecchia C, Gulie C, Negri E (1993a). Dietary factors and breast cancer risk in Vaud, Switzerland. *Nutr Cancer*, 19(3):327–35. doi:10.1080/01635589309514263 PMID:8346081

Levi F, Pasche C, La Vecchia C, Lucchini F, Franceschi S (1999). Food groups and colorectal cancer risk. *Br J Cancer*, 79(7-8):1283–7. doi:10.1038/sj.bjc.6690206 PMID:10098773

Li G, Ma D, Zhang Y, Zheng W, Wang P (2013c). Coffee consumption and risk of colorectal cancer: a meta-analysis of observational studies. *Public Health Nutr*, 16(2):346–57. doi:10.1017/S1368980012002601 PMID:22694939

Li J, Seibold P, Chang-Claude J, Flesch-Janys D, Liu J, Czene K, et al. (2011). Coffee consumption modifies risk of estrogen-receptor negative breast cancer. *Breast Cancer Res*, 13(3):R49. doi:10.1186/bcr2879 PMID:21569535

Li L, Gan Y, Wu C, Qu X, Sun G, Lu Z (2015). Coffee consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies. *BMC Cancer*, 15(1):733. doi:10.1186/s12885-015-1758-z PMID:26481317

Li Q, Kakizaki M, Sugawara Y, Tomata Y, Watanabe T, Nishino Y, et al. (2013b). Coffee consumption and the risk of prostate cancer: the Ohsaki Cohort Study. *Br J Cancer*, 108(11):2381–9. doi:10.1038/bjc.2013.238 PMID:23674088

Li XJ, Ren ZJ, Qin JW, Zhao JH, Tang JH, Ji MH, et al. (2013a). Coffee consumption and risk of breast cancer: an up-to-date meta-analysis. *PLoS One*, 8(1):e52681. doi:10.1371/journal.pone.0052681 PMID:23308117

Li YM, Peng J, Li LZ (2016). Coffee consumption associated with reduced risk of oral cancer: a meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol*, 121(4):381–389. e1. doi:10.1016/j.oooo.2015.12.006 PMID:26972538

Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, et al. (2002). Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk. *Int J Cancer*, 99(5):742–6. doi:10.1002/ijc.10402 PMID:12115510

Linos A, Linos DA, Vgotza N, Souvatzoglou A, Koutras DA (1989). Does coffee consumption protect against thyroid disease? *Acta Chir Scand*, 155(6-7):317–20. PMID:2816215

Liu H, Hu GH, Wang XC, Huang TB, Xu L, Lai P, et al. (2015a). Coffee consumption and prostate cancer risk: a meta-analysis of cohort studies. *Nutr Cancer*, 67(3):392–400. doi:10.1080/01635581.2015.1004727 PMID:25706900

Liu H, Hua Y, Zheng X, Shen Z, Luo H, Tao X, et al. (2015b). Effect of coffee consumption on the risk of gastric cancer: a systematic review and meta-analysis of prospective cohort studies. *PLoS One*, 10(5):e0128501. doi:10.1371/journal.pone.0128501 PMID:26023935

Liu J, Shen B, Shi M, Cai J (2016). Higher caffeinated coffee intake is associated with reduced malignant melanoma risk: a meta-analysis study. *PLoS One*, 11(1):e0147056. doi:10.1371/journal.pone.0147056 PMID:26816289

Löf M, Sandin S, Yin L, Adami HO, Weiderpass E (2015). Prospective study of coffee consumption and all-cause, cancer, and cardiovascular mortality in Swedish women. *Eur J Epidemiol*, 30(9):1027–34. doi:10.1007/s10654-015-0052-3 PMID:26076920

Loftfield E, Freedman ND, Graubard BI, Hollenbeck AR, Shebl FM, Mayne ST, et al. (2015). Coffee drinking and cutaneous melanoma risk in the NIH-AARP diet and health study. *J Natl Cancer Inst*, 107(2):dju421. doi:10.1093/jnci/dju421 PMID:25604135

Lowcock EC, Cotterchio M, Anderson LN, Boucher BA, El-Sohemy A (2013). High coffee intake, but not caffeine, is associated with reduced estrogen receptor negative and postmenopausal breast cancer risk with no effect modification by CYP1A2 genotype. *Nutr Cancer*, 65(3):398–409. doi:10.1080/01635581.2013.768348 PMID:23530639

Lu CM, Lan SJ, Lee YH, Huang JK, Huang CH, Hsieh CC (1999). Tea consumption: fluid intake and bladder cancer risk in Southern Taiwan. *Urology*, 54(5):823–8. doi:10.1016/S0090-4295(99)00281-2 PMID:10565741

Lu Y, Zhai L, Zeng J, Peng Q, Wang J, Deng Y, et al. (2014). Coffee consumption and prostate cancer risk: an updated meta-analysis. *Cancer Causes Control*, 25(5):591–604. doi:10.1007/s10552-014-0364-8 PMID:24584929

Lubin F, Ron E, Wax Y, Modan B (1985). Coffee and methylxanthines and breast cancer: a case-control study. *J Natl Cancer Inst*, 74(3):569–73. PMID:3856060

Lubin JH, Burns PE, Blot WJ, Ziegler RG, Lees AW, Fraumeni JF Jr (1981). Dietary factors and breast cancer risk. *Int J Cancer*, 28(6):685–9. doi:10.1002/ijc.2910280605 PMID:7333703

Lueth NA, Anderson KE, Harnack LJ, Fulkerson JA, Robien K (2008). Coffee and caffeine intake and the risk of ovarian cancer: the Iowa Women's Health Study. *Cancer Causes Control*, 19(10):1365–72. doi:10.1007/s10552-008-9208-8 PMID:18704717

Lukic M, Licaj I, Lund E, Skeie G, Weiderpass E, Braaten T (2016). Coffee consumption and the risk of cancer in the Norwegian Women and Cancer (NOWAC) Study. *Eur J Epidemiol*, 31(9):905–16. doi:10.1007/s10654-016-0142-x PMID:27010635

Luo J, Inoue M, Iwasaki M, Sasazuki S, Otani T, Ye W, et al.; JPHC Study Group (2007). Green tea and coffee intake and risk of pancreatic cancer in a large-scale, population-based cohort study in Japan (JPHC study). *Eur J Cancer Prev*, 16(6):542–8. doi:10.1097/CEJ.0b013e32809b4d30 PMID:18090127

Luqman M, Javed MM, Daud S, Raheem N, Ahmad J, Khan AU (2014). Risk factors for lung cancer in the Pakistani population. *Asian Pac J Cancer Prev*, 15(7):3035–9. doi:10.7314/APJCP.2014.15.7.3035 PMID:24815443

Lyon JL, Mahoney AW, French TK, Moser R Jr (1992). Coffee consumption and the risk of cancer of the exocrine pancreas: a case-control study in a low-risk population. *Epidemiology*, 3(2):164–70. doi:10.1097/00001648-199203000-00015 PMID:1576222

Ma X, Park Y, Mayne ST, Wang R, Sinha R, Hollenbeck AR, et al. (2010). Diet, lifestyle, and acute myeloid leukemia in the NIH-AARP cohort. *Am J Epidemiol*, 171(3):312–22. doi:10.1093/aje/kwp371 PMID:20042434

Mabuchi K, Bross DS, Kessler II (1985a). Epidemiology of cancer of the vulva. A case-control study. *Cancer*, 55(8):1843–8. doi:10.1002/1097-0142(19850415)55:8<1843::AID-CNCR2820550833>3.0.CO;2-M PMID:3978570

Mabuchi K, Bross DS, Kessler II (1985b). Risk factors for male breast cancer. *J Natl Cancer Inst*, 74(2):371–5. PMID:3856050

Mack TM, Yu MC, Hanisch R, Henderson BE (1986). Pancreas cancer and smoking, beverage consumption, and past medical history. *J Natl Cancer Inst*, 76(1):49–60. PMID:3455742

Mack WJ, Preston-Martin S, Bernstein L, Qian D (2002). Lifestyle and other risk factors for thyroid cancer in Los Angeles County females. *Ann Epidemiol*, 12(6):395–401. doi:10.1016/S1047-2797(01)00281-2 PMID:12160598

Mack WJ, Preston-Martin S, Dal Maso L, Galanti R, Xiang M, Franceschi S, et al. (2003). A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. *Cancer Causes Control*, 14(8):773–85. doi:10.1023/A:1026349702909 PMID:14674742

MacMahon B, Yen S, Trichopoulos A, Warren K, Nardi G (1981a). Coffee and cancer of the pancreas (Letter to the Editor). *N Engl J Med*, 304(11):605–6. doi:10.1056/NEJM198103123041102

MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G (1981b). Coffee and cancer of the pancreas. *N Engl J Med*, 304(11):630–3. doi:10.1056/NEJM198103123041102 PMID:7453739

Makiuchi T, Sobue T, Kitamura T, Ishihara J, Sawada N, Iwasaki M, et al. (2016). Association between green tea/coffee consumption and biliary tract cancer: A population-based cohort study in Japan. *Cancer Sci*, 107(1):76–83. doi:10.1111/cas.12843 PMID:26530716

Malerba S, Galeone C, Pelucchi C, Turati F, Hashibe M, La Vecchia C, et al. (2013b). A meta-analysis of coffee and tea consumption and the risk of glioma in adults. *Cancer Causes Control*, 24(2):267–76. doi:10.1007/s10552-012-0126-4 PMID:23247638

Malerba S, Turati F, Galeone C, Pelucchi C, Verga F, La Vecchia C, et al. (2013a). A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular diseases. *Eur J Epidemiol*, 28(7):527–39. doi:10.1007/s10654-013-9834-7 PMID:23934579

Männistö S, Pietinen P, Virtanen M, Kataja V, Uusitupa M (1999). Diet and the risk of breast cancer in a case-control study: does the threat of disease have an influence on recall bias? *J Clin Epidemiol*, 52(5):429–39. doi:10.1016/S0895-4356(99)00010-4 PMID:10360338

Mansel RE, Webster DJT, Burr M, Leger S (1982). Is there a relationship between coffee consumption and breast disease? (Abstract No. 69). *B J Surg*, 69:295–6.

Marrett LD, Walter SD, Meigs JW (1983). Coffee drinking and bladder cancer in Connecticut. *Am J Epidemiol*, 117(2):113–27. doi:10.1093/oxfordjournals.aje.a113522 PMID:6829543

Mashberg A, Boffetta P, Winkelman R, Garfinkel L (1993). Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. *Cancer*, 72(4):1369–75. doi:10.1002/1097-0142(19930815)72:4<1369::AID-CNCR2820720436>3.0.CO;2-L PMID:8339227

McCann SE, Yeh M, Rodabaugh K, Moysich KB (2009). Higher regular coffee and tea consumption is associated with reduced endometrial cancer risk. *Int J Cancer*, 124(7):1650–3. doi:10.1002/ijc.24125 PMID:19107932

McCredie M, Ford JM, Stewart JH (1988). Risk factors for cancer of the renal parenchyma. *Int J Cancer*, 42(1):13–6. doi:10.1002/ijc.2910420104 PMID:3391702

McLaughlin CC, Mahoney MC, Nasca PC, Metzger BB, Baptiste MS, Field NA (1992). Breast cancer and methylxanthine consumption. *Cancer Causes Control*, 3(2):175–8. doi:10.1007/BF00051658 PMID:1562707

McLaughlin JK, Blot WJ, Mandel JS, Schuman LM, Mehl ES, Fraumeni JF Jr (1983). Etiology of cancer of the renal pelvis. *J Natl Cancer Inst*, 71(2):287–91. PMID:6576188

McLaughlin JK, Gridley G, Block G, Winn DM, Preston-Martin S, Schoenberg JB, et al. (1988). Dietary factors in oral and pharyngeal cancer. *J Natl Cancer Inst*, 80(15):1237–43. doi:10.1093/jnci/80.15.1237 PMID:3418729

Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH (1994). Risk factors for renal cell carcinoma in Denmark. I. Role of socioeconomic status, tobacco use, beverages, and family history. *Cancer Causes Control*, 5(2):105–13. doi:10.1007/BF01830256 PMID:8167257

Mendilaharsu M, De Stefani E, Deneo-Pellegrini H, Carzoglio JC, Ronco A (1998). Consumption of tea and coffee and the risk of lung cancer in cigarette-smoking men: a case-control study in Uruguay. *Lung Cancer*, 19(2):101–7. doi:10.1016/S0169-5002(97)00075-5 PMID:9567246

Menegaux F, Ripert M, Hémon D, Clavel J (2007). Maternal alcohol and coffee drinking, parental smoking and childhood leukaemia: a French population-based case-control study. *Paediatr Perinat Epidemiol*, 21(4):293–9. doi:10.1111/j.1365-3016.2007.00824.x PMID:17564585

Menegaux F, Steffen C, Bellec S, Baruchel A, Lescoeur B, Leverger G, et al. (2005). Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. *Cancer Detect Prev*, 29(6):487–93. doi:10.1016/j.cdp.2005.06.008 PMID:16289502

Merritt MA, Tzoulaki I, Tworoger SS, De Vivo I, Hankinson SE, Fernandes J, et al. (2015). Investigation of dietary factors and endometrial cancer risk using a nutrient-wide association study approach in the EPIC and Nurses' Health Study (NHS) and NHSII. *Cancer Epidemiol Biomarkers Prev*, 24(2):466–71. doi:10.1158/1055-9965.EPI-14-0970 PMID:25662427

Mettlin C (1989). Milk drinking, other beverage habits, and lung cancer risk. *Int J Cancer*, 43(4):608–12. doi:10.1002/ijc.2910430412 PMID:2703270

Mettlin C, Graham S (1979). Dietary risk factors in human bladder cancer. *Am J Epidemiol*, 110(3):255–63. doi:10.1093/oxfordjournals.aje.a112810 PMID:582494

Michaud DS, Gallo V, Schlehofer B, Tjønneland A, Olsen A, Overvad K, et al. (2010). Coffee and tea intake and risk of brain tumors in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Am J Clin Nutr*, 92(5):1145–50. doi:10.3945/ajcn.2010.29876 PMID:20844074

Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS (2001). Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. *Cancer Epidemiol Biomarkers Prev*, 10(5):429–37. PMID:11352851

Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Curhan GC, Willett WC, et al. (1999). Fluid intake and the risk of bladder cancer in men. *N Engl J Med*, 340(18):1390–7. doi:10.1056/NEJM199905063401803 PMID:10228189

Michels KB, Holmberg L, Bergkvist L, Wolk A (2002). Coffee, tea, and caffeine consumption and breast cancer incidence in a cohort of Swedish women. *Ann Epidemiol*, 12(1):21–6. doi:10.1016/S1047-2797(01)00238-1 PMID:11750236

Michels KB, Willett WC, Fuchs CS, Giovannucci E (2005). Coffee, tea, and caffeine consumption and incidence of colon and rectal cancer. *J Natl Cancer Inst*, 97(4):282–92. doi:10.1093/jnci/dji039 PMID:15713963

Michikawa T, Inoue M, Shimazu T, Sasazuki S, Iwasaki M, Sawada N, et al. (2011). Green tea and coffee consumption and its association with thyroid cancer risk: a population-based cohort study in Japan. *Cancer Causes Control*, 22(7):985–93. doi:10.1007/s10552-011-9771-2 PMID:21562752

Milán T, Verkasalo PK, Kaprio J, Koskenvuo M (2003). Lifestyle differences in twin pairs discordant for basal cell carcinoma of the skin. *Br J Dermatol*, 149(1):115–23. doi:10.1046/j.1365-2133.2003.05352.x PMID:12890204

Miller DR, Rosenberg L, Kaufman DW, Helmrich SP, Schottenfeld D, Lewis J, et al. (1987). Epithelial ovarian cancer and coffee drinking. *Int J Epidemiol*, 16(1):13–7. doi:10.1093/ije/16.1.13 PMID:3570612

Mills PK, Beeson WL, Abbey DE, Fraser GE, Phillips RL (1988). Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer*, 61(12):2578–85. doi:10.1002/1097-0142(19880615)61:12<2578::AID-CNCR2820611232>3.0.CO;2-0 PMID:3365678

Mills PK, Beeson WL, Phillips RL, Fraser GE (1991). Bladder cancer in a low risk population: results from the Adventist Health Study. *Am J Epidemiol*, 133(3):230–9. doi:10.1093/oxfordjournals.aje.a115867 PMID:2000840

Milne E, Royle JA, Bennett LC, de Klerk NH, Bailey HD, Bower C, et al. (2011). Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: results from an Australian case-control study. *Cancer Causes Control*, 22(2):207–18. doi:10.1007/s10552-010-9688-1 PMID:21113653

Miura K, Hughes MC, Green AC, van der Pols JC (2014). Caffeine intake and risk of basal cell and squamous cell carcinomas of the skin in an 11-year prospective study. *Eur J Nutr*, 53(2):511–20. doi:10.1007/s00394-013-0556-0 PMID:23824258

Mizoo T, Taira N, Nishiyama K, Nogami T, Iwamoto T, Motoki T, et al. (2013). Effects of lifestyle and single nucleotide polymorphisms on breast cancer risk: a case-control study in Japanese women. *BMC Cancer*, 13(1):565 doi:10.1186/1471-2407-13-565 PMID:24289300

Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, et al. (1992). A multi-institute case-control study on the risk factors of developing pancreatic cancer. *Jpn J Clin Oncol*, 22(4):286–91. PMID:1434027

Momas I, Daurès JP, Festy B, Bontoux J, Grémy F (1994). Relative importance of risk factors in bladder carcinogenesis: some new results about Mediterranean habits. *Cancer Causes Control*, 5(4):326–32. doi:10.1007/BF01804983 PMID:8080944

Mommsen S, Aagaard J, Sell A (1983a). A case-control study of female bladder cancer. *Eur J Cancer Clin Oncol*, 19(6):725–9. doi:10.1016/0277-5379(83)90005-6 PMID:6683645

Mommsen S, Aagaard J, Sell A (1983b). An epidemiological study of bladder cancer in a predominantly rural district. *Scand J Urol Nephrol*, 17(3):307–12. doi:10.3109/00365598309182137 PMID:6689086

Mongraw-Chaffin ML, Cohn BA, Anglemyer AT, Cohen RD, Christianson RE (2009). Maternal smoking, alcohol, and coffee use during pregnancy and son's risk of testicular cancer. *Alcohol*, 43(3):241–5. doi:10.1016/j.alcohol.2008.12.002 PMID:19303242

Montella M, Polesel J, La Vecchia C, Dal Maso L, Crispo A, Crovatto M, et al. (2007). Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. *Int J Cancer*, 120(7):1555–9. doi:10.1002/ijc.22509 PMID:17205531

Montella M, Tramacere I, Tavani A, Gallus S, Crispo A, Talamini R, et al. (2009). Coffee, decaffeinated coffee, tea intake, and risk of renal cell cancer. *Nutr Cancer*, 61(1):76–80. doi:10.1080/01635580802670754 PMID:19116877

Morgan RW, Jain MG (1974). Bladder cancer: smoking, beverages and artificial sweeteners. *Can Med Assoc J*, 111(10):1067–70. PMID:4429932

Mori M, Harabuchi I, Miyake H, Casagrande JT, Henderson BE, Ross RK (1988). Reproductive, genetic, and dietary risk factors for ovarian cancer. *Am J Epidemiol*, 128(4):771–7. doi:10.1093/oxfordjournals.aje.a115030 PMID:3421242

Mori M, Hariharan M, Anandakumar M, Tsutsumi M, Ishikawa O, Konishi Y, et al. (1999). A case-control study on risk factors for pancreatic diseases in Kerala, India. *Hepatogastroenterology*, 46(25):25–30. PMID:10228760

Morrison AS, Buring JE, Verhoek WG, Aoki K, Leck I, Ohno Y, et al. (1982). Coffee drinking and cancer of the lower urinary tract. *J Natl Cancer Inst*, 68(1):91–4. PMID:6948130

Mucci LA, Dickman PW, Steineck G, Adami HO, Augustsson K (2003). Dietary acrylamide and cancer of the large bowel, kidney, and bladder: absence of an association in a population-based study in Sweden. *Br J Cancer*, 88(1):84–9. doi:10.1038/sj.bjc.6600726 PMID:12556964

Mucci LA, Lindblad P, Steineck G, Adami HO (2004). Dietary acrylamide and risk of renal cell cancer. *Int J Cancer*, 109(5):774–6. doi:10.1002/ijc.20011 PMID:14999788

Muñoz N, Plummer M, Vivas J, Moreno V, De Sanjosé S, Lopez G, et al. (2001). A case-control study of gastric cancer in Venezuela. *Int J Cancer*, 93(3):417–23. doi:10.1002/ijc.1333 PMID:11433408

Muñoz SE, Navarro A, Lantieri MJ, Fabro ME, Peyrano MG, Ferraroni M, et al. (1998). Alcohol, methylxanthine-containing beverages, and colorectal cancer in Córdoba, Argentina. *Eur J Cancer Prev*, 7(3):207–13. doi:10.1097/00008469-199806000-00005 PMID:9696929

Nagano J, Kono S, Preston DL, Moriwaki H, Sharp GB, Koyama K, et al. (2000). Bladder-cancer incidence in relation to vegetable and fruit consumption: a prospective study of atomic-bomb survivors. *Int J Cancer*, 86(1):132–8. doi:10.1002/(SICI)1097-0215(20000401)86:1<132::AID-IJC21>3.0.CO;2-M PMID:10728607

Naganuma T, Kuriyama S, Akhter M, Kakizaki M, Nakaya N, Matsuda-Ohmori K, et al. (2007). Coffee consumption and the risk of colorectal cancer: a prospective cohort study in Japan. *Int J Cancer*, 120(7):1542–7. doi:10.1002/ijc.22505 PMID:17205519

Naganuma T, Kuriyama S, Kakizaki M, Sone T, Nakaya N, Ohmori-Matsuda K, et al. (2008). Coffee consumption and the risk of oral, pharyngeal, and esophageal cancers in Japan: the Miyagi Cohort Study. *Am J Epidemiol*, 168(12):1425–32. doi:10.1093/aje/kwn282 PMID:18974083

Nakamura K, Nagata C, Wada K, Tamai Y, Tsuji M, Takatsuka N, et al. (2011). Cigarette smoking and other lifestyle factors in relation to the risk of pancreatic cancer death: a prospective cohort study in Japan. *Jpn J Clin Oncol*, 41(2):225–31. doi:10.1093/jjco/hyq185 PMID:21075833

Naldi L, Gallus S, Tavani A, Imberti GL, La Vecchia C; Oncology Study Group of the Italian Group for Epidemiologic Research in Dermatology(2004). Risk of melanoma and vitamin A, coffee and alcohol: a case-control study from Italy. *Eur J Cancer Prev*, 13(6):503–8. doi:10.1097/00008469-200412000-00007 PMID:15548944

Negri E, Bosetti C, La Vecchia C, Fioretti F, Conti E, Franceschi S (1999). Risk factors for adenocarcinoma of the small intestine. *Int J Cancer*, 82(2):171–4. doi:10.1002/(SICI)1097-0215(19990719)82:2<171::AID-IJC3>3.0.CO;2-T PMID:10389747

Nilsson LM, Johansson I, Lenner P, Lindahl B, Van Guelpen B (2010). Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study. *Cancer Causes Control*, 21(10):1533–44. doi:10.1007/s10552-010-9582-x PMID:20512657

Nishi M, Ohba S, Hirata K, Miyake H (1996). Dose-response relationship between coffee and the risk of pancreas cancer. *Jpn J Clin Oncol*, 26(1):42–8. doi:10.1093/oxfordjournals.jjco.a023177 PMID:8551666

Nkondjock A, Ghadirian P, Kotsopoulos J, Lubinski J, Lynch H, Kim-Sing C, et al. (2006). Coffee consumption and breast cancer risk among BRCA1 and BRCA2 mutation carriers. *Int J Cancer*, 118(1):103–7. doi:10.1002/ijc.21296 PMID:16032702

Nomura A, Heilbrun LK, Stemmermann GN (1986). Prospective study of coffee consumption and the risk of cancer. *J Natl Cancer Inst*, 76(4):587–90. doi:10.1093/jnci/76.4.587 PMID:3457196

Nomura A, Stemmermann GN, Heilbrun LK (1981). Coffee and pancreatic cancer. *Lancet*, 2(8243):415. doi:10.1016/S0140-6736(81)90849-7 PMID:6115175

Nomura AM, Kolonel LN, Hankin JH, Yoshizawa CN (1991). Dietary factors in cancer of the lower urinary tract. *Int J Cancer*, 48(2):199–205. doi:10.1002/ijc.2910480208 PMID:2019466

Norell SE, Ahlbom A, Erwald R, Jacobson G, Lindberg-Navier I, Olin R, et al. (1986). Diet and pancreatic cancer: a case-control study. *Am J Epidemiol*, 124(6):894–902. doi:10.1093/oxfordjournals.aje.a114479 PMID:3776972

Nyberg F, Agrenius V, Svartengren K, Svensson C, Pershagen G (1998). Dietary factors and risk of lung cancer in never-smokers. *Int J Cancer*, 78(4):430–6. doi:10.1002/(SICI)1097-0215(19981109)78:4<430::AID-IJC7>3.0.CO;2-V PMID:9797130

Oba S, Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, et al. (2006). The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. *Cancer Lett*, 244(2):260–7. doi:10.1016/j.canlet.2005.12.037 PMID:16519996

Oh JK, Sandin S, Ström P, Löf M, Adami HO, Weiderpass E (2015). Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden. *Int J Cancer*, 137(8):1979–89. doi:10.1002/ijc.29569 PMID:25885188

Ohfuji S, Fukushima W, Tanaka T, Habu D, Tamori A, Sakaguchi H, et al. (2006). Coffee consumption and reduced risk of hepatocellular carcinoma among patients with chronic type C liver disease: A case-control study. *Hepatol Res*, 36(3):201–8. doi:10.1016/j.hepres.2006.07.010 PMID:16916617

Ohishi W, Fujiwara S, Cologne JB, Suzuki G, Akahoshi M, Nishi N, et al. (2008). Risk factors for hepatocellular carcinoma in a Japanese population: a nested case-control study. *Cancer Epidemiol Biomarkers Prev*, 17(4):846–54. doi:10.1158/1055-9965.EPI-07-2806 PMID:18398026

Ohno Y, Aoki K, Obata K, Morrison AS (1985). Case-control study of urinary bladder cancer in metropolitan Nagoya. *Natl Cancer Inst Monogr*, 69:229–34. PMID:3834338

Oleske D, Golomb HM, Farber MD, Levy PS (1985). A case-control inquiry into the etiology of hairy cell leukemia. *Am J Epidemiol*, 121(5):675–83. doi:10.1093/aje/121.5.675 PMID:4014159

Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM (1989). A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. *Am J Public Health*, 79(8):1016–9. doi:10.2105/AJPH.79.8.1016 PMID:2751016

Orsi L, Rudant J, Ajrouche R, Leverger G, Baruchel A, Nelken B, et al. (2015). Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia: the ESTELLE study. *Cancer Causes Control*, 26(7):1003–17. doi:10.1007/s10552-015-0593-5 PMID:25956268

Osterlind A, Tucker MA, Stone BJ, Jensen OM (1988). The Danish case-control study of cutaneous malignant melanoma. IV. No association with nutritional factors, alcohol, smoking or hair dyes. *Int J Cancer*, 42(6):825–8. doi:10.1002/ijc.2910420604 PMID:3192325

Oze I, Matsuo K, Kawakita D, Hosono S, Ito H, Watanabe M, et al. (2014). Coffee and green tea consumption is associated with upper aerodigestive tract cancer in Japan. *Int J Cancer*, 135(2):391–400. doi:10.1002/ijc.28653 PMID:24310779

Paffenbarger RS Jr, Wing AL, Hyde RT (1978). Characteristics in youth predictive of adult-onset malignant lymphomas, melanomas, and leukemias: brief communication. *J Natl Cancer Inst*, 60(1):89–92. doi:10.1093/jnci/60.1.89 PMID:272469

Parazzini F, Moroni S, Negri E, La Vecchia C, Dal Pino D, Cavalleri E (1995). Selected food intake and risk of vulvar cancer. *Cancer*, 76(11):2291–6. doi:10.1002/1097-0142(19951201)76:11<2291::AID-CNCR2820761117>3.0.CO;2-W PMID:8635034

Park CH, Myung SK, Kim TY, Seo HG, Jeon YJ, Kim Y; Korean Meta-Analysis (KORMA) Study Group (2010). Coffee consumption and risk of prostate cancer: a meta-analysis of epidemiological studies. *BJU Int*, 106(6):762–9. doi:10.1111/j.1464-410X.2010.09493.x PMID:20590551

Parodi S, Santi I, Marani E, Casella C, Puppo A, Garrone E, et al. (2016). Lifestyle factors and risk of leukemia and non-Hodgkin's lymphoma: a case-control study. *Cancer Causes Control*, 27(3):367–75. doi:10.1007/s10552-016-0713-x PMID:26759332

Partanen T, Hemminki K, Vainio H, Kauppinen T (1995). Coffee consumption not associated with risk of pancreas cancer in Finland. *Prev Med*, 24(2):213–6. doi:10.1006/pmed.1995.1035 PMID:7597024

Patil PS, Mohandas KM, Bhatia SJ, Mehta SA (2014). Serum ferritin and the risk of hepatocellular carcinoma in chronic liver disease of viral etiology: a case-control study. *Indian J Gastroenterol*, 33(1):12–8. doi:10.1007/s12664-013-0367-5 PMID:24006121

Peters JM, Preston-Martin S, London SJ, Bowman JD, Buckley JD, Thomas DC (1994). Processed meats and risk of childhood leukemia (California, USA). *Cancer Causes Control*, 5(2):195–202. doi:10.1007/BF01830266 PMID:8167267

Peterson S, Yuan JM, Koh WP, Sun CL, Wang R, Turesky RJ, et al. (2010). Coffee intake and risk of colorectal cancer among Chinese in Singapore: the Singapore Chinese Health Study. *Nutr Cancer*, 62(1):21–9. doi:10.1080/01635580903191528 PMID:20043256

Petrick JL, Freedman ND, Graubard BI, Sahasrabuddhe VV, Lai GY, Alavanja MC, et al. (2015). Coffee consumption and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma by sex: the Liver Cancer Pooling Project. *Cancer Epidemiol Biomarkers Prev*, 24(9):1398–406. doi:10.1158/1055-9965.EPI-15-0137 PMID:26126626

Petridou E, Kedikoglou S, Koukoulomatis P, Dessypris N, Trichopoulos D (2002a). Diet in relation to endometrial cancer risk: a case-control study in Greece. *Nutr Cancer*, 44(1):16–22. doi:10.1207/S15327914NC441_3 PMID:12672637

Petridou E, Koukoulomatis P, Dessypris N, Karalis D, Michalas S, Trichopoulos D (2002b). Why is endometrial cancer less common in Greece than in other European Union countries? *Eur J Cancer Prev*, 11(5):427–32. doi:10.1097/00008469-200210000-00004 PMID:12394239

Petridou E, Trichopoulos D, Kalapothaki V, Pourtsidis A, Kogevinas M, Kalmanti M, et al. (1997). The risk profile of childhood leukaemia in Greece: a nationwide case-control study. *Br J Cancer*, 76(9):1241–7. doi:10.1038/bjc.1997.541 PMID:9365177

Pfeffer F, Avilas Rosas H, Vargas F, Villalobos JJ (1989). [Smoking, consumption of alcoholic beverages and coffee as factors associated with the development of cancer of the pancreas]. *Rev Invest Clin*, 41(3):205–8. [Spanish] PMID:2813993

Phillips RL, Snowdon DA (1985). Dietary relationships with fatal colorectal cancer among Seventh-Day Adventists. *J Natl Cancer Inst*, 74(2):307–17. PMID:3856044

Pintos J, Franco EL, Oliveira BV, Kowalski LP, Curado MP, Dewar R (1994). Maté, coffee, and tea consumption and risk of cancers of the upper aerodigestive tract in southern Brazil. *Epidemiology*, 5(6):583–90. doi:10.1097/00001648-199411000-00005 PMID:7841239

Piper JM, Matanoski GM, Tonascia J (1986). Bladder cancer in young women. *Am J Epidemiol*, 123(6):1033–42. doi:10.1093/oxfordjournals.aje.a114331 PMID:3706274

Plichart M, Menegaux F, Lacour B, Hartmann O, Frappaz D, Doz F, et al. (2008). Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE). *Eur J Cancer Prev*, 17(4):376–83. doi:10.1097/CEJ.0b013e3282f75e6f PMID:18562965

Pohlabeln H, Jöckel KH, Bolm-Audorff U (1999). Non-occupational risk factors for cancer of the lower urinary tract in Germany. *Eur J Epidemiol*, 15(5):411–9. doi:10.1023/A:1007595809278 PMID:10442466

Polesel J, Zucchetto A, Talamini R, Dal Maso L, Serraino D, La Vecchia C, et al. (2012). Re: coffee consumption and prostate cancer risk and progression in the Health Professional Follow-up Study. *J Natl Cancer Inst*, 104(21):1684–6, author reply 1686. doi:10.1093/jnci/djs383 PMID:22962694

Polychronopoulou A, Tzonou A, Hsieh CC, Kaprinis G, Rebelakos A, Toupadaki N, et al. (1993). Reproductive variables, tobacco, ethanol, coffee and somatometry as risk factors for ovarian cancer. *Int J Cancer*, 55(3):402–7. doi:10.1002/ijc.2910550312 PMID:8375923

Pozner J, Papatestas AE, Fagerstrom R, Schwartz I, Saevitz J, Feinberg M, et al. (1986). Association of tumor differentiation with caffeine and coffee intake in women with breast cancer. *Surgery*, 100(3):482–8. PMID:3738767

Rabstein S, Brüning T, Harth V, Fischer HP, Haas S, Weiss T, et al.; GENICA Network (2010). N-acetyltransferase 2, exposure to aromatic and heterocyclic amines, and receptor-defined breast cancer. *Eur J Cancer Prev*, 19(2):100–9. doi:10.1097/CEJ.0b013e328333fbb7 PMID:19996973

Radoï L, Paget-Bailly S, Menvielle G, Cyr D, Schmaus A, Carton M, et al. (2013). Tea and coffee consumption and risk of oral cavity cancer: results of a large population-based case-control study, the ICARE study. *Cancer Epidemiol*, 37(3):284–9. doi:10.1016/j.canep.2013.02.001 PMID:23453554

Radosavljević V, Janković S, Marinković J, Djokić M (2003). Fluid intake and bladder cancer. A case control study. *Neoplasma*, 50(3):234–8. PMID:12937859

Ran HQ, Wang JZ, Sun CQ (2016). Coffee consumption and pancreatic cancer risk: an update meta-analysis of cohort studies. *Pak J Med Sci*, 32(1):253–9. PMID:27022386

Rao DN, Ganesh B, Dinshaw KA, Mohandas KM (2002). A case-control study of stomach cancer in Mumbai, India. *Int J Cancer*, 99(5):727–31. doi:10.1002/ijc.10339 PMID:12115507

Raymond L, Infante F, Tuyns AJ, Voirol M, Lowenfels AB (1987). [Diet and cancer of the pancreas]. *Gastroenterol Clin Biol*, 11(6-7):488–92. [French] PMID:3609645

Rebelakos A, Trichopoulos D, Tzonou A, Zavitsanos X, Velonakis E, Trichopoulos A (1985). Tobacco smoking, coffee drinking, and occupation as risk factors for bladder cancer in Greece. *J Natl Cancer Inst*, 75(3):455–61. PMID:3861898

Ren JS, Freedman ND, Kamangar F, Dawsey SM, Hollenbeck AR, Schatzkin A, et al. (2010). Tea, coffee, carbonated soft drinks and upper gastrointestinal tract cancer risk in a large United States prospective cohort study. *Eur J Cancer*, 46(10):1873–81. doi:10.1016/j.ejca.2010.03.025 PMID:20395127

Restrepo HE, Correa P, Haenszel W, Brinton LA, Franco A (1989). A case-control study of tobacco-related cancers in Colombia. *Bull Pan Am Health Organ*, 23(4):405–13. PMID:2611462

Riman T, Dickman PW, Nilsson S, Nordlinder H, Magnusson CM, Persson IR (2004). Some life-style factors and the risk of invasive epithelial ovarian cancer in Swedish women. *Eur J Epidemiol*, 19(11):1011–9. doi:10.1007/s10654-004-1633-8 PMID:15648594

Risch HA, Burch JD, Miller AB, Hill GB, Steele R, Howe GR (1988). Dietary factors and the incidence of cancer of the urinary bladder. *Am J Epidemiol*, 127(6):1179–91. doi:10.1093/oxfordjournals.aje.a114911 PMID:3369417

Rodriguez T, Altieri A, Chatenoud L, Gallus S, Bosetti C, Negri E, et al. (2004). Risk factors for oral and pharyngeal cancer in young adults. *Oral Oncol*, 40(2):207–13. doi:10.1016/j.oraloncology.2003.08.014 PMID:14693246

Rohan TE, McMichael AJ (1988). Methylxanthines and breast cancer. *Int J Cancer*, 41(3):390–3. doi:10.1002/ijc.2910410312 PMID:3346103

Ros MM, Bas Bueno-de-Mesquita HB, Büchner FL, Aben KK, Kampman E, Egevad L, et al. (2011). Fluid intake and the risk of urothelial cell carcinomas in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*, 128(11):2695–708. doi:10.1002/ijc.25592 PMID:20715171

Rosenberg L, Miller DR, Helmrich SP, Kaufman DW, Schottenfeld D, Stolley PD, et al. (1985). Breast cancer and the consumption of coffee. *Am J Epidemiol*, 122(3):391–9. doi:10.1093/oxfordjournals.aje.a114120 PMID:4025289

Rosenberg L, Werler MM, Palmer JR, Kaufman DW, Warshauer ME, Stolley PD, et al. (1989). The risks of cancers of the colon and rectum in relation to coffee consumption. *Am J Epidemiol*, 130(5):895–903. doi:10.1093/oxfordjournals.aje.a115422 PMID:2816900

Rosenblatt KA, Thomas DB, Jimenez LM, Fish B, McTiernan A, Stalsberg H, et al. (1999). The relationship between diet and breast cancer in men (United States). *Cancer Causes Control*, 10(2):107–13. doi:10.1023/A:1008808925665 PMID:10231158

Ross JA, Potter JD, Reaman GH, Pendergrass TW, Robison LL (1996). Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United

States): a report from the Children's Cancer Group. *Cancer Causes Control*, 7(6):581–90. doi:10.1007/BF00051700 PMID:8932918

Ross RK, Paganini-Hill A, Landolph J, Gerkins V, Henderson BE (1989). Analgesics, cigarette smoking, and other risk factors for cancer of the renal pelvis and ureter. *Cancer Res*, 49(4):1045–8. PMID:2912549

Rossi M, Lipworth L, Polesel J, Negri E, Bosetti C, Talamini R, et al. (2010). Dietary glycemic index and glycemic load and risk of pancreatic cancer: a case-control study. *Ann Epidemiol*, 20(6):460–5. doi:10.1016/j.annepidem.2010.03.018 PMID:20470973

Russnes KM, Wilson KM, Epstein MM, Kasperzyk JL, Stampfer MJ, Kenfield SA, et al. (2014). Total antioxidant intake in relation to prostate cancer incidence in the Health Professionals Follow-Up Study. *Int J Cancer*, 134(5):1156–65. doi:10.1002/ijc.28438 PMID:23959920

Saito E, Inoue M, Sawada N, Shimazu T, Yamaji T, Iwasaki M, et al. (2015). Association of coffee intake with total and cause-specific mortality in a Japanese population: the Japan Public Health Center-based Prospective Study. *Am J Clin Nutr*, 101(5):1029–37. doi:10.3945/ajcn.114.104273 PMID:25762807

Sala M, Cordier S, Chang-Claude J, Donato F, Escolar-Pujolar A, Fernandez F, et al. (2000). Coffee consumption and bladder cancer in nonsmokers: a pooled analysis of case-control studies in European countries. *Cancer Causes Control*, 11(10):925–31. doi:10.1023/A:1026524014954 PMID:11142527

Sang LX, Chang B, Li XH, Jiang M (2013). Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis. *BMC Gastroenterol*, 13(1):34. doi:10.1186/1471-230X-13-34 PMID:23433483

Sanikini H, Dik VK, Siersema PD, Bhoo-Pathy N, Uiterwaal CS, Peeters PH, et al. (2015b). Total, caffeinated and decaffeinated coffee and tea intake and gastric cancer risk: results from the EPIC cohort study. *Int J Cancer*, 136(6):E720–30. doi:10.1002/ijc.29223 PMID:25236393

Sanikini H, Radoï L, Menvielle G, Guida F, Mattei F, Cénée S, et al. (2015a). Coffee consumption and risk of lung cancer: the ICARE study. *Eur J Epidemiol*, 30(1):81–5. doi:10.1007/s10654-014-9976-2 PMID:25504015

Schairer C, Brinton LA, Hoover RN (1987). Methylxanthines and breast cancer. *Int J Cancer*, 40(4):469–73. doi:10.1002/ijc.2910400406 PMID:3117709

Schmauz R, Cole P (1974). Epidemiology of cancer of the renal pelvis and ureter. *J Natl Cancer Inst*, 52(5):1431–4. doi:10.1093/jnci/52.5.1431 PMID:4831435

Schulte PA, Ringen K, Hemstreet GP, Altekruse EB, Gullen WH, Patton MG, et al. (1985). Risk assessment of a cohort exposed to aromatic amines. Initial results. *J Occup Med*, 27(2):115–21. PMID:3884754

Schulte PA, Ringen K, Hemstreet GP, Altekruse EB, Gullen WH, Tillett S, et al. (1986). Risk factors for bladder cancer in a cohort exposed to aromatic amines. *Cancer*, 58(9):2156–62. doi:10.1002/1097-0142(19861101)58:9<2156::AID-CNCR2820580933>3.0.CO;2-Y PMID:3756832

Schüz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J (2001). High-birth weight and other risk factors for Wilms tumour: results of a population-based case-control study. *Eur J Pediatr*, 160(6):333–8. doi:10.1007/PL00008443 PMID:11421411

Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE (2015). Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. *Gastroenterology*, 148(1):118–25, quiz e15. doi:10.1053/j.gastro.2014.10.005 PMID:25305507

Severson RK, Davis S, Polissar L (1982). Smoking, coffee, and cancer of the pancreas. *Br Med J (Clin Res Ed)*, 285(6336):214. doi:10.1136/bmj.285.6336.214-b PMID:6807425

Severson RK, Nomura AM, Grove JS, Stemmermann GN (1989). A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res*, 49(7):1857–60. PMID:2924323

Shafique K, McLoone P, Qureshi K, Leung H, Hart C, Morrison DS (2012). Coffee consumption and prostate cancer risk: further evidence for inverse relationship. *Nutr J*, 11(11):42. doi:10.1186/1475-2891-11-42 PMID:22695052

Sharpe CR, Siemiatycki J (2002). Consumption of non-alcoholic beverages and prostate cancer risk. *Eur J Cancer Prev*, 11(5):497–501. doi:10.1097/00008469-200210000-00013 PMID:12394248

Shen Z, Liu H, Cao H (2015). Coffee consumption and risk of gastric cancer: an updated meta-analysis. *Clin Res Hepatol Gastroenterol*, 39(2):245–53. doi:10.1016/j.clinre.2014.09.005 PMID:25459992

Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE (1994). A prospective study of pancreatic cancer in the elderly. *Int J Cancer*, 58(1):46–9. doi:10.1002/ijc.2910580109 PMID:8014014

Shimazu T, Inoue M, Sasazuki S, Iwasaki M, Kurahashi N, Yamaji T, et al.; JPHC Study Group Members of the Japan Public Health Center-based Prospective Study (2008). Coffee consumption and risk of endometrial cancer: a prospective study in Japan. *Int J Cancer*, 123(10):2406–10. doi:10.1002/ijc.23760 PMID:18711700

Shimazu T, Tsubono Y, Kuriyama S, Ohmori K, Koizumi Y, Nishino Y, et al. (2005). Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan. *Int J Cancer*, 116(1):150–4. doi:10.1002/ijc.20989 PMID:15756689

Shirlina NG, Vilms EA, Stasenko VL (2015). [Nutrition as a possible risk factor for breast cancer]. *Gig Sanit*, 94(8):48–52. [Russian] PMID:26856173

Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE (2007). Intake of coffee and tea and risk of ovarian cancer: a prospective cohort study. *Nutr Cancer*, 58(1):22–7. doi:10.1080/01635580701307945 PMID:17571963

Silverman DT, Swanson CA, Gridley G, Wacholder S, Greenberg RS, Brown LM, et al. (1998). Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. *J Natl Cancer Inst*, 90(22):1710–9. doi:10.1093/jnci/90.22.1710 PMID:9827525

Simon D, Yen S, Cole P (1975). Coffee drinking and cancer of the lower urinary tract. *J Natl Cancer Inst*, 54(3):587–91. PMID:1123851

Simons CC, Leurs LJ, Weijenberg MP, Schouten LJ, Goldbohm RA, van den Brandt PA (2010). Fluid intake and colorectal cancer risk in the Netherlands Cohort Study. *Nutr Cancer*, 62(3):307–21. doi:10.1080/01635580903407098 PMID:20358468

Sinha R, Cross AJ, Daniel CR, Graubard BI, Wu JW, Hollenbeck AR, et al. (2012). Caffeinated and decaffeinated coffee and tea intakes and risk of colorectal cancer in a large prospective study. *Am J Clin Nutr*, 96(2):374–81. doi:10.3945/ajcn.111.031328 PMID:22695871

Slattery ML, Kampman E, Samowitz W, Caan BJ, Potter JD (2000). Interplay between dietary inducers of GST and the GSTM-1 genotype in colon cancer. *Int J Cancer*, 87(5):728–33. doi:10.1002/1097-0215(20000901)87:5<728::AID-IJC16>3.0.CO;2-G PMID:10925368

Slattery ML, Schumacher MC, West DW, Robison LM (1988a). Smoking and bladder cancer. The modifying effect of cigarettes on other factors. *Cancer*, 61(2):402–8. doi:10.1002/1097-0142(19880115)61:2<402::AID-CNCR2820610233>3.0.CO;2-U PMID:3334975

Slattery ML, West DW (1993). Smoking, alcohol, coffee, tea, caffeine, and theobromine: risk of prostate cancer in Utah (United States). *Cancer Causes Control*, 4(6):559–63. doi:10.1007/BF00052432 PMID:8280834

Slattery ML, West DW, Robison LM (1988b). Fluid intake and bladder cancer in Utah. *Int J Cancer*, 42(1):17–22. doi:10.1002/ijc.2910420105 PMID:3391705

Slattery ML, West DW, Robison LM, French TK, Ford MH, Schuman KL, et al. (1990). Tobacco, alcohol, coffee, and caffeine as risk factors for colon cancer in a low-risk population. *Epidemiology*, 1(2):141–5. doi:10.1097/00001648-199003000-00010 PMID:2073501

Smith SJ, Deacon JM, Chilvers CE; UK National Case-Control Study Group (1994). Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. *Br J Cancer*, 70(1):112–9. doi:10.1038/bjc.1994.258 PMID:8018520

Snowdon DA, Phillips RL (1984). Coffee consumption and risk of fatal cancers. *Am J Public Health*, 74(8):820–3. doi:10.2105/AJPH.74.8.820 PMID:6742274

Soler M, Chatenoud L, La Vecchia C, Franceschi S, Negri E (1998). Diet, alcohol, coffee and pancreatic cancer: final results from an Italian study. *Eur J Cancer Prev*, 7(6):455–60. doi:10.1097/00008469-199812000-00005 PMID:9926293

Song F, Qureshi AA, Han J (2012). Increased caffeine intake is associated with reduced risk of basal cell carcinoma of the skin. *Cancer Res*, 72(13):3282–9. doi:10.1158/0008-5472.CAN-11-3511 PMID:22752299

Song YJ, Kristal AR, Wicklund KG, Cushing-Haugen KL, Rossing MA (2008). Coffee, tea, colas, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*, 17(3):712–6. doi:10.1158/1055-9965.EPI-07-2511 PMID:18349292

Steevens J, Schouten LJ, Verhage BA, Goldbohm RA, van den Brandt PA (2007). Tea and coffee drinking and ovarian cancer risk: results from the Netherlands Cohort Study and a meta-analysis. *Br J Cancer*, 97(9):1291–4. doi:10.1038/sj.bjc.6604008 PMID:17923877

Stensvold I, Jacobsen BK (1994). Coffee and cancer: a prospective study of 43,000 Norwegian men and women. *Cancer Causes Control*, 5(5):401–8. doi:10.1007/BF01694753 PMID:7999961

Stocks P (1957). Statistical survey of cancer in North Wales and Liverpool region. British Empire Cancer Campaign, 35th Annual Report, Part II; 496–501.

Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D (2002). Prospective study of diet and pancreatic cancer in male smokers. *Am J Epidemiol*, 155(9):783–92. doi:10.1093/aje/155.9.783 PMID:11978580

Sturgeon SR, Hartge P, Silverman DT, Kantor AF, Linehan WM, Lynch C, et al. (1994). Associations between bladder cancer risk factors and tumor stage and grade at diagnosis. *Epidemiology*, 5(2):218–25. doi:10.1097/00001648-199403000-00012 PMID:8172997

Sturgeon SR, Ziegler RG, Brinton LA, Nasca PC, Mallin K, Gridley G (1991). Diet and the risk of vulvar cancer. *Ann Epidemiol*, 1(5):427–37. doi:10.1016/1047-2797(91)90012-2 PMID:1669523

Sugiyama K, Kuriyama S, Akhter M, Kakizaki M, Nakaya N, Ohmori-Matsuda K, et al. (2010). Coffee consumption and mortality due to all causes, cardiovascular disease, and cancer in Japanese women. *J Nutr*, 140(5):1007–13. doi:10.3945/jn.109.109314 PMID:20335629

Sugiyama K, Sugawara Y, Tomata Y, Nishino Y, Fukao A, Tsuji I (2017). The association between coffee consumption and bladder cancer incidence in a pooled analysis of the Miyagi Cohort Study and Ohsaki Cohort Study. *Eur J Cancer Prev*, 26(2):125–30. doi:10.1097/CEJ.0000000000000226 PMID:26882077

Sullivan JW (1982). Epidemiologic survey of bladder cancer in greater New Orleans. *J Urol*, 128(2):281–3. doi:10.1016/S0022-5347(17)52886-4 PMID:7109090

Suzuki Y, Tsubono Y, Nakaya N, Suzuki Y, Koizumi Y, Tsuji I (2004). Green tea and the risk of breast cancer: pooled analysis of two prospective studies in Japan. *Br J Cancer*, 90(7):1361–3. doi:10.1038/sj.bjc.6601652 PMID:15054454

Takezaki T, Hirose K, Inoue M, Hamajima N, Kuroishi T, Nakamura S, et al. (1996a). Tobacco, alcohol and dietary factors associated with the risk of oral cancer among Japanese. *Jpn J Cancer Res*, 87(6):555–62. doi:10.1111/j.1349-7006.1996.tb00259.x PMID:8766517

Takezaki T, Hirose K, Inoue M, Hamajima N, Kuroishi T, Nakamura S, et al. (1996b). Risk factors of thyroid cancer among women in Tokai, Japan. *J Epidemiol*, 6(3):140–7. doi:10.2188/jea.6.140 PMID:8952218

Takezaki T, Hirose K, Inoue M, Hamajima N, Yatabe Y, Mitsudomi T, et al. (2001). Dietary factors and lung cancer risk in Japanese: with special reference to fish consumption and adenocarcinomas. *Br J Cancer*, 84(9):1199–206. doi:10.1054/bjoc.2001.1722 PMID:11336471

Talamini R, Barón AE, Barra S, Bidoli E, La Vecchia C, Negri E, et al. (1990). A case-control study of risk factor for renal cell cancer in northern Italy. *Cancer Causes Control*, 1(2):125–31. doi:10.1007/BF00053163 PMID:2102282

Tamakoshi A, Lin Y, Kawado M, Yagyu K, Kikuchi S, Iso H; JACC Study Group (2011). Effect of coffee consumption on all-cause and total cancer mortality: findings from the JACC study. *Eur J Epidemiol*, 26(4):285–93. doi:10.1007/s10654-011-9548-7 PMID:21298466

Tanaka K, Hara M, Sakamoto T, Higaki Y, Mizuta T, Eguchi Y, et al. (2007). Inverse association between coffee drinking and the risk of hepatocellular carcinoma: a case-control study in Japan. *Cancer Sci*, 98(2):214–8. doi:10.1111/j.1349-7006.2006.00368.x PMID:17233838

Tang N, Wu Y, Ma J, Wang B, Yu R (2010). Coffee consumption and risk of lung cancer: a meta-analysis. *Lung Cancer*, 67(1):17–22. doi:10.1016/j.lungcan.2009.03.012 PMID:19362749

Tang N, Zhou B, Wang B, Yu R (2009). Coffee consumption and risk of breast cancer: a metaanalysis. *Am J Obstet Gynecol*, 200(3):290.e1–9. doi:10.1016/j.ajog.2008.10.019 PMID:19114275

Tavani A, Bertuzzi M, Talamini R, Gallus S, Parpinel M, Franceschi S, et al. (2003). Coffee and tea intake and risk of oral, pharyngeal and esophageal cancer. *Oral Oncol*, 39(7):695–700. doi:10.1016/S1368-8375(03)00081-2 PMID:12907209

Tavani A, Gallus S, Dal Maso L, Franceschi S, Montella M, Conti E, et al. (2001). Coffee and alcohol intake and risk of ovarian cancer: an Italian case-control study. *Nutr Cancer*, 39(1):29–34. doi:10.1207/S15327914nc391_4 PMID:11588899

Tavani A, Negri E, Franceschi S, Talamini R, La Vecchia C (1994). Coffee consumption and risk of non-Hodgkin's lymphoma. *Eur J Cancer Prev*, 3(4):351–6. doi:10.1097/00008469-199407000-00008 PMID:7950889

Tavani A, Pregnolato A, La Vecchia C, Favero A, Franceschi S (1998). Coffee consumption and the risk of breast cancer. *Eur J Cancer Prev*, 7(1):77–82. PMID:9511854

Tavani A, Pregnolato A, La Vecchia C, Negri E, Talamini R, Franceschi S (1997a). Coffee and tea intake and risk of cancers of the colon and rectum: a study of 3,530 cases and 7,057 controls. *Int J Cancer*, 73(2):193–7. doi:10.1002/(SICI)1097-0215(19971009)73:2<193::AID-IJC5>3.0.CO;2-R PMID:9335441

Tavani A, Pregnolato A, Negri E, Franceschi S, Serraino D, Carbone A, et al. (1997b). Diet and risk of lymphoid neoplasms and soft tissue sarcomas. *Nutr Cancer*, 27(3):256–60. doi:10.1080/01635589709514535 PMID:9101555

Terry P, Bergkvist L, Holmberg L, Wolk A (2001). Coffee consumption and risk of colorectal cancer in a population based prospective cohort of Swedish women. *Gut*, 49(1):87–90. doi:10.1136/gut.49.1.87 PMID:11413115

Terry P, Lagergren J, Wolk A, Nyrén O (2000). Reflux-inducing dietary factors and risk of adenocarcinoma of the esophagus and gastric cardia. *Nutr Cancer*, 38(2):186–91. doi:10.1207/S15327914NC382_7 PMID:11525596

Terry P, Vainio H, Wolk A, Weiderpass E (2002). Dietary factors in relation to endometrial cancer: a nationwide case-control study in Sweden. *Nutr Cancer*, 42(1):25–32. doi:10.1207/S15327914NC421_4 PMID:12235647

Theodoratou E, Farrington SM, Tenesa A, McNeill G, Cetnarskyj R, Korakakis E, et al. (2014). Associations between dietary and lifestyle risk factors and colorectal cancer in the Scottish population. *Eur J Cancer Prev*, 23(1):8–17. doi:10.1097/CEJ.0b013e3283639fb8 PMID:23820601

Thomopoulos TP, Ntouvelis E, Diamantaras AA, Tzanoudaki M, Baka M, Hatzipantelis E, et al. (2015). Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis. *Cancer Epidemiol*, 39(6):1047–59. doi:10.1016/j.canep.2015.08.009 PMID:26329264

Tian C, Wang W, Hong Z, Zhang X (2013). Coffee consumption and risk of colorectal cancer: a dose-response analysis of observational studies. *Cancer Causes Control*, 24(6):1265–8. doi:10.1007/s10552-013-0200-6 PMID:23546611

Trichopoulos D, Papapostolou M, Polychronopoulou A (1981). Coffee and ovarian cancer. *Int J Cancer*, 28(6):691–3. doi:10.1002/ijc.2910280606 PMID:7333704

Tripathi A, Folsom AR, Anderson KE; Iowa Women's Health Study (2002). Risk factors for urinary bladder carcinoma in postmenopausal women. *Cancer*, 95(11):2316–23. doi:10.1002/cncr.10975 PMID:12436437

Tsubono Y, Nishino Y, Komatsu S, Hsieh CC, Kanemura S, Tsuji I, et al. (2001). Green tea and the risk of gastric cancer in Japan. *N Engl J Med*, 344(9):632–6. doi:10.1056/NEJM200103013440903 PMID:11228277

Turati F, Bosetti C, Polesel J, Zucchetto A, Serraino D, Montella M, et al. (2015). Coffee, tea, cola, and bladder cancer risk: dose and time relationships.

Urology, 86(6):1179–84. doi:10.1016/j.urology.2015.09.017 PMID:26416008

Turati F, Galeone C, Edefonti V, Ferraroni M, Lagiou P, La Vecchia C, et al. (2012). A meta-analysis of coffee consumption and pancreatic cancer. *Ann Oncol*, 23(2):311–8. doi:10.1093/annonc/mdr331 PMID:21746805

Turati F, Galeone C, La Vecchia C, Garavello W, Tavani A (2011b). Coffee and cancers of the upper digestive and respiratory tracts: meta-analyses of observational studies. *Ann Oncol*, 22(3):536–44. doi:10.1093/annonc/mdq603 PMID:20943597

Turati F, Galeone C, Talamini R, Franceschi S, Manzari M, Gallino G, et al. (2011a). Coffee, decaffeinated coffee, tea, and pancreatic cancer risk: a pooled-analysis of two Italian case-control studies. *Eur J Cancer Prev*, 20(4):287–92. doi:10.1097/CEJ.0b013e32834572e7 PMID:21403521

Tverdal A (2015). Boiled coffee consumption and the risk of prostate cancer: follow-up of 224,234 Norwegian men 20-69 years. *Br J Cancer*, 112(3):576–9. doi:10.1038/bjc.2014.645 PMID:25535729

Tverdal A, Hjellvik V, Selmer R (2011). Coffee intake and oral-oesophageal cancer: follow-up of 389,624 Norwegian men and women 40-45 years. *Br J Cancer*, 105(1):157–61. doi:10.1038/bjc.2011.192 PMID:21629248

Tworoger SS, Gertig DM, Gates MA, Hecht JL, Hankinson SE (2008). Caffeine, alcohol, smoking, and the risk of incident epithelial ovarian cancer. *Cancer*, 112(5):1169–77. doi:10.1002/cncr.23275 PMID:18213613

Tzonou A, Day NE, Trichopoulos D, Walker A, Saliaraki M, Papapostolou M, et al. (1984). The epidemiology of ovarian cancer in Greece: a case-control study. *Eur J Cancer Clin Oncol*, 20(8):1045–52. doi:10.1016/0277-5379(84)90107-X PMID:6540687

Uccella S, Mariani A, Wang AH, Vierkant RA, Cliby WA, Robien K, et al. (2013). Intake of coffee, caffeine and other methylxanthines and risk of Type I vs Type II endometrial cancer. *Br J Cancer*, 109(7):1908–13. doi:10.1038/bjc.2013.540 PMID:24022184

Ugnat A-M, Luo W, Semenciw R, Mao Y; Canadian Cancer Registries Epidemiology Research Group (2004). Occupational exposure to chemical and petrochemical industries and bladder cancer risk in four western Canadian provinces. *Chronic Dis Can*, 25(2):7–15. PMID:15554606

US Department of Health and Human Services (2014). The Health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta (GA), USA: United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014. Available from: http://www.surgeongeneral.gov/library/reports/50-years-of-progress/#fullreport [Printed with corrections].

Vassileiou A, Vlastarakos PV, Kandiloros D, Delicha E, Ferekidis E, Tzagaroulakis A, et al. (2012). Laryngeal cancer: smoking is not the only risk factor. *B-ENT*, 8(4):273–8. PMID:23409557

Vatten LJ, Solvoll K, Løken EB (1990). Coffee consumption and the risk of breast cancer. A prospective study of 14,593 Norwegian women. *Br J Cancer*, 62(2):267–70. doi:10.1038/bjc.1990.274 PMID:2386741

Veierød MB, Thelle DS, Laake P (1997). Diet and risk of cutaneous malignant melanoma: a prospective study of 50,757 Norwegian men and women. *Int J Cancer*, 71(4):600–4. doi:10.1002/(SICI)1097-0215(19970516)71:4<600::AID-IJC15>3.0.CO;2-F PMID:9178814

Vena JE, Freudenheim J, Graham S, Marshall J, Zielezny M, Swanson M, et al. (1993). Coffee, cigarette smoking, and bladder cancer in western New York. *Ann Epidemiol*, 3(6):586–91. doi:10.1016/1047-2797(93)90079-J PMID:7921304

Villanueva CM, Silverman DT, Murta-Nascimento C, Malats N, Garcia-Closas M, Castro F, et al. (2009). Coffee consumption, genetic susceptibility and bladder cancer risk. *Cancer Causes Control*, 20(1):121–7. doi:10.1007/s10552-008-9226-6 PMID:18798002

Villeneuve PJ, Johnson KC, Hanley AJ, Mao Y; Canadian Cancer Registries Epidemiology Research Group (2000). Alcohol, tobacco and coffee consumption and the risk of pancreatic cancer: results from the Canadian Enhanced Surveillance System case-control project. *Eur J Cancer Prev*, 9(1):49–58. doi:10.1097/00008469-200002000-00007 PMID:10777010

Villeneuve PJ, Johnson KC, Kreiger N, Mao Y; The Canadian Cancer Registries Epidemiology Research Group (1999). Risk factors for prostate cancer: results from the Canadian National Enhanced Cancer Surveillance System. *Cancer Causes Control*, 10(5):355–67. doi:10.1023/A:1008958103865 PMID:10530605

Vlajinac H, Jarebinski M, Adanja B (1987). Relationship of some biosocial factors to colon cancer in Belgrade (Yugoslavia). *Neoplasma*, 34(4):503–7. PMID:3658050

von Ruesten A, Feller S, Bergmann MM, Boeing H (2013). Diet and risk of chronic diseases: results from the first 8 years of follow-up in the EPIC-Potsdam study. *Eur J Clin Nutr*, 67(4):412–9. doi:10.1038/ejcn.2013.7 PMID:23388667

Wakai K, Hirose K, Takezaki T, Hamajima N, Ogura Y, Nakamura S, et al. (2004). Foods and beverages in relation to urothelial cancer: case-control study in Japan. *Int J Urol*, 11(1):11–9. doi:10.1111/j.1442-2042.2004.00740.x PMID:14678179

Wakai K, Kurozawa Y, Shibata A, Fujita Y, Kotani K, Ogimoto I, et al.; JACC Study Group (2007). Liver cancer risk, coffee, and hepatitis C virus infection: a nested case-control study in Japan. *Br J Cancer*, 97(3):426–8. doi:10.1038/sj.bjc.6603891 PMID:17637681

Wang J, Li X, Zhang D (2016). Coffee consumption and the risk of cutaneous melanoma: a meta-analysis. *Eur J Nutr*, doi:10.1007/s00394-015-1139-z PMID:26695410

Wang J, Wu X, Kamat A, Barton Grossman H, Dinney CP, Lin J (2013a). Fluid intake, genetic variants of UDP-glucuronosyltransferases, and bladder cancer risk. *Br J Cancer*, 108(11):2372–80. doi:10.1038/bjc.2013.190 PMID:23632476

Wang Y, Yu X, Wu Y, Zhang D (2012). Coffee and tea consumption and risk of lung cancer: a dose-response analysis of observational studies. *Lung Cancer*, 78(2):169–70. doi:10.1016/j.lungcan.2012.08.009 PMID:22964413

Wang ZJ, Ohnaka K, Morita M, Toyomura K, Kono S, Ueki T, et al. (2013b). Dietary polyphenols and colorectal cancer risk: the Fukuoka colorectal cancer study. *World J Gastroenterol*, 19(17):2683–90. doi:10.3748/wjg.v19.i17.2683 PMID:23674876

Washio M, Mori M, Sakauchi F, Watanabe Y, Ozasa K, Hayashi K, et al.; JACC Study Group (2005). Risk factors for kidney cancer in a Japanese population: findings from the JACC Study. *J Epidemiol*, 15(Suppl 2):S203–11. doi:10.2188/jea.15.S203 PMID:16127235

Weiderpass E, Sandin S, Lof M, Oh JK, Inoue M, Shimazu T, et al. (2014). Endometrial cancer in relation to coffee, tea, and caffeine consumption: a prospective cohort study among middle-aged women in Sweden. *Nutr Cancer*, 66(7):1132–43. doi:10.1080/01635581.2014.948214 PMID:25181598

Whittemore AS, Paffenbarger RS Jr, Anderson K, Halpern J (1983). Early precursors of pancreatic cancer in college men. *J Chronic Dis*, 36(3):251–6. doi:10.1016/0021-9681(83)90059-0 PMID:6826689

Whittemore AS, Paffenbarger RS Jr, Anderson K, Lee JE (1985). Early precursors of site-specific cancers in college men and women. *J Natl Cancer Inst*, 74(1):43–51. PMID:3855486

Whittemore AS, Wu ML, Paffenbarger RS Jr, Sarles DL, Kampert JB, Grosser S, et al. (1988). Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol*, 128(6):1228–40. doi:10.1093/oxfordjournals.aje.a115077 PMID:3195564

Wilson KM, Bälter K, Möller E, Adami HO, Andrén O, Andersson SO, et al. (2013). Coffee and risk of prostate cancer incidence and mortality in the Cancer of the Prostate in Sweden Study. *Cancer Causes Control*, 24(8):1575–81. doi:10.1007/s10552-013-0234-9 PMID:23702886

Wilson KM, Giovannucci E, Stampfer MJ, Mucci LA (2012). Dietary acrylamide and risk of prostate cancer. *Int J Cancer*, 131(2):479–87. doi:10.1002/ijc.26383 PMID:21866549

Wilson KM, Kasperzyk JL, Rider JR, Kenfield S, van Dam RM, Stampfer MJ, et al. (2011). Coffee consumption and prostate cancer risk and progression in the Health Professionals Follow-up Study. *J Natl Cancer Inst*, 103(11):876–84. doi:10.1093/jnci/djr151 PMID:21586702

Wilson KM, Mucci LA, Cho E, Hunter DJ, Chen WY, Willett WC (2009). Dietary acrylamide intake and risk of premenopausal breast cancer. *Am J Epidemiol*, 169(8):954–61.doi:10.1093/aje/kwn421PMID:19224978

Woolcott CG, King WD, Marrett LD (2002). Coffee and tea consumption and cancers of the bladder, colon and rectum. *Eur J Cancer Prev*, 11(2):137–45. doi:10.1097/00008469-200204000-00005 PMID:11984131

Wu AH, Yu MC, Tseng CC, Hankin J, Pike MC (2003). Green tea and risk of breast cancer in Asian Americans. *Int J Cancer*, 106(4):574–9. doi:10.1002/ijc.11259 PMID:12845655

Wu H, Reeves KW, Qian J, Sturgeon SR (2015a). Coffee, tea, and melanoma risk among postmenopausal women. *Eur J Cancer Prev*, 24(4):347–52. doi:10.1097/CEJ.0000000000000093 PMID:25325307

Wu S, Han J, Song F, Cho E, Gao X, Hunter DJ, et al. (2015b). Caffeine intake, coffee consumption, and risk of cutaneous malignant melanoma. *Epidemiology*, 26(6):898–908. doi:10.1097/EDE.0000000000000360 PMID:26172864

Wu W, Tong Y, Zhao Q, Yu G, Wei X, Lu Q (2015). Coffee consumption and bladder cancer: a meta-analysis of observational studies. *Sci Rep*, 5(1):9051. doi:10.1038/srep09051 PMID:25761588

Wynder EL, Dieck GS, Hall NE (1986). Case-control study of decaffeinated coffee consumption and pancreatic cancer. *Cancer Res*, 46(10):5360–3. PMID:3756885

Wynder EL, Dieck GS, Hall NE, Lahti H (1985). A case-control study of diesel exhaust exposure and bladder cancer. *Environ Res*, 37(2):475–89. doi:10.1016/0013-9351(85)90129-X PMID:2410250

Wynder EL, Goldsmith R (1977). The epidemiology of bladder cancer: a second look. *Cancer*, 40(3):1246–68. doi:10.1002/1097-0142(197709)40:3<1246::AID-CNCR2820400340>3.0.CO;2-5 PMID:332323

Wynder EL, Hall NE, Polansky M (1983). Epidemiology of coffee and pancreatic cancer. *Cancer Res*, 43(8):3900–6. PMID:6861152

Xie F, Wang D, Huang Z, Guo Y (2014). Coffee consumption and risk of gastric cancer: a large updated meta-analysis of prospective studies. *Nutrients*, 6(9):3734–46. doi:10.3390/nu6093734 PMID:25237829

Xie Y, Qin J, Nan G, Huang S, Wang Z, Su Y (2016). Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies. *Eur J Clin Nutr*, 70(2):199–206. doi:10.1038/ejcn.2015.96 PMID:26081490

Yamada H, Kawado M, Aoyama N, Hashimoto S, Suzuki K, Wakai K, et al.; JACC Study Group (2014). Coffee consumption and risk of colorectal cancer: the Japan

Collaborative Cohort Study. *J Epidemiol*, 24(5):370–8. doi:10.2188/jea.JE20130168 PMID:24857957

Yan K, Xu X, Liu X, Wang X, Hua S, Wang C, et al. (2015). The associations between maternal factors during pregnancy and the risk of childhood acute lymphoblastic leukemia: A meta-analysis. *Pediatr Blood Cancer*, 62(7):1162–70. doi:10.1002/pbc.25443 PMID:25728190

Yang TO, Crowe F, Cairns BJ, Reeves GK, Beral V (2015). Tea and coffee and risk of endometrial cancer: cohort study and meta-analysis. *Am J Clin Nutr*, 101(3):570–8. doi:10.3945/ajcn.113.081836 PMID:25733642

Yeh CC, Hsieh LL, Tang R, Chang-Chieh CR, Sung FC (2003). Risk factors for colorectal cancer in Taiwan: a hospital-based case-control study. *J Formos Med Assoc*, 102(5):305–12. PMID:12874668

Yen S, Hsieh CC, MacMahon B (1987). Extrahepatic bile duct cancer and smoking, beverage consumption, past medical history, and oral-contraceptive use. *Cancer*, 59(12):2112–6. doi:10.1002/1097-0142(19870615)59:12<2112::AID-CNCR2820590122>3.0.CO;2-H PMID:3567872

Yew YW, Lai YC, Schwartz RA (2016). Coffee consumption and melanoma: a systematic review and meta-analysis of observational studies. *Am J Clin Dermatol*, 17(2):113–23. doi:10.1007/s40257-015-0165-1 PMID:26547919

Yu MC, Mack TM, Hanisch R, Cicioni C, Henderson BE (1986). Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. *J Natl Cancer Inst*, 77(2):351–6. PMID:3461197

Yu X, Bao Z, Zou J, Dong J (2011). Coffee consumption and risk of cancers: a meta-analysis of cohort studies. *BMC Cancer*, 11(1):96. doi:10.1186/1471-2407-11-96 PMID:21406107

Zamora-Ros R, Luján-Barroso L, Bueno-de-Mesquita HB, Dik VK, Boeing H, Steffen A, et al. (2014). Tea and coffee consumption and risk of esophageal cancer: the European prospective investigation into cancer and nutrition study. *Int J Cancer*, 135(6):1470–9. doi:10.1002/ijc.28789 PMID:24535727

Zatonski WA, Boyle P, Przewozniak K, Maisonneuve P, Drosik K, Walker AM (1993). Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. *Int J Cancer*, 53(4):601–7. doi:10.1002/ijc.2910530413 PMID:8436433

Zatonski WA, La Vecchia C, Przewozniak K, Maisonneuve P, Lowenfels AB, Boyle P (1992). Risk factors for gallbladder cancer: a Polish case-control study. *Int J Cancer*, 51(5):707–11. doi:10.1002/ijc.2910510508 PMID:1612778

Zeegers MP, Dorant E, Goldbohm RA, van den Brandt PA (2001). Are coffee, tea, and total fluid consumption associated with bladder cancer risk? Results from the Netherlands Cohort Study. *Cancer Causes Control*, 12(3):231–8. doi:10.1023/A:1011245627593 PMID:11405328

Zeng SB, Weng H, Zhou M, Duan XL, Shen XF, Zeng XT (2015). Long-term coffee consumption and risk of gastric cancer: a PRISMA-compliant dose-response meta-analysis of prospective cohort studies. *Medicine (Baltimore)*, 94(38):e1640. doi:10.1097/MD.0000000000001640 PMID:26402838

Zhang M, Holman CD, Huang JP, Xie X (2007). Green tea and the prevention of breast cancer: a case-control study in Southeast China. *Carcinogenesis*, 28(5):1074–8. doi:10.1093/carcin/bgl252 PMID:17183063

Zhang X, Albanes D, Beeson WL, van den Brandt PA, Buring JE, Flood A, et al. (2010). Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. *J Natl Cancer Inst*, 102(11):771–83. doi:10.1093/jnci/djq107 PMID:20453203

Zhang Y, Wang X, Cui D (2015). Association between coffee consumption and the risk of oral cancer: a meta-analysis of observational studies. *Int J Clin Exp Med*, 8(7):11657–65. PMID:26380002

Zheng JS, Yang J, Fu YQ, Huang T, Huang YJ, Li D (2013). Effects of green tea, black tea, and coffee consumption on the risk of esophageal cancer: a systematic review and meta-analysis of observational studies. *Nutr Cancer*, 65(1):1–16. doi:10.1080/01635581.2013.741762 PMID:23368908

Zheng W, McLaughlin JK, Gridley G, Bjelke E, Schuman LM, Silverman DT, et al. (1993). A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control*, 4(5):477–82. doi:10.1007/BF00050867 PMID:8218880

Zhong S, Chen W, Yu X, Chen Z, Hu Q, Zhao J (2014). Coffee consumption and risk of prostate cancer: an up-to-date meta-analysis. *Eur J Clin Nutr*, 68(3):330–7. doi:10.1038/ejcn.2013.256 PMID:24300907

Zhou Q, Luo ML, Li H, Li M, Zhou JG (2015). Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. *Sci Rep*, 5(1):13410. doi:10.1038/srep13410 PMID:26302813

Zvrko E, Gledović Z, Ljaljević A (2008). Risk factors for laryngeal cancer in Montenegro. *Arh Hig Rada Toksikol*, 59(1):11–8. doi:10.2478/10004-1254-59-2008-1863 PMID:18407867

3. CANCER IN EXPERIMENTAL ANIMALS

In its previous evaluation (*IARC Monographs* Volume 51; IARC, 1991), the Working Group concluded that the results of animal bioassays provided *inadequate evidence* for the carcinogenicity of coffee. This section provides an evaluation of the carcinogenicity, co-carcinogenicity, and initiation–promotion studies reviewed in Volume 51 of the *IARC Monographs* and a review of any studies published since that time.

3.1 Studies of carcinogenicity

See Table 3.1.

3.1.1 Mouse

Bauer et al. (1977) reported the results of a drinking-fluid study in which three cohorts of male C57BL/6J mice were given brewed coffee (55 mice) or boiled water (54 mice) over their lifetime. Mice given coffee demonstrated lower body weights and decreased survival, even though this group had a higher food and fluid intake throughout the study. Since no histopathology was included in the study design, no conclusions could be drawn as to whether the decreased survival was related to cancer incidence. [The Working Group determined that this study was inadequate for evaluation.] Bauer et al. (1977) also mentioned that an identical study was performed with A/J mice, but provided no quantitative data from this study.

Stalder et al. (1990) reported the results of a well-designed and well-conducted 2-year bioassay to determine the possible carcinogenicity of instant coffee (given as a dietary supplement) in Swiss mice. Coffee administration was initiated after mating of parental (F_0 generation) mice and was continued throughout the F_0 and F_1 generations. Beginning after mating and continuing throughout gestation, parturition, and lactation, dams (F_0 generation) were given either basal diet (control dams) or basal diet supplemented with 1% instant coffee (1% coffee was the maximum dietary supplement that did not affect fertility in dams). At weaning, F_1 mice were randomized into groups of 150 per sex and were given diets supplemented with 1%, 2.5%, or 5% instant coffee for 2 years. Controls (born from control dams) were only given basal diet for the same period.

The consumption of a coffee-supplemented diet was associated with a statistically significant, dose-related increase in survival in both sexes. Although food intake in coffee-supplemented groups did not differ from that in sex-matched controls, coffee induced a dose-related suppression of body-weight gain in both sexes. Differences from control body weights were statistically significant in male mice given 2.5% and 5% coffee and in all three groups of female mice given coffee ($P < 0.001$ for all comparisons). [The study authors attributed decreased body weights to increased activity in groups receiving coffee supplements.]

In comparison to female mice in the dietary control group, female mice given coffee

Table 3.1 Studies of carcinogenicity in experimental animals exposed to coffee

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Dose(s) No. animals/group at start No. of surviving animals/group	Results	Significance	Comments
Full carcinogenicity Mouse, Swiss (M) In utero Fetal life + 2 yr Stalder et al. (1990)	In utero + oral (diet) Instant coffee 0 (control), 1%, 2.5%, 5% in F_1 generation diet In utero (dams given 0 (control) or 1% instant coffee in the diet) + continuous exposure (F_1 generation diet) 150, 150, 150, 150/group 32, 48, 57, 76	Liver: hepatocellular adenoma		Principal strengths: large group size (150/group), statistical analysis, in utero exposure Decreased incidences of lymphosarcoma also seen in liver, lung, pancreas, spleen, thymus, lymph nodes, and small intestine
		Tumour incidence: 46/135, 47/140, 26/142, 18/143	Incidences in 2.5% and 5% groups are significantly decreased from control; statistically significant trend towards reduced adenoma incidence with increasing dose	
		Kidney: lymphosarcoma		
		Tumour incidence: 20/135, 11/139, 7/142, 2/143	2.5% and 5% dose: statistically significant negative association; significant negative trend with dose	
		All sites: benign tumours		
		Tumour incidence: 56/136, 59/141, 44/142, 26/143	Statistically significant trend towards lower incidence with increasing dose	
		All sites: malignant tumours		
		Tumour incidence: 54/136, 45/141, 40/142, 26/143	Statistically significant trend towards lower incidence with increasing dose	
		All sites: all tumours		
		Tumour incidence: 96/136, 88/141, 77/142, 49/143	Statistically significant trend towards lower incidence with increasing dose	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Dose(s) No. animals/group at start No. of surviving animals/group	Results	Significance	Comments
Full carcinogenicity Mouse, Swiss (F) In utero Fetal life + 2 yr Stalder et al. (1990)	In utero + oral (diet) Instant coffee 0 (control), 1%, 2.5%, 5% in F_1 generation diet In utero (dams given 0 (control) or 1% instant coffee in the diet) + continuous exposure (F_1 generation diet) 150, 150, 150, 150/group 30, 49, 41, 84	Uterus: leiomyoma		Principal strengths: large group size (150/group), statistical analysis, in utero exposure Decreased incidences of lymphosarcoma also seen in liver, lung, pancreas, spleen, salivary gland, urinary bladder, thymus, lymph nodes, and large intestine
		Tumour incidence: 0/142, 2/146, 0/145, 4/140	Statistically significant trend towards increased incidence ($P < 0.05$) with increasing dose	
		Kidney: lymphosarcoma		
		Tumour incidence: 26/146, 13/146, 16/146, 3/148	Statistically significant decreased incidence in 5% coffee groups; significant negative trend with increasing dose	
		All sites: malignant tumours		
		Tumour incidence: 67/146, 41/147, 46/146, 34/149	Statistically significant trend towards decreased tumour incidence with increasing dose	
		All sites: all tumours		
		Tumour incidence: 83/146, 60/147, 67/146, 54/149	Statistically significant trend towards decreased tumour incidence with increasing dose	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Dose(s) No. animals/group at start No. of surviving animals/group	Results	Significance	Comments
Full carcinogenicity Rat, Sprague-Dawley (M) In utero Fetal life + 2 yr Palm et al. (1984)	In utero + drinking fluid Brewed coffee (in tap water) 0, 0, 25, 50, 100% In utero (dams given tap water (control) or 50% coffee as drinking-water) + continuous (F_1 generation drinking-water) exposure 55, 55, 55, 55, 55/group NR	Skin: fibrosarcoma or squamous cell carcinoma (combined) Tumour incidence: 0/55, 2/55, 7/55, 3/55, 0/55 Skin: fibrosarcoma Tumour incidence: 0/55, 1/55, 4/55, 1/55, 0/55 Skin: squamous cell carcinoma Tumour incidence: 0/55, 1/55, 3/55, 2/55, 0/55	Increase was statistically significant only in 25% coffee group ($P < 0.05$; X^2 test, vs pooled controls) NS NS	Principal strengths: in utero exposure, statistics Coffee was analysed chemically; two control groups
Full carcinogenicity Rat, Sprague-Dawley (F) In utero Fetal life + 2 yr Palm et al. (1984)	In utero + drinking fluid Brewed coffee (in tap water) 0, 0, 25%, 50%, 100% In utero (dams given tap water (control) or 50% coffee as drinking-water) + continuous (F_1 generation drinking-water) exposure 55, 55, 55, 55, 55/group NR	Mammary gland: fibroadenoma Tumour incidence: 25/55, 23/55, 23/55, 11/55, 14/55	50% and 100% dose groups: statistically significantly reduced ($P < 0.05$; X^2 test, vs pooled controls)	Principal strengths: in utero exposure, statistics Coffee was analysed chemically; two control groups

F, female; M, male; NR, not reported; NS, not significant; vs, versus; yr, year

demonstrated a statistically significant trend towards increased incidence of leiomyoma of the uterus (0/142, 2/146, 0/145, 4/140). By contrast, statistically significant and dose-related reductions in the incidence of lymphosarcoma were seen in the kidney, liver, lung, pancreas, salivary gland, spleen, thymus, lymph nodes, large intestine, and urinary bladder. In comparison to male mice in the dietary control group, male mice given coffee demonstrated statistically significant and dose-related reductions in the incidence of lymphosarcoma of the kidney, liver, lung, pancreas, thymus, lymph nodes, small intestine, and spleen. In addition, male mice given coffee demonstrated a statistically significant, dose-related reduction in the incidence of hepatocellular adenoma. Statistically significant, dose-related negative associations were seen in both sexes for level of coffee exposure and total tumour incidence, and level of coffee exposure and total incidence of malignant tumours. [The Working Group noted the possibility that the observed reductions in tumour incidence were related to the statistically significant suppression of mean body weights in male and female mice given coffee.]

3.1.2 Rat

Palm et al. (1984) reported the results of a well-designed and well-conducted 2-year bioassay of fresh brewed coffee in Sprague-Dawley rats. The green coffee mix, roast colour, grind, and freshness criteria of the ground coffee used in the study (provided vacuum-packed by the National Coffee Association of the USA) was almost identical to that of the commercial coffee commonly purchased in the USA. Coffee administration was initiated before mating of parental (F_0 generation) rats and was continued throughout the F_0 and F_1 generations. Beginning 5 weeks before mating and continuing throughout gestation, parturition, and lactation, dams (F_0 generation) were given either 50% coffee (the maximum concentration tolerated by dams) or tap water only. When F_1 rats were aged 5–6 weeks, those whose dams were given either 50% coffee or tap water only were randomized into groups (55 F_1 rats per sex per group). F_1 rats from coffee-treated dams were given 100%, 50%, or 25% fresh brewed coffee as their only fluid source for 2 years. F_1 rats from control dams were randomized into two control groups (55 F_1 rats per sex per group) to be given tap water only for 2 years.

No significant differences in mortality were seen in any group of male rats receiving coffee compared with pooled male controls. By contrast, statistically significant decreases in survival were seen in female rats given 50% and 100% coffee as their only fluid source compared with pooled female controls. Despite increases in food and fluid intake, statistically significant reductions in group mean body weight were seen in male rats given 100% coffee as their only fluid source; mean body weights in other groups were not statistically different from controls given tap water only.

When compared with sex-matched controls given water only, no statistically significant increases in the total incidence of primary tumours were seen in any group given coffee at 25%, 50%, or 100% of fluid intake. However, in statistical analyses based on the assumption that tumours were non-lethal (Mantel–Haenszel model), time-to-tumour analyses identified a statistically significant increase in the number of tumour-bearing male rats in the group given 25% coffee. By contrast, no statistically significant differences were seen in male rats given 50% coffee or 100% coffee, or in female rats given coffee at any concentration. [The Working Group noted that the increased number of tumour-bearing male rats was not related to dose.]

In comparison to sex-matched controls, the total incidence of fibrosarcoma or squamous cell carcinoma (combined) of the skin was significantly increased in male rats given 25%

coffee (7/55 vs 2/110 in pooled male controls); however, the incidences in male rats given 50% and 100% coffee (3/55 and 0/55, respectively) were not significantly different from pooled male controls. [The Working Group noted that the increased incidence of skin tumours in male rats given 25% coffee was the result of small increases in the incidences of both epithelial and mesenchymal tumours (squamous cell carcinoma and fibrosarcoma, respectively), neither of which was itself significant.] No significant differences in the incidence of skin tumours in female rats between the control group and any coffee-exposed group were observed. Statistically significant decreases in the incidence of fibroadenoma of the mammary gland were seen in female rats given 50% or 100% coffee (11/55 and 14/55, respectively, vs 48/110 in pooled female controls) (Palm et al., 1984).

Würzner et al. (1977a, b) reported the results of a 2-year study in which groups of 40 male and 40 female Sprague-Dawley rats [age not reported; weight, approximately 100 g] were given a chow diet supplemented with regular instant coffee, decaffeinated instant coffee, or decaffeinated instant coffee + caffeine for 2 years. Both spray-dried and freeze-dried instant coffees were tested; extraction rates of instant coffees given to different groups varied over the range 23.0–50.2%. Instant coffee was given at 6% of the diet, determined to be the maximum tolerated level for rats. The effective numbers of rats were 28–36 for groups of coffee-treated males and 34–39 for groups of coffee-treated females. The effective numbers of rats for the control groups were 31 males and 36 females.

No pair-wise statistical comparisons or trend tests for the effects of coffee on the incidence of specific benign or malignant tumours were performed. In general, rats given caffeinated coffee or decaffeinated coffee + caffeine had fewer tumours than controls; the reduction in the incidence of benign tumours, malignant tumours, or their combination, was significant for three groups of male rats given caffeinated coffee or decaffeinated coffee + caffeine. The only statistically significant difference in female rats was an increase in total malignant tumours in one group given caffeinated coffee; this finding was not seen in a parallel cohort of female rats that were given a comparable level of coffee exposure [interpreted by the Working Group as an isolated and not reproducible finding]. [The Working Group noted that the value of this study is limited by the lack of pair-wise statistical comparisons of tumour incidences at specific sites.]

3.2 Co-carcinogenicity and initiation–promotion studies

Co-carcinogenicity and initiation–promotion studies of coffee were previously reviewed in the *IARC Monographs* (Volume 51; IARC, 1991), where the Working Group reported being aware of various experiments (e.g. Mori & Hirono, 1977; Fujii et al., 1980; Wattenberg & Lam, 1984; Nishikawa et al., 1986) that were part of studies on the modifying effects of coffee on the activity of known carcinogens. These studies were not included in that monograph because their design was considered inadequate for revealing any effect of coffee on tumour production (short duration of exposure and/or limited numbers of animals).

See Table 3.2.

3.2.1 Rat

Mori & Hirono (1977) conducted initiation–promotion studies of coffee by giving four groups of 10 male and 10 female Sprague-Dawley rats either: a solution of brewed Brazilian coffee (2 g/100 mL water) instead of drinking-water for 480 days; a coffee solution for 120 days, a single gavage dose of cycasin at 150 mg/kg bw on day 121 followed by tap drinking-water until day 480; tap water for 120 days, cycasin on day 121, coffee for another 120 days then tap water until day 480;

Table 3.2 Co-carcinogenicity and initiation–promotion studies in experimental animals exposed to coffee

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Vehicle Dose(s) No. of animals at start No. surviving animals	Results	Significance	Comments
Initiation–promotion (tested as promoter) Rat, Sprague-Dawley (M) Age 3 wk 290 days Fujii et al. (1980)	Drinking-water Brewed coffee, Brazilian coffee Tap water Diet containing 0.025% AAF for 8 wk and then fed the basal diet alone, and given concomitantly a solution of coffee instead of drinking-water for 290 days (Group 1); AAF diet and tap water as drinking-water for 8 wk and then fed the basal diet and given coffee solution (Group 2); AAF diet and tap water as drinking-water for the first 8 wk then basal diet and tap water (Group 3); or basal diet and tap water only (Group 4). 10, 10, 10, 10/group 10, 10, 9, 10	Mammary gland: adenocarcinoma Tumour incidence: 2/10, 0/10, 0/9, 0/9	NS	Principal limitations: limited description of experimental details; small number of animals per group
Initiation–promotion (tested as promoter) Rat, Sprague-Dawley (F) Age 3 wk 290 days Fujii et al. (1980)	Drinking-water Brewed coffee, Brazilian coffee Tap water Diet containing 0.025% AAF for 8 wk and then fed the basal diet alone, and given concomitantly a solution of coffee instead of drinking-water for 290 days (Group 1); AAF diet and tap water as drinking-water for 8 wk and then fed the basal diet and given coffee solution (Group 2); AAF diet and tap water as drinking-water for the first 8 wk then basal diet and tap water (Group 3); or basal diet and tap water only (Group 4). 10, 10, 10, 10/group 9, 10, 10, 10	Mammary gland: adenocarcinoma Tumour incidence: 4/10, 7/10*, 2/10, 0/9	*P = 0.034 (Fisher exact test, vs Group 3)	Principal limitations: limited description of experimental details; small number of animals per group

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Vehicle Dose(s) No. of animals at start No. surviving animals	Results	Significance	Comments
Initiation–promotion (tested as initiator) Rat, Sprague-Dawley (F) Age 34 days 20 wk Wattenberg & Lam (1984)	Feed Green coffee beans Addition of 0, 10, or 20% green coffee beans to the diet for 14 days, 1 day before a single gavage dose of 12 mg DMBA in 1 mL olive oil: experiment 1: 0 or 10% + DMBA; experiment 2: 0 or 20% + DMBA; experiment 3: 0, 10, or 20% + DMBA 16, 16, 16, 16, 32, 16, 16/group 16, 16, 16, 16, 32, 16, 16	Mammary: tumours Tumour incidence: 13/16, 8/16, 16/16, 9/16*, 30/32, 13/16, 9/16* Tumours per rat: 1.9 ± 0.3, 0.9 ± 0.3**, 3.2 ± 0.3, 1.1 ± 0.3**, 2.7 ± 0.2, 1.9 ± 0.3**, 1.2 ± 0.3**	*$P < 0.01$ (decrease) **$P < 0.01$ (decrease)	Principal limitations: contains little experimental details on exact design, clinical observations, body weight gain, or survival In a fourth experiment, 10% green coffee beans tested as promoter significantly decreased the incidence of DMBA-induced mammary tumours
Co-carcinogenicity Rat, Sprague-Dawley (F) Age 4 wk 630 days Nishikawa et al. (1986)	Drinking-water Roasted coffee (Brazil), brewed, 2 g/100 mL Tap water Group 1: diet containing 0.01% aminopyrine and 0.1% sodium nitrite + brewed coffee solution as drinking-water; group 2: diet containing 0.01% aminopyrine and 0.1% sodium nitrite + tap water for drinking-water; group 3: diet containing 0.01% aminopyrine alone + coffee solution as drinking-water; group 4: diet containing 0.01% aminopyrine + tap water for drinking-water; group 5: basal diet + tap water 12, 12, 12, 12, 12/group 9, 9, 7, 8, 10	Liver: tumours Tumour incidence: 2/9* (all adenomas), 7/9 (adenoma, 5/9; carcinoma, 1/9; haemangiosarcoma, 1/9), 0/7, 0/8, 0/10	*$P < 0.03$ (decrease vs group 2; Fisher exact test)	
Initiation–promotion (tested as initiator) Rat, Sprague-Dawley (F) Age 24 days 22.5 wk Welsch et al. (1988)	Drinking-water Brewed coffee, full strength Water (control), full-strength, full-strength decaf., full-strength decaf. + caffeine (860 mg/L), or caffeine (860 mg/L) ad libitum in drinking-water Single i.v. dose of DMBA (2 mg/100 g bw in a lipid emulsion) given at age 53 days; dosing until age 56 days, and held an additional 18 wk 41, 40, 41, 41, 40/group NR	Mammary gland: carcinoma Tumour incidence: 38/41, 31/40, 40/41, 37/41, 36/40 Number of tumours per rat: 6.5, 2.5*, 4.9, 3.3*, 2.7* Total tumours: 266, 99, 199, 137, 109	NS *$P < 0.05$ (decrease)	Principal strengths: well-described and -conducted study Addition of caffeine was also studied

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Vehicle Dose(s) No. of animals at start No. surviving animals	Results	Significance	Comments
Initiation–promotion (tested as initiator) Rat, Sprague-Dawley (F) Age 26 days 16.5 wk Welsch et al. (1988)	Drinking-water Brewed coffee, moderate strength Water (control), moderate-strength, or moderate-strength decaf. ad libitum in drinking-water Single i.v. dose of DMBA (2 mg/100 g bw in a lipid emulsion) given at age 55 days; dosing until age 58 days and held an additional 12 wk 40, 41, 41/group NR	Mammary gland: carcinoma Tumour incidence: 37/40, 38/40, 40/41 Number of tumours per rat: 5.5, 3.3*, 6.0 Total tumours: 220, 137, 245	NS *$P < 0.05$ (decrease)	Principal strengths: well-described and -conducted study
Initiation–promotion (tested as promoter) Rat, Sprague-Dawley (F) Age 55 days Up to 21 wk Welsch et al. (1988)	Drinking-water Brewed coffee, full strength Water (control), full-strength, or full-strength decaf. Single gavage dose of DMBA (5 mg/rat in sesame oil) given at age 55 days, and then brewed coffee ad libitum as drinking-water starting at age 58 days until termination at 21 wk 82, 80, 81/group NR	Mammary gland: carcinoma Tumour incidence: 39/82, 30/80, 37/81 Number of tumours per rat: 1.0, 0.8, 1.1 Total tumours: 84, 58, 84	NS NS	Principal strengths: well-described and -conducted study
Initiation–promotion (tested as promoter) Rat, Sprague-Dawley (F) Age 54 days 18 wk Welsch et al. (1988)	Drinking-water Brewed coffee, moderate strength Water (control), moderate-strength, moderate-strength decaf., or caffeine (430 mg/L) Single gavage dose of DMBA (5 mg/rat in sesame oil) given at age 54 days, and then brewed coffee ad libitum as drinking-water starting at age 57 days until termination at 18 wk 84, 84, 84, 84/group NR	Mammary gland: carcinoma Tumour incidence: 45/84, 46/84, 50/84, 50/84 Number of tumour per rat: 1.5, 1.6, 1.8, 1.8 Total tumours: 127, 129, 147, 149	NS NS	Principal strengths: well-described and -conducted study Addition of caffeine was also studied

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Vehicle Dose(s) No. of animals at start No. surviving animals	Results	Significance	Comments
Initiation–promotion (tested as promoter) Rat, Wistar (M) Age 19 days 15 mo Woutersen et al. (1989)	Drinking-water Brewed coffee Water Low-fat (LF, 5% corn oil) diet, high-fat (HF, 25% corn oil) diet, HF diet + coffee Single i.p. injection of azaserine at 30 mg/kg bw followed or not 6 days later by brewed coffee replacing drinking-water for duration of the study 40, 40, 40/group NR	Pancreas: carcinoma Tumour incidence: Carcinoma in situ: 14/39, 11/37, 10/39 (Micro)carcinoma: 1/39, 8/37, 3/39 Acinar cell carcinoma: 2/39, 7/37, 3/39 Total tumours: 29, 57, 28* Pancreas: adenoma Tumour incidence: 10/39, 6/37, 11/39 Total tumours: 33, 176, 44**	The authors stated that the incidence of carcinomas was slightly lower ($P = 0.076$) in the coffee + HF diet group than in the HF diet group *$P < 0.05$ (decrease vs HF diet group) NS **$P < 0.001$ (decrease vs HF diet group)	Tumour incidence for carcinomas (all) NR
Co-carcinogenicity Rat, Sprague-Dawley (M) Age 24 days 32 wk Gershbein (1994)	Feed Brazilian Arabica green coffee bean oil, pressed/filtered Laboratory chow 0 or 0.10% ad libitum in the feed From day 37, 20 mg/kg bw of 1,2-dimethylhydrazine in buffered water (pH, 7.0) given by gavage 1x/wk for a total of 15 dosages 22, 14/group 15, 5	Colon: adenocarcinoma Tumour incidence: 19/22, 9/14 Total tumours: 132, 43*	[NS] *$P < 0.05$ (decrease)	Principal limitations: study limited by the poor survival

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Vehicle Dose(s) No. of animals at start No. surviving animals	Results	Significance	Comments
Co-carcinogenicity Rat, Wistar (M) Newborn 110 days Silva-Oliveira et al. (2010)	Feed Milled roasted coffee (Arabica), lyophilized extract Milled laboratory chow 0, 1.5, 0 + NDEA/AAF, 1.5 + NDEA/AAF (% in diet) Ad libitum, through mothers treated with coffee diet during lactation and then in the feed. At 42 days, chemical hepatocarcinogenesis was induced in 2 groups by means of a single i.p. dose of NDEA (200 mg/kg bw) in saline followed after 17 days by daily gavage doses of AAF (20 mg/kg bw) in propylene glycol for 4 days. A two-thirds partial hepatectomy was then performed on all animals, followed by an additional dose of AAF 2 and 4 days after the hepatectomy. The other two coffee-treated and untreated groups received propylene glycol and saline solution, respectively, rather than NDEA and AAF 10, 10, 10, 10/group NR	Liver: foci and nodules of altered hepatocytes Number persistent lesions/cm^2: NR, NR, 41.52 ± 17.14, 9.14 ± 1.59* Area (mm^2) persistent lesions/section: NR, NR, 1.93 ± 0.51, 0.15 ± 0.08*	 *$P < 0.05$ (decrease) *$P < 0.05$ (decrease)	Milled roasted coffee was extracted using boiled distilled water (6% wt/vol) that was stirred and centrifuged; the supernatant was lyophilized and then stored. Test diets contained 1.5% of the lyophilized coffee extract
Co-carcinogenicity Rat, Wistar (M) Age 6 wk 25 wk Furtado et al. (2014)	Drinking fluid Brewed coffee, 8 g of powder in 140 mL hot water with filtration Water 0, 8 g/140 mL Initial i.p. injection of 200 mg/kg bw NDEA followed 1 wk later by 1×/wk gavage doses of CCl_4 (0.5 mL/kg bw per wk during wk 2–10 followed by 1.0 mL/kg bw per wk during wk 11–24) and either water or brewed coffee (wk 2–25) ad libitum for 5 days/wk 12, 12/group NR	Liver: neoplastic lesions [mainly adenomas] Tumour incidence: 12/12, 11/12 Number of neoplastic lesions/liver area (cm^2): 6.85 ± 1.45, 4.09 ± 0.80	 NS NS	Principal limitations: exposures were for only 5 days/wk; no information on survival An additional group of NDEA/CCl_4-initiated rats received 0.1% caffeine in their drinking-water. The authors reported the mean number of neoplastic lesions per liver area was significantly lower ($P < 0.05$) in the group receiving 0.1% caffeine (1.48 ± 0.36) compared to the group receiving drinking-water

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Vehicle Dose(s) No. of animals at start No. surviving animals	Results	Significance	Comments
Co-carcinogenicity Rat, Wistar (M) Age 6 wk 25 wk Furtado et al. (2014)	Drinking fluid Instant coffee, 2% (wt/vol) in hot water Water 0, 2% Initial i.p. injection of 200 mg/kg bw NDEA followed 1 wk later by 1×/wk gavage doses of CCl_4 (0.5 mL/kg bw per wk during wk 2–10 followed by 1.0 mL/kg bw per wk during wk 11–24) and either water or instant coffee (wk 2–25) ad libitum for 5 days/wk 12, 12/group NR	Liver: neoplastic lesions [mainly adenomas] Tumour incidence: 12/12, 11/12 Number of neoplastic lesions/liver area (cm^2): 6.85 ± 1.45, 2.95 ± 0.68*	NS *$P < 0.05$ (decrease);	Principal limitations: exposures were for only 5 days/wk; no information on survival An additional group of NDEA/CCl_4-initiated rats received 0.1% caffeine in their drinking-water. The authors reported the mean number of neoplastic lesions per liver area was significantly lower ($P < 0.05$) in the group receiving 0.1% caffeine (1.48 ± 0.36) compared to the group receiving drinking-water
Co-carcinogenicity Hamster, Syrian golden (F) Age NR 18.5 wk Miller et al. (1988)	Feed Green coffee beans, Colombian Laboratory chow 0 + DMBA, 20 + DMBA, 0, 20 (% in diet) Ad libitum in feed, followed after 2-wk adjustment to diet with painting of right buccal pouch with 0.5% solution of DMBA in heavy mineral oil, 3 × /wk (total of 50 treatments) for 16.5 wk 16, 16, 4, 4/group 12, 9, 4, 4	Buccal pouch: tumours Tumour incidence: 9/12 [mainly carcinomas], 2/9 (carcinomas)*, 0/4, 0/4 Number of tumours per rat: 2.4 ± 0.6, 0.2 ± 0.2**, NR, NR Tumour mass (mm) was 4.5 ± 1.2 for DMBA only treated groups controls vs 0.4 ± 0.3** for coffee + DMBA-treated group	*[$P = 0.03$, Fisher exact test], decrease **$P < 0.01$, decrease	Principal limitations: large number of animals in DMBA+coffee treatment group died before end of study Weight at start, 70 g
Initiation–promotion (tested as promoter) Hamster, Syrian golden (M) Age 6–7 wk 12 mo Woutersen et al. (1989)	Drinking-water Brewed coffee Water LF (5% corn oil) diet, HF (25% corn oil) diet, HF diet + coffee S.c. injection of 20 mg/kg bw BOP at age 6 and 7 wk immediately followed or not by brewed coffee replacing drinking-water for duration of the study 40, 40, 40/group NR	Pancreas: carcinoma Tumour incidence: 17/36, 29/38, 22/34 Total tumours: 23, 37, 30	NS	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested Vehicle Dose(s) No. of animals at start No. surviving animals	Results	Significance	Comments
Initiation–promotion (tested as promoter) Hamster, Syrian golden (M) Age 8–10 wk 14 wk Saroja et al. (2001)	Gavage Black coffee extract (from roasted coffee beans, 8%), store bought Water 0% + DMBA, 8% + DMBA, 0%, 8% Gavage 3×/wk for 14 wk and on alternate days skin application of 0.5% DMBA (0.4 mg) in liquid paraffin on the right buccal pouch, or untreated 10, 10, 10, 10/group NR	Buccal pouch: squamous cell carcinoma Tumour incidence: 10/10, 10/10, 0/10, 0/10 Tumour multiplicity: 9.16, 12.4, 0, 0	[NS] NR	Principal limitations: no statistical analysis provided; no information on survival or body weight

AAF, 2-acetylaminofluorene; BOP, *N*-nitrosobis(2-oxopropyl)amine; bw, body weight; decaf., decaffeinated; DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; HF, high-fat; i.p., intraperitoneal; i.v., intravenous; LF, low-fat; M, male; mo, month(s); NDEA, *N*-nitrosodiethylamine; NR, not reported; NS, not significant; s.c., subcutaneous; vol, volume; vs, versus; wk, week(s); wt, weight

or tap water for 480 days with cycasin on day 121. A fifth group was given tap water only (controls). The number of rats surviving beyond 200 days was comparable in all groups. At the end of the experiment (480 days), no significant tumour findings were observed. A few single tumours were observed in various organs distributed among the groups. No tumours were observed in the coffee-only group. [The Working Group considered that the study was inadequate for evaluation because of the lack of use of a positive control.]

Fujii et al. (1980) conducted initiation–promotion studies of coffee by giving four groups of 10 male and 10 female Sprague-Dawley rats (age, 3 weeks) one of the following diets the basal diet containing 0.025% 2-acetylaminofluorene (AAF) for 8 weeks from the start of experiment then the basal diet alone, with a solution of brewed Brazilian coffee solution instead of drinking-water for the duration of the experiment (290 days; Group 1); the AAF-containing diet and tap water as drinking-water for the first 8 weeks, and then the basal diet and a coffee solution until termination of the experiment at 290 days (Group 2); the AAF-containing diet for the first 8 weeks and then the basal diet until the end of the experiment, with tap water as drinking-water for the duration (Group 3); or the basal diet and tap water only (Group 4). The number of rats surviving beyond 130 days was comparable in all groups. The incidence of adenocarcinoma of the mammary gland in female rats exposed to AAF followed by coffee (Group 2; 7/10) was significantly higher (P = 0.034, Fisher exact test) compared with that in female rats exposed to AAF only (Group 3; 2/10). The incidence of mammary gland adenocarcinoma was 4/9 in female rats of Group 1. No mammary gland tumours were observed in female rats of Group 4. No significant difference in the incidence of liver tumour was seen between the groups given AAF and coffee solution concurrently (Groups 1 or 2) and the groups given AAF alone (Group 3). [The Working Group noted the limited description of experimental details and the small number of animals per group.]

Wattenberg & Lam (1984) presented data from three experiments (with a similar study design) on the effects on mammary tumour formation in groups of 16–32 female Sprague-Dawley rats (age, 34 days) given green coffee beans at 10% or 20% of diet for 14 days, 1 day before a single gavage dose of 12 mg of 7,12-dimethylbenz[*a*]-anthracene (DMBA) in 1 mL olive oil. The experiments ended 18 weeks after DMBA administration. Limited data were reported on survival or body-weight gain. The consumption of a diet containing green coffee beans resulted in fewer rats with mammary tumours 18 weeks after DMBA administration and fewer tumours per rat. The incidences of mammary tumours for the group given 10% green coffee beans compared with the corresponding DMBA-alone control group was 8/16 (50%) versus 13/16 (81%; not significant) in experiment 1; for the group given 20% green coffee beans compared with the corresponding DMBA-alone control group, incidences of mammary tumours were 9/16 (56%) versus 16/16 (100%; $P < 0.01$, decrease) in experiment 2. In experiment 3, the incidences of mammary tumours were 30/32, 13/16, and 9/16 ($P < 0.01$, decrease) for the DMBA-treated rats given diets containing 0%, 10%, and 20% green coffee beans groups, respectively. In a fourth experiment, a diet with 10% green coffee beans tested as a promoter significantly decreased the incidence of DMBA-induced mammary tumours. [The article contained few experimental details on exact design, body-weight gain, and survival.]

Nishikawa et al. (1986) examined the effect of coffee drinking on hepatocarcinogenesis in rats concurrently administered aminopyrine and sodium nitrite in the diet. Five groups of 12 female Sprague-Dawley rats (age, 4 weeks) were given: a diet containing 0.01% aminopyrine and 0.1% sodium nitrite, and a brewed coffee solution as a drinking fluid (Group 1); a diet containing

0.01% aminopyrine and 0.1% sodium nitrite, and tap water for drinking fluid (Group 2); a diet containing 0.01% aminopyrine alone and the coffee solution as drinking fluid (Group 3); a diet containing 0.01% aminopyrine and tap water for drinking fluid (Group 4); or a basal diet and tap water (Group 5). The study was ended after 630 days. A total of 43 rats survived more than 600 days (17 rats died of pneumonia earlier). The number of rats that survived more than 600 days was considered the effective number of rats. The incidence of liver tumours in the group of rats given coffee in combination with aminopyrine and sodium nitrite (Group 1: 2/9, 22%, both adenomas) was significantly lower than that of the animals receiving aminopyrine and sodium nitrite only (Group 2: 7/9, 78%: 5/9, adenoma; 1/9, carcinoma; and 1/9, haemangiosarcoma) ($P < 0.03$, decrease; Fisher exact test).

Welsch et al. (1988) treated different groups of female Sprague-Dawley rats with regular or decaffeinated coffee in both initiation and promotion phases of DMBA-induced mammary gland tumourigenesis. Groups exposed to caffeine or decaffeinated coffee with added caffeine were also included.

In the initiation studies, groups of 40–41 female rats (age, 24–26 days) were given plain drinking-water (control) or full- or moderate-strength brewed regular or decaffeinated coffee, prepared by using 4.25 or 2.125 cups of coffee and 45 cups of water in a 55-cup coffee maker, ad libitum. There were also two additional groups that received caffeine at 860 mg/L in either the full-strength decaffeinated coffee or their drinking-water. A single intravenous dose of DMBA (2 mg/100 g bw in a lipid emulsion) was given at age 53–55 days. The coffee dosing was stopped at age 56–58 days and the rats were then held for an additional 12–18 weeks. There was no effect on body weight in any of these treated groups. The consumption of full-strength and moderate-strength caffeinated coffee reduced the number of mammary carcinomas per rat by 62% and 40% ($P < 0.05$) compared with control groups, respectively. Full- or moderate-strength decaffeinated coffee did not significantly affect the number of mammary carcinomas per rat. Caffeine alone and addition of caffeine to the full-strength decaffeinated coffee also sharply reduced the number of mammary carcinomas per rat by 58% and 49% ($P < 0.05$), respectively. Coffee and/or caffeine consumption did not significantly affect the percentage of rats with mammary carcinomas or the mean latency period of mammary tumour appearance (Welsch et al., 1988). [These studies were well described and appeared to have been well conducted.] Welsch & DeHoog (1988) conducted the same initiation studies with brewed regular or decaffeinated coffee but used a chemically defined diet containing standard (5%) or high (20%) levels of fat (corn oil) during coffee exposures and observed essentially the same results. [These studies were well described and appeared to have been well conducted.]

In the promotion studies, groups of 80–84 female rats received a single gavage dose of DMBA (5 mg/rat in sesame oil) given at age 54–55 days. At age 57–58 days, rats were given plain drinking-water (control) or full- or moderate-strength brewed regular or decaffeinated coffee, prepared by using 4.25 or 2.125 cups of coffee and 45 cups of water in a 55-cup coffee maker, ad libitum for 18–21 weeks. There was an additional group that received 430 mg/L caffeine in their drinking-water. There was no effect on body weight in any of these treated groups. The consumption of full-strength or moderate-strength caffeinated or decaffeinated coffee did not significantly affect the number of mammary carcinomas per rat. Neither coffee nor caffeine consumption significantly affected the percentage of rats with mammary carcinomas or the mean latency period of mammary tumour appearance (Welsch et al., 1988). [These studies were well described and appeared to have been well conducted.] Welsch & DeHoog (1988)

conducted the same promotion studies with brewed regular or decaffeinated coffee but used a chemically defined diet containing standard (5%) or high (20%) levels of fat (corn oil) during coffee exposures, and observed essentially the same results. [These studies were well described and appeared to have been well conducted.]

In a well-conducted study to investigate the effect of chronic coffee ingestion on pancreatic carcinogenesis promoted by dietary fat (Woutersen et al. 1989), three groups of 40 male Wistar rats (age, 19 days) were given a single intraperitoneal injection of 30 mg azaserine/kg bw in saline followed, or not, by replacement of drinking-water with brewed coffee 6 days later. The coffee was freshly prepared each day of the study by brewing 500 g of ground coffee in 10 L of distilled water. The rats were given either a low-fat (LF) control diet (5% corn oil), a high-fat (HF) diet (25% corn oil), or the HF diet plus coffee (HF+C). Mean body weight of the HF+C group was significantly lower than that of the other two groups ($P < 0.01$) from day 119 onwards. At 15 months, the numbers of pancreatic adenomas and pancreatic carcinomas reported were significantly lower in the HF+C group than in the HF group ($P < 0.001$, decrease and $P < 0.05$, decrease, respectively). [The Working Group noted that the lower body weight in the coffee-treated animals may have contributed to the reduction in pancreatic tumours observed in the treated animals.]

A group of 22 (control) or 14 (treated) male Sprague-Dawley male rats (age, 24 days) were given ad libitum feed containing 0 or 0.10% Brazilian Arabica green coffee bean oil for 32 weeks (Gershbein, 1994). From day 37 of the study, 1,2-dimethylhydrazine was given by weekly gavage at a dose of 20 mg/kg bw to both groups for a total of 15 weeks. Survival in the coffee-treated group was significantly less than that of controls (36% vs 68%). Average body weight was comparable in both groups. There was a significant decrease in the number of adenocarcinomas of the colon observed in the coffee-treated group ($P < 0.05$, decrease) compared with controls (43 vs 132). [The study was limited by the poor survival of the coffee-treated group compared with the controls.]

In a well-conducted study, Silva-Oliveira et al. (2010) investigated the effect of daily coffee ingestion on hepatocarcinogenesis in rats submitted to the resistant hepatocyte (RH) model. Four groups of 10 male newborn Wistar rats were treated with or without milled roasted coffee (*Coffea arabica*) that was extracted by stirring with boiling distilled water (6% wt/vol), centrifuging, and the supernatant lyophilized and then stored. Test diets were prepared with a concentration of 1.5% lyophilized coffee extract. At day 42 of the study, the RH model of chemical hepatocarcinogenesis was induced in one untreated group and one coffee-treated group by means of a single intraperitoneal dose of *N*-nitrosodiethylamine (NDEA, 200 mg/kg bw) in saline, followed 17 days later by daily gavage doses of AAF (20 mg/kg bw) in propylene glycol for 4 days. A two-thirds partial hepatectomy (PH) was then performed on all RH-induced coffee-treated and untreated rats, followed by an additional dose of AAF 2 and 4 days later. The other two coffee-treated and untreated groups received propylene glycol and saline solution, respectively, rather than NDEA and AAF. Coffee consumption and the induction of hepatocarcinogenesis had no effect on body-weight gain, final body weight, liver weight at PH, or on liver regeneration which varied from 108% to 126% in the groups (without statistical differences). The experiment was terminated at 110 days. In the RH model, the rats given the coffee diet had a 78.0% reduction in the total number of preneoplastic lesions, 85.5% in the number of persistent lesions, 70.5% in the number of remodelling lesions, and 92.2% and 92.0% in the total and relative areas occupied by persistent lesions, respectively. [The Working Group felt it appropriate to include this study in the evaluation because it is generally accepted that the foci and

nodules of altered hepatocytes observed in this study are the result of clonal expansion of the initiated hepatocytes and precede the appearance of malignant tumours, acting as potential precursors for subsequent steps in the carcinogenic process.]

Furtado et al. (2014) gave three groups of 12 Wistar male rats (age, 6 weeks) an initial intraperitoneal injection of NDEA at 200 mg/kg bw followed 1 week later by gavage doses of carbon tetrachloride (CCl_4) once per week (0.5 mL/kg bw per week during weeks 2–10 followed by 1.0 mL/kg bw per week during weeks 11–24) and either plain water (control), 2% (wt/vol) instant coffee, or brewed coffee (8 g/140 mL) ad libitum in their drinking-water for 5 days/week for 24 weeks (weeks 2–25). The ingestion of the coffee beverages had no effect on body weight or relative liver weights. At 25 weeks, the incidence of liver neoplastic lesions [mainly hepatocellular adenomas] in both coffee-treated groups was 11/12 (93%) compared with 12/12 (100%) in the control group. The mean number of neoplastic lesions per liver area (per cm^2) was significantly lower (2.95 ± 0.68, $P < 0.05$) in the group receiving the instant coffee in their drinking-water compared with the group receiving plain drinking-water (6.85 ± 1.45). The mean number of neoplastic lesions per liver area (per cm^2) for the brewed coffee group was also lower (4.09 ± 0.80) than controls, but not significantly. The authors reported on an additional group of NDEA/CCl_4-initiated rats that had received 0.1% caffeine in their drinking-water, which also had a significantly lower mean number of neoplastic lesions per liver area (1.48 ± 0.36, $P < 0.05$) compared with the group receiving drinking-water. [The Working Group noted the lack of survival data.]

3.2.2 Hamster

Miller et al. (1988) gave two groups of 16 female Syrian hamsters [age not provided; weight, 70 g] powdered green coffee beans in their feed at 0% or 20% ad libitum. After a 2-week adjustment period to the diet, the right buccal pouch of each group was painted with a 0.5% solution of DMBA in heavy mineral oil three times per week for the remaining 16.5 weeks of the study (a total of 50 treatments). Two other groups of four hamsters were given either the 0% or 20% green coffee diet and were treated three times per week with heavy mineral oil (a total of 50 treatments). Weight gain for the hamsters given coffee + DMBA was less than that of the hamsters given DMBA only throughout the study. There was a significant decrease in survival in all DMBA-treated groups, mostly due to respiratory infections. At 18.5 weeks, the incidence of buccal pouch tumours in the group given coffee + DMBA was 2/9 (22%) (carcinomas) [$P = 0.03$, decrease; Fisher exact test] compared with 9/12 (75%) [mainly carcinomas] in the DMBA-only group. The average number of tumours was 0.2 ± 0.2 versus 2.4 ± 0.6 and the calculated value for tumour mass (number of tumours times the average diameter of the tumours in millimetres) was 0.4 ± 0.3 versus 4.5 ± 1.2 for groups given coffee + DMBA and DMBA only, respectively. Since tumour mass takes into account tumour number and size, the differences in these values are significant ($P < 0.01$). No tumours were seen in the buccal pouches of hamsters given the 0% or 20% green coffee diet and not treated with DMBA. [The Working Group noted the poor survival of hamsters treated with coffee + DMBA.]

In a well-conducted study to investigate the effect of chronic coffee ingestion on dietary fat-promoted pancreatic carcinogenesis, Woutersen et al. (1989) treated three groups of 34–38 male Syrian hamsters (age, 6–7 weeks) with *N*-nitrosobis(2-oxopropyl) amine (BOP) at a dose of 20 mg /kg bw in saline by subcutaneous injection at age 6 and 7 weeks. The hamsters were fed a low-fat (LF) control diet (5% corn oil), a high-fat (HF) diet (25% corn oil), or a HF diet plus coffee (HF+C). For the latter group, drinking-water was replaced by brewed coffee after BOP injection.

The coffee was prepared fresh each day of the study by brewing 500 g of ground coffee in 10 L of distilled water. Body-weight gain of the hamsters maintained on the HF+C diet was comparable to the LF controls, while the mean body weight of the HF group was significantly higher than that of the LF controls. At 12 months, there was no significant difference in the incidence or total number of pancreatic carcinomas between the HF+C group and the HF group.

Saroja et al. (2001) gave two groups of 10 male Syrian hamsters (age, 8–10 weeks) black coffee extract (from roasted coffee beans obtained from a local Indian market) at 0% (untreated) or 8% by gavage three times per week for 14 weeks. On alternate days these groups were given 0.5% DMBA (0.4 mg) in liquid paraffin painted on the right buccal pouch. Two other groups of 10 hamsters were either untreated or given 8% black coffee extract. No information was provided for survival or weight gain or loss in any groups. The incidence of buccal pouch tumours in the DMBA-treated groups and the groups given coffee plus DMBA was 100% (10/10). The mean number of tumours per animal was 12.4 versus 9.16, the mean tumour volume was 300 mm^3 versus 240 mm^3, and the calculated value for mean tumour burden (calculated by multiplying mean tumour volume by mean number of tumours) was 3720 mm^3 versus 2198 mm^3 for coffee+DMBA-treated animals and for DMBA-treated animals, respectively. No tumours were seen in hamsters not given DMBA or in those given only coffee. [The Working Group noted the lack of information on survival or body weight. This study was not suitable for evaluation because no error terms were provided for the mean number of tumours and no statistical analysis was reported.]

References

Bauer AR Jr, Rank RK, Kerr R, Straley RL, Mason JD (1977). The effects of prolonged coffee intake on genetically identical mice. *Life Sci*, 21(1):63–70. doi:10.1016/0024-3205(77)90425-8 PMID:886913

Fujii M, Mori H, Nishikawa A, Takahashi M (1980). Effect of coffee on carcinogenicity of N-2-fluorenylacetamide. *Acta Sehol Med Univ Gifu*, 28:295–8.

Furtado KS, Polletini J, Dias MC, Rodrigues MA, Barbisan LF (2014). Prevention of rat liver fibrosis and carcinogenesis by coffee and caffeine. *Food Chem Toxicol*, 64:20–6. doi:10.1016/j.fct.2013.11.011 PMID:24275088

Gershbein LL (1994). Action of dietary trypsin, pressed coffee oil, silymarin and iron salt on 1,2-dimethylhydrazine tumorigenesis by gavage. *Anticancer Res*, 14(3A):1113–6. PMID:8074460

IARC (1991). Coffee, tea, mate, methylxanthines and methylglyoxal. *IARC Monogr Eval Carcinog Risks Hum*, 51:41–199. Available from: http://publications.iarc.fr/69 PMID:1674554

Miller EG, Formby WA, Rivera-Hidalgo F, Wright JM (1988). Inhibition of hamster buccal pouch carcinogenesis by green coffee beans. *Oral Surg Oral Med Oral Pathol*, 65(6):745–9. doi:10.1016/0030-4220(88)90022-9 PMID:3135522

Mori H, Hirono I (1977). Effect of coffee on carcinogenicity of cycasin. *Br J Cancer*, 35(3):369–71. doi:10.1038/bjc.1977.51 PMID:851512

Nishikawa A, Tanaka T, Mori H (1986). An inhibitory effect of coffee on nitrosamine-hepatocrcinogenesis with aminopyrine and sodium nitrite in rats. *J Nutr Growth Cancer*, 3:161–6.

Palm PE, Arnold EP, Nick MS, Valentine JR, Doerfler TE (1984). Two-year toxicity/carcinogenicity study of fresh-brewed coffee in rats initially exposed in utero. *Toxicol Appl Pharmacol*, 74(3):364–82. doi:10.1016/0041-008X(84)90290-4 PMID:6740685

Saroja M, Balasenthil S, Ramachandran CR, Nagini S (2001). Coffee enhances the development of 7,12-dimethylbenz[a]anthracene (DMBA)-induced hamster buccal pouch carcinomas. *Oral Oncol*, 37(2):172–6. doi:10.1016/S1368-8375(00)00084-1 PMID:11167145

Silva-Oliveira EM, Fernandes PA, Moraes-Santos T (2010). Effect of coffee on chemical hepatocarcinogenesis in rats. *Nutr Cancer*, 62(3):336–42. doi:10.1080/01635580903407205 PMID:20358471

Stalder R, Bexter A, Würzner HP, Luginbühl H (1990). A carcinogenicity study of instant coffee in Swiss mice. *Food Chem Toxicol*, 28(12):829–37. doi:10.1016/0278-6915(90)90056-S PMID:2148922

Wattenberg LW, Lam LK (1984). Protective effects of coffee constituents on carcinogenesis in experimental animals. In: MacMahon B, Sugimura T, editors. Coffee

and Health (Banbury Report 17). Cold Spring Harbor, New York: CSH Press; pp. 137–145.

Welsch CW, DeHoog JV (1988). Influence of caffeine consumption on 7,12-dimethylbenz(a)anthracene-induced mammary gland tumorigenesis in female rats fed a chemically defined diet containing standard and high levels of unsaturated fat. *Cancer Res*, 48(8):2074–7. PMID:3127045

Welsch CW, DeHoog JV, O'Connor DH (1988). Influence of caffeine and/or coffee consumption on the initiation and promotion phases of 7,12-dimethylbenz(a)anthracene-induced rat mammary gland tumorigenesis. *Cancer Res*, 48(8):2068–73. PMID:3127044

Woutersen RA, van Garderen-Hoetmer A, Bax J, Scherer E (1989). Modulation of dietary fat-promoted pancreatic carcinogenesis in rats and hamsters by chronic coffee ingestion. *Carcinogenesis*, 10(2):311–6. doi:10.1093/carcin/10.2.311 PMID:2643485

Würzner HP, Lindström E, Vuataz L, Luginbühl H (1977a). A 2-year feeding study of instant coffees in rats. I. Body weight, food consumption, haematological parameters and plasms chemistry. *Food Cosmet Toxicol*, 15(1):7–16. doi:10.1016/S0015-6264(77)80256-3 PMID:852786

Würzner HP, Lindström E, Vuataz L, Luginbühl H (1977b). A 2-year feeding study of instant coffees in rats. II. Incidence and types of neoplasms. *Food Cosmet Toxicol*, 15(4):289–96. doi:10.1016/S0015-6264(77)80199-5 PMID:590890

4. MECHANISTIC AND OTHER RELEVANT DATA

4.1 Toxicokinetic data

4.1.1 Humans

(a) Absorption

(i) Caffeine

Table 4.1 (web only; available at: http://publications.iarc.fr/566) summarizes pharmacokinetics parameters maximum plasma concentration (C_{max}), time to peak concentration (T_{max}), and the area under the curve (AUC) of caffeine from studies in humans.

Several studies in humans have shown rapid and dose-dependent absorption of caffeine in subjects administered coffee. Coffee consumption significantly increased caffeine in plasma in a single-blind, three-stage clinical trial of 11 men and 36 women, all regular coffee consumers (4.0 ± 1.7 cups/day) who had abstained from coffee consumption for 1 month (Kempf et al., 2010). [Two smokers were included in the analysis. There were no data on caffeine content in coffee used in the study.] Caffeine was rapidly absorbed, reaching C_{max} 1.2 h after consumption, in a study of healthy non-smokers (7 men, 5 women) who ingested a single dose of 70 mg caffeine as a green/roasted coffee blend dissolved in water (Martínez-López et al., 2014). [The 70 mg dose was selected to avoid possible saturation processes and nonlinear kinetics reported with higher caffeine doses.] A caffeine mean peak level of 9.7 ± 1.2 µg/mL and time to peak of 42 ± 5 minutes was reported in subjects administered coffee (400 mg caffeine) in a randomized, double-blind, single-dose, placebo-controlled, study of caffeine pharmacokinetics in 8 men and 5 women characterized as regular coffee and cola consumers (1 smoker) (Liguori et al., 1997).

Studies in humans given caffeine added to decaffeinated instant coffee (Gelal et al., 2003) or caffeine as a capsule or gum (Kaplan et al., 1997; Kamimori et al., 2002; Skinner et al., 2014) reported rapid, dose-dependent absorption.

An in vitro study using human skin membrane [of less relevance to pharmacokinetics of caffeine from coffee] demonstrated absorption of caffeine (100 µg/m^2) with time to maximum rate of 1.2 ± 0.2 hour to 5.2 ± 1.2 hour (van de Sandt et al., 2004).

(ii) Phenolic acids

Table 4.2 (web only; available at: http://publications.iarc.fr/566) is a summary of pharmacokinetics parameters C_{max}, T_{max}, and AUC of phenolic acids from studies in humans.

Hydroxycinnamic acids are rapidly absorbed after coffee consumption. Peak absorption of caffeic acid (CA) was reached 1 hour after giving 200 mL of brewed coffee to 10 healthy men who were non-smoking moderate coffee drinkers (2–4 cups/day of coffee (Nardini et al., 2002). 5-Caffeoylquinic acid (5-CQA) was the major hydroxycinnamic acid present in plasma, contributing 40.7% of AUC in 6 non-smoking healthy volunteers (2 men, 4 women) given 190 mL of decaffeinated brewed coffee (Monteiro et al., 2007). Two plasma concentration peaks

were observed in all subjects for all hydroxycinnamic acids. [Biphasic concentration peaks could be attributed to either enterohepatic circulation or to colonic metabolism.] Stalmach et al. (2009) identified 12 different compounds related to chlorogenic acid (CGA) in 11 non-smoking subjects (8 men, 3 women) who followed a polyphenol-free diet for 48 hour before administration of 200 mL of instant coffee. The T_{max} of up to 1 hour was indicative of small intestine absorption.

In the study of Kempf et al. (2010) reported above, significant increases were seen in coffee-derived compounds including CA, ferulic acid (FA), and isoferulic acid (iFA) after daily consumption. In two reports (Renouf et al., 2010a, b), CA, FA, and iFA reached C_{max} approximately 1 hour after administration of 4 g of instant coffee in 9 healthy non-smoking coffee consumers (4 men, 5 women). [Plasma was sampled up to 12 hours after coffee consumption; data on certain late-appearing phenolic acids was therefore lacking.]

In a similar randomized, crossover study of 10 healthy non-smoking coffee consumers (4 men, 6 women) (Renouf et al., 2014), phenolic acids appeared rapidly in the plasma, but the overall level of hydroxycinnamic acids remained low (AUC < 10 μM min, C_{max} < 100 nM). The hydroxycinnamic acid AUC values increased during dose escalation. [The exclusion criterion for smoking was > 5 cigarettes/day.]

In a study of 9 healthy volunteers (4 men, 5 women) who consumed a single dose of 400 mL instant coffee, dimethoxycinnamic acid was found in plasma exclusively as a free aglycone, with a C_{max} of 496 ± 110 nM reached 30 minutes after dosing (Farrell et al., 2012). [Smoking status of the subjects was not assessed.]

Several studies investigated absorption of hydroxycinnamic acids after coffee administration in individuals with an ileostomy (Stalmach et al., 2010; Erk et al., 2012, 2014b). In 3 men and 2 women, 71 ± 7% of hydroxycinnamic acids ingested as a single 200 mL dose of instant coffee drink was recovered in the form of parent compound and its metabolites in ileostomy effluent (Stalmach et al., 2010). In two studies, 5 women with ileostomies were given a single dose of decaffeinated coffee containing either hydroxycinnamic acids (4525 μmol, 2219 μmol, or 1053 μmol) (Erk et al., 2012) or CQAs (746 μmol) (Erk et al., 2014b). For hydroxycinnamic acids, 68.8 ± 9.0% and 77.4 ± 4.3% of the high and low ingested dose, respectively, were recovered in the ileal fluid [suggesting that one third of the ingested amount is absorbed in the small intestine]. For CQAs, the recovery rate was 76.2%.

In a further study of 10 non-smoking healthy volunteers (5 men, 5 women) given 170 mg of hydroxycinnamic acids via decaffeinated green coffee extract in a capsule in plasma (Farah et al., 2008), apparent bioavailability of chlorogenic acids varied considerably over the range 7.8–72.1% (mean: 33 ± 23%) [no data on regular coffee consumption were provided.]

In a study using instant coffee in vitro (Farrell et al., 2011), rapid and time-dependent membrane permeation of dimethoxycinnamic acid was seen in Caco-2 cells. Paracellular diffusion was the main transport mechanisms of hydroxycinnamic acids, and the monocarboxylic acid transporter was a mediator of CA disposition (Konishi & Kobayashi, 2004).

(iii) Other compounds

After a single dose (350 mL) of filtered coffee given to healthy non-smoking regular coffee consumers who had abstained from caffeine for 10 days, a higher maximum concentration of trigonelline was reached later in women (n = 6, C_{max} = 6547 nmol/L, T_{max} = 3.17 hours) as compared with men (n = 7, C_{max} = 5479 nmol/L, T_{max} = 2.29 hours) (Lang et al., 2010). No difference was observed for *N*-methylpyridinium.

De Roos et al. (1998) reported dose-dependent absorption of diterpenes in 9 healthy volunteers (4 men, 5 women) with an ileostomy after coffee

consumption. [No data on smoking and regular coffee consumption were available.]

(b) Distribution

A high volume of distribution was reported in a study of healthy non-smoking regular coffee drinkers (7 men and 6 women) who ingested a single 350 mL dose of coffee after a 10-day washout period (Lang et al., 2010). The volume of distribution (i.e., the theoretic-al volume that would be necessary to contain the total amount of an administered dose) was 123 L and 148 L for trigonelline and 211 L and 214 L for *N*-methylpyridinium, for women and men, respectively.

(c) Metabolism

(i) Caffeine

A general schematic of caffeine metabolism is presented in Fig. 4.1.

In the study of Martínez-López et al. (2014) described in Section 4.1.1 (a) (i) above, paraxanthine (PX) was the major metabolite followed by 1-methyluric acid (1-MU) and 1-methylxanthine (1-MX). All detected metabolites were present in plasma from the first sampling time (30 minutes after coffee consumption). [Data on regular coffee consumption were not provided.]

In 9 (7 men, 2 women) healthy non-smoking regular coffee drinkers (≥ 4 cups per day) administered caffeine (0, 4.2, or 12 mg/kg per day in decaffeinated coffee in three randomized treatment blocks of 5 days each), the higher caffeine dose resulted in plasma AUC values for all evaluated metabolites that were at least 3.3-fold higher (Denaro et al., 1990). The metabolism of caffeine under long-term dosing conditions decreased in a dose-dependent manner, leading to the accumulation of methylxanthines.

Additional studies on the modulating effect of coffee on metabolizing enzymes can be found in Section 4.1.3 of this monograph.

(ii) Phenolic acids

A general schematic of chlorogenic acids metabolism is presented in Fig. 4.2.

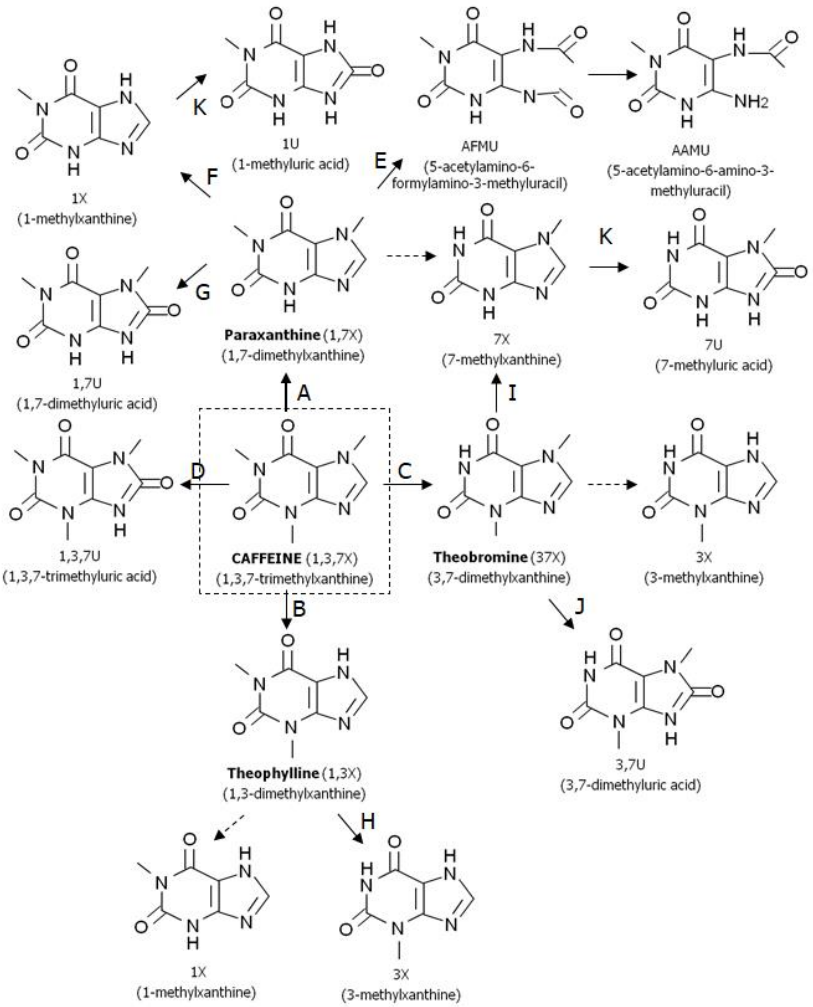
In the study of Farah et al. (2008) described in Section 4.1.1 (a) (ii) above, the hydroxycinnamic acids metabolites CA, FA, and iFA and *p*-coumaric acids contributed about 20.3% of the total phenolics detected in plasma. On the other hand, sinapic, gallic, *p*-hydroxybenzoic, and dihydrocaffeic (DHCA) acids were the major phenolic compounds found in urine (approximately 82%). [Plasma was not sampled 8 hours after dosing, when concentrations of hydroxycinnamic acids in some of the subjects were still high. No data on regular coffee consumption were available.]

In the study of Erk et al. (2012) described in Section 4.1.1 (a) (ii) above, sulfation was the dominant form of conjugation and significant inter-individual variation in metabolism of hydroxycinnamic acids was observed. [Only women were included in the study. Most of the observed inter-individual differences came from a single outlier.]

In two studies conducted by Renouf et al. (Renouf et al., 2010a, b), DHCA and dihydroferulic acid (DHFA) reached maximum plasma concentration (approximately 200 nM and 550 nM, respectively) 10 hours after ingestion. [Plasma was sampled up to 12 hours after the coffee consumption; the complete kinetics of certain late-appearing phenolic acids was therefore lacking.]

Fumeaux et al. (2010) identified and characterized several hydroxycinnamic acids for the first time in the plasma and urine of 11 healthy volunteers given a single dose of hydroxycinnamic acids of 412 µmol consumed as instant coffee. Four were identified in plasma (CA and DHCA 3′-sulfate, and FA and DHFA 4′-sulfate), and ten in urine (CA 3′- and 4′-sulfates, DHCA 3′-O-glucuronide and 3′-sulfate, FA 4′-sulfate, iFA 3′-sulfate, DHFA 4′-O-glucuronide and

Fig. 4.1 Important metabolic pathways for caffeine and its metabolites



A, F: CYP1A2; B, D: CYP1A2, CYP2C8, CYP2C9, CYP2E1, CYP3A4; C: CYP1A2, CYP2E1, E: NAT2; G: CYP1A2, CYP2A6; H: methylxanthine N1 demethylase; I: methylxanthine N3 demethylase; J, K: xanthine oxidase
Compiled by the Working Group

4′-sulfate, FA and dihydroisoferulic acid 3′-O-glucuronides). [Sex, smoking status, and regular coffee consumption of study subjects were not reported.]

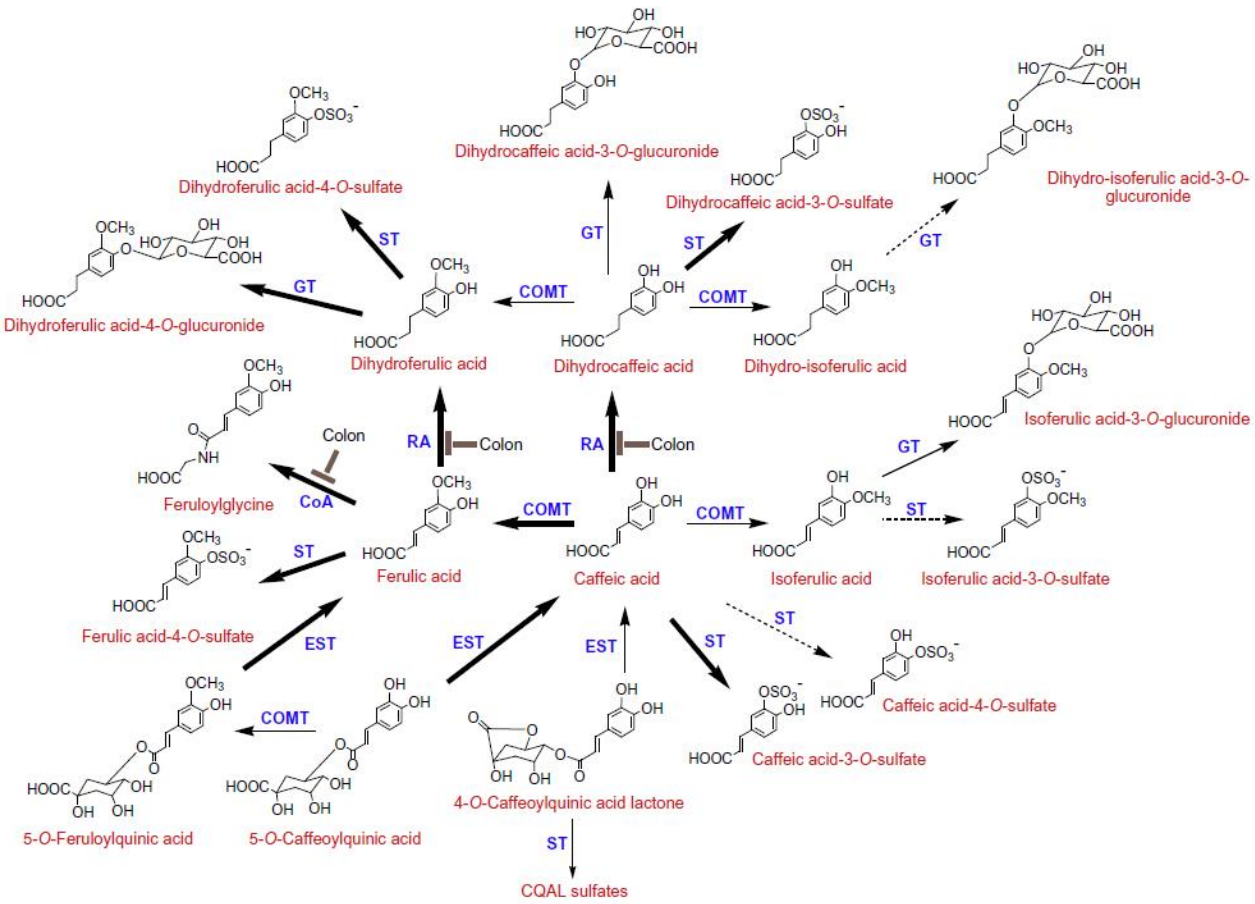
Several previously unidentified coffee metabolites were detected by Redeuil et al. (2011) in the plasma of 9 healthy non-smoking regular coffee consumers (4 men and 5 women) after the administration of a single 400 mL dose of instant coffee. A total of 22 phenolic acid derivatives and 12 CGA derivatives were detected, including 19 newly identified substances such as feruloylquinic acid lactone (FQA), sulfated and glucuronidated forms of FQA lactone, and sulfated forms of coumaric acid.

(d) Elimination

(i) Caffeine

Martínez-López et al. (2014) detected 11 caffeine metabolites in urine after a single dose of green/roasted coffee, with 1-methyluric acid as the major compound representing 67.7%

Fig. 4.2 Metabolism of chlorogenic acids after the ingestion of coffee in humans



5-O-CQA and 5-O-FQA are illustrated structures, but their respective 3- and 4-isomers would be metabolized in a similar manner, and likewise for 4- and 3-O-CQAL. COMT, catechol-O-methyltransferase; ET, esterase; RA, reductase; GT, UDP-glucuronyltransferase; ST, sulfuryl-O-transferase; Co-A, co-enzyme A. Bold arrows indicate major routes, dotted arrows minor pathways. Steps blocked in subjects with an ileostomy and hence occurring in the colon are indicated.
From Stalmach et al. (2010), with permission from Elsevier

of the total urinary metabolites. Unmetabolized caffeine represented about 2.7% of the total amount of urinary metabolites, with a urinary T_{max} of 6.00 ± 2.71 hours. [Data on regular coffee consumption were not reported.]

In the study of Denaro et al. (1990) reported in Section 4.1.1 (c) (i) above, elimination of caffeine was dose-dependent; a higher caffeine dose was associated with a progressive decrease in caffeine clearance (0.118 ± 0.049 L/h/kg, 0.069 ± 0.018 L/h/kg, and 0.054 0.019 L/h/kg for placebo, low caffeine dose, and high caffeine dose, respectively) and a consequent increase in the half-life of caffeine (4.0 ± 1.4 hours, 6.1 ± 1.6 hours, and 8.7 ± 2.3 hours for placebo, low caffeine dose, and high caffeine dose, respectively).

Förster et al. (2005) showed increased urinary levels of free pentosidine (from 3.9 ± 1.2 µg/day to 10.2 ± 2.9 µg/day) in 18 healthy volunteers

(7 men, 11 women) given coffee. On the contrary, the elimination of free pyrraline was not affected by coffee consumption. [No data were available on smoking and coffee consumption habits.]

Other studies in which caffeine was administered as a capsule or gum demonstrated urinary elimination of caffeine and its metabolites (Kaplan et al., 1997; Kamimori et al., 2002; Gelal et al., 2003; Skinner et al., 2014).

(ii) Phenolic acids

In the study of Farah et al. (2008) described in Section 4.1.1 (a) (ii) above, the only intact hydroxycinnamic acids identified in urine were 5-CQA and 4-CQA. DHCA, sinapic, gallic, and *p*-hydroxybenzoic acids were the major (85%) phenolic compounds.

In 5 non-smokers (men) who consumed 4 g of instant coffee powder dissolved in water, significant urinary elimination of FA, iFA, DHFA, and vanillic acid was observed (Rechner et al., 2001).

In the study of Monteiro et al. (2007) described in Section 4.1.1 (a) (ii) above, the only intact CGA identified in urine was 5-CQA. Gallic and dihydrocaffeic acid represented the most abundant phenolic acids in urine, comprising about 56% of the total urinary concentration of all detected compounds. [No data on regular coffee consumption were provided.]

After ingestion of 200 mL of instant coffee by 11 non-smokers (8 men, 3 women), the major urinary CGA-related compound was DHCA-3-*O*-sulfate (Stalmach et al., 2009). In the study described above by the same group (Stalmach et al., 2010) in 5 ileostomy volunteers (3 men, 2 women), sulfated FA, CA, and DHCA and glucuronidated iFA were the main compounds in the 24-h ileostomy effluent after a single dose of instant coffee.

In 5 non-smoking volunteers (2 men, 3 women) given instant coffee in water or milk, the main coffee compounds identified in urine were hippuric, 3,4-dihydroxyphenylacetic, dihydrocaffeic, vanillic, and gallic acids (Duarte & Farah, 2011).

(iii) Other compounds

In 13 healthy non-smokers (7 men, 6 women) given a single 350 mL oral dose of coffee, the plasma half-life ($t_{1/2}$) of trigonelline and *N*-methylpyridinium was 4.65 hours versus 5.5 hours and 2.35 hours versus 2.15 hours in men compared with women, respectively (Lang et al., 2010). Differences between the sexes were also observed in terms of the extent of elimination, the 8-hour urinary excretion being slightly less in women than in men.

Habitual coffee consumption did not alter the concentration of two trigonelline metabolites, N^1-methyl-2-pyridone-5-carboxamide and N^1-methyl-4-pyridone-5-carboxamide, in urine samples of healthy volunteers 4 hours after consumption of a cup of coffee (Wong et al., 2002).

In 9 ileostomists (4 men, 5 women) consuming French-press coffee, only free kahweol and cafestol were found in 14-hour ileostomy effluent (De Roos et al., 1998). Both diterpenes were present in 24-hour urine in either glucuronidated or sulfated form.

4.1.2 Experimental systems

(a) Absorption

(i) In vivo

In Wistar rats given coffee or coffee and milk for 3 weeks, the absorption of CQA was found to be weak and not disrupted by the addition of milk, regardless of the fat content (Dupas et al., 2006). [Only skimmed and semi-skimmed milk was used in the study.]

Several studies evaluated absorption in rats treated with phenolic acids. Almost all ingested CGA (98.6%) remained intact in the small intestine 6 hours after administration in Wistar rats, suggesting poor absorption from the gastrointestinal tract (Azuma et al., 2000). In rats given

CGA, intact CGA was detected in urine samples, indicating that it was absorbed in its native form (Gonthier et al., 2003). In rats given CA, the major compounds in both urine and plasma were CGA metabolites of microbial origin (*m*-coumaric acid and derivatives of phenylpropionic, benzoic, and hippuric acids), accounting for 57.4% (mol/mol) of the CGA intake. In Sprague-Dawley rats, CA was rapidly absorbed with a peak plasma concentration (C_{max}) of 7870 ± 2480 ng/mL achieved 0.33 ± 0.13 hours after the oral administration of a 20 mg/kg dose (Wang et al., 2015).

In C57BL/6J mice treated with a single dose of cafestol (1.5 mg dose of [^{3}H]-labelled compound), cafestol was efficiently absorbed into the portal vein as the parent compound, a glucuronide, and an unidentified metabolite (Cruchten et al., 2010).

(ii) In vitro and ex vivo

In an ex vivo experiment with pig jejunal mucosa, hydroxycinnamic acids (at concentrations achievable in the gut lumen, 0.02–3.5 mM) were absorbed by passive diffusion in the jejunum with active efflux transport, mediated by MDR1 and MDR2 (Erk et al., 2014a). Using an in vitro Dunkin-Hartley guinea-pig stomach cell model, FQA and diCQA (dicaffeoylquinic acid) permeated across the gastric barrier as intact compounds with a relative permeability coefficient (P_{app}) of approximately 0.2 cm/s and 2–10 cm/s, respectively (Farrell et al., 2011).

The net absorption of CGA and CA accounted for 8% and 19.5% of their respective perfused flux using an in situ intestinal perfusion model derived from rat (ileum/jejunum) (Lafay et al., 2006). In a model of digestion model in vitro, the most abundant compound detected after digestion of coffee was caffeine (94%), followed by 5-CQA, 4-CQA, and 3-CQA (87.9–92.0%) (Cha et al., 2012).

(b) Distribution

In C57BL/6J mice given a single dose of cafestol (1.5 mg dose of ^{3}H-labelled compound), almost all radioactivity was found in small intestines and liver; trace amounts were detected in kidneys and none in other organs (van Cruchten et al., 2010).

(c) Metabolism

(i) In vivo

In Wistar rats given hydroxycinnamic acids, CA, or quinic acid (250 µmol/day) in the diet for 8 days, the major compounds in both urine and plasma were CGA metabolites of microbial origin (*m*-coumaric acid and derivatives of phenylpropionic, benzoic, and hippuric acids), accounting for 57.4% (mol/mol) of the CGA intake (Gonthier et al., 2003).

In mice given cafestol via the portal vein, epoxy-glutathione, glutathione, and glucuronide conjugates were identified (van Cruchten et al., 2010). With ^{3}H-labelled cafestol intravenously injected to mice (van Cruchten et al., 2010), the most abundant cafestol metabolites in bile (41%) was the glucuronide conjugate. The same metabolite was also detected in portal blood 18 minutes after administration.

(ii) In vitro

In a study of the metabolism of caffeine (100 mM) in vitro using rat P450s and liver microsomes, CYP1A2 was the most important enzyme overall (Kot & Daniel, 2008a). The main oxidation pathway (70%) was 8-hydroxylation, with CYP1A2 and CYP3A2 catalysing 72% and 15% of the reaction, respectively.

Hydrolysis of CGA was shown to take place in the gut mucosa, using an in situ intestinal perfusion model derived from rat (ileum/jejunum) (Lafay et al., 2006).

CA was shown to be methylated by catechol-*O*-methyltransferase in gastric cells, with iFA as the major metabolite, using a Dunkin-Hartley guinea-pig stomach cell model (Farrell et al., 2011).

(d) Elimination

When given as a single dose to Sprague-Dawley rats, CA was rapidly eliminated with $t_{1/2}$ values of about 1 hour after intravenous (1 mg/kg) or oral (20 mg/kg) administration (Wang et al., 2015).

In C57BL/6J mice, 20% of the administered radiolabelled cafestol dose was detected in bile 5 hours after intravenous administration (van Cruchten et al., 2010). Within 48 hours after oral administration, all radiolabel was eliminated.

4.1.3 Modulation of metabolic enzymes

(a) Humans

(i) In vivo

Several studies investigated the effect of coffee consumption on cytochrome P4501A2 (CYP1A2) activity. An increase of almost 2-fold (6.26 vs 3.94, $P = 0.01$) in CYP1A2 activity was seen in regular coffee consumers (1–10 cups/day) compared with non-consumers (< 1 cup/day) in a case–control study involving 43 adenocarcinoma patients and 47 controls matched by sex, age, and ethnicity (Le Marchand et al., 1997). In a study of 100 Serbian and 149 Swedish healthy volunteers, daily consumption of at least 3 cups of coffee was associated with significantly increased caffeine metabolism and CYP1A2 enzyme activity (Djordjevic et al., 2008). Additional genotyping of subjects for *CYP1A2* revealed that a significant association between heavy coffee consumption and high CYP1A2 enzyme activity exists only in carriers of –163 A/A genotype, suggesting that the –163A allele (rs762551) is a recessive factor necessary for the *CYP1A2* induction (Djordjevic et al., 2010). The effect of the single nucleotide polymorphism (SNP) –163C > A on *CYP1A2* inducibility persisted after adjusting for smoking and oral contraceptive use in women ($P \leq 0.022$). In a similar study with 194 Swedish and 150 Korean healthy volunteers, Ghotbi et al. (2007) reported a significantly lower rate of caffeine metabolism in Koreans as compared with Swedes ($P < 0.0001$). Increased caffeine metabolism was detected in cigarette smokers and carriers of –163C > A *CYP1A2* polymorphism ($P \leq 0.0007$), while sex-specific effects were not observed.

The effect of coffee on phase II metabolizing enzymes was also reported. In 10 healthy volunteers who consumed 1 L/day of filtered or unfiltered coffee over a period of 5 days, a significant increase in glutathione *S*-transferase (GST) enzymatic activity and immunoassays for GSTA and GSTP isozymes revealed that the induction can be assigned exclusively to the latter (Steinkellner et al., 2005). The same inductive effect was observed with both filtered and unfiltered coffee preparations [suggesting that coffee diterpenes kahweol and cafestol, known to be removed from coffee by paper filtration, are not responsible for the GST induction]. In contrast, colorectal GST activity was not affected by coffee consumption in 64 healthy regular coffee consumers drinking 1 L/day of unfiltered coffee for two intervention periods of 2 weeks (Grubben et al., 2000).

(ii) In vitro

In an assay in vitro using cultured lymphocytes from 239 healthy Japanese volunteers, regular coffee consumption increased the expression of aryl hydrocarbon hydroxylase (AHH) (Kiyohara & Hirohata, 1997).

In human colon carcinoma Caco-2 cells, coffee inhibited sulfotransferase (SULT) activity in a dose-dependent manner, an inhibitory effect that could not be attributed to caffeine (Okamura et al., 2005). Neither coffee nor caffeine affected glucuronidation, that is, UDP-glucuronosyl transferase (UGT) activity. Exposure of Caco-2 cells to 5% coffee resulted in an 81.4% decrease in SULT activity (Saruwatari et al., 2008). Likewise, Isshiki et al. (2013) also reported a 60% and 25% reduction of the expression of *SULT1E1* gene and SULT activity, respectively, in Caco-2 cells treated with 2.5% coffee for 24 hours.

Filtered coffee, decaffeinated coffee, and instant coffee induced UGT1A expression in HepG2 and Caco-2 cells (Kalthoff et al., 2010), indicating that the observed upregulation is independent of caffeine, kahweol, or cafestol content.

Kahweol and cafestol slightly increased overall GST activity and significantly increased the level of GST-mu protein in transformed liver epithelial cell lines (THLE) (Cavin et al., 2001). Similarly, kahweol and cafestol decreased sulfotransferase SULT1A1 by 38%, while GST and UGT activity increased by 1.4- and 1.2-fold, respectively, in human HepG2 cells (Majer et al., 2005).

In human lymphoblastoid cell lines (LCLs), caffeine caused a significant downregulation in *CYP1A1* levels (by 1.29-fold), but had no effect on *CYP1A2* (Amin et al., 2012). Likewise, caffeine did not alter the expression of the *CYP1A2* in primary human hepatocytes (Vaynshteyn & Jeong, 2012).

(b) Experimental systems

(i) In vivo

In wildtype mice, coffee (3% and 6%) increased hepatic levels of GSTA1 (5-fold and 6-fold, respectively), GSTA4 (3-fold and 4-fold, respectively), and CYP1A2 (3-fold in the 6% coffee group), while GSTA3 and UGT1A6 were unaffected (Higgins et al., 2008). On the contrary, in Nrf2 null mice, both the normal constitutive expression of enzymes and the alteration in their level and activity in the liver was diminished; only the UGT1A6 level was increased by 4-fold in *nrf2*$^{-/-}$ mice fed 6% coffee. In the small intestine of the wildtype mice, induction followed the same Nrf2-dependent pattern.

In Fischer rats fed a coffee-containing diet (0%, 1%, or 5% w/w) for 2 weeks, there was a strong, concentration-dependent induction of CYP1A2 (by up to 16-fold) (Turesky et al., 2003). In addition, coffee (5%) (but not caffeine) increased rGSTA1 and rGSTA3 (by 1.4- and 2.6-fold, respectively), and UGT (2-fold). Similarly, Abraham et al. (1998) showed that coffee caused a modest increase in GST activity in Swiss albino mice.

Coffee significantly increased enzyme expression in different organs of humanized UGT transgenic mice, ranging from 10-fold for liver UGT1A1 to 11-fold and 14-fold for stomach UGT1A1 and UGT1A6, respectively (Kalthoff et al., 2010). Several studies (Huber et al., 2003, 2004, 2008) have demonstrated that coffee given to rats for 10–20 days induced hepatic GST and UGT activities (up to 30% and approximately 2-fold, respectively), as well as hepatic CYP1A1, CYP1A2, CYP2B1, and CYP2B2 (ranging from 2-fold for CYP2B2 to 6-fold for CYP1A2).

In male Fischer 344 rats, caffeine (0.04%) significantly increased the CYP1A2 protein level by 3.8-fold (Chen et al., 1996). Similarly, caffeine (20 mg/kg) given to Swiss albino mice for 8 weeks increased the level of CYP1A2 in the brain (Singh et al., 2009). Kahweol/cafestol (47% kahweol, 47% cafestol, 5% isomeric derivatives) increased GST and UGT activity in rat liver and kidney (Huber et al., 2002).

(ii) In vitro

In rat primary hepatocytes, caffeine (50 µM for 72 hours) resulted in an increase of 9-fold in *Cyp1a2* expression (Vaynshteyn & Jeong, 2012). A mixture of kahweol and cafestol (52.5:47.5) for 48 hours inhibited CYP3A2 and activated GST in a dose-dependent manner in primary rat hepatocytes (Cavin et al., 2001).

CA significantly inhibited both human (Uwai et al., 2011) and rat (Uwai et al., 2013) organic anion transporters (OATs) expressed in *Xenopus laevis* oocytes. CGA significantly inhibited only hOAT3, while quinic acid was without effect on the transporters.

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

(a) Humans

The results of investigations on the effect of coffee drinking by exposed humans and in human cells in vitro are listed in Table 4.3 and Table 4.4, respectively.

(i) Exposed humans

See Table 4.3.

DNA damage

A protective effect on DNA damage in lymphocytes was found in studies conducted with coffee containing increased amounts of chlorogenic acids (green coffee bean extract) and *N*-methylpyridinium (Bakuradze et al., 2011, 2014, 2015, 2016).

While several other studies found no protective effect on DNA damage in unexposed lymphocytes, it was demonstrated that lymphocytes isolated from coffee consumers exhibited reduced DNA damage after in vitro exposure to DNA-damaging agents (Steinkellner et al., 2005; Bichler et al., 2007). In contrast to the protective effects seen in peripheral lymphocytes, non-smoking, coffee-consuming men had an approximately 20% higher percentage tail DNA under neutral, but not alkaline, conditions compared with men who consumed no caffeine (Schmid et al., 2007).

Oxidative and other DNA damage end-points reported in studies of oxidative stress markers are discussed in Section 4.2.2.

Cytogenetic effects

One study reported a significant increase in lymphocyte chromosomal aberrations with coffee intake, independent of smoking status or folate levels (Chen et al., 1989). In sperm cells, a statistically significant positive association was found between drinking coffee daily and the lack of chromosome X or Y. In addition, coffee drinking 1–6 times per week was associated with an additional chromosome 18 (Jurewicz et al., 2014).

In splenectomized individuals, consumption of caffeinated (but not decaffeinated) coffee was associated with an approximately 2-fold higher frequency of micronuclei (MN) in reticulocytes and erythrocytes (Smith et al., 1990). In an Italian lifestyle study described by Barale et al. (1998), no increase of MN formation was found in coffee drinkers compared with non-drinkers.

Several studies that reported on the relationship between coffee consumption and sister-chromatid exchange (SCE) in lymphocytes focused on a variety of lifestyle factors rather than primarily on the effects of coffee. [The Working Group noted shortcomings regarding the study design.] Reidy et al. (1988) reported a positive linear relationship between SCE) and coffee consumption that was similar for male smokers (n = 30) and non-smokers (n = 30). [The Working Group noted a lack of details on coffee consumption.] Similarly, coffee intake was associated with a significant increase in SCE in a study of women of the Republic of Korea (Shim et al., 1989). However, a follow-up report from the same group found no effect of coffee consumption on SCE in male smokers (Shim et al., 1995). A borderline increase in SCE frequencies with coffee drinking was reported by Barale et al. (1998), and no difference in spontaneous SCE between coffee drinkers and non-drinkers was reported in another study in Italy (Sbrana et al., 1995). Finally, reporting on a cross-sectional study of twins, Hirsch et al. (1992) found that individuals who consumed at least 5 cups/day of coffee had half the number of SCE/cell (after adjusting for smoking) compared with those who drank < 5 cups/day.

Gene mutations

Several studies from one research group (Porta et al., 1999, 2009; Morales et al., 2007) reported an association between coffee consumption and

Table 4.3 Genetic and related effects of drinking coffee in exposed humans

Cell type	End-point	Test system	Description of exposure and controls	Response	Comments	Reference
Lymphocytes	DNA damage	Comet assay	33 male non-smoking subjects consumed 750 mL/day of coffee for 4 wk	(PE) ($P < 0.001$)		Bakuradze et al. (2011)
Lymphocytes	DNA damage	Comet assay	84 non-smoking subjects consumed 750 mL/day of coffee for 4 wk	(PE) ($P < 0.001$)		Bakuradze et al. (2014)
Lymphocytes	DNA damage	Comet assay	84 male non-smoking subjects; 42 consumed 750 mL/day of coffee and 42 controls consumed water only for 4 wk	(PE) ($P = 0.0002$)		Bakuradze et al. (2015)
Lymphocytes	DNA damage	Comet assay	13 male non-smoking subjects; sampling every 2 h before and after coffee drinking; 200 mL every 2 h (total 800 mL)	(PE) $P < 0.001$		Bakuradze et al. (2016)
Lymphocytes	DNA damage	Comet assay	10 healthy subjects (3 men, 7 women) consumed 1 L/day of unfiltered coffee for 5 days	– (PE)	Reduction in DNA damage induced by BPDE ($P = 0.0001$)	Steinkellner et al. (2005)
Lymphocytes	DNA damage	Comet assay	8 healthy men and women; 600 mL/day coffee (400 mL paper- and 200 mL metal-filtered) for 5 days	– SC (PE)	Reduction in DNA damage induced by H_2O_2 or Trp-P-2 ($P < 0.05$)	Bichler et al. (2007)
Sperm	DNA damage	Comet assay	80 healthy male non-smokers: 58 coffee drinkers vs 22 non-drinkers	+ coffee drinkers vs non-drinkers ($P = 0.005$)	+ for neutral, but not alkaline, assay	Schmid et al. (2007)
Lymphocytes	Chromosomal damage	Chromosomal aberration	25 subjects who consumed > 4 cups/day of coffee vs 34 subjects < 4 cups/day of coffee	+ ($P < 0.019$)		Chen et al. (1989)
Sperm	Chromosomal damage	Chromosomal aberration, aneuploidy (FISH)	212 healthy men	+		Jurewicz et al. (2014)
Reticulocytes and erythrocytes	Chromosomal damage	Micronucleus formation	44 splenectomized subjects (26 men, 18 women); 29 drank 1–2 cups/day of coffee, 10 drank decaffeinated coffee (< 1 cup/day), 12 drank tea	+ reticulocytes ($P = 0.05$), erythrocytes ($P = 0.03$)	No effect with decaffeinated coffee	Smith et al. (1990)
Lymphocytes	Chromosomal damage	Micronucleus formation	564 female coffee drinkers vs 165 non-drinkers; 414 male coffee drinkers vs 107 non-drinkers	–		Barale et al. (1998)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	30 smoking and 30 non-smoking men	+ Coffee intake vs abstinence ($P = 0.0006$)	Linear increase with cups of coffee intake ($P < 0.01$)	Reidy et al. (1988)

Table 4.3 (continued)

Cell type	End-point	Test system	Description of exposure and controls	Response	Comments	Reference
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	11 coffee-drinking (1–2 cups/day) women vs 41 women non-drinkers	+ ($P < 0.01$)	Few coffee consumers	Shim et al. (1989)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	14 male smokers who drank coffee (> 2–3 cups/day for 6 mo) vs 14 male non-drinking smokers	–	Few coffee consumers	Shim et al. (1995)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	564 coffee-drinking women vs 165 non-drinkers; 414 coffee drinker men vs 107 non-drinkers	–		Barale et al. (1998)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	86 coffee drinkers versus 22 non-drinkers	–		Sbrana et al. (1995)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	In a study of twins, 29 coffee drinkers who consumed ≥ 5 cups/day vs 195 consuming < 5 cups/day	+ ($P < 0.001$)	Linear increase with cups of coffee ($P < 0.001$)	Hirsch et al. (1992)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	86 coffee drinkers versus 22 non-drinkers	–		Sbrana et al. (1995)
Tumour	K-*RAS* mutation	DNA analysis, PCR	121 patients with pancreatic cancer (70 men and 51 women)	+ ($P = 0.018$)	Increase with cups of coffee consumed, but not duration	Porta et al. (1999)
Tumour	K-*RAS* mutation	DNA analysis, PCR	107 pancreatic cancer patients with (83 cases) or without (24 cases) K-*RAS* mutation	+ ($P = 0.026$)	Increase with cups of coffee ($P = 0.038$)	Morales et al. (2007)
Tumour	K-*RAS* mutation	DNA analysis, PCR	103 pancreatic ductal adenocarcinoma patients	+ ($P < 0.015$)	Increase with cups of coffee consumed	Porta et al. (2009)

+, positive; –, negative; BPDE, (±)-anti-benzo[*a*]pyrene-7,8-dihydrodiol-9,10-epoxide; FISH, fluorescence in situ hybridization; h, hour; PCR, polymerase chain reaction; PE, protective effect; SC, standard conditions; Trp-P-2, amine 3-amino-1-methyl-5H-pyrido[4,3-*b*]indole-acetate; wk, week(s); vs, versus

Table 4.4 Genetic and related effects of coffee in human cells in vitro

Tissue, cell line	Coffee type and preparation	End-point	Test	Results		Concentration (LEC or HIC)	Comments	Reference
				Without activation	With metabolic activation			
HT29 and HepG2 cells	Green coffee extract	DNA damage	DNA strand break, comet assay	– (PE)	NT	6 µg/mL	Reduction in H_2O_2-induced DNA damage	Glei et al. (2006)
Peripheral lymphocytes	Metal filtered coffee, French press method	DNA damage	DNA strand break, comet assay	+ (PE)	NT	50 µL/mL	Coffee increased DNA damage and reduced H_2O_2-induced DNA damage	Bichler et al. (2007)
HeLa cells	Spent coffee grounds	DNA damage	DNA strand break, comet assay	– (PE)	NT	333 µg/mL	Reduction in H_2O_2-induced DNA damage	Bravo et al. (2013)
p53R cells (colorectal cell line expressing *TP53* reporter gene)	Brewed coffees (regular and decaffeinated)	DNA damage	p53 activation assay	+	NT	1:20		Hossain et al. (2013)
Transformed liver epithelial cell lines expressing CYP 1A2, 3A4, and 2B6	Coffee diterpenes: cafestol and kahweol	DNA damage	DNA adduct	(PE)	NT	1 µg/mL	Reduction in AFB1-DNA adducts formation	Cavin et al. (2001)
Primary hepatocytes	Coffee (caffeinated and decaffeinated)	DNA damage	DNA adducts	(PE)	NT	200 µg/mL	Reduction in AFB1-DNA adduct formation	Cavin et al. (2008)
Lymphocytes	Instant coffee (caffeinated and decaffeinated)	Chromosomal damage	Chromosomal aberration	+	+	2.5 mg/mL	Lower in the presence of S9	Aeschbacher et al. (1985)
Peripheral lymphocytes	Brewed coffee	Chromosomal damage	Sister-chromatid exchange	+	NT	0.2 mg/mL		Tucker et al. (1989)
Liver HepG2 cell line	Coffee diterpenes: cafestol and kahweol (C+K)	Chromosomal damage	MN formation	– (PE)	NT	0.3 µg/mL	Inhibited MN induced by PhIP or NDMA	Majer et al. (2005)

+, positive; – negative; AFB1, aflatoxin B_1; C+K, cafestol and kahweol; H_2O_2, hydrogen peroxide; HIC, highest ineffective concentration; LEC, lowest effective concentration; MN, micronucleus; NDMA, *N*-nitrosodimethlyamine; NT, not tested; PE, protective effect; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine

K-*RAS* mutations in ductal adenocarcinoma of the pancreas. Mutations in K-*RAS* on codon 12 were found in tumours from 94 of 121 patients (77.7%), and were more common among regular coffee drinkers than non-regular coffee drinkers (82.0% vs 55.6%, $P = 0.018$, $n = 107$, adjusted for smoking and alcohol drinking) (Porta et al., 1999). Similar results were obtained in two follow-up studies that also adjusted for other lifestyle factors and exposures to organochlorine chemicals (Morales et al., 2007; Porta et al., 2009).

Mutagenicity of urine

Aeschbacher & Chappuis (1981) found no evidence of mutagenicity in Salmonella strains TA98 and TA100 of polar and non-polar fractions with urine samples from 6 coffee drinkers and 6 non-drinkers. However, chromosomal damage in Chinese hamster ovary (CHO) cells was induced by fractions prepared from urine of coffee drinkers (Dunn & Curtis, 1985).

(ii) Human cells in vitro

See Table 4.4.

Coffee increased DNA damage by comet assay in one study (Bichler et al. 2007) and reduced the DNA damage induced by H_2O_2 in several studies using different cell types (Bichler et al. 2007; Bravo et al., 2013), as did a green coffee extract (Glei et al., 2006). Coffee increased TP53 activation, via a stably transfected luciferase reporter, in a human colorectal cell line (Hossain et al., 2013). Although reportedly confirmed in comet and histone γH2AX phosphorylation experiments, the latter results were not shown. [The Working Group noted that this study is difficult to interpret.]

Coffee protected against aflatoxin-induced DNA adducts in transformed human liver epithelial cells (Cavin et al., 2001), as did two diterpenes (cafestol and kahweol) in human primary hepatocytes (Cavin et al., 2008). Similar protection by the diterpenes was seen against MN induced by 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) and *N*-nitrosodimethylamine (NDMA) (Majer et al., 2005).

In human lymphocytes, coffee induced chromosomal aberrations in the absence of a metabolic activation system (S9), but S9 reduced the clastogenic properties (Aeschbacher et al., 1985). Tucker et al. (1989) reported a significant increase in SCE with brewed coffee, an effect reduced by bisulfite addition. [The Working Group noted that this suggested that bicarbonyls (which are complexed by bisulfite) may have accounted for this effect.]

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.5.

Several in vivo studies tested coffee in combination with genotoxic agents. Turesky et al. (2003) found evidence for coffee-associated reduction of PhIP-induced DNA adducts in the liver of rats. Ferk et al. (2014) found a significant reduction of DNA damage induced by aflatoxin B_1 in the liver of rats with paper- and metal-filtered coffee brews, whereas a decaffeinated coffee brew had a lesser effect.

A significant dose-dependent increase in 8-OHdG levels, as well as an increase in the concentrations of CGA in the urine, was found in Wistar rats given freeze-dried coffee (Sakamoto et al., 2003). Salomone et al. (2014) showed that coffee reduced the hepatic levels of 8-OHdG and other markers of oxidative stress in rats fed a high-fat diet. A study in ICR mouse by Morii et al. (2009) reported no effect of instant coffee consumption (0.1% w/v) on DNA oxidation, on the activity of superoxide dismutase (SOD), or on 8-OHdG repair-associated gene expression (*Ogg1*).

A protective effect of coffee on the induction of MN in mouse bone marrow was reported by Abraham and co-workers. A significant inhibition of MN formation by coffee was observed after co-treatment with dimethylbenz[*a*]anthracene,

Table 4.5 Genetic and related effects of coffee in non-human mammalian cells in vivo

Species, strain, sex	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regiment	Comments	Reference
Rat, Fischer-344, male	Liver, colon, pancreas	DNA damage	DNA adducts	(PE) against PhIP	1% lyophilized coffee	Diet, 14 day, sampling 24 h after PhIP treatment	$P < 0.01$; PhIP detected (0.75 mg/kg bw); DNA adducts in liver, colon, pancreas; liver adducts decreased by 50%; 1% coffee protects against PhIP in liver, 5% in pancreas	Turesky et al. (2003)
Rat, Him-OFA, male	Liver	DNA damage	DNA strand breaks, comet assay	(PE) against AFB1	Metal-filtered coffee: 9.65 g/day; paper-filtered coffee or decaffeinated coffee: 19.3 g/day	Orally, 8 day, sampling 4 h after AFB1 (2 mg/kg bw)		Ferk et al. (2014)
Rat, Wistar, male	Urine	Oxidized DNA damage	8-OHdG	+	0.62% (125 mg/day) freeze-dried coffee	Orally in diet, 130 d		Sakamoto et al. (2003)
Rat, Wistar, male	Liver	Oxidized DNA damage	8-OHdG	(PE), high-fat diet	1.5 mL/animal Paper-filtered decaffeinated coffee	Orally as solution, 12 wk		Salomone et al. (2014)
Mouse, ICR, male	Liver	Oxidized DNA damage	8-OHdG	–	0.1% w/v instant coffee	Orally as solution, up to 8 mo		Morii et al. (2009)
Mouse, Swiss, male/female	Bone marrow	Chromosomal damage	MN formation	– (PE) against MMC, CP, PCZ but not adriamycin	500 mg/kg bw coffee/instant coffee	Gavage, 1×, sampled after 25–28 h		Abraham (1989)
Mouse, Swiss, female	Fetal liver, blood, maternal bone marrow	Chromosomal damage	MN formation	(PE) against CP, NEU and MMC	350 mg/kg bw during gestation (15–16 days)	Gavage; 1×, sampled after 22 or 28 h	Protective effect in embryos and dams	Abraham (1995)
Mouse, Swiss albino, male	Bone marrow	Chromosomal damage	MN formation	– (PE) against urethane	125 mg/kg bw filtered coffee	Gavage, 1×, sampled after 24 or 48 h	Coffee increased GST	Abraham et al. (1998)

Table 4.5 (continued)

Species, strain, sex	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regiment	Comments	Reference
Mouse, Swiss, male	Bone marrow	Chromosomal damage	MN formation	(PE) against DMBA, AFB1, B[*a*]P, UR, CP	250 mg/kg bw instant coffee	Gavage, 2× (2 h, 20 h before i.p. carcinogen treatment), sampled 24 h or 48 h after last dose		Abraham (1991)
Mouse, Swiss, male	Bone marrow	Chromosomal damage	MN formation	– (PE) against DMBA, B[*a*]P, UR, CP, MMC	140 mg/kg bw decaffeinated, caffeinated instant coffee	Gavage, 1×/10 d, sampled 24 h or 48 h after dose	Same result with 2 g/100 mL oral	Abraham & Singh (1999)
Mouse, MS/Ae	Bone marrow	Chromosomal damage	MN formation	– (PE) against MU + $NaNO_2$	150–1000 mg/kg bw instant coffee	Orally, 1×, sampled 24 h after dose	No PE against MNU	Aeschbacher & Jaccaud (1990)
Mouse, Swiss, OF-1, male	Bone marrow	Chromosomal damage	MN formation	–	3000 mg/kg bw instant coffee	Gavage, 1×/5 days, sampled 6 h after dose		Aeschbacher et al. (1984)
Chinese hamster, male	Bone marrow	Chromosomal damage	Sister-chromatid exchange	–	2500 mg/kg bw instant coffee	Gavage, 1×, sampled 25–26 h after dose		Aeschbacher et al. (1984)

+, positive; –, negative; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; AFB1, aflatoxin B_1; B[*a*]P, benzo[*a*]pyrene; bw, body weight; CP, cyclophosphamide; DMBA, dimethylbenz[α]anthracene; GST, glutathione *S*-transferase; h, hour(s); HID, highest ineffective dose; i.p., intraperitoneally; LED, lowest effective dose; MMC, mitomycin C; MN, micronucleus; mo, month(s); MNU, *N*-methylnitrosourea; MU, methyl urea; $NaNO_2$, sodium nitrite; NEU, *N*-nitroso-*N*-ethylurea; PCZ, procarbazine; PE, protective effect; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; UR, urethane; wk, week(s)

aflatoxin B_1, benzo[*a*]pyrene, cyclophosphamide, mitomycin, procarbazine, and urethane, but not adriamycin (Abraham, 1989, 1991; Abraham et al., 1998). Oral administration of coffee to pregnant mice before administration of cyclophosphamide, *N*-nitroso-*N*-ethyl urea, or mitomycin C reduced the formation of MN in the fetal liver and blood and in maternal bone marrow (Abraham, 1995). Coffee was also protective against urethane-mediated reduction in the activity of the detoxifying enzyme glutathione *S*-transferase (Abraham et al., 1998). In a comparative study of caffeinated and decaffeinated brews, both displayed similar protective effects against chemically-induced MN (Abraham & Singh, 1999). Notably, several of these studies included coffee-only control groups; no evidence for induction of MN by coffee itself was detected.

Coffee administered in a dose equivalent to the consumption of 5 cups of coffee had a protective effect on nitrosourea-induced MN in bone marrow cells in mice (Aeschbacher & Jaccaud, 1990). In addition, no prevention of MN induced by exogenous *N*-methylnitrosourea was found, suggesting that the protective effect of coffee may be through prevention of endogenous nitrosation (Aeschbacher & Jaccaud, 1990). The same group reported that instant coffee had no effect on MN and SCE in mice or in Chinese hamsters (Aeschbacher et al., 1984).

(ii) Non-human mammalian cells in vitro

See Table 4.6.

Overall, experiments with coffee or its constituents in mammalian cells fall into two categories: the first group concerns the effect of coffee per se on damage of the genetic material, and the second group deals with the protective effects towards chemical carcinogen-associated damage.

In a CHO cell line (AUXB1), coffee induced SCE; this was reduced by bisulfite addition but not by catalase and peroxidase (Tucker et al., 1989). In CHO-K1 cells, SCE frequencies were increased with caffeinated or decaffeinated coffee (brewed and instant), although decaffeinated coffee was less potent and only positive in the absence of S9 (Santa-Maria et al., 2001). No increase was seen with green coffee prepared from unroasted beans (with and without S9).

In Chinese hamster lung (CHL) cells, a mutagenic effect of instant coffee was suppressed by sodium bisulfite, a scavenger of carbonyls (Nakasato et al., 1984).

Protection by coffee against PhIP as measured by the single-cell gel electrophoresis assay was seen in the Chinese hamster fibroblast V79 cell line expressing CYP1A2 and sulfotransferase SULT1C1 (Edenharder et al., 2002).

Caffeine-containing instant coffee protected against DNA damage and MN induced by different genotoxic chemicals, such as *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG), mitomycin C, methyl methanesulfonate, and γ-radiation in mouse lymphoma cells (Abraham et al. (2004). No difference in the protective properties of caffeinated and decaffeinated brews against MNNG was detected (Abraham & Stopper, 2004). Coffee itself was devoid of genotoxic activity, and no reduction of MN was detected when cells were exposed to the mutagen before coffee.

(iii) Non-mammalian experimental systems

See Table 4.7.

No clear effects were found in germ cell assays in *Drosophila melanogaster*, but moderate activities were detected regarding the induction of mosaic spots in the wings in repair-proficient and also repair-deficient cells (Graf & Würgler, 1986). Coffee had a protective effect when administered in combination with a variety of genotoxins such as urethane, cyclophosphamide, mitomycin C, and diethylnitrosamine (Abraham, 1994; Abraham & Graf, 1996).

The majority of studies with *Salmonella typhimurium* and other bacterial tester strains were published before 1990 and were reviewed by the

Table 4.6 Genetic and related effects of coffee in non-human mammalian cells in vitro

Species	Cell model	End-point	Test system	Results		Concentration (LEC or HIC)	Reference
				Without metabolic activation	With metabolic activation		
Chinese hamster	CHO (AUXBI)	Chromosomal damage	Sister-chromatid exchange	+	NT	0.1–1.2 mg/mL; brewed coffee	Tucker et al. (1989)
Chinese hamster	CHO-K1	Chromosomal damage	Sister-chromatid exchange	+	+	10 mg/mL; blend or instant coffee	Santa-Maria et al. (2001)
Chinese hamster	CHO-K1	Chromosomal damage	Sister-chromatid exchange	–	–	10 mg/mL; roasted, green coffee	Santa-Maria et al. (2001)
Chinese hamster	CHO-K1	Chromosomal damage	Sister-chromatid exchange	+	–	10 mg/mL; blend or instant decaffeinated coffee	Santa-Maria et al. (2001)
Chinese hamster	Lung fibroblasts V79-rCYP1A2-rSULT1C1	DNA damage	Comet assay	– (PE) against PhIP	NT	2% v/v; coffee (not specified)	Edenharder et al. (2002)
Mouse	Lymphoma L5178Y	DNA damage	Comet assay	– (PE) against MNNG and MMS	NT	125 µg/mL; caffeinated instant coffee	Abraham & Stopper (2004); Abraham et al. (2004)
Mouse	Lymphoma L5178Y	Gene mutation	*Tk*$^{\pm}$ locus	– (PE) against MNNG	NT	125 µg/mL; caffeinated instant coffee	Abraham et al. (2004)
Mouse	Lymphoma L5178Y	Chromosomal aberration	MN formation	–	NT	250 µg/mL; caffeinated instant coffee	Abraham & Stopper (2004)
Mouse	Lymphoma L5178Y	Chromosomal aberration	MN formation	–	NT	125 µg/mL; caffeinated instant coffee or filtered and unfiltered instant coffee 60 µg/mL boiled coffee	Abraham et al. (2004); Abraham & Stopper (2004)
Mouse	Lymphoma L5178Y	Chromosomal aberration	MN formation	– (PE) against MNNG	NT	60–250 µg/mL; caffeinated, decaffeinated, filtered, unfiltered instant coffee, and boiled coffee	Abraham & Stopper (2004)
Mouse	Lymphoma L5178Y	Chromosomal aberration	MN formation	– (PE) against MNNG; MMS; MMC; γ- radiation.	NT	125 µg/mL; caffeinated instant coffee	Abraham et al. (2004)

+, positive; –, negative; HIC, highest ineffective concentration; LEC, lowest effective concentration; MMC, mitomycin C; MMS, methyl methanesulfonate; MN, micronucleus; MNNG, *N*-methyl-*N*-nitro-*N*-nitrosoguanidine; NT, not tested; PE, protective effect; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine

Working Group in a previous *IARC Monograph* on coffee (IARC, 1991).

The first description of an investigation of the effects of coffee on *Salmonella typhimurium* strains was published by Nagao et al. (1979). Regular, instant, and decaffeinated instant coffee were mutagenic in strain TA100 but not TA98, and only without metabolic activation. Similar results were reported by Aeschbacher & Würzner (1980), with positive results in TA100 but not in other tester strains (TA98, TA1535, TA1537, TA1538). Subsequent host-mediated assays in which bacterial indicator cells were injected into host animals (mice received instant coffee at 6 /kg bw) and subsequently recovered from the liver yielded consistently negative results.

Many subsequent studies attempted to discern the components accounting for mutagenicity in the Ames assay, determining that the addition of glutathione reduced mutagenicity (Kosugi et al., 1983; Friederich et al., 1985). The first evidence that methylglyoxal accounts for the bacterial mutagenicity of coffee beverages was provided by the studies of Kasai et al. (1982) and Fujita et al. (1985a). Later studies confirmed this assumption; that is, it was shown that the addition of glyoxalase reduced the mutagenicity of methylglyoxal and also the mutagenic activity of coffee brews by up to 80% (Friederich et al., 1985). [The Working Group noted that the compounds accounting for the induction of bacterial mutagenesis may be inactivated under in vivo conditions in humans.]

Apart from methylglyoxal, other dicarbonyls (in particular glyoxal and ethylglyoxal) are also present in coffee brews (Nagao et al., 1986). These compounds are less mutagenic in TA100 than methylglyoxal itself and are present in lower quantities; nevertheless, they may contribute to a certain extent to the overall effects of coffee.

A systematic comparison of the effects of a broad variety of components indicated that the effects (in TA100 and TA102) were mainly caused by dicarbonyls and not by other constituents such as furans, heterocycles, and sulfur-containing compounds (Aeschbacher et al., 1989). Another coffee constituent that may be involved in the bacterial mutagenesis is trigonelline (Wu et al., 1997). In contrast to coffee, however, trigonelline compounds were highly active in TA98 and its derivative strains (YG1024) in the presence of S9 mix. One investigation (Johansson et al., 1995) of instant coffee found some evidence of mutagenicity in TA98 with S9, which may be due to trigonelline reaction products. The mutagenic activity of instant coffee was seen in TA98, YG1024, and YG1029 with S9 (the latter strains overexpress *N*-acetyltransferase, which catalyses the activation of heterocyclic aromatic amines) (Johansson et al., 1995).

The mutagenic activity of instant coffee in strain TA100 increased significantly after nitrosation, and involved compounds such as chlorogenic acid, cathechol, and caffeic acid (Duarte et al., 2000). However, whereas coffee and coffee components inhibit the nitrosation of methylurea under in vitro conditions, the reduced formation of *N*-nitroso compounds was observed in vivo (Stich et al., 1982, 1984).

Evidence for the genotoxic properties of coffee was also found in several other bacterial test systems, for example in assays for phage induction with *Escherichia coli* (Suwa et al., 1982; Kosugi et al., 1983) and in experiments with *Escherichia coli* WP2 *uvrA* and *Escherichia coli* WP2 *uvrA*/pKM101 (Kosugi et al., 1983). Based on a comparison of coffee components using the L-arabinose resistance assay, methylglyoxal, glyoxal, caffeic acid, and caffeine contributed little, if at all, to the bacterial mutagenicity of coffee, whereas hydrogen peroxide content could explain 40–60% of the genotoxic activity of the brews (Dorado et al., 1987). These findings are in contrast to results obtained with Ames tester strains, which are more responsive to methylglyoxal (Ariza et al., 1988). The assumption that the peroxide accounts for the effects of coffee in the L-arabinose resistance test was further

Table 4.7 Genetic and related effects of coffee in non-mammalian experimental systems

Experimental system Species, strain	End-point	Test[a]	Results		Type of coffee	Concentration (LEC or HIC)	Comments	Reference
			Without activation	With metabolic activation				
Drosophila melanogaster	Germ cells mutation	Sex-linked recessive lethals	–	NA	Instant coffee	4%		Graf & Würgler (1986)
Drosophila melanogaster	Germ cells mutation	Dominant lethal sex chromosome loss	–	NA	Home-brew coffee	3%		Graf & Würgler (1986)
Drosophila melanogaster	Somatic mutation	SMART	+ + –	NA	Instant coffee Home-brew coffee Decaffeinated	4% 3% 20%	Moderate effect	Graf & Würgler (1986)
Drosophila melanogaster	Somatic mutation	SMART	– (PE) against DEN, MMC, UR, CP	NA	Instant coffee	2%		Abraham (1994); Abraham & Graf (1996)
Salmonella typhimurium TA100	Gene mutation	Reverse mutation	+ +	– –	Coffee from roasted beans Instant caffeinated and decaffeinated coffee	4.7–21 mg/plate 1 mg/plate		Nagao et al. (1979)
Salmonella typhimurium TA98	Gene mutation	Reverse mutation	–	–	Coffee from roasted beans, instant caffeinated and decaffeinated coffee	5–35 mg/plate		Nagao et al. (1979)
Salmonella typhimurium TA98, TA1535, TA1537, TA1538	Gene mutation	Reverse mutation	–	–	Brewed, instant coffee	35 mg/plate		Aeschbacher & Würzner (1980)
Salmonella typhimurium TA100	Gene mutation	Reverse mutation	+	–	Brewed, instant coffee	5–15 mg/plate		Aeschbacher & Würzner (1980)

Table 4.7 (continued)

Experimental system Species, strain	End-point	Test[a]	Results		Type of coffee	Concentration (LEC or HIC)	Comments	Reference
			Without activation	With metabolic activation				
Salmonella typhimurium TA100	Gene mutation	Reverse mutation	+ + +	NT NT NT	Brewed coffee Instant coffee Instant decaffeinated	10 mg/plate 7.5 mg/plate 5 mg/plate	Suppression of the mutagenic properties of all brews by scavenging of 1,2-dicarbonyl diacetyl and glyoxal L-ascorbic acid increased the effect of coffee	Suwa et al. (1982)
Escherichia coli K12	Prophage induction	Plaque formation	+	NT	Instant coffee, decaffeinated instant	20 mg/plate		Suwa et al. (1982)
Salmonella typhimurium TA100	Gene mutation	Reverse mutation	+	NT	Coffee from roasted beans	15 mg/plate	No effects of green coffee	Kosugi et al. (1983)
Escherichia coli K12	Prophage induction	Plaque formation	+ –	NT	Coffee from roasted beans Coffee from green beans	20–30 mg/plate 60 mg/plate	No effects of green coffee	Kosugi et al. (1983)
Escherichia coli WP2*uvr*A/pKM101	Gene mutation	Reverse mutation	+ –	NT	Coffee from roasted beans Coffee from green beans	40 mg/plate 75 mg/plate	No effects of green coffee	Kosugi et al. (1983)
Salmonella typhimurium TA100, TA102	Gene mutation	Reverse mutation	+ (TA100) + (TA102)	– (TA100) – (TA102)	Instant coffee Instant coffee	7 mg/plate 10 mg/plate	Reduction of mutagenic effect by glutathione	Friederich et al. (1985)
Salmonella typhimurium TA100	Gene mutation	Reverse mutation	+ + (TA100) + (TA102) – (TA104) – (YG1024)	NT – (TA100) + (TA102) – (TA104) – (YG1024)	Instant coffee Instant coffee Instant coffee Instant coffee Instant coffee	10 mg/plate 10 mg/plate NR NR NR	Methylglyoxal in coffee caused only a moderate effect. Reduction of the coffee effects by catalase	Fujita et al. (1985a)

Table 4.7 (continued)

Experimental system Species, strain	End-point	Test[a]	Results		Type of coffee	Concentration (LEC or HIC)	Comments	Reference
			Without activation	With metabolic activation				
Salmonella typhimurium TA100, TA102	Gene mutation	Reverse mutation	+ (TA100) + (TA102)	NT NT	Instant coffee Instant coffee	10 mg/plate 20 mg/plate		Aeschbacher et al. (1989)
Salmonella typhimurium TA98, TA100	Gene mutation	Reverse mutation	+ (TA98) – (TA100)	NT NT	Fractions of instant coffee	Fractions from 250 mg/mL		Kato et al. (1994)
Salmonella typhimurium TA98, YG1024, YG1029	Gene mutation	Reverse mutation	NT NT NT NT NT NT	+ (TA98) + (YG1024) + (YG1029) + (TA98) + (YG1024) + (YG1029)	Extracts of grain-based coffee Extracts of instant coffee	0.75 gEq/plate 0.2 gEq/plate NR 0.75 gEq/plate 0.2 gEq/plate NR	Higher sensitivity in YG1024 with S9 mix	Johansson et al. (1995)
Escherichia coli K12 (catalase proficient UC1217 and catalase deficient UC1218)	Gene mutation	*Lac* I Test	+	NT	Instant coffee	4 mg/plate (UC1218); 15 mg/plate (UC1217)	Similar spectrum of mutations (coffee vs H_2O_2)	Ruiz-Laguna & Pueyo (1999)
Salmonella typhimurium TA102, TA104	Gene mutation	Reverse mutation	+ (TA102) + (TA104)	NT NT	Paper-filtered coffees	5 mg/plate 5 mg/plate		Dorado et al. (1987)
Salmonella typhimurium (L-Arabinose resistant) BA1, BA3, BA9, BA13	Gene mutation	Forward mutation	+ (BA13) + (BA13) + (B13)	NT NT NT	Coffee beans Ground coffee Instant coffee	1 mg/plate 1 mg/plate 0.5 mg/plate	Instant coffee was more active than ground coffee	Dorado et al. (1987)
Salmonella typhimurium (L-Arabinose resistant) BA13	Gene mutation	Forward mutation	+ + +	NT NT NT	Ground coffee static Ground coffee agitated Instant coffee agitated	0.5 mg/plate 0.5 mg/plate 0.5 mg/plate	Caffeine was not mutagenic	Ariza et al. (1988)
Salmonella typhimurium (L-Arabinose resistant) BA13	Gene mutation	Forward mutation	+	–	Instant coffee	2.5 mg/plate	Only one dose tested; reduction of mutagenicity by addition of catalase	Ariza & Pueyo (1991)

Table 4.7 (continued)

Experimental system Species, strain	End-point	Test[a]	Results		Type of coffee	Concentration (LEC or HIC)	Comments	Reference
			Without activation	With metabolic activation				
Plasmid pBR322 DNA	DNA damage	DNA strand breaks	–	NT	Instant coffee	0.8 mg/assay		Kato et al. (1994)
Plasmid pBR322 DNA	DNA damage	DNA strand breaks	+	NT	Fractions of instant coffee	Fractions from 100 mg/mL		Kato et al. (1994)
Plasmid pBR322 DNA	DNA damage	DNA strand breaks	+	NT	Fractions of instant coffee	Fractions from 100 mg/mL		Hiramoto et al. (1998)

[a] Unless otherwise indicated, the experiments were plate incorporation assays

+, positive results; –, negative results; cat. def., catalase deficient; cat. pro., catalase proficient; CP, cyclophosphamide; DEN, diethylnitrosamine; gEq, gram equivalent; HIC, highest ineffective concentration; LEC, lowest effective concentration; MMC, mitomycin C; NA, none applicable; NR, not reported; NT, not tested; PE, protective effect; SMART, somatic mutation and recombinant test; UR, urethane

confirmed by experiments showing that the addition of catalase attenuates the activity of the beverage (Ariza et al., 1988; Ariza & Pueyo, 1991). Ruiz-Laguna & Pueyo (1999) compared mutation spectra induced by coffee and H_2O_2 in the *LacI* gene in catalase-deficient and -proficient *E. coli* strains. Coffee caused a similar spectrum of mutational events as H_2O_2, which was in turn different from the spontaneous spectrum.

(iv) Acellular systems

Chlorogenic acid, caffeic acid, pyrogallol, and hydroquinone cause a pH-dependent degradation of deoxyribose (Kato et al., 1994; Duarte et al., 1999). In isolated bacteriophage (PM2) DNA treated with Maillard products (isolated from coffee extracts) and a Fe^{2+} catalysed Fenton reaction, DNA single-strand breaks were detected (Wijewickreme & Kitts, 1998). Hydroxyhydroquinone was identified as the active component of coffee inducing DNA damage (Hiramoto et al., 1998).

4.2.2 Oxidative stress and antioxidant status

This section describes the effects of coffee on oxidative stress and on antioxidant status. In contrast to potentially enhancing oxidative stress, coffee also has antioxidant properties that might reduce oxidative stress. The antioxidant properties of coffee and its constituents, for example chlorogenic acids, have been demonstrated using various assays including ferric ion-reducing antioxidant power (FRAP), total peroxyl radical-trapping antioxidant parameter (TRAP), 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azino-bis 3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and oxygen radical antioxidant capacity (ORAC) (reviewed in Liang & Kitts, 2014). In cell- and animal-based studies, coffee is also able to induce mRNA and protein expression of antioxidant enzymes via the Nrf2/ARE (antioxidant response element) pathway, thus enhancing endogenous defence mechanisms.

(a) Exposed humans

See Table 4.8.

(i) Cross-sectional studies

Several cross-sectional studies investigated the effects of coffee consumption on oxidative DNA damage. Coffee drinking (0 to > 4 cups/day) was inversely associated with DNA damage as measured by 8-hydroxydeoxyguanosine (8-OHdG) (van Zeeland et al., 1999; Hori et al., 2014). Hori et al. (2014) adjusted for smoking status. In the latter study, the association was attenuated in women after adjusting for ferritin. [Coffee is known to inhibit iron absorption and therefore might decrease iron-induced oxidative damage.] In another study, coffee and tea consumption significantly decreased DNA damage as measured by 8-oxodeoxyguanosine (8-OxodG), another marker for DNA damage (Lodovici et al., 2005). However, the effects of coffee and tea were not separately studied. Coffee drinking was associated with decreased derivatives of reactive oxygen metabolites (d-ROM), a measure of lipid peroxidation, in men only in a large cross-sectional study of 9877 Japanese subjects (Ishizaka et al., 2013). The highest quartile of coffee consumption (≥ 5 cups/day) had a significantly lower d-ROM than the lowest quartile. d-ROM was increased in male current smokers compared with male never-smokers. Antioxidant status was not affected by coffee in either men or women, but was decreased in male smokers compared with male never-smokers (Ishizaka et al., 2013).

(ii) Randomized controlled trials

Several randomized controlled trials (RCTs) studied the effects of coffee drinking on various markers of DNA damage and lipid peroxidation. Consumption of filtered coffee (800 mL/day) for 5 days significantly decreased DNA damage as measured by the comet assay (Mišík et al., 2010). Another study using 800 mL of instant coffee enriched with CGA did not find significant effects

with this assay (Hoelzl et al., 2010). Mišík et al. (2010) also measured a range of oxidative stress markers, such as nitrotyrosine (3-NT), oxidized low-density lipoprotein (oxLDL), thiobarbituric acid-reactive substances (TBARS), 8-epi-prostaglandin F2α (PGF2α), and reactive oxygen species (ROS), but none of these changed significantly. In the study of Hoelzl et al. (2010), plasma 3-NT and urinary PGF2α decreased significantly. Coffee significantly decreased 8-OHdG in a crossover trial comparing coffee drinking (4 cups/day) and abstinence in 37 patients with chronic hepatitis (Cardin et al., 2013). However, advanced protein oxidation products (AOPP) did not change. Coffee with reduced hydroxyhydroquinone (HHQ), a roasting product of coffee beans, decreased lipid peroxidation (F2-isoprostanes) (Ochiai et al., 2009). In contrast, roasting did not appear to affect PGF2α and oxLDL as there were no differences between light- and medium-roast coffee (each 480 mL) (Corrêa et al., 2012).

Markers of antioxidant status were studied in several randomized controlled trials with coffee. A significant increase in glutathione (GSH) was reported by Ochiai et al. (2009), which is in line with the simultaneous decrease in lipid peroxidation mentioned in the paragraph above. In another study, a range of markers of the antioxidant status did not change, such as total antioxidant capacity (TAC), total glutathione (tGSH), and the activities of the antioxidant enzymes SOD and glutathione peroxisidase (GPx) (Mišík et al., 2010). This is consistent with the lack of effect on oxidative stress markers (see paragraph above), although DNA damage decreased significantly. Light- and medium-roast coffee both increased markers of antioxidant status, including SOD, GPx, and catalase (CAT), total antioxidant status (TAS), and oxygen radical absorbance capacity (ORAC) (Corrêa et al., 2012). In a crossover trial of 64 healthy subjects, coffee (1 L/day) did not change the activity of GST in the mucosa, but increased GSH in mucosa and plasma (Grubben et al., 2000).

(iii) Interventions (≥ 7 days)

No effects on lipid peroxidation and antioxidant enzymes were seen in a study comparing the consumption of 0, 3, or 6 cups of filtered coffee (Mursu et al., 2005). Yukawa et al. (2004) found that coffee drinking (150 mL daily for 7 days) reduced lipid peroxidation in plasma in 11 participants; the lag time of LDL oxidation increased substantially, whereas TBARS decreased.

The effects of light- and dark-roast coffee (500 mL daily for 4 weeks) on antioxidant enzymes and antioxidants in erythrocytes were studied by Kotyczka et al. (2011). Dark-roast coffee decreased SOD and GPx activity, but increased CAT activity and tGSH and tocopherol. Light-roast coffee increased SOD, GPx, and CAT activity, but did not change tGSH and tocopherol. Light- and dark-roast coffee (500 mL) did not significantly increase the expression of transcription factor Nrf2 and the antioxidant enzyme NAD(P)H:quinone oxidoreductase 1 (NQO1) regulated by Nrf2 (Boettler et al., 2011). However, a later study (Boettler et al., 2012) reported that the consumption of 750 mL/day of coffee for 4 weeks increased expression of Nrf2 in peripheral blood lymphocytes in male volunteers (n = 18). Similar findings were reported by Volz et al. (2012) in a pilot intervention study. Daily consumption of 750 mL of coffee for 4 weeks by healthy male volunteers (n = 29) increased NRF2 transcription in peripheral blood lymphocytes.

(iv) Acute interventions

In several studies, the concentration of H_2O_2 in urine increased 3–10-fold 1–2 hours after consumption of coffee (Long & Halliwell, 2000; Hiramoto et al., 2002; Ziobro & Bartosz, 2003; Halliwell et al., 2004). [This may suggest that H_2O_2 is absorbed from coffee, enters the circulation, and may reach tissues.] In subjects who drank green tea and instant coffee containing the same concentrations of H_2O_2, Halliwell et al. (2004) found that, in contrast to coffee, none of the subjects showed a rise in urinary H_2O_2

Table 4.8 Effects of drinking coffee on oxidative stress markers in exposed humans

Tissue	Cell type	End-points	Test	Description of exposure[a] and controls	Response[b]/ significance	Comments	Reference
Cross-sectional studies							
Blood	Lymphocytes	DNA damage	8-OxodG	Cross-sectional; 87 men (18–60 yr): 30 smokers, 29 non-smokers, 28 secondary smokers	Coffee and tea consumption decreased 8-OxodG [$P < 0.05$]; 8-OxodG higher in smokers than non-smokers [$P < 0.0001$]	Tea and coffee not separated	Lodovici et al. (2005)
Blood	Leukocytes	DNA damage	8-OHdG	Cross-sectional; 102 (51 M, 51 F) healthy Italians (24–45 yr); 0 to > 4 cups/day	Coffee and smoking inversely associated with 8-OHdG		van Zeeland et al. (1999)
Urine	–	DNA damage	8-OHdG	Cross-sectional, 507 (298 M, 209 F) healthy (21–67 yr); < 1, 1, 2–3, ≥ 4 cups/day)	Coffee inversely associated with 8-OHdG in women [P-trend < 0.05] but adjustment for ferritin attenuated the association		Hori et al. (2014)
Plasma	–	Redox status	d-ROM, BAP	Cross-sectional, 9877 (7633, 2627 F, 5006 M) Japanese subjects (mean, 59 ± 10 yr); quartiles of coffee intake (0, 1–2, 3–4, ≥ 5 cups/day)	Decrease in d-ROM [$P < 0.001$ for trend] with coffee intake in men only; in male current smokers vs never smokers, d-ROM increased [$P < 0.001$] while BAP decreased [$P < 0.001$]		Ishizaka et al. (2013)
Randomized controlled trials							
Blood	Leukocytes	DNA damage	8-OHdG, AOPP	RCT crossover, 37 (29 M, 8 F) patients with chronic hepatitis C (58 ± 11 yr); 4 cups/day unfiltered coffee, abstinence; 30 days	Coffee vs no coffee decreased 8-OHdG [$P < 0.05$] but AOPP was not changed	No placebo	Cardin et al. (2013)
Blood, plasma, urine	Lymphocytes	DNA damage, redox status	Comet assay, various ROS measures	RCT crossover, 38 (14 M, 24 F) healthy non-smokers (28 ± 8 yr); filtered coffee (800 mL); 5 days, washout 5 wk	Coffee vs water decreased DNA damage (+FPG) [$P < 0.05$]; no significant change: 3-NT, oxLDL, TBARS, PGF2α, ROS, TAC, tGSH, SOD, GPx	No placebo	Mišík et al. (2010)

Table 4.8 (continued)

Tissue	Cell type	End-points	Test	Description of exposure[a] and controls	Response[b]/ significance	Comments	Reference
Blood, plasma, urine	Lymphocytes	DNA damage, lipid peroxidation, protein nitrosation	Comet assay, PGF2α, 3-NT	RCT crossover, 36 (13 M, 16 F) healthy non-smoking subjects (27 yr); 800 mL unfiltered coffee, 800 mL water; 5 days, washout 5 wk	Coffee vs water decreased plasma 3-NT ($P < 0.02$) and urinary PGF2α ($P < 0.02$); no change in DNA damage (+FPG)	No placebo	Hoelzl et al. (2010)
Plasma, urine	–	Lipid peroxidation, antioxidants	F2-isoprostanes, tGSH	RCT, placebo, double-blind, parallel; 9 on coffee (184 mL), 12 on placebo (184 mL); 8 wk	Coffee decreased isoprostanes [$P < 0.05$] and increased tGSH [$P < 0.05$]	Coffee with reduced HHQ	Ochiai et al. (2009)
Plasma	Erythrocytes	Redox status	TAS, ORAC, oxLDL, PGF2α, activity SOD, GPx, CAT	RCT crossover; 20 (6 M, 14 F) healthy non-smoking (20–65 yr); 480 mL paper-filtered coffee light roast for 4 wk, 480 mL paper-filtered coffee medium roast for 4 wk, no washout in between	Coffee increased TAS [$P < 0.01$], ORAC [$P < 0.01$], SOD [$P < 0.01$], GPx [$P < 0.01$], and CAT [$P < 0.01$]; PGF2α and oxLDL were not changed	No placebo	Corrêa et al. (2012)
Colorectal tissue, plasma	Mucosa	Glutathione status	GST activity, GSH	RCT crossover, 64 (31 M, 33 F) healthy subjects (43 ± 11 yr); 1 L/day unfiltered coffee, no coffee; 2 wk, washout 8 wk	Coffee vs no coffee GSH content but not GST activity increased in mucosa ($P = 0.01$) and plasma ($P = 0.003$)	No placebo	Grubben et al. (2000)
Interventions (≥ 7 days)							
Plasma, serum	–	Lipid peroxidation, antioxidant enzymes	F2-isoprostanes, hydroxy fatty acids, LDL-conjugated dienes, activity GPx and PON	Intervention, parallel, 43 healthy non-smoking men (26 ± 6 yr); 0, 3, or 6 cups filtered coffee, 3 wk; acute intervention (in 35 of the subjects) 0, 1, or 2 cups filtered coffee	No change in lipid peroxidation or antioxidant enzyme activity	Subjects not randomized across three treatment groups	Mursu et al. (2005)
Plasma	–	Lipid peroxidation	Lag time LDL oxidation, TBARS	11 healthy male students (20–31 yr); wash-in (water, 7 days); coffee (150 mL, 7 days); washout (water, 7 days)	Coffee increased LDL oxidation lag time [$P < 0.001$] and decreased TBARS [$P < 0.005$]; both returned to baseline after washout		Yukawa et al. (2004)

Table 4.8 (continued)

Tissue	Cell type	End-points	Test	Description of exposure[a] and controls	Response[b]/ significance	Comments	Reference
Blood	Erythrocytes	Antioxidant enzymes, antioxidants	SOD, GPx, CAT activity; erythrocyte GSH, tocopherol, MDA	30 healthy subjects; 2 wk washout, 4 wk 500 mL light-roast filtered coffee daily, 2 wk washout, 4 wk dark-roast filtered coffee daily	Light roast increased SOD, GPx, and CAT [all $P < 0.05$]; no change in tGSH, Toc, and MDA Dark roast decreased SOD and GPx activity, and increased CAT, tGSH (total GSH), and Toc (tocopherol) concentrations [all $P < 0.05$]; no change: MDA	Tocepherol not defined	Kotyczka et al. (2011)
Blood	Peripheral blood lymphocytes	mRNA, NQO1, and Nrf2	RT–PCR	27 healthy non-smoking subjects (26 ± 1 yr); 2 wk washout, 4 wk 500 mL light-roast filtered coffee, 2 wk washout, 4 wk dark-roast filtered coffee	No change in Nrf2, NQO1		Boettler et al. (2011)
Acute interventions							
Urine	–	Oxidative stress	H_2O_2	4 subjects (26–49 yr); 1 cup instant coffee; 0, 50, 100 min	Increased urinary H_2O_2		Long & Halliwell (2000)
Urine	–	Oxidative stress	H_2O_2	10 (2 F, 8 M) healthy subjects (20–70 yr); 187 mL canned coffee; 1–4 h	Increased urinary H_2O_2		Hiramoto et al. (2002)
Urine	–	Oxidative stress, antioxidants	H_2O_2	8 healthy subjects; 200 mL instant coffee; 0, 60 min	Increased urinary H_2O_2; no change in antioxidants		Ziobro & Bartosz (2003)
Urine	–	Oxidative stress	H_2O_2	9 subjects; 200 mL instant coffee; 0, 1, 2, 3, 4 h	Increased urinary H_2O_2		Halliwell et al. (2004)
Plasma	–	Lipid peroxidation	Lag time LDL oxidation	10 (5 F, 5 M) healthy (24–35 yr); 200 mL filtered coffee; 0, 30, 60 min	Coffee increased LDL oxidation lag time [$P < 0.05$]	No control	Natella et al. (2007)
Plasma	–	Antioxidants	TRAP, SH groups, crocin test, ascorbic acid	Acute intervention, 10 healthy non-smoking (age NR; 200 mL coffee; 0, 1, 2 h	Coffee increased uric acid [$P < 0.005$] and TRAP [$P < 0.05$] but not ascorbic acid or total SH	No control	Natella et al. (2002)

Table 4.8 (continued)

Tissue	Cell type	End-points	Test	Description of exposure[a] and controls	Response[b]/ significance	Comments	Reference
Plasma/ serum	–	Antioxidants	FRAP, TRAP, ascorbic acid, tocopherols (α, γ), albumin, bilirubin, uric acid	Acute intervention, randomized crossover, 10 (7 F, 3 M) healthy subjects (22–57 yr); 200 mL instant coffee, 200 mL water; 0, 90 min; 7 days washout	Coffee increased FRAP and TRAP [both $P < 0.05$] but did not change ascorbic acid, α-tocopherol, or γ-tocopherol		Moura-Nunes et al. (2009)

[a] Unless otherwise specified, the term coffee is used to mean brewed, caffeinated coffee

[b] +, positive; –, negative; differences: coffee vs control

3-NT, 3-nitrotyrosine; 8-OHdG, 8-hydroxydeoxyguanosine; 8-OxodG, 8-oxodeoxyguanosine; AOPP, advanced oxidation protein products; BAP, biological antioxidant potential; CAT, catalase; d-ROM, derivatives of reactive oxygen metabolites; F, female; FPG, formamidopyrimidine-DNA *N*-glycosylase; FRAP, ferric-reducing antioxidant parameter; GPx, glutathione peroxidase; GSH, glutathione; GST, glutathione *S*-transferase; h, hour; HHQ, hydroxyhydroquinone; LDL, low-density lipoprotein; M, male; MDA, malondialdehyde; min, minute; mo, month(s); NQO1, NAD(P)H:quinone oxidoreductase 1; Nrf2, nuclear factor-erythroid-2-related factor; ORAC, oxygen radical absorbance capacity; oxLDL, oxidized LDL; PGF2α, 8-epi-prostaglandin F2α; PON, paraoxonase; RCT, randomized controlled trial; ROS, reactive oxygen species; RT–PCR, real time polymerase chain reaction; SH, sulfhydryl; SOD, superoxide dismutase; TAC, total antioxidant capacity; TAS, total antioxidant status; TBARS, thiobarbituric acid-reactive substances; tGSH, total glutathione; Toc, tocopherol; TRAP, total radical-trapping antioxidant parameter; vs, versus; wk, week(s); yr, year(s)

after green tea. [The Working Group took note of Halliwell's hypothesis that H_2O_2 of coffee is not excreted into urine, but very likely originates from the hydroxyhydroquinone present in coffee, which is subsequently oxidized in urine to produce H_2O_2.]

The lag time of LDL oxidation increased by 1 hour after consumption of 200 mL of coffee (Natella et al., 2007). Regarding measures of antioxidant status, uric acid and TRAP in plasma increased, whereas ascorbic acid and total sulfhydryl groups did not change 2 hours after coffee consumption (Natella et al., 2002). The antioxidant capacity (TRAP and FRAP) of plasma also increased 90 minutes after coffee consumption, but individual antioxidants including ascorbic acid and tocopherols did not change significantly (Moura-Nunes et al., 2009).

(b) Human cells in vitro

Colon-derived HT-29 and CaCo-2 cells exposed to coffee and coffee extracts showed protection against induced ROS (Bakuradze et al., 2010). Light-roasted coffee induced electrophile response element (EpRE)-dependent antioxidant enzymes γ-glutamylcysteine ligase (γ-GCL), NQO1, and GSR (Bakuradze et al., 2010). Roasted coffee extracts increased the expression of GPx in CaCo-2 cells by more than 10-fold (Yazheng & Kitts, 2012). Roasted coffee induced other antioxidant enzymes such as sulfiredoxin, thioredoxin reductase, and peroxiredoxin.

Exposure of hepatocytes (HepG2) to an unfiltered dark-roast coffee extract induced EpRE by more than 10-fold, but the filtered extract had a slightly lesser effect (Paur et al., 2010). [The Working Group noted that coffee components first have to be absorbed in the gastrointestinal tract, and are very likely metabolized upon absorption before they reach lymphocytes and hepatocytes. Some coffee components, for example phenolics, will be extensively metabolized during their passage through the gastrointestinal tract and upon their subsequent absorption.]

Treatment of human hepatoma (HepG2), colon carcinoma (Caco-2), and oesophagus carcinoma (KYSE70) cells with regular and decaffeinated coffee for 24 hours significantly increased expression of NRF2 (Kalthoff et al., 2010). Similar findings were reported in several other studies (Paur et al., 2010; Boettler et al., 2011; Volz et al., 2012; Sauer et al., 2013). In particular, Paur et al. (2010) demonstrated that treatment of hepatoma HepG2 cells with dark-roast coffee extract for 17 hours significantly increased expression of NRF2.

A coffee extract enriched by *N*-methylpyridinium and CGAs, each known as a potent activator of the Nrf2/ARE pathway, increased nuclear Nrf2 translocation and enhanced the transcription of ARE-dependent genes NAD(P)H:quinone oxidoreductase (*NQO1*) and *GSTA1* in HT29 human colon carcinoma cells (Volz et al., 2012).

(c) Non-human mammals in vivo

(i) Rat

See Table 4.9 (web only; available at: http://publications.iarc.fr/566).

Biomarkers of DNA damage (8-OHdG) and lipid peroxidation (F2-isoprostanes) in rat urine after long-term exposure (up to 130 days) of a coffee dose equivalent to 9 and 20 cups/day were determined (Sakamoto et al., 2003). Only 8-OHdG increased, and the increase was dependent upon dose. In another subchronic study, Morakinyo et al. (2013) reported no significant effects on TBARS.

In several experiments in rats, the effects of coffee were studied after induction of oxidative stress using a variety of stressors: a high-fat diet (Vitaglione et al., 2010; Salomone et al., 2014); exercise (Viana et al., 2012); carbon tetrachloride (CCl_4) (Ozercan et al., 2006; Poyrazoglu et al., 2008); and dimethylnitrosamine (DMN) (Shin et al. 2010). For instance, a high-fat diet increased F2-isoprostanes and 8-OHdG, both of

which were suppressed by coffee (Salomone et al., 2014). Exercise increased carbonyls, a measure of protein oxidation, and TBARS (Viana et al., 2012). Coffee partly normalized the effects of exercise on carbonyls and TBARS, but decaffeinated coffee had no effect. Carbon tetrachloride ($CCl_{4)}$ increased TBARS in plasma and liver, and unfiltered coffee was able to partly suppress the effect of CCl_4 on lipid peroxidation (Poyrazoglu et al., 2008). Coffee normalized the DMN-induced effects on TBARS (Shin et al. 2010).

Regarding antioxidant status, Morakinyo et al. (2013) found no effects of coffee on tGSH and SOD after 12 weeks of coffee. In an acute study, Vicente et al. (2011) showed that the activity of GPx, SOD, and CAT in liver increased significantly after only 1 hour, and returned to basal levels > 4 hours later. ORAC did not change. Decaffeinated coffee increased GSH and glutathione disulfide (GSSG) (Vitaglione et al., 2010). Coffee normalized the DMN-induced reduction of tGSH and SOD (Shin et al., 2010). In male Wistar rats, 2.0 mL/day of regular coffee for 28 days increased the expression of Nrf2 in the liver by 2.3-fold Vicente et al. (2014).

(ii) Mouse

See Table 4.9 (web only; available at: http://publications.iarc.fr/566).

No significant changes in 8-OHdG levels were observed in the livers of coffee-fed mice (Morii et al., 2009).

Activation of the EpRE by coffee was studied in transgenic EpRE/luciferase mice after induction by lipopolysaccharide (LPS). Coffee increased whole-body luminescence, especially that of the liver (Paur et al., 2010). A related experiment studied Nrf2 transcription by comparing the effects of coffee in *nrf2*$^{+/+}$ and *nrf2*$^{-/-}$ mice (Higgins et al., 2008). In nrf2$^{+/+}$ mice, coffee significantly increased the mRNA and protein expression of GST and NQO1. Moreover, patterns of GST and NQO1 expression in the liver, colon, and small intestine were different (Higgins et al., 2008).

Coffee did not significantly impact the expression of a range of antioxidant enzymes in the liver (Morii et al., 2009). In another study, both regular (caffeinated) and decaffeinated coffee significantly increased the content of sulfhydryls and the activity of GST in the liver. However, a dose–response relation could not be demonstrated (Abraham & Singh, 1999).

4.2.3 Chronic inflammation and immunosuppression

(a) Chronic inflammation

(i) Exposed humans

Cross-sectional studies

See Table 4.10 (web only; available at: http://publications.iarc.fr/566).

C-reactive protein (CRP) as a single biomarker of inflammation has been studied in cross-sectional studies of coffee consumption, ranging from large studies of thousands of subjects (Maki et al., 2010; Pham et al., 2011) to studies involving about 100 subjects (Kotani et al., 2010). In a healthy Japanese population of 10 325 subjects, the men (4407) in the highest quintiles of coffee consumption (> 7 cups/day) had 20% lower levels of high-sensitivity CRP (hsCRP) compared with men in the lowest quintile (0 cups/day) (Maki et al., 2010; Pham et al., 2011). In 7574 healthy men and women of the Republic of Korea, there was no difference in serum CRP levels between the highest and the lowest quartile of coffee intake (Lee et al., 2014). In a multiple regression model, Rebello et al. (2011) found that coffee drinking had no effect on hsCRP levels in 4139 healthy Asian men and women. Arsenault et al. (2009) found lower hsCRP values in the highest quartile of coffee intake in 344 healthy women. In 114 healthy Japanese, coffee drinkers had lower hsCRP values than non-drinkers of coffee (Kotani et al., 2010).

In a European population of 3042 healthy men and women (M/F: 50/50), levels of

inflammatory biomarkers (C-reactive protein, CRP; interleukin-6, IL-6; tumour necrosis factor alpha, TNF-α; and serum amyloid-A, SAA) were higher in the highest quartile of coffee intake compared with the lowest quartile for both men and women (Zampelas et al., 2004). Leukocyte counts were also higher in the highest quartile.

In a cross-sectional study of 1393 women of the US Nurses' Health Study I cohort, caffeinated and decaffeinated coffee consumption was inversely related to a range of inflammatory biomarkers (Lopez-Garcia et al., 2006). In drinkers of caffeinated coffee, CRP and E-selectin levels were lower in women with type 2 diabetes, but not in healthy women. For decaffeinated coffee, both CRP and E-selectin levels were lower in non-diabetics, whereas no difference was observed in women with diabetes (Lopez-Garcia et al., 2006).

IL-6 and plasminogen-activator inhibitor type 1 (PAI-1) were increased among 30 drinkers of high quantities of coffee (> 4 cups/day) compared with 30 drinkers of low quantities of coffee (< 1 cup/day) in a study of hypertensive smokers (Tsioufis et al., 2006).

A large number (77) of inflammatory and immune biomarkers were measured in 1728 older non-Hispanic white US subjects (age, 55–74 years). After correction for multiple comparisons and the exclusion of markers with < 25% detectability, only the soluble tumour necrosis factor receptor II (sTNFRII) was found to be significantly lower in drinkers of high quantities of coffee (> 2.5 cups/day) (Loftfield et al., 2015).

Prospective studies

See Table 4.10 (web only; available at: http://publications.iarc.fr/566).

In 2040 subjects from the prospective Nurses' Health Study, coffee drinking (highest quartile of intake ≥ 4 cups/day) was inversely associated with CRP and TNFα receptor-2 levels (Williams et al., 2008).

A prospective nested case–control study on coffee drinking and the primary form of liver cancer, hepatocellular carcinoma, included 125 cases of hepatocellular carcinoma and 250 controls (Aleksandrova et al., 2015). The multivariable-adjusted relative risk (RR) for subjects drinking ≥ 4 cups/day compared with < 2 cups/day was 0.25 (95% CI, 0.11–0.62) (*P* for trend = 0.006). Additionally, coffee drinking was inversely associated with IL-6, and that IL-6 attenuated the association of coffee with hepatocellular carcinoma.

Randomized controlled clinical trials

See Table 4.10 (web only; available at: http://publications.iarc.fr/566).

The effect of roasting was studied on a range of inflammatory markers in subjects who drank 3–4 cups/day of light- or medium-roasted coffee (150 mL/cup) for 4 weeks. Only three markers changed: soluble vascular cell adhesion molecule-1 (sVACM-1) increased after both the light- and medium-roasted coffee; fibrinogen increased only after the medium-roasted coffee; and sE-selectin increased only after the consumption of the light-roasted coffee (Corrêa et al., 2013).

Kempf et al. (2010) studied the effect of coffee (4 and 8 cups/day) drinking in subjects with an elevated risk of type 2 diabetes, and measured six inflammatory markers; 1 month of coffee drinking was followed by 1 month of abstinence. Only IL-18 was significantly lower at the end of the coffee-drinking period.

A study of the acute effects of caffeinated and decaffeinated coffee (200 mL) found no effect on plasma/serum IL-6 and IL-18 (Gavrieli et al., 2011).

(ii) Human cells in vitro

Coffee extract and a synthetic mixture of roasting products both induced the nuclear translocation of nuclear factor κB (NF-κB) in macrophages (NR8383) and intact human gut tissue, whereas only the roast products had an effect on Caco-2 cells (Sauer et al., 2011).

Filtered and unfiltered coffee extracts inhibited LPS-induced activation of NF-κB in U937 cells transfected with a NF-κB–luciferase construct (Paur et al., 2010). Dark-roasted coffee extracts had a larger effect than light-roasted extracts. In agreement with changes in luminescence, NF-κB protein and mRNA levels changed together with the mRNA of several NF-κB target genes. [The Working Group noted that these results were obtained after direct exposure to coffee extracts.]

(iii) Experimental systems

See Table 4.11 (web only; available at: http://publications.iarc.fr/566).

In the rat, the effects of coffee on the expression and tissue concentration of several inflammatory cytokines were studied after the induction of inflammation using a variety of stressors: a mutant strain that accumulates iron and copper in the liver (Katayama et al., 2014); a high-fat diet (Vitaglione et al., 2010); DMN to induce liver fibrosis (Shin et al., 2010); and LPS (Sakamoto et al., 2001). In the liver of the Long Evans Cinnamon (LEC) rat, coffee suppressed IL-6 protein and mRNA levels as well as TNF-α mRNA. However, it did not affect TNF-α protein levels or IL-1β mRNA expression (Katayama et al., 2014). Decaffeinated coffee significantly lowered hepatic concentrations of TNF-α and IFN-γ, and increased those of IL-4, IL-6, and the anti-inflammatory IL-10 in Wistar rats fed a high-fat diet (Vitaglione et al., 2010). LPS-induced serum changes in TNF-α and IL-6 were not inhibited by coffee (Sakamoto et al., 2001).

In mice, coffee decreased mRNA levels of IL-6 in adipose tissue (Matsuda et al., 2011) and reduced serum levels of IL-1α, IL-6, and TNF-α (Guo et al., 2014). Other experiments evaluated coffee on inflammation induced by LPS (Paur et al., 2010), a high-fat diet (Fukushima et al., 2009), and diabetes (Yamauchi et al., 2010) in the mouse. In mice transfected with a NF-κB–luciferase construct, coffee reduced whole-body luminescence that had been induced with LPS (Paur et al., 2010). Coffee and pure caffeine reduced mRNA levels of various inflammatory cytokines in fat (MCP-1, IL-6, and TNF-α) and in serum (TNF-α) in diabetic mice (Yamauchi et al., 2010). Fukushima et al. (2009) showed that the increased expression in MCP-1 and IL-1β that is induced by a high-fat diet is partly inhibited by coffee. There were no clear differences between caffeinated and decaffeinated coffee.

Rat macrophages were exposed to roasted and non-roasted coffee in studies in vitro; only the roasted coffee increased the expression of NF-κB (Muscat et al., 2007). In mouse splenocytes, freeze-dried coffee attenuated the induction of interleukins by ovalbumin (Goto et al., 2011).

(b) Immunosuppression

(i) Exposed humans

See Table 4.12 (web only; available at: http://publications.iarc.fr/566).

In a cross-sectional study of 1728 older United States non-Hispanic white people (age, 55–74 years), a large number (77) of immune and inflammatory markers was compared between coffee drinkers and non-drinkers of coffee (Loftfield et al., 2015). The immune markers interferon gamma (IFNγ), fractalkine (CX3CL1), microphage inflammatory protein-1β (MIP-1β/CCL4), fibroblast growth factor-2 (FGF-2), and sTNFRII were found to be lower in coffee drinkers.

In an exploratory study with 15 subjects, consumption of 5 cups/day of coffee for 5 weeks had no effect on total T- and B-cell counts, but increased the counts of natural killer cells (Melamed et al., 1990). Coffee drinking suppressed lectin-stimulated transformation of lymphocytes, and stimulated the chemotaxis activity of mononuclear leukocytes.

(ii) Experimental systems

Goto et al. (2011) exposed splenocytes from mice to coffee extracts and observed a decrease in ovalbumin-induced cell proliferation.

4.2.4 Receptor-mediated mechanisms

(a) Nuclear receptor signalling pathways

(i) Humans

No data from exposed humans were available to the Working Group.

In studies in vitro, treatment with regular and decaffeinated coffee for 24 hours significantly increased expression of aryl hydrocarbon receptor (AhR) in hepatoma (HepG2), colon carcinoma (Caco-2), and oesophagus carcinoma (KYSE70) cells (Kalthoff et al., 2010). Similarly, Ishikawa et al. (2014) reported that coffee is a strong activator of AhR expression in vitro.

The coffee component cafestol, at a concentration of 20 μM activated the farnesoid X receptor (FXR) and pregnane X receptor (PXR) in human liver HepG2 cells (Ricketts et al., 2007).

The coffee component HHQ was a putative ligand of the peroxisome proliferator-activated receptor γ (PPARγ) Shashni et al. (2013). Coffee treatment of human MCF-7 and MDA-MB-231 breast cancer cells inhibited PPARγ-dependent glycolytic enzymes.

(ii) Experimental systems

Decaffeinated coffee increased the level of PPARα in the livers of male Wistar rats fed a high-fat diet (Vitaglione et al., 2010).

In mouse 3T3-L1 cells, coffee extract (1.25%, 2.5%, and 5.0% v/v for 6 days) reduced *Pparγ* gene expression in a dose-dependent manner (Aoyagi et al., 2014). PPARγ protein was reduced in cells treated with 2.5% (v/v) coffee extract.

In a model system in vitro, cafestol activated human FXR in the monkey kidney CV-1 cell line (Ricketts et al. (2007).

(b) Sex hormone pathways

Kotsopoulos et al. (2009a) reported an inverse correlation between coffee intake and the level of luteal and free estradiol in 524 premenopausal women from the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII), but not luteal progesterone level. No association between coffee intake and estrogen and androgen levels was found in 713 postmenopausal women from the NHS and NHSII. In contrast, a significant increase in the level of estradiol associated with coffee consumption in women aged > 40 years who consumed > 1 cup/day of coffee (Lucero et al., 2001).

Several studies found a positive association between coffee and/or caffeine intake and the level of sex hormone-binding globulin (SHBG) in postmenopausal women. In the largest study involving 13 547 postmenopausal women from the Women's Health Initiative, intake of regular coffee, but not decaffeinated coffee, was positively associated with the SHBG plasma level Goto et al. (2014). Similarly, in the Rancho Bernardo Study of 728 postmenopausal women, caffeine intake increased plasma level of SHBG and estrone. In contrast, Wedick et al. (2012) did not find an association between caffeinated coffee consumption and SHBG; however, the sample size in that study was small (n = 42). Svartberg et al. (2003) reported a positive association between coffee consumption and the levels of total testosterone and SHBG. In contrast, as part of a Danish pregnancy study, the sons of women who consumed 4–7 cups/day of coffee during pregnancy had lower testosterone levels than the sons of mothers drinking 0–3 cups/day (P = 0.04) Ramlau-Hansen et al., 2008).

Sisti et al. (2015) demonstrated that coffee consumption modulates the 2-hydroxylation pathway, the major pathway in estrogen metabolism. This was evidenced by a positive association between coffee intake of > 4 cups/day and the

levels of 2-hydroxyestrone and 2-hydroxyestradiol in urine of premenopausal women.

Several studies in vitro demonstrated that coffee is a potent inhibitor of the estrogen SULT reaction, a major pathway for the inactivation of estrogens (Kauffman, 2004), in human colon carcinoma Caco-2 cells (Okamura et al., 2005; Saruwatari et al., 2008; Isshiki et al., 2013). In two separate studies, incubation of human colon carcinoma Caco-2 cells with coffee extract resulted in a dose-dependent inhibition of SULT activity (Okamura et al., 2005) in general, and estrogen SULT sulfation activity towards 17β-estradiol in particular (Saruwatari et al., 2008). In addition, treatment of Caco-2 cells with 2.5% (v/v) coffee extract for 24 hours resulted in a 60% reduction of *SULTE1* gene expression and a 25% reduction in cytosolic estrogen SULT activity (Isshiki et al., 2013).

In the treatment of estrogen receptor α (ERα) -positive human breast cancer MCF7 cells with coffee constituents, caffeine at concentrations of 0.2, 1.0, and 5 mM or caffeic acid at concentrations of 2, 10, and 50 μM for 72 hours suppressed the expression of ERα (Rosendahl et al., 2015). In contrast, Ezechiáš et al. (2016) did not detect antiestrogen or antiandrogen effects of caffeine at a concentration of 8 μM on the human breast cancer T47D cell line.

(c) Glucocorticoid hormone pathways

Humans

Consumption of regular coffee (with a caffeine concentration of 3.0 mg/kg bw) increased plasma cortisol concentration at 60 minutes and thereafter in healthy young men Gavrieli et al. (2011). In contrast, in a randomized pilot crossover study, consumption of 4 cups/day of green coffee by healthy volunteers for 2 weeks significantly decreased urinary free cortisol level; it was also found that both black coffee and green coffee reduced urinary cortisol/cortisone ratio (Revuelta-Iniesta & Al-Dujaili, 2014).

Oral consumption of caffeine at 3.3 mg/kg bw, which is equivalent to 2–3 cups of coffee, significantly elevated cortisol level after 60 minutes Lovallo et al. (1996).

In a study in vitro, treatment of human embryonic kidney HEK-293 cells with 0.5% coffee extract for 40 minutes inhibited endogenous 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) activity, resulting in blockage of 11β-HSD1-dependent cortisol formation and preventing nuclear translocation of glucocorticoid receptor (Atanasov et al., 2006).

(d) Gastrointestinal hormone pathways

(i) Humans

Acquaviva et al. (1986) studied the effect of coffee on the release of gastrin in healthy volunteers and demonstrated a strong gastrin-releasing property of coffee. Drinking 100 mL of decaffeinated coffee resulted in a prompt and lasting elevation of total gastrin. The stimulatory effect of coffee consumption, especially regular coffee, was reported on the release of three other gastrointestinal hormones, glucagon-like peptide 1 (GLP-1), and cholecystokinin (Douglas et al., 1990; Johnston et al., 2003; Olthof et al., 2011).

In a study in vitro, Fujii et al. (2015) demonstrated that treatment of human caecum NCI-H716 cells with 0.05% and 0.1% of extract of coffee polyphenols for 2 hours resulted in a dose-dependent increase of GLP-1 secretion.

(ii) Experimental systems

Treatment of male C57BL/6J mice with extract of coffee polyphenols by gavage increased GLP-1 in portal vein blood (Fujii et al., 2015).

(e) Adipose-derived hormone pathways

(i) Humans

A positive association between the consumption of ≥ 4 cups/day of regular coffee and plasma adiponectin level has been reported in diabetic and non-diabetic women (Williams

et al., 2008). Several other independent studies have demonstrated a similar positive association between coffee consumption and plasma adiponectin concentrations (Imatoh et al., 2011; Pham et al., 2015). In a cross-sectional study comprising Japanese workers (2554 men, 763 women), coffee consumption was positively and significantly associated with adiponectin level (Yamashita et al., 2012). Specifically, individuals who consumed ≥ 4 cups/day of coffee had a significantly greater plasma adiponectin level as compared with those who consumed 1 cup/day. Furthermore, coffee consumption in Japanese men was not only associated with a greater adiponectin level, but that there was also a positive dose-dependent significant association between coffee consumption and plasma adiponectin level (Imatoh et al., 2011). Indeed, individuals who consumed 1–2 cups/day of coffee had a greater plasma adiponectin level (6.43 μg/mL; n = 220) than individuals who consumed 1–5 cups/week of coffee (5.91 μg/mL; n = 181). In a randomized parallel-arm controlled-intervention trial, consumption of regular coffee (5 cups/day for 8 weeks) increased plasma adiponectin levels (Wedick et al., 2011). Contrary to the positive association between coffee consumption and greater adiponectin level, several reports have shown that coffee consumption was linked to low leptin levels in plasma (Yamashita et al., 2012; Imatoh et al., 2015).

(ii) Experimental systems

In male Wistar rats fed a high-fat diet for a month and decaffeinated coffee or solutions of coffee polyphenols in drinking-water (the daily amount of coffee or coffee polyphenols corresponded to 6 cups of espresso coffee or 2 cups of filtered coffee), the expression of adiponectin receptor 2 (*Adipo-R2*) in the livers was increased as compared with rats fed a high-fat diet alone (Vitaglione et al., 2010).

Treatment of mouse 3T3-L1 cells with 2.5 or 5% (v/v) coffee reduced the adiponectin gene in a dose-dependent manner (Aoyagi et al., 2014).

4.2.5 Alterations of cell proliferation, death, or nutrient supply

(a) Coffee, cell death, and cell proliferation

(i) Humans

Grubben et al. (2000) studied the effect of unfiltered coffee on the extent of cell proliferation in colorectal mucosa in healthy volunteers in a crossover randomized trial. A total of 64 healthy volunteers (31 men and 33 women; age, 43 ± 11 years) were randomly assigned to two groups. The study consisted of two intervention periods of 2 weeks each separated by a washout period of 8 weeks. One group drank 1 L/day each (6 cups/day) of unfiltered regular coffee; the other group did not drink coffee. Colorectal biopsies were taken on day 15 of each intervention period. When comparing proliferation cell nuclear antigen (PCNA) immunostaining results from the control and experimental groups, no effect of coffee drinking on cell proliferation in colorectal mucosa was found.

In vitro, an antiproliferative effect of various dilutions of four different regular or decaffeinated coffee brands was shown in human ovarian carcinoma A2780 cells after 48 hours of treatment. The magnitude of inhibitory activity varied among the different brands of coffee (Tai et al., 2010).

Several studies have examined the antiproliferative and cytotoxic effects of the coffee-specific diterpenes kahweol and cafestol in various human cancer cell lines. Kahweol (20–80 μM for 24 hours and 48 hours) treatment of human HN22 and HSC4 oral squamous cancer cell lines significantly decreased cell viability in a dose- and time-dependent manner (Chae et al., 2014). Cárdenas et al. (2014) showed a potent proapoptotic effect of kahweol in several human cancer

cell lines (HT-29 colon adenocarcinoma, HL-60 leukaemia, and MDA-MB-231 breast cancer cells). In MDA-MB-231 breast cancer cells, a dose-dependent increase of the subG1 cell population was accompanied by a dose-dependent decrease of cells in the G2/M phase. Additionally, treatment of MDA-MB-231 breast cancer cells with kahweol induced caspase 3/7 activity. Several independent studies (e.g. Oh et al., 2009; Choi et al., 2015) reported similar proapoptotic effects of kahweol on various human cancer cells.

A proapoptotic activity in human cancer cells was also reported for another coffee-specific diterpene: cafestol. Choi et al. (2011) demonstrated dose-dependent cafestol-induced antiproliferative and proapoptotic effects in human Caki renal carcinoma cells. Kotowski et al. (2015) reported a dose-dependent reduction in cell viability and the induction of apoptosis in three cafestol-treated human head and neck squamous cell carcinoma cell lines: SCC25, CAL27, and FaDu.

(ii) Experimental systems

Lina et al. (1993) showed that drinking coffee diluted 10 times (10%) or undiluted coffee brew (100%) for 2 weeks and 6 weeks did not alter cell proliferation in the urinary bladders of male Wistar rats. Miura et al. (2004) investigated the effect of instant coffee on the growth of rat hepatoma AH109A cells using a tumour-implant model in vivo. Donryu rats with subcutaneously implanted AH109A cells fed a diet containing 0.1% of instant coffee powder for 2 weeks exhibited a suppressive effect on the in vivo growth of AH109A cells, with significantly smaller tumour sizes in coffee-fed rats.

Chlorogenic acid (30 µM and 60 µM for 24 hours) significantly decreased the cell viability of B16 murine melanoma cells (Li et al. (2014). Instant coffee inhibited the proliferation of rat hepatoma AH109A cells assessed by [methyl-^{3}H]-labelled thymidine incorporation (Miura et al. (1997). Moreover, an antiproliferative effect on AH109A cells was reported for the serum obtained from rats given instant coffee solution at 100 mg/mL per 100 g bw by gavage. In a subsequent study, Miura et al. (2004) instant coffee was proapoptotic in AH109A cells.

(b) Autophagy

(i) Humans

No data were available to the Working Group.

(ii) Experimental systems

Two studies investigated the effect of coffee and caffeine on autophagy in vivo. In the first study, short-term administration of 3% (w/v) regular or decaffeinated coffee by gavage to female C57BL/6 mice rapidly induced autophagy in multiple organs, including liver, heart, and muscle (Pietrocola et al., 2014). A similar autophagy-inducing effect of regular or decaffeinated coffee in the livers was also observed after the longer-term (for 2 weeks) administration of 3% (w/v) coffee in drinking-water. Autophagy induced by coffee was independent of caffeine content and accompanied by the inhibition of the enzymatic activity of mTORC1. In a second study, administration of 0.05% (w/v) of caffeine for 4 weeks in the drinking-water of male C57/BL6 mice maintained on a high-fat diet resulted in a marked increase in LC3-II protein levels (Sinha et al., 2014).

(c) Angiogenesis

(i) Humans

No data in exposed humans were available to the Working Group.

An antiangiogenic effect of cafestol (Wang et al., 2012) and kahweol (Cárdenas et al., 2011) was reported in human umbilical vein endothelial cells (HUVEC) and human HT-1080 fibrosarcoma cells.

(ii) Experimental systems

Using the mouse aortic ring assay, 5 μM of kahweol inhibited microvessel sprouting by 40% after 10 days of treatment, whereas 25 μM almost completely inhibited this angiogenic effect (Cárdenas et al., 2011).

In zebrafish (*Danio rerio*), 75 μM of kahweol inhibited intersegmental vessel formation after 24 hours of treatment (Cárdenas et al., 2011). Similarly, kahweol at 50 μM inhibited angiogenesis in treated eggs in the chicken chorioallantoic membrane assay (Cárdenas et al., 2011).

4.2.6 Other mechanisms

(a) DNA repair

No human data on coffee were available to the Working Group.

In male ICR mice given 0.1% instant coffee solution in drinking-water for 35 weeks, no changes in the hepatic expression of 8-OHdG repair-associated genes was found (Morii et al., 2009). In male Fischer rats given kahweol and cafestol in the diet for 10 days, a marked and dose-dependent increase in the hepatic levels of O^6-methylguanine-DNA methyltransferase (MGMT) was seen (Huber et al., 2003). Similarly, "Turkish" coffee given in drinking-water for 10 days significantly increased hepatic MGMT activity.

Several studies in vitro have shown that caffeine inhibits DNA repair. Caffeine was shown to inhibit the ataxia telangiectasia mutated (ATM) activity in human HeLa cells and lymphoblasts by Blasina et al. (1999). In human fibroblasts, caffeine compromised the non-homologous end-joining pathway and sensitized the cells to X-ray exposure (Kawata et al., 2005). In rodent cells, caffeine inhibited DNA replication (Schlegel & Pardee, 1986) and the homology-directed repair of DNA double-strand breaks (Wang et al., 2004), and delayed replication fork progression (Johansson et al., 2006).

(b) Epigenetic alterations

No data for coffee were available to the Working Group.

In human MCF-7 and MDA-MB-231 breast cancer cells in vitro, Lee & Zhu (2006) reported demethylation of the promoter region of the retinoic acid receptor β (*RARβ*) gene by caffeic acid and chlorogenic acid.

In rodents, prenatal caffeine exposure induced epigenetic alterations. When given to pregnant Wistar rats, caffeine reduced hepatic methylation of DNA and histones in the offspring (Tan et al., 2012) and induced the expression of DNA methyltransferase and histone deacetylase genes in fetal adrenals (Ping et al., 2014).

Lee & Zhu (2006) demonstrated concentration-dependent inhibition of DNA methylation catalysed by prokaryotic SssI DNA methyltransferase and human DNMT1 by caffeic acid and chlorogenic acid.

4.3 Genetic susceptibility

The literature on the genetic modifiers of coffee consumption-associated traits is diverse and can be subdivided into two broad categories: studies of polymorphisms that are associated with coffee consumption patterns and coffee drinking preference; and studies of genetic variants as factors of susceptibility or resistance to certain cancers in humans. While the data for the latter category are sparse and come from a relatively small number of molecular epidemiology studies, there is strong evidence from several large-scale genome-wide association studies (GWAS) and meta-analyses that habitual coffee consumption is associated with a limited number of modifier alleles.

4.3.1 Genetic mediators of habitual coffee consumption

Coffee and caffeine consumption patterns are highly heritable (as high as 58%) traits (Yang et al., 2010). Coffee consumption habits are strongly associated with polymorphisms in genes involved in metabolism and pharmacological mechanisms of the action of caffeine. Specifically, cytochrome P450 (CYP)1A2, which is almost exclusively responsible for the oxidative metabolism of caffeine in humans (Kot & Daniel, 2008b), and AhR, a nuclear receptor that is responsible for the upregulation of xenobiotic metabolizing enzymes by coffee (Kalthoff et al., 2010), are two genes that exhibit strong associations with coffee and caffeine consumption. For instance, a meta-analysis (Sulem et al., 2011) of four GWASs of coffee consumption assessed from a questionnaire (0 to ≥ 4 cups/day) completed by around 6000 coffee drinkers from Germany, Iceland, the Netherlands, and the USA found two sequence variants to be significantly associated with increased coffee consumption: rs2472297-T located between *CYP1A1* and *CYP1A2* at 15q24; and rs6968865-T near *AHR* at 7p21. The association of these SNPs with coffee consumption was observed in both smokers and non-smokers. [The Working Group noted that the lack of effect of smoking indicates that, even though components of cigarette smoke may affect the same metabolism pathways, the effect of caffeine alone is pronounced.] Similarly, Amin et al. (2012) reported a significant association for two SNPs in the 15q24 region between *CYP1A1* and *CYP1A2* genes in a meta-analysis of GWASs, as assessed by questionnaires, from eight Caucasian cohorts (over 18 000 individuals). Importantly, significant associations between SNPs in *AHR* and *CYP1A1-CYP1A2* and caffeine and coffee consumption from GWASs in European populations were also replicated in an ethnically distinct Costa Rican population (Josse et al., 2012).

A more recent genome-wide meta-analysis of over 100 000 coffee consumers and non-consumers of European and African-American ancestry, in which intake was assessed in terms of the number of cups of predominantly regular coffee consumed per day, Cornelis et al. (2015) confirmed eight loci, including six novel loci, that are located in or near genes potentially involved in the pharmacokinetics (*ABCG2*, *AHR*, *POR*, and *CYP1A2*) and pharmacodynamics (*BDNF* and *SLC6A4*) of caffeine. [The Working Group noted that these studies demonstrate that coffee consumption is strongly associated with polymorphisms in genes that are involved in metabolism and the pharmacological mechanisms of the action of caffeine.]

4.3.2 Genetic modifiers of cancer-associated effects of coffee

(a) Cancer of the breast

Rabstein et al. (2010) studied the modifier effects of *N*-acetyltransferase 2 (*NAT2*) polymorphisms and several lifestyle factors, including coffee consumption, on the risks of developing estrogen receptor (ER) and progesterone receptor (PR) -positive or -negative breast tumours in 1020 cases and 1047 population controls in Germany. In slow acetylators, frequent consumption of coffee (> 4 cups/day vs none) was associated with higher risks of receptor-negative tumours [risk of developing ER-negative tumours: OR, 2.55; 95% CI, 1.22–5.33].

Two studies investigated whether the variation in *CYP1A2* modifies associations between caffeine and coffee consumption and breast cancer risk. In a cohort of 3062 cases and 3427 controls, Lowcock et al. (2013) found that while high coffee consumption, but not total caffeine intake, may be associated with reduced risk of ER-negative and postmenopausal breast cancers, these effects were independent of *CYP1A2* genotype. Similarly, the *CYP1A2* genotype did not

affect breast cancer risk in *BRCA1* mutation carriers (Kotsopoulos et al., 2007).

(b) Cancer of the ovary

Goodman et al. (2003) published the results of a small molecular epidemiology study that examined genetic modifiers of risk of cancer of the ovary (164 cases of epithelial cancer of the ovary and 194 controls) in association with coffee consumption; subjects were stratified into non-drinkers, and moderate (< 7 cups/week) and heavy (> 7 cups/week) drinkers. A modest positive association between caffeine and coffee consumption and an increased risk of ovarian cancer was reported, as well as some evidence that the risk may be modified by *CYP1A2* genotype. A positive significant trend (P = 0.04) in the odds of ovarian cancer associated with coffee (using a threshold of 7 cups/week) and caffeine intake was observed among women with the *CYP1A2* A/A genotype but not among women with any C allele. [The Working Group noted that this small study would not change the overall evaluation of inadequate evidence for the carcinogenicity of coffee.]

Kotsopoulos et al. (2009b) used data and biological specimens from the Nurses' Health Studies and the New England-based case–control study of ovarian cancer (1354 ovarian cancer cases and 1851 controls) to investigate the relationship between genetic polymorphisms in caffeine-metabolizing enzymes, coffee consumption (evaluated using a dietary questionnaire; subjects stratified as consuming < 2.5 cups/day or ≥ 2.5 cups/day of coffee), and the risk of ovarian cancer. The study found no relationship between coffee consumption and ovarian cancer risk in the overall population. Two SNPs in CYP19 (CYP19013 A and CYP19027 G) were found to be associated with an 18% increased (P for trend = 0.02) and 15% decreased (P for trend = 0.05) risk of ovarian cancer, respectively. However, variants in CYP1A1, CYP1A2, or CYP2A6 could not account for the inconsistent reports of coffee intake and ovarian cancer risk.

(c) Cancer of the bladder

A hospital-based case–control study of association between genetic polymorphisms, coffee drinking, and risk of cancer of the bladder (197 cases and 211 controls) (Covolo et al., 2008) found no association between the genetic polymorphisms in NAT1, NAT2, GSTM1, GSTT1, GSTP1, SULT1A1, XRCC1, XRCC3, and XPD, risk of bladder cancer, and coffee consumption (evaluated from the dietary questionnaire). The only positive finding in this study was a significantly increased risk of bladder cancer (OR, 3.18; 95% CI, 1.06–9.55) among GSTP1 105–114 Val carriers who regularly consumed large quantities of coffee (> 3 cups/day).

A hospital-based case–control study of bladder cancer risk factors (185 cases and 180 controls, all Caucasian men) found no interaction between polymorphisms in CYP1A2, risk of bladder cancer, and coffee consumption (determined in cups/day) from a lifetime dietary questionnaire (Pavanello et al., 2010).

(d) Cancer of the colorectum

A study of 1579 incident cases of adenocarcinoma of the colon and 1898 population-based controls showed that consumption of coffee (intake was evaluated from a questionnaire as part of the diet history) was not associated with colon cancer, and that GSTM1 variants did not modify this association (Slattery et al., 2000).

A nested case–control study of 1252 cases and 2175 controls from 477 071 participants (70.2% women) of the European Investigation into Cancer and Nutrition (EPIC) cohort examined potential effect modification by CYP1A2 and NAT2 for the relationship between colorectal cancer and coffee consumption (based on the recorded number of cups per day/week/month) from a country-specific dietary questionnaire (Dik et al., 2014). In this study, total coffee

consumption (high vs zero/low) was not associated with risk of colorectal cancer (HR, 1.06; 95% CI, 0.95–1.18) or subsite cancers. High-consumption subjects with slow CYP1A2 or NAT2 activity had a similar risk compared with non-consumers/low-consumption subjects with a fast CYP1A2 or NAT2 activity.

(e) Leukaemia

A hospital-based case–control study of 280 cases of acute childhood leukaemia and 288 controls examined various gene–environment interactions for the polymorphisms of CYP1A1, GSTM1, GSTP1, GSTT1, and NQO1 and maternal coffee consumption during pregnancy identified from a dietary questionnaire; subjects were stratified into three groups: never drinkers, < 3 cups/day, and ≥ 3 cups/day (Clavel et al., 2005). Overall, the polymorphisms were not associated with the risk of leukaemia; however, it was observed that the association between maternal coffee consumption during pregnancy and leukaemia was weaker among children with the heterozygous or homozygous mutant *NQO1* genotype than for those with the wildtype genotype. No *P* value for interaction was given.

Another study of the associations between childhood acute leukaemia and maternal caffeinated beverage consumption during pregnancy (764 acute leukaemia cases and 1681 controls in France) also explored the interactions between caffeinated beverage consumption and polymorphisms of metabolism enzymes (NAT2, ADH1C, CYP2E1) (Bonaventure et al., 2013). While it was found that regular maternal coffee consumption during pregnancy was weakly associated with childhood acute leukaemia (OR, 1.2 [95% CI, 1.0–1.5]; $P = 0.02$) no significant gene–environment interactions with coffee drinking were observed.

(f) Melanoma

A hospital-based case–control study of 304 incident cases of cutaneous melanoma and 305 controls explored the relationship between *GSTM1* and *GSTT1* positive and null individuals and coffee consumption (evaluated from a dietary questionnaire as never/occasional, 1, 2, or > 2 cups/day) (Fortes et al., 2013). A high frequency of coffee drinking (more than once per day) was associated with a protective effect for cutaneous melanoma (OR, 0.46; 95% CI, 0.31–0.68) after adjusting for sex, age, education, hair colour, common naevi, skin phototype, and sunburn episodes in childhood. When the subjects were stratified by *GSTM1* and *GSTT1* genotype, the inverse association for coffee was high for subjects with both *GSTM1* and *GSTT1* null polymorphisms.

4.4 Other effects

4.4.1 Humans

(a) Preneoplastic lesions

(i) Adenoma of the colorectum

Several studies have reported a decreased risk of adenomas of the colorectum with coffee drinking (Kato et al., 1990; Almendingen et al., 2001; Budhathoki et al., 2015). However, other reports have found no association (Baron et al., 1997; Nagata et al., 2001), or have suggested increased risks (Lee et al., 1993). Only two studies considered how coffee was prepared. One US-based investigation (Baron et al., 1997) considered caffeinated versus decaffeinated coffee, and found no association with consumption of either beverage. An investigation in Japan (Kono et al., 1991) reported a borderline significant trend of decreasing adenoma risks with increasing intake of instant (but not brewed) coffee.

One large investigation that had no evident selection biases reported significant trends of decreased risks with increased coffee intake. The

trends became apparent only after controlling for confounding factors (Budhathoki et al., 2015). The odds ratio for drinking > 291 mL/day of coffee versus < 26 mL/day was 0.67 (95% CI, 0.48–0.93).

[The Working Group noted that many of the studies regarding coffee and adenomas are subject to possible selection bias in the choice of controls (Kato et al., 1990; Olsen & Kronborg, 1993; Hoshiyama et al., 2000; Almendingen et al., 2001; Nagata et al., 2001) and/or insufficient adjustment for likely confounding factors such as cigarette smoking (Kato et al., 1990; Lee et al., 1993; Hoshiyama et al., 2000). Additionally, no studies addressed the association of coffee drinking with preinvasive lesions in the pathway to serrated colorectal cancer (Bettington et al., 2013).]

One case–control study of adenoma (Lee et al., 1993) assessed the association between colorectal cancer and estimated total caffeine intake from coffee, tea, and carbonated beverages. Although this study reported an association with coffee drinking in women, there was no association with caffeine intake. [The Working Group noted the inadequate control for possible confounding factors, such as cigarette smoking, in this study.]

(ii) Barrett oesophagus

One multicentre hospital-based case–control study investigated the association between coffee drinking and biopsy-confirmed Barrett oesophagus in patients admitted for non-neoplastic, non-gastroenterological conditions (Conio et al., 2002). In unadjusted analyses, there was no difference in the prevalence of coffee drinking between cases and controls (Conio et al., 2002). A second study investigated the association between coffee drinking and Barrett oesophagus in patients who underwent oesophagogastroduodenoscopy; controls without Barrett oesophagus underwent colonoscopy or oesophagogastroduodenoscopy. The authors found an association between Barrett oesophagus and coffee drinking in unadjusted analyses, but no association after multivariable adjustment (Sajja et al., 2016). [The Working Group noted that both studies were susceptible to selection bias in the choice of controls.]

(b) Metabolic effects

Multiple single-dose clinical trials have shown that caffeinated coffee increases insulin resistance and impairs glucose homeostasis (Beaudoin & Graham, 2011). However, the few trials that have investigated longer-term (≥ 1 month) consumption did not observe such metabolic impairments (Kempf et al., 2010; Wedick et al., 2011). Studies that investigated decaffeinated coffee have reported conflicting findings (see review by Beaudoin & Graham, 2011).

Clinical trials that have manipulated caffeine intake have also found that caffeine alone (MacKenzie et al., 2007) or caffeine added to decaffeinated coffee (Gavrieli et al., 2013; Robertson et al., 2015) interferes with glucose homeostasis. It is not clear if the effects of caffeine on glucose regulation are dependent upon dose (Gavrieli et al., 2013; Robertson et al., 2015).

One clinical trial (van Dijk et al., 2009) assessed the effects of the coffee constituents chlorogenic acid (1 g) and trigonelline (500 mg) in a glucose tolerance test. Both compounds reduced early circulating glucose and insulin levels compared with placebo, with no effect on the areas under the concentration curves.

Observational studies clearly show an inverse association between diabetes and coffee intake (Higdon & Frei, 2006; Natella & Scaccini, 2012; Cano-Marquina et al., 2013; Jiang et al., 2014). A meta-analysis of 26 cohort studies involving 50 595 cases of type 2 diabetes reported that risk decreased by 12% (95% CI, 10–14%) and 11% (95% CI, 2–18%) for every 2 cups/day increment in coffee and decaffeinated coffee intake, respectively (Jiang et al., 2014). [The Working Group noted that the differences between the acute and chronic effects may involve acclimation to caffeine and/or the effects of other substances in coffee that improve insulin resistance.]

(c) Liver diseases

Observational studies have found that coffee drinking protects against, or improves the prognosis of, liver diseases associated with hepatocellular carcinoma (Saab et al., 2014). A meta-analysis of coffee drinking and risk of hepatic fibrosis and cirrhosis included eight studies investigating cirrhosis, seven investigating advanced hepatic fibrosis, and one investigating both (Liu et al., 2015). Overall, 3034 coffee consumers and 132 076 non-consumers were studied in the investigations. The pooled odds ratio for hepatic cirrhosis in coffee consumers compared with non-consumers was 0.61 (95% CI, 0.45–0.84). For advanced fibrosis, the odds ratio was 0.73 (95% CI, 0.58–0.92). There were statistically significant inverse associations for both alcohol-associated cirrhosis and cirrhosis associated with hepatitis C. [The Working Group noted the heterogeneity in this meta-analysis.] Decaffeinated coffee does not appear to be associated with cirrhosis/liver fibrosis (Modi et al., 2010; Khalaf et al., 2015). [The Working Group noted the inadequate consideration of smoking in the paper by Khalaf et al. (2015), and the lack of control for smoking in the study by Modi et al. (2010).]

Coffee consumption may also be associated with lower severity of non-alcoholic fatty liver disease (NAFLD) (Chen et al., 2014a; Wadhawan & Anand, 2016). Decaffeinated coffee did not appear to have the same associations (Modi et al., 2010; Dickson et al., 2015; Khalaf et al., 2015). However, coffee consumption was not associated with the prevalence of ultrasound-diagnosed NAFLD (Zelber-Sagi et al., 2015). A meta-analysis of observational studies reported that caffeine consumption is not associated with the prevalence of NAFLD (Shen et al., 2016). However, caffeine is associated with a reduced severity of disease in affected patients (Molloy et al., 2012; Shen et al., 2016).

There are suggestions that coffee intake ameliorates the severity of chronic hepatitis C (Wadhawan & Anand, 2016). In cross-sectional studies of hepatitis C patients, coffee intake has been inversely associated with degree of fibrosis and other measures of liver injury (Liu et al., 2015). A cohort study showed that fibrosis in patients who drank coffee progressed less quickly than those who did not (Freedman et al., 2009); coffee-drinking patients also responded better to peginterferon and ribavirin therapy (Freedman et al., 2011). In a randomized open-label crossover trial, 40 patients with hepatitis C were randomized to either 4 cups/day of coffee for 1 month or abstinence. Coffee intake caused a reduction in plasma procollagen type III, a measure of fibrosis and collagen synthesis (Cardin et al., 2013). Inverse associations between caffeine intake and transaminase levels, fibrosis, and disease activity in hepatitis C patients have also been reported (Costentin et al., 2011; Khalaf et al., 2015).

4.4.2 Experimental systems

Most of the experimental animal studies on the effect of coffee and its ingredients on insulin resistance and insulin secretion were conducted in different mouse models of type 2 diabetes. Using spontaneously diabetic male KK-A^y mice, Yamauchi et al. (2010) demonstrated that ingestion of diluted black coffee as drinking-water (black coffee/water = 1:1 v/v) for 5 weeks improved insulin resistance. The similar effect of regular coffee, decaffeinated green coffee bean extract, and chlorogenic acid on improving insulin resistance have been reported in C57BL/6 mice (Rustenbeck et al., 2014; Song et al., 2014; Ma et al., 2015) and male Sprague-Dawley rats (Shearer et al., 2007) fed a high-fat diet. Coffee ingestion increased insulin sensitivity via the induction of Akt serine phosphorylation in liver and skeletal muscle (Kobayashi et al., 2012; Jia et al., 2014) and increasing insulin-receptor substrate-1 (IRS-1) tyrosine phosphorylation

(Jia et al., 2014). In contrast, Tan et al. (2012) reported that intragastrical administration of caffeine at 120 mg /kg bw per day to pregnant Wistar rats from gestational day 11 to 20 reduced the expression of insulin-like growth factor 1 receptor (IGF-1R) and IRS-1 in the fetal livers.

Potentiation of liver toxicity induced by carbon tetrachloride by intake of unfiltered coffee has been reported in Sprague-Dawley rats (Poyrazoglu et al., 2008). Another study found that coffee prevented liver toxicity in rats injected with lipopolysaccharide (Sakamoto et al., 2000), however. Both caffeinated and decaffeinated instant coffee protected rats against liver fibrosis after dimethylnitrosamine injection (Shin et al., 2010). Similar findings were reported for brewed coffee (but not instant coffee) in rats treated with diethylnitrosamine and carbon tetrachloride (Furtado et al., 2014). In a study where male Wistar rats were given an extract of Colombian coffee, the coffee-treated rats had lower liver weight, less portal fibrosis, and less collagen deposition than those given water (Panchal et al., 2012).

References

Abraham SK (1989). Inhibition of in vivo genotoxicity by coffee. *Food Chem Toxicol*, 27(12):787–92. doi:10.1016/0278-6915(89)90109-9 PMID:2514131

Abraham SK (1991). Inhibitory effects of coffee on the genotoxicity of carcinogens in mice. *Mutat Res*, 262(2):109–14. doi:10.1016/0165-7992(91)90115-K PMID:1900350

Abraham SK (1994). Antigenotoxicity of coffee in the Drosophila assay for somatic mutation and recombination. *Mutagenesis*, 9(4):383–6. doi:10.1093/mutage/9.4.383 PMID:7968582

Abraham SK (1995). Inhibitory effects of coffee on transplacental genotoxicity in mice. *Mutat Res*, 347(1):45–52. doi:10.1016/0165-7992(95)90032-2 PMID:7596367

Abraham SK, Graf U (1996). Protection by coffee against somatic genotoxicity in Drosophila: role of bioactivation capacity. *Food Chem Toxicol*, 34(1):1–14. doi:10.1016/0278-6915(95)00087-9 PMID:8603789

Abraham SK, Singh SP (1999). Anti-genotoxicity and glutathione *S*-transferase activity in mice pretreated with caffeinated and decaffeinated coffee. *Food Chem Toxicol*, 37(7):733–9. doi:10.1016/S0278-6915(99)00053-8 PMID:10496374

Abraham SK, Singh SP, Kesavan PC (1998). In vivo antigenotoxic effects of dietary agents and beverages co-administered with urethane: assessment of the role of glutathione S-transferase activity. *Mutat Res*, 413(2):103–10. doi:10.1016/S1383-5718(98)00008-4 PMID:9639686

Abraham SK, Stopper H (2004). Anti-genotoxicity of coffee against *N*-methyl-*N*-nitro-*N*-nitrosoguanidine in mouse lymphoma cells. *Mutat Res*, 561(1–2):23–33. doi:10.1016/j.mrgentox.2004.03.010 PMID:15238227

Abraham SK, Vukicevic V, Stopper H (2004). Coffee-mediated protective effects against directly acting genotoxins and gamma-radiation in mouse lymphoma cells. *Cell Biol Toxicol*, 20(2):121–32. doi:10.1023/B:CBTO.0000027936.89301.b3 PMID:15242187

Acquaviva F, DeFrancesco A, Andriulli A, Piantino P, Arrigoni A, Massarenti P, et al. (1986). Effect of regular and decaffeinated coffee on serum gastrin levels. *J Clin Gastroenterol*, 8(2):150–3. doi:10.1097/00004836-198604000-00009 PMID:3745848

Aeschbacher HU, Chappuis C (1981). Non-mutagenicity of urine from coffee drinkers compared with that from cigarette smokers. *Mutat Res*, 89(2):161–77. doi:10.1016/0165-1218(81)90122-1 PMID:7027029

Aeschbacher HU, Jaccaud E (1990). Inhibition by coffee of nitrosourea-mediated DNA damage in mice. *Food Chem Toxicol*, 28(9):633–7. doi:10.1016/0278-6915(90)90171-I PMID:2272561

Aeschbacher HU, Meier H, Ruch E, Würzner HP (1984). Investigation of coffee in sister chromatid exchange and micronucleus tests in vivo. *Food Chem Toxicol*, 22(10):803–7. doi:10.1016/0278-6915(84)90118-2 PMID:6541618

Aeschbacher HU, Ruch E, Meier H, Würzner HP, Munoz-Box R (1985). Instant and brewed coffees in the in vitro human lymphocyte mutagenicity test. *Food Chem Toxicol*, 23(8):747–52. doi:10.1016/0278-6915(85)90269-8 PMID:4043880

Aeschbacher HU, Wolleb U, Löliger J, Spadone JC, Liardon R (1989). Contribution of coffee aroma constituents to the mutagenicity of coffee. *Food Chem Toxicol*, 27(4):227–32. doi:10.1016/0278-6915(89)90160-9 PMID:2659457

Aeschbacher HU, Würzner HP (1980). An evaluation of instant and regular coffee in the Ames mutagenicity test. *Toxicol Lett*, 5(2):139–45. doi:10.1016/0378-4274(80)90163-0 PMID:7008262

Aleksandrova K, Bamia C, Drogan D, Lagiou P, Trichopoulou A, Jenab M, et al. (2015). The association of coffee intake with liver cancer risk is mediated by biomarkers of inflammation and hepatocellular injury: data from the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*, 102(6):1498–508. doi:10.3945/ajcn.115.116095 PMID:26561631

Almendingen K, Hofstad B, Trygg K, Hoff G, Hussain A, Vatn M (2001). Current diet and colorectal adenomas: a case-control study including different sets of traditionally chosen control groups. *Eur J Cancer Prev*, 10(5):395–406. doi:10.1097/00008469-200110000-00003 PMID:11711754

Amin N, Byrne E, Johnson J, Chenevix-Trench G, Walter S, Nolte IM, et al.; kConFab Investigators (2012). Genome-wide association analysis of coffee drinking suggests association with CYP1A1/CYP1A2 and NRCAM. *Mol Psychiatry*, 17(11):1116–29. doi:10.1038/mp.2011.101 PMID:21876539

Aoyagi R, Funakoshi-Tago M, Fujiwara Y, Tamura H (2014). Coffee inhibits adipocyte differentiation via inactivation of PPARγ. *Biol Pharm Bull*, 37(11):1820–5. doi:10.1248/bpb.b14-00378 PMID:25212747

Ariza RR, Dorado G, Barbancho M, Pueyo C (1988). Study of the causes of direct-acting mutagenicity in coffee and tea using the Ara test in *Salmonella typhimurium*. *Mutat Res*, 201(1):89–96. doi:10.1016/0027-5107(88)90114-5 PMID:3047575

Ariza RR, Pueyo C (1991). The involvement of reactive oxygen species in the direct-acting mutagenicity of wine. *Mutat Res*, 251(1):115–21. doi:10.1016/0027-5107(91)90221-9 PMID:1944368

Arsenault BJ, Earnest CP, Després JP, Blair SN, Church TS (2009). Obesity, coffee consumption and CRP levels in postmenopausal overweight/obese women: importance of hormone replacement therapy use. *Eur J Clin Nutr*, 63(12):1419–24. doi:10.1038/ejcn.2009.112 PMID:19756031

Atanasov AG, Dzyakanchuk AA, Schweizer RA, Nashev LG, Maurer EM, Odermatt A (2006). Coffee inhibits the reactivation of glucocorticoids by 11beta-hydroxysteroid dehydrogenase type 1: a glucocorticoid connection in the anti-diabetic action of coffee? *FEBS Lett*, 580(17):4081–5. doi:10.1016/j.febslet.2006.06.046 PMID:16814782

Azuma K, Ippoushi K, Nakayama M, Ito H, Higashio H, Terao J (2000). Absorption of chlorogenic acid and caffeic acid in rats after oral administration. *J Agric Food Chem*, 48(11):5496–500. doi:10.1021/jf000483q PMID:11087508

Bakuradze T, Boehm N, Janzowski C, Lang R, Hofmann T, Stockis JP, et al. (2011). Antioxidant-rich coffee reduces DNA damage, elevates glutathione status and contributes to weight control: results from an intervention study. *Mol Nutr Food Res*, 55(5):793–7. doi:10.1002/mnfr.201100093 PMID:21462335

Bakuradze T, Lang R, Hofmann T, Eisenbrand G, Schipp D, Galan J, et al. (2015). Consumption of a dark roast coffee decreases the level of spontaneous DNA strand breaks: a randomized controlled trial. *Eur J Nutr*, 54(1):149–56. doi:10.1007/s00394-014-0696-x PMID:24740588

Bakuradze T, Lang R, Hofmann T, Schipp D, Galan J, Eisenbrand G, et al. (2016). Coffee consumption rapidly reduces background DNA strand breaks in healthy humans: Results of a short-term repeated uptake intervention study. *Mol Nutr Food Res*, 60(3):682–6. doi:10.1002/mnfr.201500668 PMID:26632023

Bakuradze T, Lang R, Hofmann T, Stiebitz H, Bytof G, Lantz I, et al. (2010). Antioxidant effectiveness of coffee extracts and selected constituents in cell-free systems and human colon cell lines. *Mol Nutr Food Res*, 54(12):1734–43. doi:10.1002/mnfr.201000147 PMID:20589861

Bakuradze T, Montoya Parra GA, Riedel A, Somoza V, Lang R, Dieminger N, et al. (2014). Four-week coffee consumption affects energy intake, satiety regulation, body fat, and protects DNA integrity *Food Res Int*, 63:420–7. doi:10.1016/j.foodres.2014.05.032

Barale R, Chelotti L, Davini T, Del Ry S, Andreassi MG, Ballardin M, et al. (1998). Sister chromatid exchange and micronucleus frequency in human lymphocytes of 1,650 subjects in an Italian population: II. Contribution of sex, age, and lifestyle. *Environ Mol Mutagen*, 31(3):228–42. doi:10.1002/(SICI)1098-2280(1998)31:3<228::AID-EM4>3.0.CO;2-G PMID:9585261

Baron JA, Greenberg ER, Haile R, Mandel J, Sandler RS, Mott L (1997). Coffee and tea and the risk of recurrent colorectal adenomas. *Cancer Epidemiol Biomarkers Prev*, 6(1):7–10. PMID:8993790

Beaudoin MS, Graham TE (2011). Methylxanthines and human health: epidemiological and experimental evidence. *Handbook Exp Pharmacol*, 200:509–48. doi:10.1007/978-3-642-13443-2_21 PMID:20859811

Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V (2013). The serrated pathway to colorectal carcinoma: current concepts and challenges. *Histopathology*, 62(3):367–86. doi:10.1111/his.12055 PMID:23339363

Bichler J, Cavin C, Simic T, Chakraborty A, Ferk F, Hoelzl C, et al. (2007). Coffee consumption protects human lymphocytes against oxidative and 3-amino-1-methyl-5H-pyrido[4,3-b]indole acetate (Trp-P-2) induced DNA-damage: results of an experimental study with human volunteers. *Food Chem Toxicol*, 45(8):1428–36. doi:10.1016/j.fct.2007.02.001 PMID:17376579

Blasina A, Price BD, Turenne GA, McGowan CH (1999). Caffeine inhibits the checkpoint kinase ATM. *Curr Biol*, 9(19):1135–8. doi:10.1016/S0960-9822(99)80486-2 PMID:10531013

Boettler U, Volz N, Pahlke G, Teller N, Kotyczka C, Somoza V, et al. (2011). Coffees rich in chlorogenic acid or N-methylpyridinium induce chemopreventive phase II-enzymes via the Nrf2/ARE pathway in vitro and in vivo. *Mol Nutr Food Res*, 55(5):798–802. doi:10.1002/mnfr.201100115 PMID:21448860

Boettler U, Volz N, Teller N, Haupt LM, Bakuradze T, Eisenbrand G, et al. (2012). Induction of antioxidative Nrf2 gene transcription by coffee in humans: depending on genotype? *Mol Biol Rep*, 39(6):7155–62. doi:10.1007/s11033-012-1547-6 PMID:22314914

Bonaventure A, Rudant J, Goujon-Bellec S, Orsi L, Leverger G, Baruchel A, et al. (2013). Childhood acute leukemia, maternal beverage intake during pregnancy, and metabolic polymorphisms. *Cancer Causes Control*, 24(4):783–93. doi:10.1007/s10552-013-0161-9 PMID:23404349

Bravo J, Arbillaga L, de Peña MP, Cid C (2013). Antioxidant and genoprotective effects of spent coffee extracts in human cells. *Food Chem Toxicol*, 60:397–403. doi:10.1016/j.fct.2013.08.002 PMID:23948352

Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Tsugane S (2015). Coffee intake and the risk of colorectal adenoma: The colorectal adenoma study in Tokyo. *Int J Cancer*, 137(2):463–70. doi:10.1002/ijc.29390 PMID:25500898

Cano-Marquina A, Tarín JJ, Cano A (2013). The impact of coffee on health. *Maturitas*, 75(1):7–21. doi:10.1016/j.maturitas.2013.02.002 PMID:23465359

Cárdenas C, Quesada AR, Medina MA (2011). Anti-angiogenic and anti-inflammatory properties of kahweol, a coffee diterpene. *PLoS ONE*, 6(8):e23407 doi:10.1371/journal.pone.0023407 PMID:21858104

Cárdenas C, Quesada AR, Medina MÁ (2014). Insights on the antitumor effects of kahweol on human breast cancer: decreased survival and increased production of reactive oxygen species and cytotoxicity. *Biochem Biophys Res Commun*, 447(3):452–8. doi:10.1016/j.bbrc.2014.04.026 PMID:24732357

Cardin R, Piciocchi M, Martines D, Scribano L, Petracco M, Farinati F (2013). Effects of coffee consumption in chronic hepatitis C: a randomized controlled trial. *Dig Liver Dis*, 45(6):499–504. doi:10.1016/j.dld.2012.10.021 PMID:23238034

Cavin C, Mace K, Offord EA, Schilter B (2001). Protective effects of coffee diterpenes against aflatoxin B_1-induced genotoxicity: mechanisms in rat and human cells. *Food Chem Toxicol*, 39(6):549–56. doi:10.1016/S0278-6915(00)00168-X PMID:11346484

Cavin C, Marin-Kuan M, Langouët S, Bezençon C, Guignard G, Verguet C, et al. (2008). Induction of Nrf2-mediated cellular defenses and alteration of phase I activities as mechanisms of chemoprotective effects of coffee in the liver. *Food Chem Toxicol*, 46(4):1239–48. doi:10.1016/j.fct.2007.09.099 PMID:17976884

Cha KH, Song DG, Kim SM, Pan CH (2012). Inhibition of gastrointestinal lipolysis by green tea, coffee, and gomchui (Ligularia fischeri) tea polyphenols during simulated digestion. *J Agric Food Chem*, 60(29):7152–7. doi:10.1021/jf301047f PMID:22730927

Chae JI, Jeon YJ, Shim JH (2014). Anti-proliferative properties of kahweol in oral squamous cancer through the regulation specificity protein 1. *Phytother Res*, 28(12):1879–86. doi:10.1002/ptr.5217 PMID:25196544

Chen AT, Reidy JA, Annest JL, Welty TK, Zhou HG (1989). Increased chromosome fragility as a consequence of blood folate levels, smoking status, and coffee consumption. *Environ Mol Mutagen*, 13(4):319–24. doi:10.1002/em.2850130407 PMID:2737183

Chen L, Bondoc FY, Lee MJ, Hussin AH, Thomas PE, Yang CS (1996). Caffeine induces cytochrome P4501A2: induction of CYP1A2 by tea in rats. *Drug Metab Dispos*, 24(5):529–33. PMID:8723732

Chen S, Teoh NC, Chitturi S, Farrell GC (2014a). Coffee and non-alcoholic fatty liver disease: brewing evidence for hepatoprotection? [Review.] *J Gastroenterol Hepatol*, 29(3):435–41. doi:10.1111/jgh.12422 PMID:24199670

Choi DW, Lim MS, Lee JW, Chun W, Lee SH, Nam YH, et al. (2015). The cytotoxicity of kahweol in HT-29 human colorectal cancer cells is mediated by apoptosis and suppression of heat shock protein 70 expression. *Biomol Ther (Seoul)*, 23(2):128–33. doi:10.4062/biomolther.2014.133 PMID:25767680

Choi MJ, Park EJ, Oh JH, Min KJ, Yang ES, Kim YH, et al. (2011). Cafestol, a coffee-specific diterpene, induces apoptosis in renal carcinoma Caki cells through down-regulation of anti-apoptotic proteins and Akt phosphorylation. *Chem Biol Interact*, 190(2–3):102–8. doi:10.1016/j.cbi.2011.02.013 PMID:21334318

Clavel J, Bellec S, Rebouissou S, Ménégaux F, Feunteun J, Bonaïti-Pellié C, et al. (2005). Childhood leukaemia, polymorphisms of metabolism enzyme genes, and interactions with maternal tobacco, coffee and alcohol consumption during pregnancy. *Eur J Cancer Prev*, 14(6):531–40. doi:10.1097/00008469-200512000-00007 PMID:16284498

Conio M, Filiberti R, Blanchi S, Ferraris R, Marchi S, Ravelli P, et al.; Gruppo Operativo per lo Studio delle Precancerosi Esofagee (GOSPE) (2002). Risk factors for Barrett's esophagus: a case-control study. *Int J Cancer*, 97(2):225–9. doi:10.1002/ijc.1583 PMID:11774268

Cornelis MC, Byrne EM, Esko T, Nalls MA, Ganna A, Paynter N, et al.; Coffee and Caffeine Genetics Consortium; International Parkinson's Disease Genomics Consortium (IPDGC); North American Brain Expression Consortium (NABEC); UK Brain Expression Consortium (UKBEC) (2015). Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. *Mol Psychiatry*, 20(5):647–56. doi:10.1038/mp.2014.107 PMID:25288136

Corrêa TA, Monteiro MP, Mendes TM, Oliveira DM, Rogero MM, Benites CI, et al. (2012). Medium light and medium roast paper-filtered coffee increased antioxidant capacity in healthy volunteers: results of a randomized trial. *Plant Foods Hum Nutr*, 67(3):277–82. doi:10.1007/s11130-012-0297-x PMID:22766993

Corrêa TA, Rogero MM, Mioto BM, Tarasoutchi D, Tuda VL, César LA, et al. (2013). Paper-filtered coffee increases cholesterol and inflammation biomarkers independent of roasting degree: a clinical trial. *Nutrition*, 29(7–8):977–81. doi:10.1016/j.nut.2013.01.003 PMID:23510568

Costentin CE, Roudot-Thoraval F, Zafrani ES, Medkour F, Pawlotsky JM, Mallat A, et al. (2011). Association of caffeine intake and histological features of chronic hepatitis C. *J Hepatol*, 54(6):1123–9. doi:10.1016/j.jhep.2010.08.027 PMID:21145804

Covolo L, Placidi D, Gelatti U, Carta A, Scotto Di Carlo A, Lodetti P, et al. (2008). Bladder cancer, GSTs, NAT1, NAT2, SULT1A1, XRCC1, XRCC3, XPD genetic polymorphisms and coffee consumption: a case-control study. *Eur J Epidemiol*, 23(5):355–62. doi:10.1007/s10654-008-9238-2 PMID:18365755

Cruchten ST, de Waart DR, Kunne C, Hooiveld GJ, Boekschoten MV, Katan MB, et al. (2010). Absorption, distribution, and biliary excretion of cafestol, a potent cholesterol-elevating compound in unfiltered coffees, in mice. *Drug Metab Dispos*, 38(4):635–40. doi:10.1124/dmd.109.030213 PMID:20047988

De Roos B, Meyboom S, Kosmeijer-Schuil TG, Katan MB (1998). Absorption and urinary excretion of the coffee diterpenes cafestol and kahweol in healthy ileostomy volunteers. *J Intern Med*, 244(6):451–60. doi:10.1111/j.1365-2796.1998.00386.x PMID:9893098

Denaro CP, Brown CR, Wilson M, Jacob P 3rd, Benowitz NL (1990). Dose-dependency of caffeine metabolism with repeated dosing. *Clin Pharmacol Ther*, 48(3):277–85. doi:10.1038/clpt.1990.150 PMID:2401126

Dickson JC, Liese AD, Lorenzo C, Haffner SM, Watkins SM, Hamren SJ, et al. (2015). Associations of coffee consumption with markers of liver injury in the insulin resistance atherosclerosis study. *BMC Gastroenterol*, 15(1):88 doi:10.1186/s12876-015-0321-3 PMID:26215323

Dik VK, Bueno-de-Mesquita HB, Van Oijen MG, Siersema PD, Uiterwaal CS, Van Gils CH, et al. (2014). Coffee and tea consumption, genotype-based CYP1A2 and NAT2 activity and colorectal cancer risk-results from the EPIC cohort study. *Int J Cancer*, 135(2):401–12. doi:10.1002/ijc.28655 PMID:24318358

Djordjevic N, Ghotbi R, Bertilsson L, Jankovic S, Aklillu E (2008). Induction of CYP1A2 by heavy coffee consumption in Serbs and Swedes. *Eur J Clin Pharmacol*, 64(4):381–5. doi:10.1007/s00228-007-0438-6 PMID:18157525

Djordjevic N, Ghotbi R, Jankovic S, Aklillu E (2010). Induction of CYP1A2 by heavy coffee consumption is associated with the CYP1A2 -163C>A polymorphism. *Eur J Clin Pharmacol*, 66(7):697–703. doi:10.1007/s00228-010-0823-4 PMID:20390257

Dorado G, Barbancho M, Pueyo C (1987). Coffee is highly mutagenic in the L-arabinose resistance test in Salmonella typhimurium. *Environ Mutagen*, 9(3):251–60. doi:10.1002/em.2860090304 PMID:3552646

Douglas BR, Jansen JB, Tham RT, Lamers CB (1990). Coffee stimulation of cholecystokinin release and gallbladder contraction in humans. *Am J Clin Nutr*, 52(3):553–6. PMID:2393014

Duarte GS, Farah A (2011). Effect of simultaneous consumption of milk and coffee on chlorogenic acids' bioavailability in humans. *J Agric Food Chem*, 59(14):7925–31. doi:10.1021/jf201906p PMID:21627318

Duarte MP, Laires A, Gaspar J, Leão D, Oliveira JS, Rueff J (1999). Genotoxicity of instant coffee: possible involvement of phenolic compounds. *Mutat Res*, 442(1):43–51. doi:10.1016/S1383-5718(99)00057-1 PMID:10366772

Duarte MP, Laires A, Gaspar J, Oliveira JS, Rueff J (2000). Genotoxicity of instant coffee and of some phenolic compounds present in coffee upon nitrosation. *Teratog Carcinog Mutagen*, 20(4):241–9. doi:10.1002/1520-6866(2000)20:4<241::AID-TCM6>3.0.CO;2-4 PMID:10910474

Dunn BP, Curtis JR (1985). Clastogenic agents in the urine of coffee drinkers and cigarette smokers. *Mutat Res*, 147(4):179–88. doi:10.1016/0165-1161(85)90056-1 PMID:4022032

Dupas C, Marsset Baglieri A, Ordonaud C, Tomé D, Maillard MN (2006). Chlorogenic acid is poorly absorbed, independently of the food matrix: A Caco-2 cells and rat chronic absorption study. *Mol Nutr Food Res*, 50(11):1053–60. doi:10.1002/mnfr.200600034 PMID:17054098

Edenharder R, Sager JW, Glatt H, Muckel E, Platt KL (2002). Protection by beverages, fruits, vegetables, herbs, and flavonoids against genotoxicity of 2-acetylaminofluorene and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) in metabolically competent V79 cells. *Mutat Res*, 521(1–2):57–72. doi:10.1016/S1383-5718(02)00212-7 PMID:12438004

Erk T, Hauser J, Williamson G, Renouf M, Steiling H, Dionisi F, et al. (2014a). Structure- and dose-absorption relationships of coffee polyphenols. *Biofactors*, 40(1):103–12. doi:10.1002/biof.1101 PMID:23553742

Erk T, Renouf M, Williamson G, Melcher R, Steiling H, Richling E (2014b). Absorption and isomerization of caffeoylquinic acids from different foods using ileostomist volunteers. *Eur J Nutr*, 53(1):159–66. doi:10.1007/s00394-013-0512-z PMID:23503803

Erk T, Williamson G, Renouf M, Marmet C, Steiling H, Dionisi F, et al. (2012). Dose-dependent absorption of chlorogenic acids in the small intestine assessed by coffee consumption in ileostomists. *Mol Nutr Food Res*, 56(10):1488–500. doi:10.1002/mnfr.201200222 PMID:22945604

Ezechiáš M, Janochová J, Filipová A, Křesinová Z, Cajthaml T (2016). Widely used pharmaceuticals present in the environment revealed as in vitro antagonists for human estrogen and androgen receptors. *Chemosphere*, 152:284–91. PMID:26978704

Farah A, Monteiro M, Donangelo CM, Lafay S (2008). Chlorogenic acids from green coffee extract are highly bioavailable in humans. *J Nutr*, 138(12):2309–15. doi:10.3945/jn.108.095554 PMID:19022950

Farrell TL, Dew TP, Poquet L, Hanson P, Williamson G (2011). Absorption and metabolism of chlorogenic acids in cultured gastric epithelial monolayers. *Drug Metab Dispos*, 39(12):2338–46. doi:10.1124/dmd.111.040147 PMID:21937734

Farrell TL, Gomez-Juaristi M, Poquet L, Redeuil K, Nagy K, Renouf M, et al. (2012). Absorption of dimethoxycinnamic acid derivatives in vitro and pharmacokinetic profile in human plasma following coffee consumption. *Mol Nutr Food Res*, 56(9):1413–23. doi:10.1002/mnfr.201200021 PMID:22865606

Ferk F, Huber WW, Grasl-Kraupp B, Speer K, Buchmann S, Bohacek R, et al. (2014). Protective effects of coffee against induction of DNA damage and pre-neoplastic foci by aflatoxin B_1. *Mol Nutr Food Res*, 58(2):229–38. doi:10.1002/mnfr.201300154 PMID:24039089

Förster A, Kühne Y, Henle T (2005). Studies on absorption and elimination of dietary maillard reaction products. *Ann N Y Acad Sci*, 1043(1):474–81. doi:10.1196/annals.1333.054 PMID:16037269

Fortes C, Mastroeni S, Boffetta P, Antonelli G, Pilla MA, Bottà G, et al. (2013). The protective effect of coffee consumption on cutaneous melanoma risk and the role of GSTM1 and GSTT1 polymorphisms. *Cancer Causes Control*, 24(10):1779–87. doi:10.1007/s10552-013-0255-4 PMID:23860951

Freedman ND, Curto TM, Lindsay KL, Wright EC, Sinha R, Everhart JE; HALT-C TRIAL GROUP (2011). Coffee consumption is associated with response to peginterferon and ribavirin therapy in patients with chronic hepatitis C. [Multicenter Study Randomized Controlled Trial Research Support, NIH, Extramural Research Support, Non-US Gov't.] *Gastroenterology*, 140(7):1961–9. doi:10.1053/j.gastro.2011.02.061 PMID:21376050

Freedman ND, Everhart JE, Lindsay KL, Ghany MG, Curto TM, Shiffman ML, et al.; HALT-C Trial Group (2009). Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. *Hepatology*, 50(5):1360–9. doi:10.1002/hep.23162 PMID:19676128

Friederich U, Hann D, Albertini S, Schlatter C, Würgler FE (1985). Mutagenicity studies on coffee. The influence of different factors on the mutagenic activity in the Salmonella/mammalian microsome assay. *Mutat Res*, 156(1–2):39–52. doi:10.1016/0165-1218(85)90005-9 PMID:3889626

Fujii Y, Osaki N, Hase T, Shimotoyodome A (2015). Ingestion of coffee polyphenols increases postprandial release of the active glucagon-like peptide-1 (GLP-1(7–36)) amide in C57BL/6J mice. *J Nutr Sci*, 4:e9 doi:10.1017/jns.2014.71 PMID:26097706

Fujita Y, Wakabayashi K, Nagao M, Sugimura T (1985a). Characteristics of major mutagenicity of instant coffee. *Mutat Res*, 142(4):145–8. doi:10.1016/0165-7992(85)90013-2 PMID:3885016

Fukushima Y, Kasuga M, Nakao K, Shimomura I, Matsuzawa Y (2009). Effects of coffee on inflammatory cytokine gene expression in mice fed high-fat diets. *J Agric Food Chem*, 57(23):11100–5. doi:10.1021/jf901278u PMID:19899759

Fumeaux R, Menozzi-Smarrito C, Stalmach A, Munari C, Kraehenbuehl K, Steiling H, et al. (2010). First synthesis, characterization, and evidence for the presence of hydroxycinnamic acid sulfate and glucuronide conjugates in human biological fluids as a result of coffee consumption. *Org Biomol Chem*, 8(22):5199–211. doi:10.1039/c0ob00137f PMID:20842300

Furtado KS, Polletini J, Dias MC, Rodrigues MA, Barbisan LF (2014). Prevention of rat liver fibrosis and carcinogenesis by coffee and caffeine. *Food Chem Toxicol*, 64:20–6. doi:10.1016/j.fct.2013.11.011 PMID:24275088

Gavrieli A, Fragopoulou E, Mantzoros CS, Yannakoulia M (2013). Gender and body mass index modify the effect of increasing amounts of caffeinated coffee on postprandial glucose and insulin concentrations; a randomized, controlled, clinical trial. [Randomized Controlled Trial Research Support, Non-US Gov't.] *Metabolism*, 62(8):1099–106. doi:10.1016/j.metabol.2013.02.003 PMID:23498899

Gavrieli A, Yannakoulia M, Fragopoulou E, Margaritopoulos D, Chamberland JP, Kaisari P, et al. (2011). Caffeinated coffee does not acutely affect energy intake, appetite, or inflammation but prevents serum cortisol concentrations from falling in healthy men. *J Nutr*, 141(4):703–7. doi:10.3945/jn.110.137323 PMID:21346100

Gelal A, Guven H, Balkan D, Artok L, Benowitz NL (2003). Influence of menthol on caffeine disposition and pharmacodynamics in healthy female volunteers. *Eur J Clin Pharmacol*, 59(5–6):417–22. doi:10.1007/s00228-003-0631-1 PMID:12915954

Ghotbi R, Christensen M, Roh HK, Ingelman-Sundberg M, Aklillu E, Bertilsson L (2007). Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype-phenotype relationship in Swedes and Koreans. *Eur J Clin Pharmacol*, 63(6):537–46. doi:10.1007/s00228-007-0288-2 PMID:17370067

Glei M, Kirmse A, Habermann N, Persin C, Pool-Zobel BL (2006). Bread enriched with green coffee extract has chemoprotective and antigenotoxic activities in human cells. *Nutr Cancer*, 56(2):182–92. doi:10.1207/s15327914nc5602_9 PMID:17474864

Gonthier MP, Verny MA, Besson C, Rémésy C, Scalbert A (2003). Chlorogenic acid bioavailability largely depends on its metabolism by the gut microflora in rats. *J Nutr*, 133(6):1853–9. PMID:12771329

Goodman MT, Tung KH, McDuffie K, Wilkens LR, Donlon TA (2003). Association of caffeine intake and CYP1A2 genotype with ovarian cancer. *Nutr Cancer*, 46(1):23–9. doi:10.1207/S15327914NC4601_03 PMID:12925300

Goto A, Chen BH, Song Y, Cauley J, Cummings SR, Farhat GN, et al. (2014). Age, body mass, usage of exogenous estrogen, and lifestyle factors in relation to circulating sex hormone-binding globulin concentrations in postmenopausal women. *Clin Chem*, 60(1):174–85. doi:10.1373/clinchem.2013.207217 PMID:24048437

Goto A, Song Y, Chen BH, Manson JE, Buring JE, Liu S (2011). Coffee and caffeine consumption in relation to sex hormone-binding globulin and risk of type 2 diabetes in postmenopausal women. *Diabetes*, 60(1):269–75. doi:10.2337/db10-1193 PMID:21030499

Graf U, Würgler FE (1986). Investigation of coffee in Drosophila genotoxicity tests. *Food Chem Toxicol*, 24(8):835–42. doi:10.1016/0278-6915(86)90073-6 PMID:3096848

Grubben MJ, Van Den Braak CC, Broekhuizen R, De Jong R, Van Rijt L, De Ruijter E, et al. (2000). The effect of unfiltered coffee on potential biomarkers for colonic cancer risk in healthy volunteers: a randomized trial. *Aliment Pharmacol Ther*, 14(9):1181–90. doi:10.1046/j.1365-2036.2000.00826.x PMID:10971235

Guo Y, Niu K, Okazaki T, Wu H, Yoshikawa T, Ohrui T, et al. (2014). Coffee treatment prevents the progression of sarcopenia in aged mice in vivo and in vitro. *Exp Gerontol*, 50:1–8. doi:10.1016/j.exger.2013.11.005 PMID:24269808

Halliwell B, Long LH, Yee TP, Lim S, Kelly R (2004). Establishingbiomarkersofoxidativestress:themeasurement of hydrogen peroxide in human urine. *Curr Med Chem*, 11(9):1085–92. doi:10.2174/0929867043365404 PMID:15134507

Higdon JV, Frei B (2006). Coffee and health: a review of recent human research. *Crit Rev Food Sci Nutr*, 46(2):101–23. doi:10.1080/10408390500400009 PMID:16507475

Higgins LG, Cavin C, Itoh K, Yamamoto M, Hayes JD (2008). Induction of cancer chemopreventive enzymes by coffee is mediated by transcription factor Nrf2. Evidence that the coffee-specific diterpenes cafestol and kahweol confer protection against acrolein. *Toxicol Appl Pharmacol*, 226(3):328–37. doi:10.1016/j.taap.2007.09.018 PMID:18028974

Hiramoto K, Kida T, Kikugawa K (2002). Increased urinary hydrogen peroxide levels caused by coffee drinking. *Biol Pharm Bull*, 25(11):1467–71. doi:10.1248/bpb.25.1467 PMID:12419961

Hiramoto K, Li X, Makimoto M, Kato T, Kikugawa K (1998). Identification of hydroxyhydroquinone in coffee as a generator of reactive oxygen species that break DNA single strands. *Mutat Res*, 419(1–3):43–51. doi:10.1016/S1383-5718(98)00123-5 PMID:9804887

Hirsch BA, Sentz KK, McGue M (1992). Genetic and environmental influences on baseline SCE. *Environ Mol Mutagen*, 20(1):2–11. doi:10.1002/em.2850200103 PMID:1639080

Hoelzl C, Knasmüller S, Wagner KH, Elbling L, Huber W, Kager N, et al. (2010). Instant coffee with high chlorogenic acid levels protects humans against oxidative damage of macromolecules. *Mol Nutr Food Res*, 54(12):1722–33. doi:10.1002/mnfr.201000048 PMID:20589860

Hori A, Kasai H, Kawai K, Nanri A, Sato M, Ohta M, et al. (2014). Coffee intake is associated with lower levels of oxidative DNA damage and decreasing body iron storage in healthy women. *Nutr Cancer*, 66(6):964–9. doi:10.1080/01635581.2014.932398 PMID:25062326

Hoshiyama Y, Kono S, Sasaba T, Shigematsu T, Kawaguchi T (2000). Relation of cigarette smoking, alcohol use, and dietary habits to colon adenomas: a case-control study in Saitama, Japan. *Asian Pac J Cancer Prev*, 1(2):139–46. PMID:12718681

Hossain MZ, Gilbert SF, Patel K, Ghosh S, Bhunia AK, Kern SE (2013). Biological clues to potent DNA-damaging activities in food and flavoring. *Food Chem Toxicol*, 55:557–67. doi:10.1016/j.fct.2013.01.058 PMID:23402862

Huber WW, Prustomersky S, Delbanco E, Uhl M, Scharf G, Turesky RJ, et al. (2002). Enhancement of the chemoprotective enzymes glucuronosyl transferase and glutathione transferase in specific organs of the rat by the coffee components kahweol and cafestol. *Arch Toxicol*, 76(4):209–17. doi:10.1007/s00204-002-0322-1 PMID:12029384

Huber WW, Rossmanith W, Grusch M, Haslinger E, Prustomersky S, Peter-Vörösmarty B, et al. (2008). Effects of coffee and its chemopreventive components kahweol and cafestol on cytochrome P450 and sulfotransferase in rat liver. *Food Chem Toxicol*, 46(4):1230–8. doi:10.1016/j.fct.2007.09.094 PMID:17983700

Huber WW, Scharf G, Nagel G, Prustomersky S, Schulte-Hermann R, Kaina B (2003). Coffee and its chemopreventive components kahweol and cafestol increase the activity of O^6-methylguanine-DNA methyltransferase in rat liver–comparison with phase II xenobiotic metabolism. *Mutat Res*, 522(1–2):57–68. doi:10.1016/S0027-5107(02)00264-6 PMID:12517412

Huber WW, Teitel CH, Coles BF, King RS, Wiese FW, Kaderlik KR, et al. (2004). Potential chemoprotective effects of the coffee components kahweol and cafestol palmitates via modification of hepatic N-acetyltransferase and glutathione S-transferase activities. *Environ Mol Mutagen*, 44(4):265–76. doi:10.1002/em.20052 PMID:15468054

IARC (1991). Coffee, tea, mate, methylxanthines and methylglyoxal. *IARC Monogr Eval Carcinog Risks Hum*, 51:1–513. Available from: http://publications.iarc.fr/69 PMID:1674554

Imatoh T, Kamimura S, Miyazaki M (2015). Coffee but not green tea consumption is associated with prevalence and severity of hepatic steatosis: the impact on leptin level. *Eur J Clin Nutr*, 69(9):1023–7. doi:10.1038/ejcn.2015.23 PMID:25804274

Imatoh T, Tanihara S, Miyazaki M, Momose Y, Uryu Y, Une H (2011). Coffee consumption but not green tea consumption is associated with adiponectin levels in Japanese males. *Eur J Nutr*, 50(4):279–84. doi:10.1007/s00394-010-0136-5 PMID:20953616

Ishikawa T, Takahashi S, Morita K, Okinaga H, Teramoto T (2014). Induction of AhR-mediated gene transcription by coffee. *PLoS One*, 9(7):e102152 doi:10.1371/journal.pone.0102152 PMID:25007155

Ishizaka Y, Yamakado M, Toda A, Tani M, Ishizaka N (2013). Relationship between coffee consumption, oxidant status, and antioxidant potential in the Japanese general population. *Clin Chem Lab Med*, 51(10):1951–9. doi:10.1515/cclm-2013-0146 PMID:23612669

Isshiki M, Ohta H, Tamura H (2013). Coffee reduces SULT1E1 expression in human colon carcinoma Caco-2 cells. *Biol Pharm Bull*, 36(2):299–304. doi:10.1248/bpb.b12-00902 PMID:23370358

Jia H, Aw W, Egashira K, Takahashi S, Aoyama S, Saito K, et al. (2014). Coffee intake mitigated inflammation and obesity-induced insulin resistance in skeletal muscle of high-fat diet-induced obese mice. *Genes Nutr*, 9(3):389 doi:10.1007/s12263-014-0389-3 PMID:24599575

Jiang X, Zhang D, Jiang W (2014). Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies. *Eur J Nutr*, 53(1):25–38. doi:10.1007/s00394-013-0603-x PMID:24150256

Johansson F, Lagerqvist A, Filippi S, Palitti F, Erixon K, Helleday T, et al. (2006). Caffeine delays replication fork progression and enhances UV-induced homologous recombination in Chinese hamster cell lines. *DNA Repair (Amst)*, 5(12):1449–58. doi:10.1016/j.dnarep.2006.07.005 PMID:16968677

Johansson MA, Knize MG, Jägerstad M, Felton JS (1995). Characterization of mutagenic activity in instant hot beverage powders. *Environ Mol Mutagen*, 25(2):154–61. doi:10.1002/em.2850250209 PMID:7698108

Johnston KL, Clifford MN, Morgan LM (2003). Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. *Am J Clin Nutr*, 78(4):728–33. PMID:14522730

Josse AR, Da Costa LA, Campos H, El-Sohemy A (2012). Associations between polymorphisms in the AHR and CYP1A1-CYP1A2 gene regions and habitual caffeine consumption. *Am J Clin Nutr*, 96(3):665–71. doi:10.3945/ajcn.112.038794 PMID:22854411

Jurewicz J, Radwan M, Sobala W, Radwan P, Jakubowski L, Hawuła W, et al. (2014). Lifestyle factors and sperm aneuploidy. *Reprod Biol*, 14(3):190–9. doi:10.1016/j.repbio.2014.02.002 PMID:25152516

Kalthoff S, Ehmer U, Freiberg N, Manns MP, Strassburg CP (2010). Coffee induces expression of glucuronosyltransferases by the aryl hydrocarbon receptor and Nrf2 in liver and stomach. *Gastroenterology*, 139(5):1699–710. doi:10.1053/j.gastro.2010.06.048 PMID:20600030

Kamimori GH, Karyekar CS, Otterstetter R, Cox DS, Balkin TJ, Belenky GL, et al. (2002). The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. *Int J Pharm*, 234(1–2):159–67. doi:10.1016/S0378-5173(01)00958-9 PMID:11839447

Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Cotreau MM, Harmatz JS, et al. (1997). Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. *J Clin Pharmacol*, 37(8):693–703. doi:10.1002/j.1552-4604.1997.tb04356.x PMID:9378841

Kasai H, Kumeno K, Yamaizumi Z, Nishimura S, Nagao M, Fujita Y, et al. (1982). Mutagenicity of methylglyoxal in coffee. *Gan*, 73(5):681–3. PMID:6762317

Katayama M, Donai K, Sakakibara H, Ohtomo Y, Miyagawa M, Kuroda K, et al. (2014). Coffee consumption delays the hepatitis and suppresses the inflammation related gene expression in the Long-Evans Cinnamon rat. *Clin Nutr*, 33(2):302–10. doi:10.1016/j.clnu.2013.05.006 PMID:23755843

Kato I, Tominaga S, Matsuura A, Yoshii Y, Shirai M, Kobayashi S (1990). A comparative case-control study of colorectal cancer and adenoma. *Jpn J Cancer Res*, 81(11):1101–8. doi:10.1111/j.1349-7006.1990.tb02520.x PMID:2125036

Kato T, Hiramoto K, Kikugawa K (1994). Possible occurrence of new mutagens with the DNA breaking activity in coffee. *Mutat Res*, 306(1):9–17. doi:10.1016/0027-5107(94)90163-5 PMID:7512207

Kauffman FC (2004). Sulfonation in pharmacology and toxicology. *Drug Metab Rev*, 36(3–4):823–43. PMID:15554249

Kawata T, Ito H, Saito M, Uno T, Okayasu R, Liu C, et al. (2005). Caffeine sensitizes nondividing human fibroblasts to x rays by inducing a high frequency of misrepair. *Radiat Res*, 164(4 Pt 2):509–13. doi:10.1667/RR3382.1 PMID:16187758

Kempf K, Herder C, Erlund I, Kolb H, Martin S, Carstensen M, et al. (2010). Effects of coffee consumption on subclinical inflammation and other risk factors for type 2 diabetes: a clinical trial. *Am J Clin Nutr*, 91(4):950–7. doi:10.3945/ajcn.2009.28548 PMID:20181814

Khalaf N, White D, Kanwal F, Ramsey D, Mittal S, Tavakoli-Tabasi S, et al. (2015). Coffee and caffeine are associated with decreased risk of advanced hepatic fibrosis among patients with hepatitis C. *Clin Gastroenterol*

Hepatol, 13(8):1521, e3. doi:10.1016/j.cgh.2015.01.030 PMID:25777972

Kiyohara C, Hirohata T (1997). Environmental factors and aryl hydrocarbon hydroxylase activity (CYP1A1 phenotype) in human lymphocytes. *J Epidemiol*, 7(4):244–50. doi:10.2188/jea.7.244 PMID:9465551

Kobayashi M, Matsuda Y, Iwai H, Hiramitsu M, Inoue T, Katagiri T, et al. (2012). Coffee improves insulin-stimulated Akt phosphorylation in liver and skeletal muscle in diabetic KK-A(y) mice. *J Nutr Sci Vitaminol (Tokyo)*, 58(6):408–14. doi:10.3177/jnsv.58.408 PMID:23419399

Konishi Y, Kobayashi S (2004). Transepithelial transport of chlorogenic acid, caffeic acid, and their colonic metabolites in intestinal caco-2 cell monolayers. *J Agric Food Chem*, 52(9):2518–26. doi:10.1021/jf035407c PMID:15113150

Kono S, Shinchi K, Ikeda N, Yanai F, Imanishi K (1991). Physical activity, dietary habits and adenomatous polyps of the sigmoid colon: a study of self-defense officials in Japan. *J Clin Epidemiol*, 44(11):1255–61. doi:10.1016/0895-4356(91)90158-6 PMID:1941019

Kosugi A, Nagao M, Suwa Y, Wakabayashi K, Sugimura T (1983). Roasting coffee beans produces compounds that induce prophage lambda in E. coli and are mutagenic in *E. coli* and *S. typhimurium*. *Mutat Res*, 116(3–4):179–84. doi:10.1016/0165-1218(83)90058-7 PMID:6220221

Kot M, Daniel WA (2008a). Relative contribution of rat cytochrome P450 isoforms to the metabolism of caffeine: the pathway and concentration dependence. *Biochem Pharmacol*, 75(7):1538–49. doi:10.1016/j.bcp.2007.12.017 PMID:18279840

Kot M, Daniel WA (2008b). Caffeine as a marker substrate for testing cytochrome P450 activity in human and rat. *Pharmacol Rep*, 60(6):789–97. PMID:19211970

Kotani K, Sakane N, Yamada T, Taniguchi N (2010). Association between coffee consumption and the estimated glomerular filtration rate in the general Japanese population: preliminary data regarding C-reactive protein concentrations. *Clin Chem Lab Med*, 48(12):1773–6. doi:10.1515/CCLM.2010.347 PMID:20731617

Kotowski U, Heiduschka G, Seemann R, Eckl-Dorna J, Schmid R, Kranebitter V, et al. (2015). Effect of the coffee ingredient cafestol on head and neck squamous cell carcinoma cell lines. *Strahlenther Onkol*, 191(6):511–7. doi:10.1007/s00066-014-0807-x PMID:25575980

Kotsopoulos J, Eliassen AH, Missmer SA, Hankinson SE, Tworoger SS (2009a). Relationship between caffeine intake and plasma sex hormone concentrations in premenopausal and postmenopausal women. *Cancer*, 115(12):2765–74. doi:10.1002/cncr.24328 PMID:19384973

Kotsopoulos J, Ghadirian P, El-Sohemy A, Lynch HT, Snyder C, Daly M, et al. (2007). The CYP1A2 genotype modifies the association between coffee consumption and breast cancer risk among BRCA1 mutation carriers. *Cancer Epidemiol Biomarkers Prev*, 16(5):912–6. doi:10.1158/1055-9965.EPI-06-1074 PMID:17507615

Kotsopoulos J, Vitonis AF, Terry KL, De Vivo I, Cramer DW, Hankinson SE, et al. (2009b). Coffee intake, variants in genes involved in caffeine metabolism, and the risk of epithelial ovarian cancer. *Cancer Causes Control*, 20(3):335–44. doi:10.1007/s10552-008-9247-1 PMID:18941913

Kotyczka C, Boettler U, Lang R, Stiebitz H, Bytof G, Lantz I, et al. (2011). Dark roast coffee is more effective than light roast coffee in reducing body weight, and in restoring red blood cell vitamin E and glutathione concentrations in healthy volunteers. *Mol Nutr Food Res*, 55(10):1582–6. doi:10.1002/mnfr.201100248 PMID:21809439

Lafay S, Morand C, Manach C, Besson C, Scalbert A (2006). Absorption and metabolism of caffeic acid and chlorogenic acid in the small intestine of rats. *Br J Nutr*, 96(1):39–46. doi:10.1079/BJN20061714 PMID:16869989

Lang R, Wahl A, Skurk T, Yagar EF, Schmiech L, Eggers R, et al. (2010). Development of a hydrophilic liquid interaction chromatography-high-performance liquid chromatography-tandem mass spectrometry based stable isotope dilution analysis and pharmacokinetic studies on bioactive pyridines in human plasma and urine after coffee consumption. *Anal Chem*, 82(4):1486–97. doi:10.1021/ac902616k PMID:20073472

Le Marchand L, Franke AA, Custer L, Wilkens LR, Cooney RV (1997). Lifestyle and nutritional correlates of cytochrome CYP1A2 activity: inverse associations with plasma lutein and alpha-tocopherol. *Pharmacogenetics*, 7(1):11–9. doi:10.1097/00008571-199702000-00002 PMID:9110357

Lee WC, Neugut AI, Garbowski GC, Forde KA, Treat MR, Waye JD, et al. (1993). Cigarettes, alcohol, coffee, and caffeine as risk factors for colorectal adenomatous polyps. *Ann Epidemiol*, 3(3):239–44. doi:10.1016/1047-2797(93)90025-Y PMID:8275195

Lee WJ, Zhu BT (2006). Inhibition of DNA methylation by caffeic acid and chlorogenic acid, two common catechol-containing coffee polyphenols. *Carcinogenesis*, 27(2):269–77. doi:10.1093/carcin/bgi206 PMID:16081510

Lee Y, Kang D, Lee SA (2014). Effect of dietary patterns on serum C-reactive protein level. *Nutr Metab Cardiovasc Dis*, 24(9):1004–11. doi:10.1016/j.numecd.2014.05.001 PMID:24998076

Li HR, Habasi M, Xie LZ, Aisa HA (2014). Effect of chlorogenic acid on melanogenesis of B16 melanoma cells. *Molecules*, 19(9):12940–8. doi:10.3390/molecules190912940 PMID:25157464

Liang N, Kitts DD (2014). Antioxidant property of coffee components: assessment of methods that define mechanisms of action. *Molecules*, 19(11):19180–208. doi:10.3390/molecules191119180 PMID:25415479

Liguori A, Hughes JR, Grass JA (1997). Absorption and subjective effects of caffeine from coffee, cola and capsules. *Pharmacol Biochem Behav*, 58(3):721–6. doi:10.1016/S0091-3057(97)00003-8 PMID:9329065

Lina BA, Rutten AA, Woutersen RA (1993). Effect of coffee drinking on cell proliferation in rat urinary bladder epithelium. *Food Chem Toxicol*, 31(12):947–51. doi:10.1016/0278-6915(93)90003-H PMID:8282278

Liu F, Wang X, Wu G, Chen L, Hu P, Ren H, et al. (2015). Coffee consumption decreases risks for hepatic fibrosis and cirrhosis: a meta-analysis. [Research Support, Non-US Gov't.] *PLoS One*, 10(11):e0142457 doi:10.1371/journal.pone.0142457 PMID:26556483

Lodovici M, Caldini S, Luceri C, Bambi F, Boddi V, Dolara P (2005). Active and passive smoking and lifestyle determinants of 8-oxo-7,8-dihydro-2′ -deoxyguanosine levels in human leukocyte DNA. *Cancer Epidemiol Biomarkers Prev*, 14(12):2975–7. doi:10.1158/1055-9965.EPI-04-0906 PMID:16365019

Loftfield E, Shiels MS, Graubard BI, Katki HA, Chaturvedi AK, Trabert B, et al. (2015). Associations of coffee drinking with systemic immune and inflammatory markers. *Cancer Epidemiol Biomarkers Prev*, 24(7):1052–60. doi:10.1158/1055-9965.EPI-15-0038-T PMID:25999212

Long LH, Halliwell B (2000). Coffee drinking increases levels of urinary hydrogen peroxide detected in healthy human volunteers. *Free Radic Res*, 32(5):463–7. doi:10.1080/10715760000300461 PMID:10766414

Lopez-Garcia E, van Dam RM, Qi L, Hu FB (2006). Coffee consumption and markers of inflammation and endothelial dysfunction in healthy and diabetic women. *Am J Clin Nutr*, 84(4):888–93. PMID:17023717

Lovallo WR, Al'Absi M, Blick K, Whitsett TL, Wilson MF (1996). Stress-like adrenocorticotropin responses to caffeine in young healthy men. *Pharmacol Biochem Behav*, 55(3):365–9. doi:10.1016/S0091-3057(96)00105-0 PMID:8951977

Lowcock EC, Cotterchio M, Anderson LN, Boucher BA, El-Sohemy A (2013). High coffee intake, but not caffeine, is associated with reduced estrogen receptor negative and postmenopausal breast cancer risk with no effect modification by CYP1A2 genotype. *Nutr Cancer*, 65(3):398–409. doi:10.1080/01635581.2013.768348 PMID:23530639

Lucero J, Harlow BL, Barbieri RL, Sluss P, Cramer DW (2001). Early follicular phase hormone levels in relation to patterns of alcohol, tobacco, and coffee use. *Fertil Steril*, 76(4):723–9. doi:10.1016/S0015-0282(01)02005-2 PMID:11591405

Ma Y, Gao M, Liu D (2015). Chlorogenic acid improves high fat diet-induced hepatic steatosis and insulin resistance in mice. *Pharm Res*, 32(4):1200–9. doi:10.1007/s11095-014-1526-9 PMID:25248334

MacKenzie T, Comi R, Sluss P, Keisari R, Manwar S, Kim J, et al. (2007). Metabolic and hormonal effects of caffeine: randomized, double-blind, placebo-controlled crossover trial. *Metabolism*, 56(12):1694–8. doi:10.1016/j.metabol.2007.07.013 PMID:17998023

Majer BJ, Hofer E, Cavin C, Lhoste E, Uhl M, Glatt HR, et al. (2005). Coffee diterpenes prevent the genotoxic effects of 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP) and N-nitrosodimethylamine in a human derived liver cell line (HepG2). *Food Chem Toxicol*, 43(3):433–41. doi:10.1016/j.fct.2004.11.009 PMID:15680679

Maki T, Pham NM, Yoshida D, Yin G, Ohnaka K, Takayanagi R, et al. (2010). The relationship of coffee and green tea consumption with high-sensitivity C-reactive protein in Japanese men and women. *Clin Chem Lab Med*, 48(6):849–54. doi:10.1515/CCLM.2010.161 PMID:20441477

Martínez-López S, Sarriá B, Baeza G, Mateos R, Bravo-Clemente L (2014). Pharmacokinetics of caffeine and its metabolites in plasma and urine after consuming a soluble green/roasted coffee blend by healthy subjects. *Food Res Int*, 64:125–33. doi:10.1016/j.foodres.2014.05.043

Matsuda Y, Kobayashi M, Yamauchi R, Ojika M, Hiramitsu M, Inoue T, et al. (2011). Coffee and caffeine improve insulin sensitivity and glucose tolerance in C57BL/6J mice fed a high-fat diet. *Biosci Biotechnol Biochem*, 75(12):2309–15. doi:10.1271/bbb.110452 PMID:22146708

Melamed I, Kark JD, Spirer Z (1990). Coffee and the immune system. *Int J Immunopharmacol*, 12(1):129–34. doi:10.1016/0192-0561(90)90076-Y PMID:2303315

Mišík M, Hoelzl C, Wagner KH, Cavin C, Moser B, Kundi M, et al. (2010). Impact of paper filtered coffee on oxidative DNA-damage: results of a clinical trial. *Mutat Res*, 692(1–2):42–8. doi:10.1016/j.mrfmmm.2010.08.003 PMID:20709087

Miura Y, Furuse T, Yagasaki K (1997). Inhibitory effect of serum from rats administered with coffee on the proliferation and invasion of rat ascites hepatoma cells. *Cytotechnology*, 25(1–3):221–5. doi:10.1023/A:1007915917201 PMID:22358895

Miura Y, Ono K, Okauchi R, Yagasaki K (2004). Inhibitory effect of coffee on hepatoma proliferation and invasion in culture and on tumor growth, metastasis and abnormal lipoprotein profiles in hepatoma-bearing rats. *J Nutr Sci Vitaminol (Tokyo)*, 50(1):38–44. doi:10.3177/jnsv.50.38 PMID:15228216

Modi AA, Feld JJ, Park Y, Kleiner DE, Everhart JE, Liang TJ, et al. (2010). Increased caffeine consumption is associated with reduced hepatic fibrosis. *Hepatology*, 51(1):201–9. doi:10.1002/hep.23279 PMID:20034049

Molloy JW, Calcagno CJ, Williams CD, Jones FJ, Torres DM, Harrison SA (2012). Association of coffee and caffeine consumption with fatty liver disease,

nonalcoholic steatohepatitis, and degree of hepatic fibrosis. *Hepatology*, 55(2):429–36. doi:10.1002/hep.24731 PMID:21987293

Monteiro M, Farah A, Perrone D, Trugo LC, Donangelo C (2007). Chlorogenic acid compounds from coffee are differentially absorbed and metabolized in humans. *J Nutr*, 137(10):2196–201. PMID:17884997

Morakinyo AO, Adekunbi DA, Dada KA, Adegoke OA (2013). Coffee consumption attenuates insulin resistance and glucose intolerance in rats fed on high-sucrose diet. *Niger J Physiol Sci*, 28(2):179–85. PMID:24937394

Morales E, Porta M, Vioque J, López T, Mendez MA, Pumarega J, et al.; PANKRAS II Study Group (2007). Food and nutrient intakes and K-ras mutations in exocrine pancreatic cancer. *J Epidemiol Community Health*, 61(7):641–9. doi:10.1136/jech.2007.060632 PMID:17568059

Morii H, Kuboyama A, Nakashima T, Kawai K, Kasai H, Tamae K, et al. (2009). Effects of instant coffee consumption on oxidative DNA damage, DNA repair, and redox system in mouse liver. *J Food Sci*, 74(6):H155–61. doi:10.1111/j.1750-3841.2009.01192.x PMID:19723199

Moura-Nunes N, Perrone D, Farah A, Donangelo CM (2009). The increase in human plasma antioxidant capacity after acute coffee intake is not associated with endogenous non-enzymatic antioxidant components. *Int J Food Sci Nutr*, 60(Suppl 6): 173–81. doi:10.1080/09637480903158893 PMID:19750404

Mursu J, Voutilainen S, Nurmi T, Alfthan G, Virtanen JK, Rissanen TH, et al. (2005). The effects of coffee consumption on lipid peroxidation and plasma total homocysteine concentrations: a clinical trial. *Free Radic Biol Med*, 38(4):527–34. doi:10.1016/j.freeradbiomed.2004.11.025 PMID:15649655

Muscat S, Pelka J, Hegele J, Weigle B, Münch G, Pischetsrieder M (2007). Coffee and Maillard products activate NF-kappaB in macrophages via H2O2 production. *Mol Nutr Food Res*, 51(5):525–35. doi:10.1002/mnfr.200600254 PMID:17427264

Nagao M, Fujita Y, Wakabayashi K, Nukaya H, Kosuge T, Sugimura T (1986). Mutagens in coffee and other beverages. *Environ Health Perspect*, 67:89–91. doi:10.1289/ehp.866789 PMID:3757962

Nagao M, Takahashi Y, Yamanaka H, Sugimura T (1979). Mutagens in coffee and tea. *Mutat Res*, 68(2):101–6. doi:10.1016/0165-1218(79)90137-X PMID:390384

Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S (2001). Diet and colorectal adenoma in Japanese males and females. *Dis Colon Rectum*, 44(1):105–11. doi:10.1007/BF02234831 PMID:11805576

Nakasato F, Nakayasu M, Fujita Y, Nagao M, Terada M, Sugimura T (1984). Mutagenicity of instant coffee on cultured Chinese hamster lung cells. *Mutat Res*, 141(2):109–12. doi:10.1016/0165-7992(84)90020-4 PMID:6493267

Nardini M, Cirillo E, Natella F, Scaccini C (2002). Absorption of phenolic acids in humans after coffee consumption. *J Agric Food Chem*, 50(20):5735–41. doi:10.1021/jf0257547 PMID:12236707

Natella F, Nardini M, Belelli F, Scaccini C (2007). Coffee drinking induces incorporation of phenolic acids into LDL and increases the resistance of LDL to ex vivo oxidation in humans. *Am J Clin Nutr*, 86(3):604–9. PMID:17823423

Natella F, Nardini M, Giannetti I, Dattilo C, Scaccini C (2002). Coffee drinking influences plasma antioxidant capacity in humans. *J Agric Food Chem*, 50(21):6211–6. doi:10.1021/jf025768c PMID:12358504

Natella F, Scaccini C (2012). Role of coffee in modulation of diabetes risk. *Nutr Rev*, 70(4):207–17. doi:10.1111/j.1753-4887.2012.00470.x PMID:22458694

Ochiai R, Chikama A, Kataoka K, Tokimitsu I, Maekawa Y, Ohishi M, et al. (2009). Effects of hydroxyhydroquinone-reduced coffee on vasoreactivity and blood pressure. *Hypertens Res*, 32(11):969–74. doi:10.1038/hr.2009.132 PMID:19713967

Oh JH, Lee JT, Yang ES, Chang JS, Lee DS, Kim SH, et al. (2009). The coffee diterpene kahweol induces apoptosis in human leukemia U937 cells through down-regulation of Akt phosphorylation and activation of JNK. *Apoptosis*, 14(11):1378–86. doi:10.1007/s10495-009-0407-x PMID:19768546

Okamura S, Suzuki K, Yanase M, Koizumi M, Tamura HO (2005). The effects of coffee on conjugation reactions in human colon carcinoma cells. *Biol Pharm Bull*, 28(2):271–4. doi:10.1248/bpb.28.271 PMID:15684482

Olsen J, Kronborg O (1993). Coffee, tobacco and alcohol as risk factors for cancer and adenoma of the large intestine. *Int J Epidemiol*, 22(3):398–402. doi:10.1093/ije/22.3.398 PMID:8359954

Olthof MR, van Dijk AE, Deacon CF, Heine RJ, van Dam RM (2011). Acute effects of decaffeinated coffee and the major coffee components chlorogenic acid and trigonelline on incretin hormones. *Nutr Metab (Lond)*, 8(1):10 doi:10.1186/1743-7075-8-10 PMID:21299855

Ozercan IH, Dagli AF, Ustundag B, Ozercan MR, Bahcecioglu IH, Celik H, et al. (2006). Does instant coffee prevent acute liver injury induced by carbon tetrachloride (CCl(4))? *Hepatol Res*, 35(3):163–8. PMID:16740402

Panchal SK, Poudyal H, Waanders J, Brown L (2012). Coffee extract attenuates changes in cardiovascular and hepatic structure and function without decreasing obesity in high-carbohydrate, high-fat diet-fed male rats. *J Nutr*, 142(4):690–7. doi:10.3945/jn.111.153577 PMID:22378327

Paur I, Balstad TR, Blomhoff R (2010). Degree of roasting is the main determinant of the effects of coffee on NF-kappaB and EpRE. *Free Radic Biol Med*, 48(9):1218–27. doi:10.1016/j.freeradbiomed.2010.02.005 PMID:20176103

Pavanello S, Mastrangelo G, Placidi D, Campagna M, Pulliero A, Carta A, et al. (2010). CYP1A2 polymorphisms, occupational and environmental exposures and risk of bladder cancer. *Eur J Epidemiol*, 25(7):491–500. doi:10.1007/s10654-010-9479-8 PMID:20559687

Pham NM, Nanri A, Yasuda K, Kurotani K, Kuwahara K, Akter S, et al. (2015). Habitual consumption of coffee and green tea in relation to serum adipokines: a cross-sectional study. *Eur J Nutr*, 54(2):205–14. doi:10.1007/s00394-014-0701-4 PMID:24752775

Pham NM, Zhenjie W, Morita M, Ohnaka K, Adachi M, Kawate H, et al. (2011). Combined effects of coffee consumption and serum γ-glutamyltransferase on serum C-reactive protein in middle-aged and elderly Japanese men and women. *Clin Chem Lab Med*, 49(10):1661–7. doi:10.1515/CCLM.2011.652 PMID:21675939

Pietrocola F, Malik SA, Mariño G, Vacchelli E, Senovilla L, Chaba K, et al. (2014). Coffee induces autophagy in vivo. *Cell Cycle*, 13(12):1987–94. doi:10.4161/cc.28929 PMID:24769862

Ping J, Wang JF, Liu L, Yan YE, Liu F, Lei YY, et al. (2014). Prenatal caffeine ingestion induces aberrant DNA methylation and histone acetylation of steroidogenic factor 1 and inhibits fetal adrenal steroidogenesis. *Toxicology*, 321:53–61. doi:10.1016/j.tox.2014.03.011 PMID:24717552

Porta M, López T, Pumarega J, Jariod M, Crous-Bou M, Marco E, et al.; PANKRAS II Study Group (2009). In pancreatic ductal adenocarcinoma blood concentrations of some organochlorine compounds and coffee intake are independently associated with *KRAS* mutations. *Mutagenesis*, 24(6):513–21. doi:10.1093/mutage/gep037 PMID:19797353

Porta M, Malats N, Guarner L, Carrato A, Rifà J, Salas A, et al.; PANKRAS II Study Group (1999). Association between coffee drinking and K-ras mutations in exocrine pancreatic cancer. *J Epidemiol Community Health*, 53(11):702–9. doi:10.1136/jech.53.11.702 PMID:10656099

Poyrazoglu OK, Bahcecioglu IH, Ataseven H, Metin K, Dagli AF, Yalniz M, et al. (2008). Effect of unfiltered coffee on carbon tetrachloride-induced liver injury in rats. *Inflammation*, 31(6):408–13. doi:10.1007/s10753-008-9092-0 PMID:19009339

Rabstein S, Brüning T, Harth V, Fischer HP, Haas S, Weiss T, et al.; GENICA Network (2010). N-acetyltransferase 2, exposure to aromatic and heterocyclic amines, and receptor-defined breast cancer. *Eur J Cancer Prev*, 19(2):100–9. doi:10.1097/CEJ.0b013e328333fbb7 PMID:19996973

Ramlau-Hansen CH, Thulstrup AM, Bonde JP, Olsen J, Bech BH (2008). Semen quality according to prenatal coffee and present caffeine exposure: two decades of follow-up of a pregnancy cohort. *Hum Reprod*, 23(12):2799–805. doi:10.1093/humrep/den331 PMID:18757446

Rebello SA, Chen CH, Naidoo N, Xu W, Lee J, Chia KS, et al. (2011). Coffee and tea consumption in relation to inflammation and basal glucose metabolism in a multi-ethnic Asian population: a cross-sectional study. *Nutr J*, 10(1):61 doi:10.1186/1475-2891-10-61 PMID:21631956

Rechner AR, Spencer JP, Kuhnle G, Hahn U, Rice-Evans CA (2001). Novel biomarkers of the metabolism of caffeic acid derivatives in vivo. *Free Radic Biol Med*, 30(11):1213–22. doi:10.1016/S0891-5849(01)00506-8 PMID:11368919

Redeuil K, Smarrito-Menozzi C, Guy P, Rezzi S, Dionisi F, Williamson G, et al. (2011). Identification of novel circulating coffee metabolites in human plasma by liquid chromatography-mass spectrometry. *J Chromatogr A*, 1218(29):4678–88. doi:10.1016/j.chroma.2011.05.050 PMID:21676405

Reidy JA, Annest JL, Chen AT, Welty TK (1988). Increased sister chromatid exchange associated with smoking and coffee consumption. *Environ Mol Mutagen*, 12(3):311–8. doi:10.1002/em.2860120305 PMID:3169009

Renouf M, Guy P, Marmet C, Longet K, Fraering AL, Moulin J, et al. (2010a). Plasma appearance and correlation between coffee and green tea metabolites in human subjects. *Br J Nutr*, 104(11):1635–40. doi:10.1017/S0007114510002709 PMID:20691128

Renouf M, Guy PA, Marmet C, Fraering AL, Longet K, Moulin J, et al. (2010b). Measurement of caffeic and ferulic acid equivalents in plasma after coffee consumption: small intestine and colon are key sites for coffee metabolism. *Mol Nutr Food Res*, 54(6):760–6. doi:10.1002/mnfr.200900056 PMID:19937852

Renouf M, Marmet C, Giuffrida F, Lepage M, Barron D, Beaumont M, et al. (2014). Dose-response plasma appearance of coffee chlorogenic and phenolic acids in adults. *Mol Nutr Food Res*, 58(2):301–9. doi:10.1002/mnfr.201300349 PMID:24039147

Revuelta-Iniesta R, Al-Dujaili EA (2014). Consumption of green coffee reduces blood pressure and body composition by influencing 11β-HSD1 enzyme activity in healthy individuals: a pilot crossover study using green and black coffee. *Biomed Res Int*, 2014:482704 doi:10.1155/2014/482704 PMID:25133164

Ricketts ML, Boekschoten MV, Kreeft AJ, Hooiveld GJ, Moen CJ, Müller M, et al. (2007). The cholesterol-raising factor from coffee beans, cafestol, as an agonist ligand for the farnesoid and pregnane X receptors. *Mol Endocrinol*, 21(7):1603–16. doi:10.1210/me.2007-0133 PMID:17456796

Robertson TM, Clifford MN, Penson S, Chope G, Robertson MD (2015). A single serving of caffeinated coffee impairs postprandial glucose metabolism in overweight men. *Br J Nutr*, 114(8):1218–25. doi:10.1017/S0007114515002640 PMID:26316273

Rosendahl AH, Perks CM, Zeng L, Markkula A, Simonsson M, Rose C, et al. (2015). Caffeine and caffeic acid inhibit growth and modify estrogen receptor and insulin-like growth factor I receptor levels in human breast cancer. *Clin Cancer Res*, 21(8):1877–87. doi:10.1158/1078-0432.CCR-14-1748 PMID:25691730

Ruiz-Laguna J, Pueyo C (1999). Hydrogen peroxide and coffee induce G:C–>T:A transversions in the lacI gene of catalase-defective *Escherichia coli*. *Mutagenesis*, 14(1):95–102. doi:10.1093/mutage/14.1.95 PMID:10474829

Rustenbeck I, Lier-Glaubitz V, Willenborg M, Eggert F, Engelhardt U, Jörns A (2014). Effect of chronic coffee consumption on weight gain and glycaemia in a mouse model of obesity and type 2 diabetes. *Nutr Diabetes*, 4(6):e123 doi:10.1038/nutd.2014.19 PMID:24979152

Saab S, Mallam D, Cox GA 2nd, Tong MJ (2014). Impact of coffee on liver diseases: a systematic review. *Liver Int*, 34(4):495–504. doi:10.1111/liv.12304 PMID:24102757

Sajja KC, El-Serag HB, Thrift AP (2016). Coffee or tea, hot or cold, are not associated with risk of Barrett's esophagus. *Clin Gastroenterol Hepatol*, 14(5):769–72. doi:10.1016/j.cgh.2015.12.007 PMID:26681488

Sakamoto W, Isomura H, Fujie K, Nishihira J, Ozaki M, Yukawa S (2003). Coffee increases levels of urinary 8-hydroxydeoxyguanosine in rats. *Toxicology*, 183(1–3):255–63. doi:10.1016/S0300-483X(02)00544-9 PMID:12504356

Sakamoto W, Nishihira J, Fujie K, Iizuka T, Handa H, Ozaki M, et al. (2001). Effect of coffee consumption on bone metabolism. *Bone*, 28(3):332–6. doi:10.1016/S8756-3282(00)00444-0 PMID:11248666

Sakamoto W, Nishihira J, Fujie K, Mizuno S, Ozaki M, Yukawa S (2000). Coffee and fitness-coffee suppresses lipopolysaccharide-induced liver injury in rats. *J Nutr Sci Vitaminol (Tokyo)*, 46(6):316–20. doi:10.3177/jnsv.46.316 PMID:11227804

Salomone F, Li Volti G, Vitaglione P, Morisco F, Fogliano V, Zappalà A, et al. (2014). Coffee enhances the expression of chaperones and antioxidant proteins in rats with nonalcoholic fatty liver disease. *Transl Res*, 163(6):593–602. doi:10.1016/j.trsl.2013.12.001 PMID:24365744

Santa-Maria A, López A, Díaz MM, Ortíz AI, Caballo C (2001). Sister chromatid exchange induced by several types of coffees in Chinese hamster ovary cells. *Teratog Carcinog Mutagen*, 21(3):207–11. doi:10.1002/tcm.1009 PMID:11301415

Saruwatari A, Isshiki M, Tamura H (2008). Inhibitory effects of various beverages on the sulfoconjugation of 17beta-estradiol in human colon carcinoma Caco-2 cells. *Biol Pharm Bull*, 31(11):2131–6. doi:10.1248/bpb.31.2131 PMID:18981586

Sauer T, Raithel M, Kressel J, Münch G, Pischetsrieder M (2013). Activation of the transcription factor Nrf2 in macrophages, Caco-2 cells and intact human gut tissue by Maillard reaction products and coffee. *Amino Acids*, 44(6):1427–39. doi:10.1007/s00726-012-1222-1 PMID:22274738

Sauer T, Raithel M, Kressel J, Muscat S, Münch G, Pischetsrieder M (2011). Nuclear translocation of NF-κB in intact human gut tissue upon stimulation with coffee and roasting products. *Food Funct*, 2(9):529–40. doi:10.1039/c1fo10055f PMID:21904755

Sbrana I, Luccini A, Landi S, Barale R (1995). Enhancement of SCE frequency by alpha-naphthoflavone in cultured lymphocytes in relation to environmental factors. *Environ Mol Mutagen*, 26(4):331–7. doi:10.1002/em.2850260409 PMID:8575422

Schlegel R, Pardee AB (1986). Caffeine-induced uncoupling of mitosis from the completion of DNA replication in mammalian cells. *Science*, 232(4755):1264–6. doi:10.1126/science.2422760 PMID:2422760

Schmid TE, Eskenazi B, Baumgartner A, Marchetti F, Young S, Weldon R, et al. (2007). The effects of male age on sperm DNA damage in healthy non-smokers. *Hum Reprod*, 22(1):180–7. doi:10.1093/humrep/del338 PMID:17053003

Shashni B, Sharma K, Singh R, Sakharkar KR, Dhillon SK, Nagasaki Y, et al. (2013). Coffee component hydroxyl hydroquinone (HHQ) as a putative ligand for PPAR gamma and implications in breast cancer. *BMC Genomics*, 14(Suppl 5):S6. doi:10.1186/1471-2164-14-S5-S6 PMID:24564733

Shearer J, Sellars EA, Farah A, Graham TE, Wasserman DH (2007). Effects of chronic coffee consumption on glucose kinetics in the conscious rat. *Can J Physiol Pharmacol*, 85(8):823–30. doi:10.1139/Y07-070 PMID:17901893

Shen H, Rodriguez AC, Shiani A, Lipka S, Shahzad G, Kumar A, et al. (2016). Association between caffeine consumption and nonalcoholic fatty liver disease: a systemic review and meta-analysis. [Review.] *Therap Adv Gastroenterol*, 9(1):113–20. doi:10.1177/1756283X15593700 PMID:26770272

Shim JS, Kang MH, Kim YH, Roh JK, Roberts C, Lee IP (1995). Chemopreventive effect of green tea (Camellia sinensis) among cigarette smokers. *Cancer Epidemiol Biomarkers Prev*, 4(4):387–91. PMID:7655335

Shim JS, Lee HK, Kim YH, Roh JK, Anderson D (1989). Sister-chromatid exchanges in 52 Korean women living in the vicinity of an industrial complex. *Mutat Res*, 224(4):511–5. doi:10.1016/0165-1218(89)90078-5 PMID:2586547

Shin JW, Wang JH, Kang JK, Son CG (2010). Experimental evidence for the protective effects of coffee against liver fibrosis in SD rats. *J Sci Food Agric*, 90(3):450–5. PMID:20355067

Singh S, Singh K, Gupta SP, Patel DK, Singh VK, Singh RK, et al. (2009). Effect of caffeine on the expression of cytochrome P450 1A2, adenosine A2A receptor and dopamine transporter in control and 1-methyl 4-phenyl 1, 2, 3, 6-tetrahydropyridine treated mouse

striatum. *Brain Res*, 1283:115–26. doi:10.1016/j.brainres.2009.06.002 PMID:19520064

Sinha RA, Farah BL, Singh BK, Siddique MM, Li Y, Wu Y, et al. (2014). Caffeine stimulates hepatic lipid metabolism by the autophagy-lysosomal pathway in mice. *Hepatology*, 59(4):1366–80. doi:10.1002/hep.26667 PMID:23929677

Sisti JS, Hankinson SE, Caporaso NE, Gu F, Tamimi RM, Rosner B, et al. (2015). Caffeine, coffee, and tea intake and urinary estrogens and estrogen metabolites in premenopausal women. *Cancer Epidemiol Biomarkers Prev*, 24(8):1174–83. doi:10.1158/1055-9965.EPI-15-0246 PMID:26063478

Skinner TL, Jenkins DG, Leveritt MD, McGorm A, Bolam KA, Coombes JS, et al. (2014). Factors influencing serum caffeine concentrations following caffeine ingestion. *J Sci Med Sport*, 17(5):516–20. doi:10.1016/j.jsams.2013.07.006 PMID:23932441

Slattery ML, Kampman E, Samowitz W, Caan BJ, Potter JD (2000). Interplay between dietary inducers of GST and the GSTM-1 genotype in colon cancer. *Int J Cancer*, 87(5):728–33. doi:10.1002/1097-0215(20000901)87:5<728::AID-IJC16>3.0.CO;2-G PMID:10925368

Smith DF, MacGregor JT, Hiatt RA, Hooper NK, Wehr CM, Peters B, et al. (1990). Micronucleated erythrocytes as an index of cytogenetic damage in humans: demographic and dietary factors associated with micronucleated erythrocytes in splenectomized subjects. *Cancer Res*, 50(16):5049–54. PMID:2379170

Song SJ, Choi S, Park T (2014). Decaffeinated green coffee bean extract attenuates diet-induced obesity and insulin resistance in mice. *Evid Based Complement Alternat Med*, 2014:718379 doi:10.1155/2014/718379 PMID:24817902

Stalmach A, Mullen W, Barron D, Uchida K, Yokota T, Cavin C, et al. (2009). Metabolite profiling of hydroxycinnamate derivatives in plasma and urine after the ingestion of coffee by humans: identification of biomarkers of coffee consumption. *Drug Metab Dispos*, 37(8):1749–58. doi:10.1124/dmd.109.028019 PMID:19460943

Stalmach A, Steiling H, Williamson G, Crozier A (2010). Bioavailability of chlorogenic acids following acute ingestion of coffee by humans with an ileostomy. *Arch Biochem Biophys*, 501(1):98–105. doi:10.1016/j.abb.2010.03.005 PMID:20226754

Steinkellner H, Hoelzl C, Uhl M, Cavin C, Haidinger G, Gsur A, et al. (2005). Coffee consumption induces GSTP in plasma and protects lymphocytes against (+/-)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide induced DNA-damage: results of controlled human intervention trials. *Mutat Res*, 591(1–2):264–75. doi:10.1016/j.mrfmmm.2005.04.016 PMID:16099480

Stich HF, Dunn BP, Pignatelli B, Ohshima H, Bartsch H (1984). Dietary phenolics and betel nut extracts as modifiers of *N*-nitrosation in rat and man. *IARC Sci Publ*, (57):213–22. PMID:6533010

Stich HF, Rosin MP, Bryson L (1982). Inhibition of mutagenicity of a model nitrosation reaction by naturally occurring phenolics, coffee and tea. *Mutat Res*, 95(2–3):119–28. doi:10.1016/0027-5107(82)90251-2 PMID:6750379

Sulem P, Gudbjartsson DF, Geller F, Prokopenko I, Feenstra B, Aben KK, et al. (2011). Sequence variants at CYP1A1-CYP1A2 and AHR associate with coffee consumption. *Hum Mol Genet*, 20(10):2071–7. doi:10.1093/hmg/ddr086 PMID:21357676

Suwa Y, Nagao M, Kosugi A, Sugimura T (1982). Sulfite suppresses the mutagenic property of coffee. *Mutat Res*, 102(4):383–91. doi:10.1016/0165-1218(82)90101-X PMID:6217422

Svartberg J, Midtby M, Bønaa KH, Sundsfjord J, Joakimsen RM, Jorde R (2003). The associations of age, lifestyle factors and chronic disease with testosterone in men: the Tromsø Study. *Eur J Endocrinol*, 149(2):145–52. doi:10.1530/eje.0.1490145 PMID:12887292

Tai J, Cheung S, Chan E, Hasman D (2010). Antiproliferation effect of commercially brewed coffees on human ovarian cancer cells in vitro. *Nutr Cancer*, 62(8):1044–57. doi:10.1080/01635581.2010.492083 PMID:21058192

Tan Y, Liu J, Deng Y, Cao H, Xu D, Cu F, et al. (2012). Caffeine-induced fetal rat over-exposure to maternal glucocorticoid and histone methylation of liver IGF-1 might cause skeletal growth retardation. *Toxicol Lett*, 214(3):279–87. doi:10.1016/j.toxlet.2012.09.007 PMID:22995397

Tsioufis C, Dimitriadis K, Vasiliadou C, Taxiarchou E, Vezali E, Tsiamis E, et al. (2006). Heavy coffee consumption in conjunction with smoking is accompanied by increased inflammatory processes and impaired thrombosis/fibrinolysis system in essential hypertensive subjects. *J Hum Hypertens*, 20(6):470–2. doi:10.1038/sj.jhh.1002014 PMID:16554843

Tucker JD, Taylor RT, Christensen ML, Strout CL, Hanna ML (1989). Cytogenetic response to coffee in Chinese hamster ovary AUXB1 cells and human peripheral lymphocytes. *Mutagenesis*, 4(5):343–8. doi:10.1093/mutage/4.5.343 PMID:2687627

Turesky RJ, Richoz J, Constable A, Curtis KD, Dingley KH, Turteltaub KW (2003). The effects of coffee on enzymes involved in metabolism of the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in rats. *Chem Biol Interact*, 145(3):251–65. doi:10.1016/S0009-2797(03)00022-X PMID:12732453

Uwai Y, Kawasaki T, Nabekura T (2013). Caffeic acid inhibits organic anion transporters OAT1 and OAT3 in rat kidney. *Drug Metabol Drug Interact*, 28(4):247–50. doi:10.1515/dmdi-2013-0050 PMID:24166669

Uwai Y, Ozeki Y, Isaka T, Honjo H, Iwamoto K (2011). Inhibitory effect of caffeic acid on human organic anion transporters hOAT1 and hOAT3: a novel candidate for food-drug interaction. *Drug Metab Pharmacokinet*, 26(5):486–93. doi:10.2133/dmpk.DMPK-11-RG-020 PMID:21697612

van Cruchten ST, de Haan LH, Mulder PP, Kunne C, Boekschoten MV, Katan MB, et al. (2010). The role of epoxidation and electrophile-responsive element-regulated gene transcription in the potentially beneficial and harmful effects of the coffee components cafestol and kahweol. *J Nutr Biochem*, 21(8):757–63. doi:10.1016/j.jnutbio.2009.05.001 PMID:19616929

van de Sandt JJ, van Burgsteden JA, Cage S, Carmichael PL, Dick I, Kenyon S, et al. (2004). In vitro predictions of skin absorption of caffeine, testosterone, and benzoic acid: a multi-centre comparison study. *Regul Toxicol Pharmacol*, 39(3):271–81. doi:10.1016/j.yrtph.2004.02.004 PMID:15135208

van Dijk AE, Olthof MR, Meeuse JC, Seebus E, Heine RJ, van Dam RM (2009). Acute effects of decaffeinated coffee and the major coffee components chlorogenic acid and trigonelline on glucose tolerance. *Diabetes Care*, 32(6):1023–5. doi:10.2337/dc09-0207 PMID:19324944

van Zeeland AA, de Groot AJ, Hall J, Donato F (1999). 8-Hydroxydeoxyguanosine in DNA from leukocytes of healthy adults: relationship with cigarette smoking, environmental tobacco smoke, alcohol and coffee consumption. *Mutat Res*, 439(2):249–57. doi:10.1016/S1383-5718(98)00192-2 PMID:10023075

Vaynshteyn D, Jeong H (2012). Caffeine induces CYP1A2 expression in rat hepatocytes but not in human hepatocytes. *Drug Metab Lett*, 6(2):116–9. doi:10.2174/1872312811206020116 PMID:23167901

Viana AL, Fonseca M, Meireles EL, Duarte SM, Rodrigues MR, Paula FB (2012). Effects of the consumption of caffeinated and decaffeinated instant coffee beverages on oxidative stress induced by strenuous exercise in rats. *Plant Foods Hum Nutr*, 67(1):82–7. doi:10.1007/s11130-011-0267-8 PMID:22173821

Vicente SJ, Ishimoto EY, Cruz RJ, Pereira CD, Torres EA (2011). Increase of the activity of phase II antioxidant enzymes in rats after a single dose of coffee. *J Agric Food Chem*, 59(20):10887–92. doi:10.1021/jf202390x PMID:21942680

Vicente SJ, Ishimoto EY, Torres EA (2014). Coffee modulates transcription factor Nrf2 and highly increases the activity of antioxidant enzymes in rats. *J Agric Food Chem*, 62(1):116–22. doi:10.1021/jf401777m PMID:24328189

Vitaglione P, Morisco F, Mazzone G, Amoruso DC, Ribecco MT, Romano A, et al. (2010). Coffee reduces liver damage in a rat model of steatohepatitis: the underlying mechanisms and the role of polyphenols and melanoidins. *Hepatology*, 52(5):1652–61. doi:10.1002/hep.23902 PMID:21038411

Volz N, Boettler U, Winkler S, Teller N, Schwarz C, Bakuradze T, et al. (2012). Effect of coffee combining green coffee bean constituents with typical roasting products on the Nrf2/ARE pathway in vitro and in vivo. *J Agric Food Chem*, 60(38):9631–41. doi:10.1021/jf302258u PMID:22946519

Wadhawan M, Anand AC (2016). Coffee and liver disease. [Review.] *J Clin Exp Hepatol*, 6(1):40–6. doi:10.1016/j.jceh.2016.02.003 PMID:27194895

Wang H, Boecker W, Wang H, Wang X, Guan J, Thompson LH, et al. (2004). Caffeine inhibits homology-directed repair of I-SceI-induced DNA double-strand breaks. *Oncogene*, 23(3):824–34. doi:10.1038/sj.onc.1207168 PMID:14737117

Wang S, Yoon YC, Sung MJ, Hur HJ, Park JH (2012). Antiangiogenic properties of cafestol, a coffee diterpene, in human umbilical vein endothelial cells. *Biochem Biophys Res Commun*, 421(3):567–71. doi:10.1016/j.bbrc.2012.04.046 PMID:22525673

Wang X, Li W, Ma X, Chu Y, Li S, Guo J, et al. (2015). Simultaneous determination of caffeic acid and its major pharmacologically active metabolites in rat plasma by LC-MS/MS and its application in pharmacokinetic study. *Biomed Chromatogr*, 29(4):552–9. doi:10.1002/bmc.3313 PMID:25164780

Wedick NM, Brennan AM, Sun Q, Hu FB, Mantzoros CS, van Dam RM (2011). Effects of caffeinated and decaffeinated coffee on biological risk factors for type 2 diabetes: a randomized controlled trial. *Nutr J*, 10(1):93 doi:10.1186/1475-2891-10-93 PMID:21914162

Wedick NM, Mantzoros CS, Ding EL, Brennan AM, Rosner B, Rimm EB, et al. (2012). The effects of caffeinated and decaffeinated coffee on sex hormone-binding globulin and endogenous sex hormone levels: a randomized controlled trial. *Nutr J*, 11(1):86 doi:10.1186/1475-2891-11-86 PMID:23078574

Wijewickreme AN, Kitts DD (1998). Modulation of metal-induced genotoxicity by Maillard reaction products isolated from coffee. *Food Chem Toxicol*, 36(7):543–53. doi:10.1016/S0278-6915(98)00007-6 PMID:9687961

Williams CJ, Fargnoli JL, Hwang JJ, van Dam RM, Blackburn GL, Hu FB, et al. (2008). Coffee consumption is associated with higher plasma adiponectin concentrations in women with or without type 2 diabetes: a prospective cohort study. *Diabetes Care*, 31(3):504–7. doi:10.2337/dc07-1952 PMID:18070989

Wong P, Bachki A, Banerjee K, Leyland-Jones B (2002). Identification of N1-methyl-2-pyridone-5-carboxamide and N1-methyl-4-pyridone-5-carboxamide as components in urine extracts of individuals consuming coffee. *J Pharm Biomed Anal*, 30(3):773–80. doi:10.1016/S0731-7085(02)00384-9 PMID:12367703

Wu X, Skog K, Jägerstad M (1997). Trigonelline, a naturally occurring constituent of green coffee beans behind the mutagenic activity of roasted coffee? *Mutat Res*, 391(3):171–7. doi:10.1016/S1383-5718(97)00065-X PMID:9268042

Yamashita K, Yatsuya H, Muramatsu T, Toyoshima H, Murohara T, Tamakoshi K (2012). Association of coffee consumption with serum adiponectin, leptin, inflammation and metabolic markers in Japanese workers: a cross-sectional study. *Nutr Diabetes*, 2(4):e33 doi:10.1038/nutd.2012.6 PMID:23169586

Yamauchi R, Kobayashi M, Matsuda Y, Ojika M, Shigeoka S, Yamamoto Y, et al. (2010). Coffee and caffeine ameliorate hyperglycemia, fatty liver, and inflammatory adipocytokine expression in spontaneously diabetic KK-Ay mice. *J Agric Food Chem*, 58(9):5597–603. doi:10.1021/jf904062c PMID:20405946

Yang A, Palmer AA, de Wit H (2010). Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology (Berl)*, 211(3):245–57. doi:10.1007/s00213-010-1900-1 PMID:20532872

Yazheng L, Kitts DD (2012). Activation of antioxidant response element (ARE)-dependent genes by roasted coffee extracts. *Food Funct*, 3(9):950–4. doi:10.1039/c2fo30021d PMID:22699814

Yukawa GS, Mune M, Otani H, Tone Y, Liang XM, Iwahashi H, et al. (2004). Effects of coffee consumption on oxidative susceptibility of low-density lipoproteins and serum lipid levels in humans. *Biochemistry (Mosc)*, 69(1):70–4. doi:10.1023/B:BIRY.0000016354.05438.0f PMID:14972021

Zampelas A, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C (2004). Associations between coffee consumption and inflammatory markers in healthy persons: the ATTICA study. *Am J Clin Nutr*, 80(4):862–7. PMID:15447891

Zelber-Sagi S, Salomone F, Webb M, Lotan R, Yeshua H, Halpern Z, et al. (2015). Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population. *Transl Res*, 165(3):428–36. doi:10.1016/j.trsl.2014.10.008 PMID:25468486

Ziobro A, Bartosz G (2003). A comparison of the total antioxidant capacity of some human body fluids. *Cell Mol Biol Lett*, 8(2):415–9. PMID:12813575

5. SUMMARY OF DATA REPORTED

5.1 Exposure data

Coffee as a beverage has been consumed in many parts of the world for centuries. Coffee is prepared from the fruit seeds (called beans) of several species of the genus *Coffea* L. (Rubiaceae family). The two main types of cultivated coffee are commonly called Arabica and Robusta. After harvesting, the fruits are processed to obtain the beans which are then roasted and ground before brewing. There are variations in the way each of these steps are conducted, depending on the local farmer, industry, and consumer preferences. The quality and chemical composition of the beans can be affected at all stages of the processing.

The chemical composition of the beverage varies depending on the ratio of coffee to water, particle size, duration of brewing, percolation pressure, and filtration. Coffee contains compounds numbering several hundred. The concentration of caffeine, one of the major pharmacologically active compounds, is highly variable due to various factors such as coffee tree species and preparation method (average, 0.4 g/L). Decaffeinated coffee is also produced. Heat-induced contaminants such as acrylamide and furan regularly occur in coffee beans and brewed coffee.

Coffee production and consumption were both estimated to be about 9 million tonnes worldwide in 2015. Together, the European Union countries account for 28% of consumption; major individual consuming countries are the USA (16%), Brazil (13%), Japan (5.6%), and the Russian Federation (2.2%). In terms of per capita consumption, European countries are the major consumers. At an individual consumer level, there exists an extremely large variation in frequency of coffee drinking and portion size. Consumption has been stable in countries with high per capita consumption and has increased in countries that are currently lower per capita consumers; the latter countries are mainly situated in Africa, Asia, and Oceania.

Questionnaires used to assess coffee consumption vary in several ways, including: methods of dietary assessment and/or measurement used; whether questionnaires are validated/calibrated; differentiation between caffeinated and decaffeinated coffee; method of preparation; inclusion of serving or portion sizes; and ability to assess intake in terms of grams or litres per day.

5.2 Human carcinogenicity data

5.2.1 Bladder

In 1991 (*IARC Monographs* Volume 51), the Working Group concluded that there was limited evidence for the carcinogenicity of coffee drinking in humans. This evaluation was based on an increased risk of cancer of the bladder that was observed in several hospital-based case–control studies, with few cohort studies available. Two concerns with these older case–control studies are: (1) that coffee-drinking habits were assessed after case diagnosis and could be affected by

development of bladder cancer; and (2) the use of hospital-based controls in the majority of studies, with often unreported conditions that may affect coffee drinking, which can in turn introduce bias in reported coffee drinking and a subsequent overestimation of the risk. Bias in the observed estimates could therefore not be ruled out. Several large prospective cohort studies and population-based case–control studies have been published since 1991, with adjustment for tobacco smoking and/or results in non-smokers, and were available for this updated review.

The current Working Group examined the association between coffee intake and risk of cancer of the bladder in nearly 80 cohort and case–control studies conducted in Asia, Europe, South America, and the USA. In evaluating the evidence from these epidemiological studies, the Working Group placed the greatest weight on the cohort studies. This evaluation was complemented with information from population-based case–control studies, which were considered more informative than hospital-based studies. Studies that did not consider smoking as a confounder were excluded from evaluation.

Eleven cohort studies from Europe, Japan, and the USA reported on the association between coffee drinking and risk of cancer of the bladder with inconsistent results. There was no consistent evidence of a positive or inverse dose–response relationship with the quantity of coffee consumed. Within the studies that reported sex-specific results, associations among women were generally null or inverse and more often positive among men. The findings among women are particularly informative, in that those associations are less likely to be confounded by smoking and occupational exposure compared with associations among men. Of the two cohort studies that reported on non-smokers, one reported a non-significant positive association and the other a non-significant inverse association. Both were based on very small numbers of non-smokers.

Among the 14 independent population-based case–control studies, the findings were also inconsistent. Increased risks were reported in several studies, mostly among men. Modest positive associations were observed in several studies of non-smokers, but none were statistically significant.

In conclusion, there was no consistent evidence of an association or dose–response relationship between coffee drinking and cancer of the bladder. The majority of positive studies did not adequately adjust for smoking, and studies among non-smokers were limited by small sample size. Moreover, most studies did not adjust for occupational exposures. Sex-specific associations were more often positive among men. Among women, where confounding by occupational exposures and smoking is less likely, the associations were generally null or inverse. Residual confounding by smoking or occupational exposure therefore cannot be ruled out.

5.2.2 Pancreas

Evidence of the association between coffee drinking and cancer of the pancreas was available from 20 cohort studies and 22 case–control studies that controlled for smoking, of which 14 were population-based and 8 hospital-based. The review of epidemiological studies was restricted to those that adjusted for smoking. Cohort studies and population-based case–control studies, adjusting for multiple confounders, showed no overall association with total coffee drinking or with decaffeinated coffee drinking. The most important set of studies on which this conclusion is based is a pooled analysis of cohort studies with comparable methodology which found no association, including in non-smokers. A high-quality meta-analysis also showed no association with coffee intake in cohort studies or in case–control studies that adjusted for smoking. Several large cohort studies published after this meta-analysis

similarly found null associations. Overall, based on many large studies, there is no evidence of an association between coffee drinking and risk of pancreatic cancer.

5.2.3 Liver

A total of 14 cohort studies and 11 case–control studies conducted in Asia, Europe and North America examined the association between coffee consumption and the risk of cancer of the liver. All cohort studies adjusted for smoking and alcohol intake and, where possible, for hepatitis virus infection status and diabetes. All cohort studies observed inverse associations, which were statistically significant in most studies. Separate analyses by sex and by hepatitis C virus and/or hepatitis B virus infection status yielded similar results. Most case–control studies also observed inverse or null associations. In a 2015 pooling project of cohort studies in the USA (over 860 cases of hepatocellular carcinoma), the risk in the highest compared with the lowest category of coffee consumption was reduced by about 25%. The Working Group concluded that a consistent, statistically significant, inverse association between coffee drinking and risk of liver cancer has been observed in multiple studies.

5.2.4 Breast

Evidence of the association between coffee consumption and risk of cancer of the breast was available from 23 cohort and 22 case–control studies. Most of the reviewed studies showed no association, and several reported statistically significant inverse associations between coffee intake and breast cancer overall or among subgroups of premenopausal or postmenopausal women. The most recent meta-analysis of about one million women and more than 50 000 breast cancer cases reported a modestly decreased risk for the highest compared with lowest levels of coffee consumption, with an indication of an inverse dose–response relationship. Studies published after this meta-analysis reported null or inverse associations overall and among postmenopausal women. An inverse association was also observed in the recent large cohort study (2016). Inverse associations were reported in a small number studies among women with *BRCA1* mutations. One population-based case–control study among non-carriers of *BRCA1/2* mutations reported a positive association.

5.2.5 Uterus (endometrium)

Evidence of the association between drinking coffee and risk of endometrial cancer was available from 20 informative studies (12 cohort and 8 case–control studies) where body mass index and smoking were taken into account. Evidence from four of the largest cohort studies (the Swedish Mammography Cohort, the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study, the Nurses' Health Study (NHS) and NHS II, and European Prospective Investigation into Cancer and Nutrition (EPIC)) with over 6000 cases showed an inverse association with coffee drinking. The Million Women Study, including another 4000 cases, found a null association. Evidence from case–control studies is consistent with that of cohort studies, suggesting an inverse or a null association. A meta-analysis published in 2012 found a 30% lower risk of endometrial cancer among coffee drinkers, consistent with the majority of cohort and case–control studies.

5.2.6 Prostate

Evidence from ten cohort studies and four case–control studies of the association between coffee drinking and cancer of the prostate was evaluated. The greatest weight was given to studies of aggressive and fatal prostate cancer to reduce the potential for bias from screening. No case–control or cohort studies found positive

associations with the risk of total prostate cancer. Recent meta-analyses of cohort and case–control studies estimated inverse associations for fatal prostate cancer and no association for advanced prostate cancer. Studies conducted worldwide consistently indicated no increased risk of prostate cancer associated with coffee drinking, with inverse or null associations observed in all studies.

5.2.7 Oral cavity and pharynx

Evidence of the association between coffee drinking and cancers of the oral cavity and/or pharynx was available from more than 20 cohort and case–control studies in Europe, Japan, and the USA. Inverse associations were observed in the majority of informative studies, and these were statistically significant in about one half of the studies. An inverse dose–response relationship was also seen in a recent pooled analysis of case–control studies, as well as in four meta-analyses of cohort and case–control studies. Although data from several studies that combined results for the oral cavity and pharynx were suggestive of inverse associations, the Working Group concluded that these tumours are distinct entities and that the available data do not permit conclusions to be drawn about either cancer site.

5.2.8 Childhood leukaemia

Seven case–control studies have reported on the association between maternal coffee consumption during pregnancy and the risk of childhood leukaemia. The Working Group considered that the earliest two studies were of limited quality due to low participation fractions and uninformative exposure categories. Four of the remaining studies were conducted in France by the same research group (with no overlap of study populations). The first of these was hospital based and reported an increased risk with a significant dose–response trend. A second study by this team 2 years later used a population-based approach and reported an odds ratio slightly and non-significantly above unity. The third French study showed an increased risk with a significant dose–response trend, while the results of the fourth study were largely null. An Australian study found no evidence of an increased risk. The most recent meta-analysis of this association reported an overall increased risk for high levels of coffee consumption, but was limited by the fact that the highest exposure level varied widely across studies (from ≥ 4 times per week to ≥ 8 times per day). The lack of consistency among the findings of the studies, particularly those conducted within the same country by the same group, led the Working Group to evaluate the evidence for this site as inconclusive.

5.2.9 Lung

More than 20 cohort and case–control studies have reported on the association between coffee consumption and risk of lung cancer. Only studies that controlled for smoking were reviewed, but the level of adjustment for smoking was nevertheless inadequate in most of the older studies. Four recent large-scale studies (three cohort studies and one large population-based case–control study) performed careful adjustment for smoking. Positive associations between lung cancer and coffee drinking were substantially attenuated after these adjustments; they remained positive in the cohort studies, however, while they became null in the case–control study. In the most recent meta-analysis, coffee drinking was not associated with lung cancer when smoking was controlled. Among non-smokers, cohort, case–control studies and a meta-analysis did not find an association between coffee drinking and lung cancer. The Working Group concluded that the positive association between coffee drinking and lung cancer observed in some studies was probably explained by residual confounding due to smoking.

5.2.10 Larynx

Associations between coffee drinking and cancer of the larynx were evaluated in seven case–control studies, including a large pooled analysis, and one cohort study. The results of these studies were inconsistent. A significantly increased risk was observed in four case–control studies, but none of these studies had adequately controlled for smoking and alcohol use. No evidence of an association was observed in studies that tightly controlled for smoking and alcohol drinking, or in the pooled analysis of case–control studies. No evidence of excess risk of laryngeal cancer among coffee drinkers was observed in the prospective cohort.

5.2.11 Ovary

The evidence for the relation between coffee consumption and risk of cancer of the ovary is based on some 10 cohort and about 20 case–control studies. Evidence from the majority of the cohort studies, including the largest one and a meta-analysis, suggests no association. The evidence from case–control studies is inconsistent; although the majority of studies suggest a null association, some others show (mostly non-statistically significant) positive associations. Given the inconsistency of the results among studies, the Working Group found the evidence to be inconclusive.

5.2.12 Stomach

A total of 12 cohort studies and 14 case–control studies of the association between coffee drinking and gastric cancer reported inconsistent results, with no consistent evidence of a positive or inverse association between coffee intake and gastric cancer observed.

5.2.13 Oesophagus

Data on the association between coffee drinking and cancer of the oesophagus were available from three adequate cohort studies and eight case–control studies conducted in Europe, Asia, and the Americas that adjusted for tobacco smoking and alcohol drinking. Virtually all of these studies observed no association between coffee drinking and the risk of cancer of the oesophagus. One cohort study from Japan observed an inverse association with borderline statistical significance. No notable differences were observed between squamous cell and adenocarcinomas of the oesophagus. The two most recent case–control studies observed decreased risk. Two meta-analyses also suggested no association between coffee intake and oesophageal cancer.

5.2.14 Kidney

For renal cell carcinoma, four cohort studies (including a pooled analysis of prospective cohort studies) and five case–control studies were considered informative. The largest study pooled data from 13 prospective cohorts and found no overall association; significant inverse associations among women and among never-smokers were observed, with comprehensive adjustment for confounders. One large, well-conducted population-based case–control study found a significant positive association, and the remaining studies were either null or significantly inverse.

For renal pelvis cancer, only two population-based case–control studies were considered informative. Neither found a significant association between coffee intake and risk of renal pelvis cancer; however, confidence intervals were wide and there was limited adjustment for confounding.

5.2.15 Colorectum

Approximately 50 prospective cohort, case–control, and pooling studies have been conducted to evaluate the association between coffee drinking and cancer of the colorectum. Ten cohort studies that were considered to be the most informative, with case numbers in the hundreds to over one thousand, found null associations between coffee consumption and colorectal cancer. Three cohort studies found an increased risk of either colon or rectal cancer. A pooled analysis of 13 cohort studies of colon cancer (over 5600 cases) found no association. Two subsequent large cohort studies conducted in the USA and Europe found inverse and null associations of colorectal cancer with coffee drinking, respectively. The findings from case–control studies were mixed, with inverse associations in most studies and positive or null associations in others.

5.2.16 Skin

Thirteen studies – seven cohort studies and six case–control studies – reported inconsistent results for an association between coffee consumption and risk of cutaneous malignant melanoma. Of the cohort studies, four reported largely null findings while three reported inverse associations. In both of the cohort studies that presented results for men and women separately, the risk ratios for coffee drinking were significantly decreased for women and non-significantly increased for men. Of the case–control studies, four reported no association while two reported reduced risks with increased coffee consumption. A meta-analysis of these studies reported summary risk ratios for the highest versus lowest category of coffee intake that were significantly reduced among women and non-significantly elevated among men. Three cohort studies and three case–control studies have reported on the association between coffee consumption and risk of non-melanoma skin cancer. All of the studies reported null or inverse associations with coffee drinking.

5.2.17 Other cancer sites

Associations between coffee drinking and all cancers combined and cancers at several other sites – including Wilms tumour, brain cancer (in both adults and children), lympho-haematopoietic cancer in adults, cancers of the gallbladder and biliary tract, cancers of the small intestine, vulva, testis and thyroid, soft-tissue sarcoma, and breast cancer in men – were examined in only a few studies for each cancer site. The sparse evidence available for these cancers did not permit conclusions to be drawn.

5.3 Animal carcinogenicity data

Chronic studies to evaluate the potential carcinogenicity of coffee have been performed in male and female mice in one study (by transplacental/perinatal exposures followed by feeding), and in male and female rats in two studies (one feeding study and one study by transplacental/perinatal exposures followed by exposure to coffee-containing drinking fluid).

In the transplacental/perinatal/feeding study in mice, females exposed to coffee demonstrated a significant trend towards increased incidence of uterine leiomyoma. By contrast, coffee exposure was associated with significant, dose-related reductions in the incidences of total tumours and malignant tumours in both sexes. Significant and dose-related reductions in lymphosarcoma incidence were seen at several sites in both sexes, and males exposed to coffee also demonstrated a significant, dose-related reduction in the incidence of hepatocellular adenoma.

In the feeding study in rats, the animals fed caffeinated coffee or decaffeinated coffee plus caffeine demonstrated fewer tumours than sex-matched controls. A significant increase in

the total number of malignant tumours was seen in one group of females fed caffeinated coffee; however, since this increase was not seen in another group of females receiving comparable exposure to coffee, the Working Group interpreted it as an isolated and not reproducible finding.

In the transplacental/perinatal/drinking-fluid study in rats, the incidence of skin fibrosarcoma or squamous cell carcinoma (combined) was significantly increased in males given a low dose, but not in the groups receiving a medium or high dose. However, the individual incidences of skin fibrosarcoma and skin squamous cell carcinoma did not differ from controls in any dose group. No significant increases in total tumour incidence were seen in rats exposed to coffee. Significant decreases in the incidences of mammary gland fibroadenoma were seen in females exposed to coffee.

Coffee was tested for carcinogenicity in initiation–promotion or co-carcinogenicity studies as either: brewed or instant coffee in male or female rats by oral administration in the drinking fluid in seven studies; or as green beans, pressed oil from green beans, or a lyophilized roasted coffee extract in male or female rats by oral administration in the feed in three studies. Coffee was also tested as brewed coffee in one drinking-fluid study and one gavage study in male hamsters, and as green beans in one feeding study in female hamsters. These studies were designed to investigate the potential of coffee to mitigate the effect of different known carcinogens; because of the potency of the carcinogen used, these studies were often of relatively short duration or used small numbers of animals.

Of the 13 studies reviewed, only one reported a significant increase in tumours. When 2-acetylaminofluorene was used as an initiator and coffee used as a promoter in a drinking-fluid study, there was a significant increase in the incidence of adenocarcinomas of the mammary gland in female rats. In seven of the rat studies and one of the hamster studies, coffee caused a significant reduction in the incidence and/or multiplicity of the tumours induced in various organs by the different carcinogens; the organs included the mammary gland (two studies), liver (three studies), pancreas (one study), and colon (one study) in rats, and the buccal pouch (one study) in hamsters.

5.4 Mechanistic and other relevant data

Coffee has many constituents and numerous studies have examined their pharmacokinetics. After oral administration of coffee, absorption of caffeine, trigonelline, diterpenes, chlorogenic acids, and related compounds (hydroxycinnamates) occurs within hours and is dependent upon compound and dose. An in vivo study in mice showed that cafestol is efficiently absorbed. Upon ingestion of coffee, the major hydroxycinnamic acids that were identified in the plasma of humans were 5-*O*-caffeoylquinic acid and ferulic acid. For trigonelline, absorption is faster in women than in men. In human in vivo studies, the distribution of caffeine varies significantly with body weight and fat mass, but is not dependent on either the dose or the formulation. Trigonelline and related compounds have a high volume of distribution in humans consuming coffee.

The metabolism of caffeine in humans is rapid and dependent upon dose, with higher doses resulting in the formation of other methylxanthines. In vivo human studies reported interethnic differences in caffeine metabolism, in which multiple enzymes are involved. The main metabolic pathway in humans is CYP1A2-catalysed 3-*N*-demethylation. Smoking and heavy coffee drinking induce caffeine metabolism. The main metabolic pathway in rats is 8-hydroxylation, also mediated by CYP1A2. For hydroxycinnamic acids, sulfation is the main

conjugation pathway and more than 30 different derivatives were identified in humans. In mice, the major metabolite of cafestol is a glucuronide conjugate. Studies in rodents demonstrated that hydrolysis of chlorogenic acid can occur in the stomach and gut mucosa.

Multiple human studies showed induction of CYP1A2 as a consequence of coffee consumption. In addition, increased activity of GSTP but not GSTT was observed. Contrary to studies in humans in vivo, coffee and its constituents directly inhibit multiple enzymes in vitro, including CYP1A2, CYP3A4, CYP2B6, sulfotransferases (SULT), and catechol-*O*-methyltransferase (COMT); however, UDP-glucuronosyl transferases (UGT) was observed to be upregulated. In both rats and mice, coffee induces several metabolizing enzymes in many tissues. Coffee constituents may have opposing effects on the induction of metabolizing enzymes.

Human in vivo data showed that the elimination of caffeine and hydroxycinnamic acids is dose dependent, with higher doses associated with decreases of caffeine clearance. The extent of trigonelline elimination after coffee consumption is lower in women compared with men. 5-*O*-caffeoylquinic acid and 4-*O*-caffeoylquinic acid were the only unmetabolized hydroxycinnamic acids detected in the urine of humans after coffee consumption, whereas the most abundant phenolic acids were gallic and dihydrocaffeic acids. In studies in humans in vivo, kahweol and cafestol were eliminated in the urine and faeces. A study in rats in vivo reported efficient elimination of cafestol through bile.

With respect to the key characteristics of carcinogens, there is *weak* evidence that coffee drinking induces oxidative stress. Findings in humans in many studies of various designs, including randomized controlled trials, consistently demonstrated no effects. A variety of end-points have been evaluated. An exception is the increase of H_2O_2 in urine after consuming coffee, found in three acute interventions. In two studies in human intestinal cells in vitro, no pro-oxidant activity was detected. In lymphocytes directly exposed to coffee without metabolic activation, increased oxidative DNA damage was found. One study in rats detected increased excretion of 8-hydroxydeoxyguanosine (8-OHdG) but not F2-isoprostanes in urine upon exposure to high doses of coffee for up to 130 days. Several other studies in rats of shorter duration or of co-exposures to other oxidative stress-promoting factors showed protection by coffee on oxidative stress markers.

There is *strong* evidence that coffee drinking induces antioxidant effects. Largely consistent protective effects were seen in many human studies of various designs, including randomized controlled trials. Some of these studies examined antioxidant status while others demonstrated a general reduction in oxidative stress markers. Similar antioxidant properties of coffee were demonstrated in studies using human intestinal cell lines and lymphocytes. In several studies of short-term exposures in experimental animals, increased antioxidant enzyme activity, glutathione, and sulfhydryls in liver or plasma have been reported. Coffee induces activity of nuclear factor-erythroid-2-related factor (Nrf2). Finally, many different assays in cell-free systems of both coffee and its constituents demonstrated free radical scavenging activity.

There is *weak* evidence that coffee drinking induces chronic inflammation. In many human studies of various designs, including randomized controlled trials, coffee drinking had no consistent effect on proinflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6). In rodent models of proinflammatory conditions, coffee induced anti-inflammatory cytokines and suppressed the activation of NF-κB.

There is *weak* evidence that coffee drinking is genotoxic. The few studies in humans that have reported chromosomal damage in coffee drinkers have limitations in study design or

else present conflicting results. Some studies found protective effects of coffee drinking on oxidative DNA damage or strand breaks in lymphocytes; however, some studies showed no effect, or suggested that coffee drinking may be associated with genetic alterations in lymphocytes and sperm cells. In human cells, results in vitro are conflicting. Studies in rodents in vivo have shown no evidence that coffee induces chromosomal damage. Furthermore, many studies demonstrated protective effects of coffee towards genotoxicity induced by several carcinogens in many organs. There is some evidence in mammalian cells in vitro for induction of sister-chromatid exchanges after exposure to coffee; however, consistent negative findings were reported for micronuclei and in the comet assay. Bacterial mutagenesis assays with various coffee brews are consistently positive in absence of metabolic activation. In these experiments, formation of hydrogen peroxide from coffee is one likely mechanism for these effects as addition of antioxidants or antioxidant enzymes reduced the bacterial mutagenic effects of the brews. Another mechanism of mutagenesis in bacterial systems is through the effect of methylglyoxal, a substance that is present in coffee brews and other food products and beverages.

There is *weak* evidence that coffee constituents alter DNA repair or cause genomic instability. In the few available studies in vitro, caffeine inhibited several DNA repair pathways. One study in rats showed the induction of O^6-methylguanine-DNA methyltransferase (MGMT) in liver by kahweol and cafestol. There are no studies of coffee drinking and this key characteristic.

There is *weak* evidence that coffee constituents induce epigenetic alterations. In one study in human cell lines, caffeic and chlorogenic acids induced promotor demethylation of the retinoic acid receptor β. In three studies in rats, caffeine administration to pregnant dams reduced methylation of DNA and histones and induced expression of DNA methyltransferases and histone deacetylases in various tissues in the offspring. In one study in mouse myoblasts, caffeine induced hyperacetylation of histone H3. There are no studies of coffee drinking and this key characteristic.

There is *weak* evidence that coffee consumption alter cell proliferation, and there is moderate evidence that coffee consumption increases cell death through apoptosis. One intervention study in humans found that consuming large quantities of coffee had no effect on cell proliferation in colorectal mucosa. In many human cancer cell lines, coffee and coffee constituents exerted antiproliferative and proapoptotic effects. There is some evidence in humans and animals in vitro for antiangiogenic effects for the coffee constituents caffeine, cafestol, and kahweol. Two rodent studies of oral ingestion of coffee or caffeine reported increased cell proliferation in urinary bladder and ventral prostate, whereas another study showed a suppressive effect using a tumour-implant model. One study of short- or long-term oral administration of regular or decaffeinated coffee demonstrated increased autophagy in multiple organs, including liver, heart, and muscle.

There is *weak* evidence that coffee consumption modulates receptor-mediated effects. In several studies in human cells in vitro, coffee and coffee constituents had a direct stimulatory effect on nuclear receptors, including aryl hydrocarbon receptor (AhR), farnesoid X receptor (FXR), and pregnane X receptor (PXR). Increased levels of sex hormone-binding globulin (SHBG) were seen in coffee-consuming postmenopausal women and in men; however, results were inconsistent with respect to effects on androgens and estrogens. There is some evidence in humans in vivo and in vitro that coffee can modulate estrogen metabolism. Coffee modulates plasma levels of cortisol in both humans and rats, and a similar effect was observed in human cells in vitro. Studies in humans in vivo and human cells

in vitro and animals in vivo showed that coffee and coffee-derived phenolics stimulate excretion of gastrin and other gastrointestinal hormones. There is a positive association between coffee consumption and plasma adiponectin levels in humans. Coffee consumption lowers leptin in plasma in humans.

Coffee and/or caffeine preference is a highly heritable trait. Several large-scale genome-wide association studies (GWAS) and meta-analyses point to a small number of alleles, most notably polymorphisms in *AHR* and *CYP1A* genes, that are very strongly and consistently associated with the patterns of coffee consumption. A small number of studies examined genetic modifiers of the purported positive or inverse associations between coffee drinking and various human cancers. Most of these studies report no effect of genetic modifiers under investigation, while others are often conflicting with respect to the directionality of the effect.

There is *moderate* evidence regarding the association between coffee drinking and risk of colorectal adenomas. An inverse association between coffee drinking and risk of colorectal adenomas was found in several studies; however, possible uncontrolled confounding and selection biases cannot be excluded. The few studies regarding Barrett oesophagus suggest no association with coffee intake.

There is evidence that coffee drinking is associated with a beneficial effect on liver fibrosis and cirrhosis.

Impairment of glucose metabolism has been found in single-dose studies; however, both human and animal studies show that, in the longer term, coffee and caffeine may improve glucose metabolism.

6. EVALUATION

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of drinking coffee.

There is *evidence suggesting lack of carcinogenicity* of drinking coffee in humans for cancers of the pancreas, liver, female breast, uterine endometrium, and prostate. Inverse associations with drinking coffee have been observed with cancers of the liver and uterine endometrium.

6.2 Cancer in experimental animals

There is *inadequate evidence* in experimental animals for the carcinogenicity of coffee.

6.3 Overall evaluation

Drinking coffee is *not classifiable as to its carcinogenicity to humans* (*Group 3*).

DRINKING MATE AND VERY HOT BEVERAGES

1. Exposure Data

Beverages, or drinks, are liquids intended for human consumption. Hundreds of different drinks are consumed by humans to replenish water loss or to receive nutrients and energy, as well as for social and cultural purposes. The major component of all drinks is water.

There is no universally accepted definition of hot or very hot beverages, and the standards may vary according to the type of beverage and geographical location. High temperatures, in addition to helping dissolve chemical constituents and flavour compounds, partly inactivate pathogenic microorganisms and toxins, warm the body, and optimize the taste and sense of satisfaction provided by certain beverages. Tea and coffee are the most common hot drinks consumed worldwide but there is a long list of others, including alcoholic and non-alcoholic drinks. Notable examples include mate, hot chocolate, diverse herbal infusions, hot mulled wine or cider, hot calvados (an apple liqueur produced in France), and hot sake (a Japanese alcoholic drink made from rice). Other hot liquids consumed by humans include bouillon, other hot broths, and hot soups.

The carcinogenicity of mate was reviewed in Volume 51 (IARC, 1991). Since that time, pertinent new data for mate and other hot beverages have become available and are reviewed in this volume.

1.1 Identification of the agent

1.1.1 Very hot beverages

Hot beverages are typically served between 71 °C and 85 °C (Brown & Diller, 2008). In general, they are consumed at temperatures lower than the initial serving temperature, typically between 50 °C and 70 °C. However, the consumers' choice of the drinking temperature may vary to a wide degree. A study taking into account consumer preference and scalding hazards suggested that the optimal temperature for drinking coffee is approximately 58 °C (Brown & Diller, 2008). [Sensory acceptance may be negatively influenced at temperatures below 60 °C (see Section 4).]

Standard methods for preparing test samples of hot beverages specify different temperatures according to the beverage. The International Organization for Standardization (ISO) standard for preparation of a liquor of tea for use in sensory tests specifies that boiling water should be used for preparation, and that the temperature should be in the range of 65–80 °C when milk is added (ISO, 1980). The ISO standard for the preparation of coffee samples for use in sensory analysis specifies that the beverage must be allowed to cool to a temperature of 55 °C or below, and that the first tasting is usually at a temperature between 50 °C and 55 °C (ISO, 2008).

There is a wide variation in temperature preferences across geographical regions. The Royal Society for Chemistry in the United Kingdom has

suggested drinking tea at temperatures between 60 °C and 65 °C (Royal Society of Chemistry, 2003). A study of 300 patients with indigestion in the UK (Edwards & Edwards, 1956) found that their mean preferred tea drinking temperature was between 53 °C and 57 °C. Ghadirian (1987) compared preferred drinking temperatures for black tea between areas of the Islamic Republic of Iran with low and high incidence of cancer of the oesophagus. In the region with low incidence, 72% of subjects drank their tea at temperatures below 55 °C, whereas in the region with high incidence, 62% drank tea at temperatures over 65 °C. Another study in an area of the Islamic Republic of Iran with a high incidence of cancer of the oesophagus showed that 56% of healthy subjects drank their tea at temperatures between 60 °C and 69 °C, while 39% drank tea below 60 °C and 5% at 70 °C or higher (Islami et al., 2009a). Finally, when studying 188 people in the Kilimanjaro region of the United Republic of Tanzania, Munishi et al. (2015) found that the mean temperature of tea at the first sip was approximately 71 °C.

In a study in the USA (Lee & O'Mahony, 2002), 300 consumers were asked to mix a hot coffee with cooler coffee until the desired temperature for drinking was reached. The chosen mean preferred drinking temperature was 60 °C with a range of 37–88 °C.

A study in Pelotos, Brazil, showed that the median drinking temperature for mate was 69.5 °C (Victora et al., 1990). Men drank mate at significantly higher temperatures than women (71.1 °C vs 67.6 °C, $P < 0.001$).

[The Working Group noted that the variation in mean drinking temperature in these studies was quite substantial. This may be partly due to variations in participant populations (e.g. in the study of Edwards & Edwards (1956) on patients with indigestion) or measurement methods (e.g. measuring when the first sip is taken vs another time point). However, differences in taste preferences in different geographical regions most likely account for most variation. In view of the few representative studies that were available, the Working Group considered that beverages drunk at temperatures in the range of 50–65 °C be classified as "hot beverages" and beverages above 65 °C as "very hot beverages".]

1.1.2 Mate

(a) Introduction

The term "mate" is used ambiguously in the literature for the infusion, that is, the consumed beverage (sometimes referred to as mate tea or yerba mate), the dried leaves from which it is made, and the plant that produces the leaves. Where unambiguous terminology is needed in this monograph mate will refer to the consumed beverage, while the other materials will be specified as "mate tree" or "mate leaves", for example. The term "mate de coca", which is sometimes used to define an infusion of coca leaves, is a misnomer and should be avoided.

The mate plant is native to the area of South America between latitudes 18° S and 35° S, from the Atlantic Ocean to the Paraguay River. This area includes northern Argentina, the south of Brazil, Paraguay, and Uruguay. Mate was originally consumed by indigenous populations of Argentina, Paraguay, and regions near Brazil and Uruguay before the Spanish arrived in the 16th century (IARC, 1991; Bracesco et al., 2011). Jesuit priests began cultivation of selected varieties of the mate tree in the 17th century and introduced the practice of drinking mate as a hot beverage (Graham, 1984; IARC, 1991; EMA, 2010).

(b) Botanical data and nomenclature

Botanical name: *Ilex paraguariensis* A. St.-Hil
Family: Aquifoliaceae
Genus: *Ilex*
Common names: erva mate, yerba mate, maté, Jesuits' tea, Brazilian tea, Paraguay tea (GRIN 2016)

Fig. 1.1 *Ilex paraguariensis* A. St.-Hil

Reproduced with permission from Dr Roland Spohn, www.spohns.de

(c) Description

Mate is prepared from the leaves of *Ilex paraguariensis*, a subtropical dioecious evergreen tree. The mate tree is a flower- and fruit-producing plant. The tree is usually cultivated as a shrub 3–6 m tall with numerous stems. The leaves are dark green, 15–20 cm in length, and short-stalked with an acuminate tip and finely dentated edges. It has small white flowers, which grow in forked clusters in the axils of the leaves, and violet-black berries, each of which contains four to eight seeds (Graham, 1984; Vázquez & Moyna, 1986; IARC, 1991; Fig. 1.1).

1.2 Production and use

The production and use of mate are reviewed in this monograph. Parallel information for coffee is provided in the monograph on Coffee Drinking in the present volume.

1.2.1 Mate

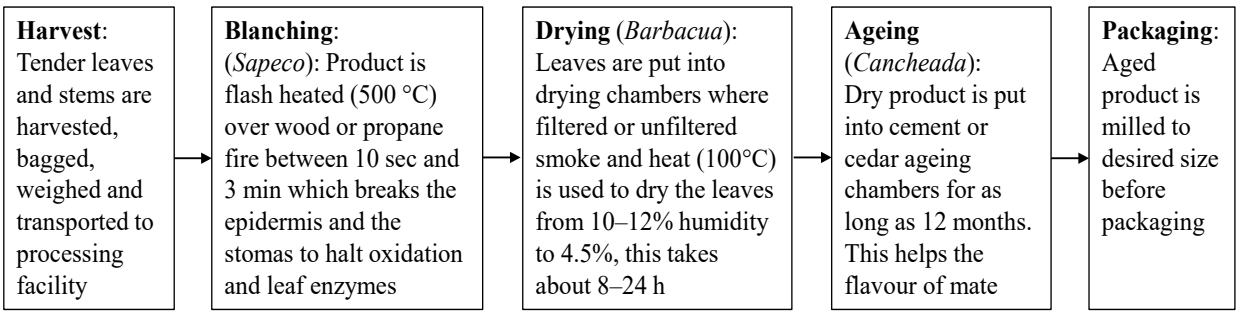
(a) Production

The cultivation and harvesting of mate is conducted by various methods depending on the region. The three primary methods of cultivation and harvest are: (1) extractive exploitation of the natural forest, (2) mixed system, and (3) cultivated plantations (Giberti, 1994).

Mate leaves are harvested when the trees are 4–6 years old. Leaves and small stems are harvested, either manually or mechanically, weighed, bagged, and transported to a processing facility (Heck & de Mejia, 2007).

The leaves are processed before reaching the consumer. Fresh mate leaves may undergo several of the following stages: blanching/flash-heating, roasting, drying, ageing, milling, and packaging. The conditions for each of these stages vary widely depending on the country or region, producer, and the final objective for the desired style and flavour of the finished drink. The overall process

Fig. 1.2 Processing of *Ilex paraguariensis* leaves into mate tea products



Created using data from Schmalko & Alzamora (2001)

is generally the same, however (Fig. 1.2; Heck & de Mejia, 2007).

Post-harvesting steps and their important effects on the chemical properties of mate are described below.

(i) Flash-heating

Flash-heating, which is a dry process, is sometimes called "blanching" or "scorching". This phase of the process consists of rapidly heating the mate leaves with the objective of inactivating enzymes (i.e. polyphenol oxidase), slowing down the natural decomposition of the plant material, and preserving sensory qualities. Traditionally, this process was performed by direct exposure to an open wood fire or propane in a rotating oven. At present, most old stoves have been replaced by automatic conveyor-belt dehumidifiers blowing hot air into the leaves (Peralta & Schmalko, 2007; Zaions et al., 2014). During industrial flash-heating with hot gases at temperatures above 500 °C, the leaves lose about 70% of their water content (Schmalko & Alzamora, 2001).

(ii) Drying

Traditionally, two systems are used to dry the leaves: *carijo* (scorched) and *barbacua* (smoke or hot air) (Fig. 1.3). When using the *carijo* method, the heat of the fire goes directly to the leaves. If the *barbacua* process is employed, the hot air (about 100 °C) or filtered or unfiltered smoke reaches the leaves indirectly through a tunnel under the earth.

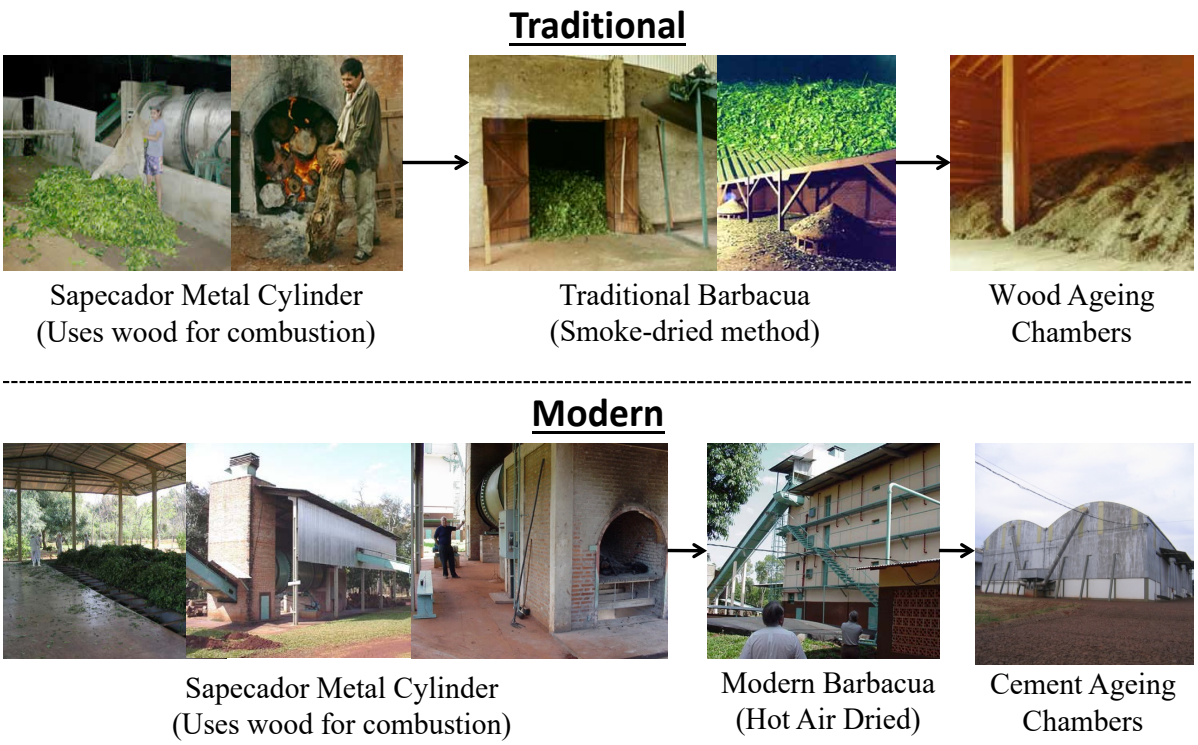
(iii) Ageing

Dried leaves may also be aged to develop specific colours and flavours, especially popular in Chile and Uruguay (Zaions et al., 2014). In the traditional ageing process, dried leaves that have been cut into smaller pieces are left in ageing chambers for a minimum of six months and up to one year or more. Ageing significantly increases the concentration of some of the components, such as methylxanthines and total phenolics (see Section 1.4), as well as the antioxidant activity of mate extracts (Blum-Silva et al., 2015). Improved methods for preserving the characteristics of the mate during storage have recently been developed (e.g. Prestes et al., 2014). The ageing step may be omitted for consumption in Brazil, where green leaves are preferred (Zaions et al., 2014).

(b) Use

The consumption of mate has expanded to millions of consumers in South America, but also to some countries in North America, Europe, and the Middle East. In South America, mate is drunk in social settings and can have important ritualistic connotations (Bracesco et al., 2011).

Fig. 1.3 Drying of mate leaves



Created by Ricardo Avalos for Dr E. Demejia, used with permission

Mate has also been used in traditional herbal medicinal products for centuries in South America and for several decades in European countries and the USA (EMA, 2010). More recently, mate leaves or extracts have been used as an ingredient in so-called energy drinks and in dietary supplements in the USA and Europe (Heck & de Mejia, 2007; Bracesco et al., 2011; Winkler et al., 2014).

(i) Hot mate

The method of preparing the mate infusion varies considerably from one region to another. In Argentina, southern Brazil, Chile, Paraguay, and Uruguay, mate is traditionally prepared for consumption by placing the dried and ground mate leaves into a hollow calabash gourd known commonly as a mate, *cuia*, or *guampa* (Fig. 1.4). Hot water [70–80 °C (158–176 °F)] is added and the resulting infusion is drawn by mouth with a metal straw called a *bombilla*. The *bombilla* acts as both a straw and a sieve. The submerged end is flared, with small holes or slots that allow the brewed liquid to be sipped while preventing aspiration of solid material (Bracesco et al., 2011). The gourd may be refilled with hot water many times before the mate leaves become washed out and lose their flavour. Consumption of around 1–2 L of brewed mate per day is common (Bracesco et al., 2011).

In addition to the traditional mate preparation, "teabag"-type infusions of mate are common, particularly in importing countries (e.g. Asia, Europe, and the USA).

Fig. 1.4 Mate in a traditional calabash gourd

(ii) Cold mate

Mate drinks made from toasted or green mate leaves can be prepared from loose or bagged leaves, with added sugar, and consumed cold. Ready-to-drink commercial mate products for cold consumption are also available.

(iii) Other mate products

Mate has traditionally been used as a medicinal product for symptoms of fatigue or a sensation of weakness, as a diuretic, and for minor urinary complaints (EMA, 2010).

New mate products have recently been developed due to the availability of mate powder extract. Mate extracts are an ingredient in various foods (sport liquid gel/chew and sweets) and energy drinks as a source of caffeine (Heckman et al., 2010a, b). A survey of the German market in 2014 detected 26 mate-containing products, predominantly alcohol-free soft drinks and energy drinks (Winkler et al., 2014).

Mate products are also marketed in Europe and North America as dietary supplements in tablet form. For example, the US Dietary Supplements Label Database lists more than 70 products that contain *Ilex paraguariensis* on the label (NLM, 2016).

(c) Chemical composition

(i) Major constituents

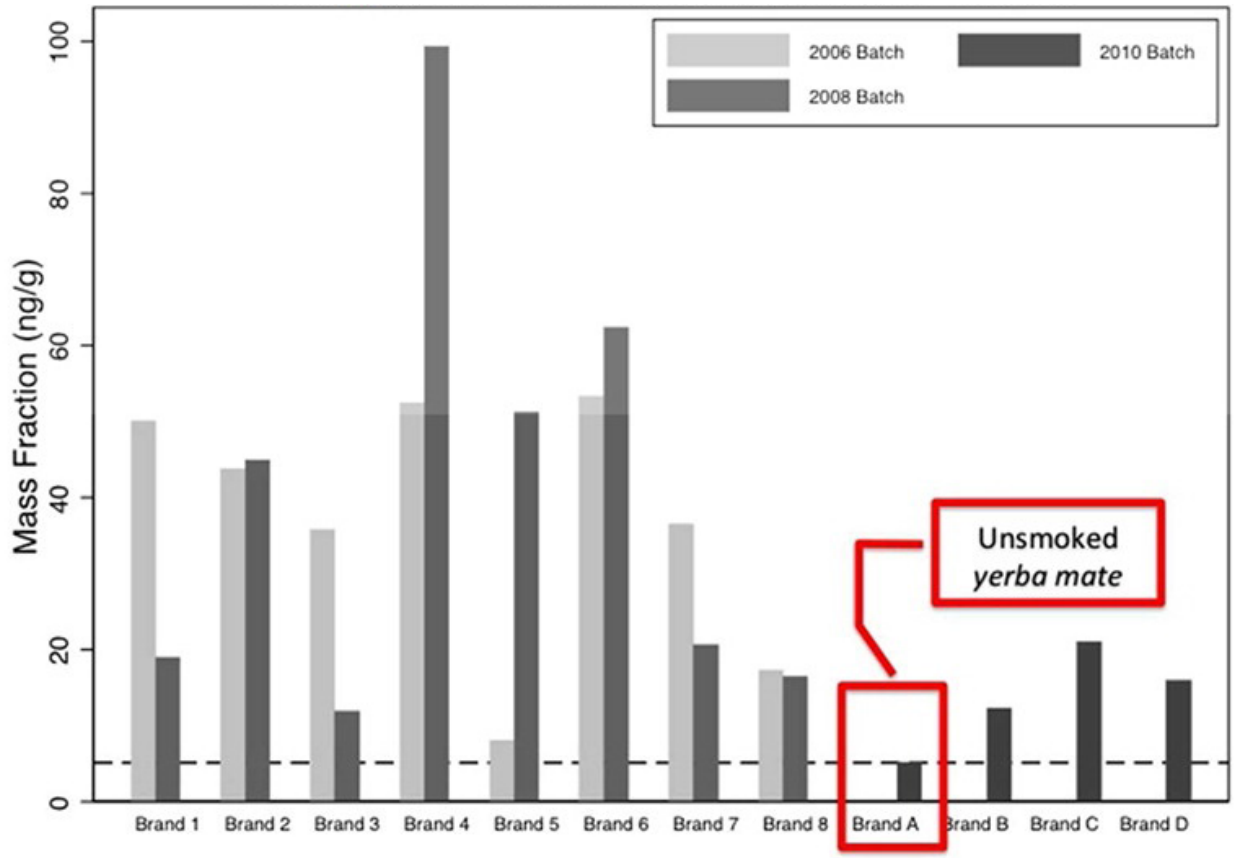
Similar to coffee (see monograph on Coffee Drinking in this volume) and *Camellia sinensis* tea (see IARC, 1991), caffeine is one of the principal components in mate with pharmacological effects; the mild stimulating effect of this beverage may be the reason for its popularity (Lachenmeier et al., 2012).

Depending on preparation, the chemical composition of the mate beverage may vary largely: the caffeine concentration in the final beverage is 270–540 mg/L (Heckman et al., 2010b).

Very few studies have reported on chlorogenic acid contents in mate. Marques & Farah (2009) reported concentrations in the order of 0.5 g/L of total chlorogenic acids in green mate and 0.1 g/L in toasted mate. In contrast, total polyphenol content in 13 traditional products were reported to range from 3.4 g to 7.4 g of chlorogenic acid equivalent (CH) per litre of freshly prepared mate, and from 0.02 g to 1.80 g of CH/L in 11 non-traditional mate beverages (Gonzalez de Mejia et al., 2005). [The Working Group concluded that the difference is likely related to the presence of additional ingredients such as sugars, fruit pieces, amino acids, vitamins, and flavouring agents in non-traditional mate beverages.]

[The Working Group noted that no systematic or representative data are available on mate composition, and the limited knowledge is based on single-sample studies. In addition, available studies vary largely in the method of preparation of the beverage for analysis in terms of origin of the leaves used, amount of leaves per litre of water, temperature, brewing time, and filtration. Further, not all studies report information in enough detail for comparison.]

Fig. 1.5 Benzo[*a*]pyrene concentration in processed mate leaves sampled in 2006, 2008, and 2010



The dashed line shows the benzo[*a*]pyrene content of the mate brand that never touched smoke (Brand A, marked with square). Adapted with permission from Golozar et al. (2012). Significant variation in the concentration of carcinogenic polycyclic aromatic hydrocarbons in yerba maté samples by brand, batch, and processing method. *Environmental Science & Technology*. Copyright (2012) American Chemical Society

(ii) Potential contaminants

Depending on the processing method (especially the drying steps), the content of polycyclic aromatic hydrocarbons (PAH) in mate leaf material sampled at fresh, partially dried, and dried stages of production may vary to a large degree (0.4–9 mg/kg total PAHs) (Vieira et al., 2010). Another study reported median total PAH contents of 0.6–3.7 mg/kg in samples of commercial mate leaf brands in 2008 and 2010; the significant variation observed was dependent on batch and processing method, including whether products were produced with or without exposure to smoke (Golozar et al., 2012). The content of benzo[*a*]pyrene, most probably from exposure to smoke during the mate manufacturing, ranged over 11.9–99.3 µg/kg of product. The samples processed without exposure to smoke had the lowest benzo[*a*]pyrene content (Fig. 1.5; Golozar et al., 2012).

Kamangar et al. (2008) reported that approximately 37% of the total PAH content (21 PAH analysed) found in the leaves of commercial mate material from Brazil [no details about samples provided] may be transferred into the mate infusion (Kamangar et al., 2008). A total PAH content of 0.6–2.3 µg/L was detected in prepared mate from Brazil [no details about samples provided],

Table 1.1 Compounds that may be present in mate and that have been evaluated previously by IARC

Agent	Concentration in mate	*IARC Monographs* evaluation of carcinogenicity			*IARC Monographs* Volume (year)
		In animals	In humans	IARC Group	
Caffeine	0.5–2% in the leaves	Inadequate	Inadequate	3	51 (1991)
Theobromine	Less than 1% in the leaves	No data	Inadequate	3	51 (1991)
Benzo[*a*]pyrene	Traces	Sufficient	No data	1	100F (2012)
Naphthalene	Traces	Sufficient	Inadequate	2B	82 (2002)
Acenaphthene	Traces	Inadequate	No data	3	92 (2010)
Phenanthrene	Traces	Inadequate	No data	3	92 (2010)
Caffeic acid	Traces	Sufficient	No data	2B	56 (1993)

No systematic data were available on concentrations of these agents in mate tea; mate also contains traces of several additional polycyclic aromatic hydrocarbons evaluated in *IARC Monographs* Volume 92 in 2010 into Groups 2A, 2B, and 3

with naphthalene, acenaphthene, and phenanthrene having the highest concentrations (Zuin et al., 2005).

Based on analyses of the PAH metabolite 1-hydroxypyrene glucuronide (1-OHPG) in 199 healthy adults, mate drinking was statistically significantly associated with higher urine concentrations of 1-OHPG (Fagundes et al., 2006).

Of the compounds evaluated in the *IARC Monographs* that have been described to occur in mate (Table 1.1), benzo[*a*]pyrene was evaluated as *carcinogenic to humans* (Group 1).

[The Working Group noted that the data available on PAH occurrence in mate leaves and mate infusion were based on small studies with non-representative sampling. No systematic monitoring data on PAH exposure related to mate consumption were available to the Working Group. Information on other potentially production-related contaminants such as acrylamide or furan was also unavailable.]

1.3 Production and consumption data

The major worldwide producers of mate leaves are Brazil (primarily southern Brazil), Argentina, and Paraguay. The total world production of processed mate leaves for 2012 was 821 534 tonnes, comprising 513 256 tonnes (62%) from Brazil, 250 928 tonnes (31%) from Argentina and 57 350 tonnes (7%) from Paraguay (FAO, 2016). Fig. 1.6 highlights the regions of South America where mate is produced commercially (Heck & de Mejia, 2007). Table 1.2 provides data describing the trends in production of mate leaves during 2002–2012.

Table 1.3 lists the average volume of production, exports, and imports of mate leaves during 2010–2013 in the main mate-producing countries. Brazil and Argentina have largely increased their production in recent years. The main destination countries for exports were Uruguay, Syrian Arab Republic, Chile, and Brazil (FAO, 2016).

Data on per capita consumption of mate beverages were not systematically available to the Working Group.

1.4 Methods of measurement and exposure assessment

1.4.1 Beverage temperature

Over the past few decades, many epidemiological studies have investigated the association between the consumption of hot drinks and

Fig. 1.6 Map of South America showing growing regions for *Ilex paraguariensis*

1 Argentina; 2 Brazil, 3 Paraguay, 4 Uruguay
Adapted from Heck & de Mejia (2007). Yerba mate tea (Ilex paraguariensis): a comprehensive review on chemistry, health implications, and technological considerations. *Journal of Food Science*, 72: R138–R151

cancer. Exposure to hot drinks has been assessed using various methods, including: asking direct questions of participants, administering structured questionnaires, and measurement of the drinking temperature of consumed beverages.

While it would be desirable to directly measure the temperature at which drinks are consumed, studies have instead typically relied on questionnaires to assess the participants' preference for drinking temperature as well as the type, duration, and frequency of drinking (Islami et al., 2009b). For example, participants may be asked to describe their usual temperature preference by subjective categories such as "cold", "warm", "hot", or "very hot".

Data on the volume consumed per day or drinking frequency, total duration of drinking, sip volume, and drinking temperature could also be valuable. However, in a systematic review of hot drinks in relation to cancer of the oesophagus based on 59 published studies, Islami et al. (2009b) concluded that many of the studies did not collect data on several of these factors or did not report the results, as investigating the effects of hot drinks was not the main aim of most studies. Furthermore, few studies adjusted the results of drinking temperature for the amount consumed and vice versa. The potential for interviewer or recall bias is also a concern, given the subjective nature of questions about temperature

Table 1.2 Trends in production of mate, 2002–2012

Country	Production (× 1000 tonnes)										
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Brazil	513.5	501.7	403.3	429.7	434.5	438.5	434.7	443.1	602.6	443.6	513.3
Argentina	285.0	285.0	251.9	265.1	280.0	290.0	237.9	228.5	250.7	245.4	250.9
Paraguay	136.6	89.0	76.7	74.0	86.1	87.5	76.7	76.7	85.5	85.5	57.3

Official data from the Food and Agriculture Organization of the United Nations (FAO, 2016)

Table 1.3 Production, exports, and imports of mate for the main producing countries and selected importing countries (average for 2010–2013)

Country	Production[a] (tonnes)	Exports[b] (tonnes)	Imports[c] (tonnes)
Brazil	518 725	35 716	2 899
Argentina	247 518	36 110	184
Paraguay	78 541	666	87
Uruguay	—	203	31 691
Syrian Arab Republic	—	81	23 495
Chile	—	—	6 599
Germany	—	474	977
Lebanon	—	—	1 144
France	—	380	582

[a] Official data from the Food and Agriculture Orgnization of the United Nations (FAO, 2016)
[b] From Vasconcelos de Oliveir & Dabdab Waquil (2015)
[c] Only three states in Brazil have mate drinkers in their population (lowering the per capita intake), but up to 70% of the male population in the states of Rio Grande do Sul, Santa Catarina, and Parana drink mate daily (Bracesco et al., 2011)

and the retrospective case–control design of most studies.

Very few epidemiological studies have assessed the reliability of reported temperature by using two or more measures. In a case–control study of cancer of the oesophagus and drinking hot tea, Islami et al. (2009a) used two independent questions regarding preference for tea temperature (lukewarm or warm, hot, and very hot) and time from pouring tea to drinking it (≥ 4, 2–3, and < 2 minutes). These two measures were strongly correlated (weighted kappa = 0.68), and both were strongly associated with a higher risk of cancer of the oesophagus.

In the pilot phase of a cohort study in Golestan Province of the Islamic Republic of Iran (Pourshams et al., 2010), the investigators tested two methods to measure the drinking temperature of tea; one of these showed good reliability (weighted kappa = 0.71) and was used for the actual cohort study. In brief, the investigators prepared a fresh cup of tea for each participant and measured the temperature of the tea using a digital thermometer. When the temperature was 75 °C, they asked the participants to sip the tea and say whether that was the temperature at which they usually drank tea. If not, the tea was allowed to cool by increments of 5 °C and the question was repeated until the temperature at which tea was usually drunk was reached (Islami et al., 2009a).

Islami et al. (2009a) studied the reliability of this method in the 48 524 cohort participants, and found that self-report of the drinking

temperature of tea (lukewarm or warm, hot, very hot) was positively correlated with the actual measured temperature (kappa = 0.49; $P = 0.005$) and inversely correlated with the time from pouring tea to drinking it (kappa = 0.68; $P = 0.03$).

Further methods of assessing the temperature of hot beverages were investigated in a cross-sectional study in the north of the United Republic of Tanzania, an area of high risk of cancer of the oesophagus (Munishi et al., 2015). Drinking temperatures of tea were measured using methods similar to those of the Golestan cohort study in the Islamic Republic of Iran. Participants were asked to prepare, pour, and drink tea in the normal manner. Temperatures were measured in an identical cup of tea poured at the same time. Participants started drinking the tea at a mean temperature of 70.6 °C (standard deviation, 3.9), and the temperature of the last of the tea before the full cup was consumed was 60.2 °C (standard deviation, 4.0). The two main types of tea consumed in the area were milky tea (milk and water boiled together in tea preparation) and black tea (no milk). Milky tea drinkers drank their tea 1.9 °C (95% CI, 0.9–2.9) hotter than drinkers of black tea, as black tea cooled twice as fast as milky tea. The temperature of the tea at which men started drinking was 0.9 °C (95% CI, −0.2 to 2.1) higher than that for women, and men finished their cups faster. Most participants self-reported their tea drinking as hot, but the measurements showed that over 90% of participants began drinking when the temperature of the tea was > 65 °C. A new exposure assessment tool additionally examined in this study was self-reported history of tongue/mouth burning from hot beverages. A strong positive correlation was found between a positive history and measured temperature of the beverage being consumed.

2. Cancer in Humans

2.1 Mate

See Table 2.1 and Table 2.1.2 (web only; available at: http://publications.iarc.fr/566).

A previous Working Group reviewed and evaluated the potential carcinogenicity of mate in Volume 51 (IARC, 1991). At that time, the available data included only seven relatively small case–control studies, three of which reported results on cancer of the oesophagus. In that evaluation, mate overall was considered *not classifiable as to its carcinogenicity to humans* (Group 3), while the Working Group concluded that there was *limited evidence* from studies in humans for the carcinogenicity of hot mate. Hot mate drinking was evaluated as *probably carcinogenic to humans* (Group 2A).

Since the previous evaluation, many more studies in humans have been published. All these studies have been conducted in South America, primarily in Uruguay but also in Argentina, Brazil, and Paraguay. The large majority of these studies have hospital-based case–control designs, with cases and controls coming from the same hospital, and are frequency- or individual-matched for age, sex, place of residence, and other covariates. Controls were selected from patients whose diseases were presumed to be unrelated to the case risk factors. Nearly all studies had very high (> 90%) case and control participation rates.

Some of these studies (mostly the more recent) focused on mate, while others (mostly older studies) investigated mate as part of a case–control study of several risk factors. Studies that focused on mate tend to have more extensive questions on the duration of mate drinking, typical frequency of drinking, daily quantity of consumption, and drinking temperature. More recent studies (typically those published after 1995) were more likely to use regression models to adjust for confounders and were therefore able

Table 2.1 Case–control studies on cancer of the oesophagus and drinking mate

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Cancer	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Castellsagué et al. (2000) Argentina, Brazil, Paraguay, Uruguay 1986–1992	Cases: 830 from hospitals and clinics in each study area (La Plata, Argentina; Porto Alegre and Pelotas, Brazil; Asuncion, Paraguay; Montevideo, Uruguay); histologically confirmed Controls: 1779 patients admitted to the same hospital during the same period, and matched for sex and age Exposure assessment method: questionnaire	Oesophagus (SCC)	Mate drinking status: Ever Former Current Mate amount (L/day): 0.01–0.5.0 0.51–1.00 1.01–1.50 1.51–2.00 > 2.00 Trend test *P* value, 0.0001 Mate temperature: Cold/ warm Hot Very hot Trend test *P* value, 0.008	 770 115 655 232 283 88 96 68 127 536 99 	 1.52 (1.10–2.12) 1.87 (1.25–2.80) 1.47 (1.06–2.05) 1.39 (0.98–1.98) 1.34 (0.95–1.90) 1.96 (1.27–3.03) 2.03 (1.32–3.13) 3.04 (1.84–5.02) 1.00 1.11 (0.84–1.47) 1.89 (1.24–2.86) 	Age, hospital, residence, education, cigarette smoking, alcohol intake, sex	IARC multinational study Strengths: pooled analysis of several studies with a large sample size, examining the interaction between mate amount and temperature Limitations: the question on mate temperature was about subjective perception of temperature
Szymańska et al. (2010) Seven centres in South America (Buenos Aires in Argentina; Goiania, Pelotas, Porto Alegre, Rio de Janeiro, and Sao Paolo in Brazil; and La Havana in Cuba) 1998	Cases: 80 patients with UADT cancers (including oesophageal) newly diagnosed or referred with no prior treatment in participating hospitals Controls: 240 in- or out-patients at the same hospitals as the cases Exposure assessment method: questionnaire	Oesophagus	Mate drinking status: Ever Mate temperature: Never drinker Cold/ warm Hot/very hot Trend test *P* value, 0.012	 157 9 15 56 	 3.81 (1.75–8.30) 1.00 7.52 (2.72–20.82) 3.33 (1.51–7.35) 	Age, sex, centre, education, tobacco smoking, alcohol drinking Age, sex, centre, education, tobacco pack-years, and alcohol gram-years	Limitations: the question on temperature was about subjective perception

Table 2.1 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Cancer	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sewram et al. (2003) Uruguay 1988–2000	Cases: 344 hospital-based, ascertained from the medical records of the Oncology Institute of Montevideo Controls: 469 hospital-based, from the same institute as cases Exposure assessment method: questionnaire	Oesophagus (SCC)	Mate drinking status			Age, sex, urban vs rural residence, education, smoking, alcohol intake	Limitations: the question on temperature was about subjective perception
			Ever	327	2.26 (1.19–4.27)		
			Mate temperature			As above	
			Non-drinkers	15	1.00		
			Warm/ hot	241	2.00 (1.05–3.81)		
			Very hot	54	3.98 (1.98–8.44)		
			Trend test *P* value, 0.004				
			Amount of mate consumption (L/day)			As above plus temperature and duration of consumption	
			0.01–0.50	73	1.69 (0.85–3.35)		
			0.51–1.00	152	2.47 (1.28–4.77)		
			≥ 1.01	102	2.84 (1.41–5.73)		
			Trend test *P* value, 0.02				
			Mate temperature among mate drinkers			As above plus amount and duration of mate consumption	
			Warm/ hot	241	1.00		
			Very hot	54	1.87 (1.17–3.00)		
			Mate consumption among mate drinkers (L/day):			Age, sex, urban vs rural residence, education, smoking, alcohol intake, temperature and duration of mate consumption	
			0.50–1.01	152	1.49 (1.00–2.23)		
			≥ 1.01	102	1.62 (1.01–2.62)		
			Trend test *P* value, 0.3				

Table 2.1 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Cancer	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lubin et al. (2014) Argentina, Brazil, Paraguay and Uruguay 1986–2005	Cases: 1400 hospital-based cases for IARC multinational study; in Uruguay, cases were ascertained from records of the Oncology Institute of Montevideo Controls: 3229 hospital-based; in Uruguay, patients with conditions unrelated to tobacco smoking and alcohol drinking, without recent changes in diet Exposure assessment method: questionnaire	Oesophagus (SCC)	Mate temperature			Study, age, sex, education, smoking (pack-years, cigarettes/day), alcohol consumption (drink-years, drinks/day) and for Uruguay income and urban vs rural residence Study, age, sex, education, cigarette smoking (pack-years, cigarettes/day), alcohol consumption (drink-years, mL ethanol/day) and for Uruguay income and urban vs rural residence	Pooled analysis of the IARC multinational study and another study from Uruguay (Castellsagué et al., 2000) Strengths: pooled analysis of several studies with a large sample size; examining the interaction between mate amount and temperature Limitations: the question on temperature was about subjective perception
			Never drinker	83	1.0		
			Warm	168	1.2 (0.8–1.7)		
			Hot	929	1.6 (1.2–2.2)		
			Very hot	213	2.2 (1.5–3.1)		
			Trend test *P* value, 0.01				
			Excess OR (L/day–yr) stratified by mate temperature				
			Warm	NR	0.004 (0.002–0.013)		
			Hot	NR	0.007 (0.003–0.013)		
			Very hot	NR	0.016 (0.009–0.027)		
			Trend test *P* value, < 0.01				
Dietz et al. (1998) Rio Grande do Sul, Brazil 1990–1991	Cases: 55 from the Endoscopy Service of General Hospital, Porto Alegre Controls: 110 patients undergoing endoscopy for gastroenterological complaints, with no evidence of cancer on the endoscopy Exposure assessment method: questionnaire	Oesophagus	Mate temperature			NR	Limitations: the question on tea temperature was about subjective perception of temperature
			Not hot	NR	1.00		
			Hot or very hot	39	2.55 (1.01–6.56)		

Table 2.1 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Cancer	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vassallo et al. (1985) Montevideo, Uruguay 1979–1984	Cases: 226 incident oesophageal SCC identified from the Cancer Registry at the Oncology Institute of Montevideo; histologically confirmed Controls: 469 other cancer cases from the same registry (common diagnoses were cancer of the skin, colorectum, prostate, and breast) Exposure assessment method: questionnaire; questionnaire administered at the time of admission to all patients	Oesophagus (SCC)	Mate consumption (men, L/day)			Age and tobacco and alcohol use	Limitations: controls were cancer patients
			Non-users	10	1.0		
			0.01–0.49	12	1.1 (0.2–5.0)		
			0.50–0.99	82	3.1 (1.2–7.8)		
			≥ 1	81	4.8 (1.9–12.1)		
			Trend test *P* value, < 0.000 01				
			Mate consumption (women, L/day)			Age	
			Non-users	1	1.0		
			0.01–0.49	3	2.1 (0.1–31.7)		
			0.50–0.99	20	12.5 (2.0–80.1)		
			≥ 1	13	34.6 (4.9–246.5)		

CI, confidence interval; NR, not reported; SCC, squamous cell carcinoma; UADT, upper aerodigestive tract

to adjust for more variables, and provided further details regarding dose–response.

No studies were excluded from this review; however, where data from several studies were reported in a combined analysis, the results are reported for the combined analysis rather than for individual studies. In some instances (mostly in studies from Uruguay) it was difficult to judge whether newer, larger publications included all data from older publications or only partially used older data. Such instances are mentioned where appropriate.

The results of these studies are summarized below, first for cancer of the oesophagus and then for other cancers.

2.1.1 Cancer of the oesophagus

Nine independent case–control studies of mate and cancer of the oesophagus were available to the Working Group: Vassallo et al. (1985), Victora et al. (1987), De Stefani et al. (1990a), Castelletto et al. (1994), Rolón et al. (1995), Dietz et al. (1998), Sewram et al. (2003), Szymańska et al. (2010), and De Stefani et al. (2014). There were also two pooled analyses (Castellsagué et al., 2000; Lubin et al., 2014) that may include some additional cases and controls. A summary of these studies is outlined below.

Vassallo et al. (1985) conducted a case–control study of mate consumption and cancer of the oesophagus. This study included 226 cases and 469 controls enrolled between 1979 and 1984, all from the Oncology Institute of Montevideo, Uruguay. The controls were selected from similar populations seeking medical care in the same medical facilities for other neoplastic conditions such as cancers of the skin, colorectum, prostate (for men), and breast (for women). Controls were not matched to cases for age or sex. The age-adjusted odds ratios were 6.7 (95% CI, 4.0–11.3) and 34.6 (95% CI, 4.9–247) for men and women, respectively, with a consumption of mate > 1 L/day. After adjusting for age and tobacco and alcohol consumption, there was a significant ($P < 0.000\,01$) dose–response association between mate drinking and risk of cancer of the oesophagus in men, with an odds ratio of 4.8 (95% CI, 1.9–12.1) for consuming more than 1 L/day, compared with no consumption. [No data on temperature were reported.]

Four case–control studies published between 1987 and 1995 reported on studies carried out by the International Agency for Research on Cancer (IARC) in Brazil (Victora et al., 1987), Uruguay (De Stefani et al., 1990a), Argentina (Castelletto et al., 1994) and Paraguay (Rolón et al., 1995). Individual results for these studies are not reported here, as Castellsagué et al. (2000) published a pooled analysis of these four studies plus a fifth study that had not been published previously; the pooled analysis is described in the following.

Since the five studies analysed by Castellsagué et al. (2000) were all designed and conducted by IARC, they could be combined. Cases (n = 830) were patients with histologically confirmed squamous cell carcinomas of the oesophagus, selected from major hospitals. Cases and controls were enrolled between 1986 and 1992. Case participation rates ranged over 90–99% in each of these studies. Controls (n = 1779) were selected from the same hospitals and matched to cases for sex and age (± 5 years). The combined results showed an increased risk of squamous cell carcinoma for mate drinking (OR, 1.52; 95% CI, 1.10–2.12 for any consumption). An independent increased risk was associated with both quantity and temperature of mate consumed, even after adjustment for other major risk factors such as tobacco smoking and alcohol consumption. The overall adjusted odds ratio for mate temperature (very hot vs hot/warm/cold) was 1.89 (95% CI, 1.24–2.86) and for mate quantity (> 2 L/day vs none) was 3.04 (95% CI, 1.84–5.02). The joint effect of mate temperature and mate quantity showed a higher than multiplicative pattern, with a significant P value for interaction (0.02). There

was a statistically significant dose–response relationship for mate temperature ($P = 0.008$) and for mate quantity ($P = 0.0001$). [Regarding temperature, the odds ratio for drinking very hot mate was considerably greater than for drinking hot mate.]

Dietz et al. (1998) reported a case–control study of mate drinking and cancer of the oesophagus. The cases ($n = 55$) and controls ($n = 110$) were recruited between 1990 and 1991 from an endoscopy clinic in Rio Grande do Sul, Brazil. Controls were those who underwent endoscopy because of gastroenterological problems, but had no cancer. [This may be a concern, as controls may not be representative of the entire population for their mate drinking.] Controls were matched to cases for age and sex, but no further selection criteria were discussed. Questions were asked about age, sex, and consumption of alcohol, tobacco, mate, and other foods. The interviewer was blind to the case status of the study participants. No details were provided on definitions of amount, temperature, or frequency. The study found that drinking hot or very hot mate (vs "not hot") (OR, 2.55; 95% CI, 1.01–6.56) and daily intake of mate (OR, 5.58; 95% CI, 1.11–36.5) were associated with a higher risk of cancer of the oesophagus. [It is not clear whether these findings were adjusted for other risk factors; although the text states that multivariable analyses were performed, the covariates are not listed. A limitation of the study was that the controls were selected from a group of patients who underwent endoscopy.]

Sewram et al. (2003) published the results of a case–control study of mate consumption and squamous cell carcinoma (SCC) of the oesophagus. The cases ($n = 344$) and controls ($n = 469$) were recruited in Montevideo, Uruguay, from 1988 to 2000. The cases were histologically confirmed. The controls were selected from a variety of benign conditions and were matched to cases for sex, with a response rate of 93%. After adjusting for age, smoking, alcohol consumption, and several other factors, ever consuming mate was associated with a substantial increase in risk of squamous cell carcinoma (OR, 2.26; 95% CI, 1.19–4.27). High daily consumption (> 1 L/day) was associated with a higher risk (OR, 2.84; 95% CI, 1.41–5.73) compared with non-drinkers. Both temperature and amount of mate intake were significantly associated with higher risk of oesophageal squamous cell carcinoma. Among mate drinkers, consuming very hot mate (vs warm or hot) was associated with an increased risk (OR, 1.87; 95% CI, 1.17–3:00) after adjusting for amount of mate intake and several other risk factors. Likewise, those who consumed more than 1 L/day had a higher risk (OR, 1.62; 95% CI, 1.01–2.62) compared with those who drank between 0.1 L/day and 0.5 L/day. [There may be partial overlap between this study from 1998–1992 with one of the studies in Uruguay included in the combined analysis reported by Castellsagué et al. (2000).]

Szymańska et al. (2010) examined the association between mate drinking and cancer of the oesophagus as part of a large multicentre study of cancers of the upper aerodigestive tract in South America (seven cities in Argentina, Brazil, and Cuba); however, data from only four centres in Argentina and Brazil were used, as mate consumption was very low in other centres. The study included 80 cases of cancer of the oesophagus and 240 controls, frequency-matched to cases for sex, age, and centre. Participants were queried about ever use, amount, duration, and cumulative amount of mate drinking, as well as other variables such as smoking and alcohol drinking. After adjusting for important confounders such as age, sex, centre, smoking, and alcohol consumption, mate drinking was associated with an increased risk of cancer of the oesophagus with an odds ratio of 3.81 (95% CI, 1.75–8.30). There was a dose–response relationship for quantity of daily mate intake, as well as for duration of use and cumulative consumption. Compared with non-drinkers, an increased risk of cancer of the oesophagus was reported for

drinkers of cold/warm mate (OR, 7.52; 95% CI, 2.72–20.82) and drinkers of hot/very hot mate (OR, 3.33; 95% CI, 1.51–7.35).

De Stefani et al. (2014) published a study of diet and squamous cell carcinoma of the oesophagus, in which mate was also examined. Cases (n = 234) were diagnosed microscopically between 1996 and 2005 from patients referred to four major public health hospitals in Uruguay. Controls (n = 936) were selected from the same hospitals and in the same time period from patients with non-neoplastic conditions that were not etiologically related to smoking or alcohol drinking. Controls were frequency-matched to the cases for age (in 10-year periods), sex, and place of residence (Montevideo, other counties). After adjusting for major confounders, mate consumption (third tertile vs first tertile of mate years) was associated with a higher risk of oesophageal squamous cell carcinoma (OR, 2.04; 95% CI, 1.32–3.16). [It was unclear how much overlap exists between this study and those reported earlier (Sewram et al., 2003) or later (Lubin et al., 2014); the Working Group considered it most likely that these results were covered in the analyses by Lubin et al. (2014).]

Lubin et al. (2014) pooled data from the five IARC case–control studies described above (Castellsagué et al., 2000) and a case–control study from Uruguay to study the independent effect of cumulative use of mate and its temperature on the risk of squamous cell carcinoma of the oesophagus. The additional study from Uruguay was conducted within the Oncology Institute of Montevideo and cases were enrolled from 1988 to 2005. Controls were from the same institute, selected from diseases unrelated to smoking and alcohol consumption, and matched to cases for sex and age. A total of 1400 cases and 3229 controls were included. [There seemed to be substantial overlap for cases and controls for this study and those reported in Sewram et al. (2003) and De Stefani et al. (2014); only cases and controls recruited after 2000 may be new.] Overall, there was an increase in the odds ratio for ever versus never use of mate (OR, 1.60; 95% CI, 1.2–2.2). The pooled adjusted odds ratio for drinking warm, hot, and very hot mate (vs never drinkers) were 1.2 (95% CI, 0.8–1.7), 1.6 (95% CI, 1.2–2.2), and 2.2 (95% CI, 1.5–3.1), respectively, with a P value for trend of 0.01. The excess odds ratio (EOR) was calculated based on intensity, duration, and cumulative use of mate, and it was found that EOR was mainly a function of cumulative use as measured by litres consumed per day × years of drinking (LPDY). After considering cumulative use, whether the mate consumer demonstrated high-intensity/short-duration or low-intensity/long-duration use had no effect on the results. The EOR for LPDY varied by temperature of use: EOR/LPDY estimates for consumption of warm, hot, and very hot mate were 0.004 (95% CI, 0.002–0.013), 0.007 (95% CI, 0.003–0.013), and 0.016 (95% CI, 0.009–0.027), respectively, and differed significantly (P < 0.01). There was a significant interaction (P = 0.02) between mate consumption and smoking, and the exposure–response relationship was strongest in never smokers of tobacco (EOR/LPDY, 0.018; 95% CI, 0.007–0.038). [This pooled analysis included all of the studies described above except Vassallo et al. (1985), Dietz et al. (1998), and Szymańska et al. (2010), which were not from Uruguay.]

2.1.2 Other cancers

Mate drinking has been studied in relation to cancers at several sites, including the upper aerodigestive tract (oral cavity, pharynx, hypopharynx, and larynx), lung, stomach, colon, rectum, kidney, bladder, prostate, and breast. Nearly all studies are hospital-based case–control studies, in which cases are histologically diagnosed. In general, participation rates for cases and controls are very high (> 90%). Data are typically available for major confounders, such as age, sex, place of residence, tobacco consumption, and alcohol consumption, and these factors

are adjusted for. All of the data come from South America, in particular from Uruguay where several case–control studies have been conducted for mate and a host of cancers. These studies are summarized below by cancer site.

(a) Cancers of the upper aerodigestive tract

De Stefani et al. (1987) reported the results of a case–control study of 107 patients with cancer of the larynx and 290 controls from the University Hospital of Montevideo, Uruguay. Cases were those identified between 1985 and 1986; controls were those with diseases considered not related to tobacco and alcohol, chosen from the same hospital for the same time period. Data were collected on demographic variables, tobacco and alcohol consumption, consumption of several food items, mate drinking, and other covariates. Mate drinking was associated with a 3-fold increased risk of cancer of the larynx, with an odds ratio of 3.4 (95% CI, 1.8–6.6) after controlling for the effects of age and tobacco and alcohol consumption.

De Stefani et al. (1988) reported the results of a case–control study of 108 cases of cancers of the oropharynx and 286 controls, also in Montevideo, Uruguay, with a similar design and methods, and restricted to men. Patients diagnosed with cancers of the lip, salivary gland, and nasopharynx were excluded. Mate exposure showed a significant dose–response association with risk of cancer of the oropharynx. After adjustment for age and tobacco and alcohol intake, drinking 1.00–1.99 L/day and > 2 L/day compared with drinking < 1 L/day of mate was associated with a relative risk of 2.5 (95% CI, 1.1–5.7) and 5.2 (95% CI, 2.1–13.1), respectively.

Franco et al. (1989) reported on the results of the association between mate intake and oral cavity cancers (carcinomas of the tongue, gum, floor, and other parts of the mouth). This case–control study was conducted in three metropolitan areas in Brazil (São Paulo), Curitiba, and Goiânia between 1986 and 1988. Interviews were conducted with 232 cases and 464 hospital non-cancer controls matched for 5-year age group, sex, hospital catchment area, and trimester of admission. After adjusting for tobacco and alcohol consumption, compared with drinking < 1 cup of mate per month, drinking 1–30 cups/month and > 30 cups/month was associated with odds ratios of 1.6 (95% CI, 0.8–3.3) and 1.6 (95% CI, 0.8–3.3), respectively. Most of the increased risk was seen for cancer of the tongue.

Oreggia et al. (1991) published the results of a study on mate consumption and cancer of the tongue in men. The study involved interviews with 57 cases and 353 controls identified in 1987–1989. All cases were squamous cell carcinomas. The design and methods were similar to those of De Stefani et al. (1987). Compared with consuming mate at < 1 L/day, consuming more than 2 L/day was associated with an increased risk with a crude odds ratio of 2.5 (95% CI, 1.2–5.6). After adjusting for age and tobacco use, this odds ratio was reduced to 1.8 [no confidence intervals reported. Further adjustment for other variables (e.g. alcohol drinking) was not reported.]

Pintos et al. (1994) reported on a case–control study of cancers of the upper aerodigestive tract in relation to mate drinking. Cases (n = 378) were all newly diagnosed patients with cancers of the mouth, pharynx, and larynx referred to Erasto Gaertner Hospital, Brazil, between 1987 and 1989. Controls (n = 756) were selected from this hospital or another general hospital in the same city, and matched to cases (2 : 1) for sex, age (5-year groups), and trimester of admission. Data were available for mate drinking and intensity of consumption, as well as for other potential confounders including tobacco and alcohol consumption. After adjusting for potential confounders, the odds ratio was 1.6 (95% CI, 1.2–2.2). The excess risk was mainly seen for cancers of the oral cavity (OR, 1.9; 95% CI, 1.1–3.3) and larynx (OR, 2.2; 95% CI, 1.1–4.5), but not cancer of the pharynx. There was a clear

dose–response pattern for all cancers combined (*P* for trend = 0.001) and for cancers of the oral cavity and larynx.

As part of their multisite study of mate and cancers of the upper aerodigestive tract, Szymańska et al. (2010) reported results on 628 cases of cancer of the oropharynx, 410 cancers of the hypopharynx and larynx, and 1026 controls. The design was described earlier in Section 2.1.1. Controls were frequency-matched to cases for sex, age, and centre. Participants were questioned on ever use, amount, duration, and cumulative amount of mate drinking as well as on other variables such as smoking and alcohol consumption. After adjusting for important confounders, ever drinking mate was associated with an increased risk of cancers of the oral cavity and oropharynx (OR, 1.48; 95% CI, 1.05–2.08) and hypopharynx and larynx (OR, 1.51; 95% CI, 1.05–2.18). There was some evidence of a dose–response relationship with cumulative use (litres per lifetime), which was marginally significant (*P* for trend, 0.08 and 0.07, for cancers of the oral cavity and oropharynx, and hypopharynx and larynx, respectively). There was no clear association with temperature of mate intake; in fact, the odds ratios were higher for cold/warm mate than hot/very hot mate (2.89 vs 1.15 for cancers of the oral cavity and oropharynx, and 2.33 vs 1.28 for cancers of the hypopharynx and larynx). When the study was limited to people who never smoked or drank (37 cases and 176 controls), ever drinking mate was associated with an increased risk of all cancers of the upper aerodigestive tract with an odds ratio of 2.81 (95% CI, 1.08–7.34). [These results are consistent with the findings of Lubin et al. (2014), in that associations were seen for non-smokers and non-drinkers.]

Deneo-Pellegrini et al. (2013) reported on a case–control study of mate drinking and squamous cell cancers originating from the oral cavity based on a reanalysis of data presented in a previous study (De Stefani et al., 2011). The cases (n = 696) and controls (n = 696) were all men, selected from the Cancer Institute of Montevideo, Uruguay, between 1990 and 2001. Controls were selected from conditions not related to tobacco smoking or alcohol consumption, and were frequency-matched to cases for age and place of residence. In analyses adjusted for main confounders such as tobacco and alcohol consumption, the odds ratio was 1.15 (95% CI, 0.76–1.73). There was highly significant (P < 0.001) interaction between the mate consumption variables and alcohol and tobacco use. [Some aspects of the analysis were unclear; for example, the interaction terms were not fully shown. The results are at least partially included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(b) Cancer of the lung

De Stefani et al. (1996) conducted a case–control study of mate consumption in relation to cancer of the lung. Cases were 497 men admitted to the Oncology Institute of Montevideo, Uruguay, from 1988 to 1994. Controls (n = 497) were from those admitted to the same hospital, and were frequency-matched to cases for age and place of residence. Controls were selected from among non-neoplastic conditions, or cancers that were deemed to be unrelated to mate consumption (e.g. cancer of the prostate). After adjusting for potential confounders including pack-years of cigarette smoking, mate drinking was associated with a higher risk of cancer of the lung with an odds ratio of 2.4 (95% CI, 1.3–4.3). There was a statistically significant dose–response relationship with intensity (litres per day) (P < 0.001), duration (P = 0.005), and cumulative use (P = 0.001). This association was strongest for small cell lung cancer but virtually non-existent for adenocarcinoma of the lung. [The results may have been partially included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(c) Cancer of the stomach

De Stefani et al. (1990b) conducted a case–control study of mate drinking and gastric cancer. The cases (n = 210) and controls (n = 630) were selected from those admitted to the University Hospital of Montevideo, Uruguay, during July 1985–December 1988. Cases and controls received the same detailed questionnaire from three social workers who were unaware of the objectives of the study. Mate ingestion was associated with an increased risk of cancer of the stomach in both sexes. After adjusting for age, sex, smoking duration, wine ingestion, and place of residence, compared with drinking mate at < 1 L/day, drinking 1–1.99 L/day and ≥ 2 L/day was associated with relative risks of 1.0 (95% CI, 0.1–1.5) and 2.7 (95% CI, 1.7–4.2), respectively.

(d) Cancer of the kidney

De Stefani et al. (1998) conducted a case–control study of mate drinking and renal cell carcinoma with 121 histologically verified cases admitted to a hospital in Montevideo, Uruguay, between 1988 and 1995. Controls (n = 243) were selected from the same institution, from patients who did not have any malignancy or conditions assumed to be related to mate consumption. Controls were frequency-matched to cases (2 : 1) for age, sex, and place of residence. After adjusting for potential confounders, ever drinking mate was associated with a non-significant increased risk of renal cell carcinoma with an odds ratio of 1.6 (95% CI, 0.7–3.3). There was a dose–response relationship with intensity (P = 0.003), duration (P = 0.07), and cumulative use (P = 0.02) of mate. For example, those who consumed more than 2 L of mate per day had an increased risk with an odds ratio of 3.1 (95% CI, 1.3–7.9). [The results may be partially included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(e) Cancer of the bladder

Iscovich et al. (1987) conducted a study of several risk factors, including mate drinking, in relation to cancer of the bladder in Argentina. A total of 117 cases of cancer of the bladder, 117 hospital controls, and 117 neighbourhood controls were enrolled in this study. All cases were histologically confirmed, and 93% were transitional cell carcinomas. Controls were matched to cases for sex and age. Cases and controls were recruited from patients during the period 1983–1985. Of these, 99 cases and 198 controls were included in the mate analysis. After adjusting for age and cigarette smoking, the odds ratios for mate drinking were 2.0, 0.9, and 0.8 for drinking < 10 drinks, 10–19 drinks, and ≥ 20 drinks per day compared with not drinking any mate. [No confidence intervals were provided. The Working Group estimated P for trend = 0.05, suggestive of a negative trend.]

De Stefani et al. (1991) reported a case–control study of mate drinking and transitional cell carcinoma of the bladder. The cases (n = 111) comprised patients newly diagnosed between 1987 and 1989 in two major hospitals in Montevideo, Uruguay. The controls (n = 222) were selected from patients from the same hospitals with conditions unrelated to tobacco smoking, and were matched to cases by age and sex. A strong dose–response association was observed between mate drinking and cancer of the bladder, even after adjusting for sex, age, and tobacco consumption. For example, when analysis was limited to men and adjusted for age, place of residence, social class, and type and duration of tobacco use, compared with those who consumed < 0.5 L of mate per day, those who consumed increasingly higher amounts per day had odds ratios of 3.3 (95% CI, 0.6–19.3) for 0.5–0.99 L/day, 5.2 (95% CI, 0.9–29.3) for 1.0–1.9 L/day, and 7.2 (95% CI, 1.2–41.6) for ≥ 1.5 L /day, with a P value for the trend of 0.004. The joint association of tobacco and mate with bladder cancer followed a multiplicative model.

De Stefani et al. (2007) reported the results of another hospital-based case–control study of transitional cell carcinoma of the bladder and mate drinking. Incident cases (n = 255) were recruited from patients diagnosed in one of the four major hospitals in Montevideo, Uruguay, during 1996–2000. Controls (n = 501) were selected over the same time period and in the same hospitals from patients with diseases not related to tobacco smoking or alcohol drinking and without recent changes in their diet. Controls were frequency-matched to cases for age, sex, and place of residence. Data on mate consumption were obtained by interview. Ever drinking mate was associated with an increased risk of cancer of the bladder, with an adjusted odds ratio of 2.2 (95% CI, 1.2–3.9). Intensity (litres per day) ($P < 0.01$), duration ($P < 0.01$), and cumulative consumption ($P < 0.01$) showed a dose–response relationship. There was also evidence of a trend of risk increasing with temperature (P for trend not reported). Compared with non-drinkers, those who drank mate warm, hot, and very hot had odds ratios of 2.1 (95% CI, 0.8–5.4), 2.1 (95% CI, 1.2–3.7), and 4.9 (95% CI, 2.2–11), respectively. [The results were possibly included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

Bates et al. (2007) published findings from a case–control study of mate consumption in relation to transitional cell carcinoma of the bladder. The cases (n = 114), identified by pathologists and urologists, were enrolled during 1996–2000 from patients resident in the counties of Union and Marcos Juarez, Cordoba Province, Argentina; all were histologically confirmed. Controls (n = 114) (matched according to county of residence, sex, and year of birth) were identified from voter registration lists. Data regarding consumption of beverages, smoking, and occupational and medical histories were collected by questionnaire. Separate questions concerned consumption of mate *con bombilla* and mate *cocido*. There was no overall association between mate *con bombilla* or *cocido* consumption at the time of interview, 20 years before the interview, or 40 years before the interview and risk of cancer of the bladder in analyses that controlled for smoking status, sex, and year of birth. The only significant association (OR, 3.77; 95% CI, 1.17–12.1) was for those who consumed mate *con bombilla* 20 years before the interview and were ever smokers.

(f) Cancer of the prostate

Deneo-Pellegrini et al. (2012) reported a case–control study of mate drinking and cancer of the prostate. Cases (n = 326) were recruited from four major hospitals in Montevideo, Uruguay, between 1996 and 2004. Controls (n = 652) were selected from patients from the same hospitals with diseases not related to smoking or drinking. Those with a recent dietary change were excluded. Controls were frequency-matched to cases according to age and place of residence. A detailed questionnaire was completed for both cases and controls during a face-to-face interview. After adjusting for age, place of residence, urban/rural status, education, family history of prostate cancer among first-degree relatives, body mass index, and total energy intake, mate intake was associated with a higher risk of cancer of the prostate. Compared with the first tertile, the second and third tertiles of use were associated with odds ratios of 1.40 (95% CI, 0.87–2.26) and 1.96 (95% CI, 1.17–3.31), respectively, with a P value for trend of 0.005. [The results were possibly included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(g) Cancer of the breast

Ronco et al. (2016) combined the results of two case–control studies from two hospitals in Uruguay. The overall design of this study was similar to other studies on mate from Uruguay, with cases and controls from the same hospitals and matched for age and residence. All cases and

controls were women. A total of 572 incident cases of cancer of the breast and 889 controls were interviewed with a questionnaire. After adjusting for multiple risk factors for breast cancer, odds ratios for increasing cumulative dose of mate (litres consumed per day × years of drinking) were 0.74 (95% CI, 0.51–1.07), 0.68 (95% CI, 0.47–0.98), and 0.50 (95% CI, 0.34–0.73), suggesting an inverse association between mate drinking and risk of cancer of the breast (*P* for trend < 0.001). [The data seemed to be a subsample of the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(h) Cancer at multiple sites

De Stefani et al. (2011) published the results of their case–control study of mate drinking in relation to cancers arising from 13 sites (mouth, pharynx, oesophagus, stomach, colon, rectum, larynx, lung, female breast, cervix uteri, prostate, bladder, and kidney). The study was conducted between 1990 and 2004 and included cases (*n* = 8875) selected from the four major hospitals in Montevideo, Uruguay. The numbers for each cancer site were 360 mouth, 424 pharynx, 605 oesophagus, 408 stomach, 334 colon, 428 rectum, 554 larynx, 2045 lung, 2061 female breast, 233 cervix uteri, 720 prostate, 429 bladder, and 274 kidney. Controls (*n* = 4326) were drawn from the same hospitals and the same time period and included patients with non-neoplastic conditions, unrelated to tobacco smoking or alcohol drinking, and without recent changes in their diets. Odds ratios and 95% confidence intervals were estimated using polytomous multiple regressions. Compared with not drinking any mate, drinking > 2 L/day was associated with an increased risk of cancers of the bladder (OR, 3.88; 95% CI, 2.47–6.08; *P* for trend < 0.0001), oesophagus (OR, 3.09; 95% CI, 1.95–4.91; *P* for trend < 0.0001), kidney (OR, 2.27; 95% CI, 1.39–3.72; *P* for trend < 0.0001), cervix uteri (OR, 2.1; 95% CI, 1.19–3.72; *P* for trend < 0.0001), lung (OR, 1.99; 95% CI, 1.55–2.58; *P* for trend < 0.0001), prostate (OR, 1.73; 95% CI, 1.22–2.45; 0.003), larynx (OR, 1.54; 95% CI, 1.03–2.32; *P* for trend = 0.06), and stomach (OR, 1.52; 95% CI, 1.01–2.29; *P* for trend = 0.02). In contrast, mate drinking was not associated with a higher risk of cancers of the mouth, pharynx, colon, rectum, or female breast. Hot mate drinking was significantly associated with an increased risk of cancers of the upper aerodigestive tract (OR, 1.41; 95% CI, 1.12–1.79; *P* = 0.0001), larynx (OR, 1.57; 95% CI, 1.07–2.31; *P* = 0.001), lung (OR, 1.95; 95% CI, 1.53–2.49; *P* < 0.0001), prostate (OR, 1.58; 95% CI, 1.18–2.13; *P* = 0.002), bladder (OR, 2.42; 95% CI, 1.58–3.69; *P* < 0.0001), and kidney (OR, 1.96; 95% CI, 1.22–3.14; *P* = 0.004) when compared with non-drinkers.

Combining all cancers included in this analysis, compared with non-drinkers odds ratios were 1.30 (95% CI, 1.14–1.47) for drinking < 1 L/day, 1.38 (95% CI, 1.22–1.56) for drinking 1 to < 2L/day and 1.50 (95% CI, 1.30–1.72) for drinking ≥ 2 L/day (*P* for trend < 0.0001). Combining all sites, odds ratios were 1.22 (95% CI, 1.07–1.39) for drinking warm mate and 1.46 (95% CI, 1.29–1.66) for drinking hot mate (*P* for trend < 0.0001).

2.2 Very hot beverages other than mate

Since the previous review of the carcinogenicity of coffee, tea, and mate (IARC, 1991), additional studies have reported data on the association between beverage temperature and risk of cancer. These studies concerning hot beverages other than mate are reviewed in this section. Studies on the association between hot mate drinking and cancer are described in Section 2.1.

The majority of studies of the association between drinking very hot beverages other than mate and cancer have focused on cancer of the oesophagus. The evidence is therefore reviewed in two sections: one on cancer of the oesophagus

(Section 2.2.1), and a second including all other cancers (Section 2.2.2). Beverage temperature was typically assessed through questions about participants' subjective perception of temperature. In this review, studies in which the reference group consisted only of those who did not drink the beverage of interest were given lower weight, except when two or more categories of beverage temperature were separately compared with this reference group, as this would allow risk estimates of drinking low- and high-temperature beverages to be compared.

2.2.1 Cancer of the oesophagus

See Table 2.2.

(a) Very hot tea and cancer of the oesophagus

One cohort study, 15 case–control studies, and a pooled analysis of multiple case–control studies that investigated the association between very hot tea and cancer of the oesophagus were available to the Working Group. The studies that reported results only for tea combined with other beverages are discussed in Section 2.2.1 (c).

(i) Cohort study

Kinjo et al. (1998) reported results of a prospective study of 220 272 individuals (aged 40–69 years at the baseline) in 29 public health districts in 6 prefectures in Japan. The participants were recruited in 1965 and followed up until 1981. A total of 440 deaths from cancer of the oesophagus were identified from the follow-up period of 1966–1981. Drinking hot tea (vs non-hot tea) was associated with the risk of death from cancer of the oesophagus (OR, 1.5; 95% CI, 1.1–1.9) in analyses that controlled for age, occupation, sex, locality (prefecture), green and yellow vegetable consumption, alcohol consumption, and tobacco use.

(ii) Case–control studies

Kaufman et al. (1965) studied 82 cases of cancer of the oesophagus and 73 controls in Kazakhstan, former Soviet Union, and later added 51 cases from another area. Finally, 127 cases and 72 controls were included in the analysis. Drinking (vs not drinking) very hot tea was associated with a higher risk of cancer of the oesophagus [crude OR, 3.18; 95% CI, 1.60–6.48]. In the same region, Bashirov et al. (1968) compared tea-drinking habits in 301 cases of cancer of the oesophagus (142 men and 159 women) and 301 healthy population controls. Cancer of the oesophagus was more common among those who reported drinking ≥ 7 cups of hot black tea at a single sitting than others [OR, 2.6; $P < 0.01$ in men; OR, 3.2; statistically non-significant in women]. Neither study adjusted for smoking, alcohol, or any other risk factors; however, in the study by Bashirov et al. (1968), duration of smoking and the amount of nass use (a smokeless tobacco product) in cases and controls were comparable. [The Working Group noted that it was unclear whether or not the reference groups in these two studies included those who did not drink the beverage of interest.]

De Jong et al. (1974) reported results of a hospital-based case–control study of cancer of the oesophagus among Singaporeans conducted in 1970–1972. For the 131 cancer cases included in this study (95 men and 36 women), 345 controls from non-cancer patients from the same ward and 320 controls from orthopaedic patients from a general hospital were recruited, matching for age and sex. In this study, drinking "burning hot" tea, coffee, and barley (compared with not drinking these hot drinks) was associated with a statistically significant increased risk of cancer of the oesophagus in both men and women in analyses that were only adjusted for dialect group. In the multivariate models that were adjusted for several potential confounding factors, including smoking and alcohol drinking, the authors used

Table 2.2 Epidemiological studies on cancer of the oesophagus and drinking very hot beverages other than mate

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tran et al. (2005) Linxian, China 1986–2001 Cohort	29 584 adults with no history of cancer from the general population Exposure assessment method: questionnaire (all study participants were interviewed to complete a baseline questionnaire in 1984)	Oesophagus (SCC)	Hot liquid (in summer) 0 time/year ≥ 1 Hot liquid (in winter) 0 time/year ≥ 1	 NR NR NR NR	 1.00 0.96 (0.87–1.07) 1.00 0.95 (0.87–1.04)	Age and sex	Strengths: prospective design; results for at least one specified histological subtype Limitations: the number of cases in each category of exposure was not reported
Kaufman et al. (1965)[a] Kazakhstan, former Soviet Union NR Case–control	Cases: 127 Controls: 72 Exposure assessment method: questionnaire	Oesophagus	Tea temperature Does not drink hot tea Drinks hot tea	 64 63	 1.00 [3.18 (1.60–6.48)]	None	The *P* value for the association was < 0.001. Limitations: no adjustments for some major risk factors of oesophageal cancer, notably smoking

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bashirov et al. (1968)[b] Kazakhstan, former Soviet Union NR Case–control	Cases: 301 Controls: 301 Exposure assessment method: questionnaire	Oesophagus	Glasses of hot tea at a time (men) < 7 ≥ 7 Glasses of hot tea at a time (women) < 7 ≥ 7	 NR NR NR NR	 1.00 [2.6] 1.00 [3.2]		The *P* value for the association in men was < 0.01. The association was not statistically significant in women. Limitations: no adjustments for some major risk factors of oesophageal cancer, notably smoking; however, duration of smoking and the amount of nass use (a chewing tobacco product) in cases and controls were comparable
De Jong et al. (1974) Singapore 1970–1972 Case–control	Cases: 131 patients admitted for dysphagia/weight loss who had an oesophageal tumour in radiographies; adenocarcinoma and cardia tumours excluded Controls: 665, 2 per case from the same ward as the case and 2 per case from orthopaedic units of one hospital, matched for sex and age Exposure assessment method: questionnaire	Oesophagus	Beverage temperature (men) Per unit temperature score Trend test *P* value, 0.01 Beverage temperature (women) Per unit temperature score Trend test *P* value, 0.01	 95 36 	 [2.10 (1.83–2.40)] [2.47 (1.87–3.26)] 	Birthplace, dialect group, education, smoking, alcohol drinking, and intake of bread, potatoes, and bananas	82% of cases histologically confirmed Limitations: results from multivariate analyses reported only for a combination of three types of hot beverages, not for individual beverages

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cook-Mozaffari et al. (1979) Islamic Republic of Iran 1975–1976 Case–control	Cases: 344 from Caspian Cancer Registry, northern Islamic Republic of Iran; 4% confirmed histologically Controls: 688 randomly selected from the same village or town as cases; individually matched for age, sex, and place of residence Exposure assessment method: questionnaire	Oesophagus	Tea temperature (men) Non-hot Hot Tea temperature (women) Non-hot Hot	 NR NR NR NR	 1.00 1.72 1.00 2.17	Full account of matching was taken in the presented results	Limitations: Proxy interviews for about 20% of cases. No adjustments for some major risk factors of oesophageal cancer, notably smoking. However, alcohol drinking in both sexes and smoking in women were uncommon habits in this study
Gao et al. (1994) Shanghai, China 1990–1993 Case–control	Cases: 902 from Shanghai Cancer Registry Controls: 1552 from population (Shanghai Resident Registry) Exposure assessment method: questionnaire	Oesophagus	Soup or porridge temperature (men only) Cold/neither cold nor hot Hot Burning hot Trend test *P* value, 0.001 Soup or porridge temperature (women only) Cold/neither cold nor hot Hot Burning hot Trend test *P* value, 0.001	 NR NR NR NR NR NR	 1.00 1.21 (0.88–1.66) 4.75 (3.33–6.79) 1.00 1.90 (1.29–2.79) 6.77 (4.09–11.20)	Age, education, birthplace, tea drinking, cigarette smoking, alcohol drinking, and consumption of preserved foods, vegetables, and fruit	Part of a larger study of cancers of the oesophagus, pancreas, colon, and rectum Strengths: large sample size Limitations: the number of cases in each category of soup/ porridge temperature was not reported

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Launoy et al. (1997) France, three regions 1991–1994 Case–control	Cases: 208 men admitted to university hospitals; histologically confirmed Controls: 399 men admitted to the same hospitals in rheumatology, orthopaedics, or ophthalmology units; matched for hospital and age Exposure assessment method: questionnaire	Oesophagus (SCC)	Cold calvados (calvados drunk alone, g alcohol/week)			Age, residence, occupation, education, marital status, smoking, interviewer, intake of total and specific alcoholic drinks	It would be difficult to separate the effect of temperature from that of alcohol on development of oesophageal cancer Strengths: results for at least one specified histological subtype Limitations: men only
			Non-drinker	195	1.00		
			1–5	9	1.01 (0.37–2.74)		
			≥ 6	4	0.86 (0.20–3.78)		
			Hot calvados (calvados drunk with coffee, g alcohol/week)				
			Non-drinker	124	1.00		
			1–20	24	1.40 (0.67–3.92)		
			21–40	8	1.40 (0.39–5.08)		
			≥ 41	52	2.33 (1.12–4.87)		
			Trend test *P* value, < 0.05				
			Cold spirits (spirits drunk alone, g alcohol/week)				
			Non-drinker	130	1.00		
			1–5	44	0.73 (0.42–1.27)		
			6–10	13	0.68 (0.28–1.62)		
			≥ 11	21	0.76 (0.36–1.61)		
			Hot spirits (spirits drunk with hot water or coffee, g alcohol/week)				
			Non-drinker	163	1.00		
			1–5	14	0.80 (0.33–1.94)		
			6–10	5	1.65 (0.37–7.33)		
			≥ 11	26	1.83 (0.91–4.31)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Garidou et al. (1996) Athens, Greece 1989–1991 Case–control	Cases: 99 (43 SCC, 56 adenocarcinoma) from nine collaborating hospitals; cases were histologically confirmed Controls: 200 Athens residents hospitalized for injury; individually matched for age and sex Exposure assessment method: questionnaire	Oesophagus (SCC)	Temperature preference for beverages and foods			Age, sex, birthplace, education, height, analgesics, coffee drinking, tobacco and alcohol use, and energy intake	Strengths: results for at least one specified histological subtype Limitations: small sample size
			Cold	30	1.00		
			Hot or very hot	13	1.89 (0.80–4.49)		
			Trend test *P* value, 0.15				
		Oesophagus (adenocarcinoma)	Temperature preference for beverages and foods				
			Cold	41	1.00		
			Hot or very hot	15	1.82 (0.85–3.91)		
			Trend test *P* value, 0.13				
Kinjo et al. (1998) Japan 1966–1981 Cohort	220 272 individuals from 29 public health districts in 6 prefectures Exposure assessment method: questionnaire	Oesophagus	Tea temperature			Age, sex, prefecture, occupation, green-yellow vegetable intake, and tobacco and alcohol use	Strengths: prospective design Limitations: data on histology were not available
			Not hot	344	1.00		
			Hot	96	1.5 (1.1–1.9)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Castellsagué et al. (2000) Uruguay, Argentina, Brazil, Paraguay 1985–1992 Case–control	Cases: 830 from hospitals and clinics in each study area (La Plata, Argentina; Porto Alegre and Pelotas, Brazil; Asuncion, Paraguay; Montevideo, Uruguay); histologically confirmed Controls: 1779 patients admitted to the same hospital during the same period as the cases and matched for sex and age Exposure assessment method: questionnaire	Oesophagus (SCC)	Coffee temperature			Age, sex, prefecture, occupation, green-yellow vegetable intake, and tobacco and alcohol use	Strengths: pooled analysis of several studies with a large sample size; results for at least one specified histological subtype Limitations: small number of tea drinkers in this study
			Cold–warm	48	1.00		
			Hot	146	0.54 (0.33–0.87)		
			Very hot	34	1.01 (0.52–1.98)		
			Trend test *P* value, 0.6				
			Any very hot beverage (including mate)				
			Never very hot	554	1.00		
			Ever very hot	135	2.07 (1.55–2.76)		
			Any very hot beverage (other than mate)				
			Never very hot	404	1.00		
			Ever very hot	90	2.45 (1.72–3.49)		
			Tea temperature			Age group, sex, hospital, residency, years of education, average number of cigarettes/day, and average amount of pure ethanol/day	
			Cold–warm	27	1.00		
			Hot	51	0.66 (0.35–1.25)		
			Very hot	20	3.73 (1.41–9.89)		
			Trend test *P* value, 0.11				
			Coffee with milk temperature				
			Cold–warm	72	1.00		
			Hot	206	0.89 (0.62–1.29)		
			Very hot	64	2.29 (1.37–3.81)		
			Trend test *P* value, 0.009				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cheng et al. (2000) England and Scotland 1993–1996 Case–control	Cases: 74 women with oesophageal cancer living in the study areas at the time of diagnosis Controls: 74 from population health registers; matched to cases by age and general practice Exposure assessment method: questionnaire	Oesophagus (adenocarcinoma)	Tea or coffee temperature Warm Hot Very/burning hot Trend test *P* value, 0.202	 20 42 12	 1.00 0.75 (0.32–1.76) 0.51 (0.18–1.45)	None	Only female participants Strengths: results for at least one specified histological subtype Limitations: small sample size
Nayar et al. (2000) New Delhi, India 1994–1997 Case–control	Cases: 150 outpatient and inpatient admissions in one hospital; histologically confirmed with no previous treatment Controls: 150 apparently healthy attendees to the same hospital as cases Exposure assessment method: questionnaire	Oesophagus	Tea temperature Warm Hot Burning hot	 40 78 29	 1.00 1.11 (0.62–1.96) 1.27 (0.60–2.69)	None	Possible overlap with Srivastava et al. (1995, 1997)

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sharp et al. (2001) England and Scotland 1993–1996 Case–control	Cases: 159 women, histologically confirmed Controls: 159 women from population; individually matched by age and general practice Exposure assessment method: questionnaire	Oesophagus (SCC)	Tea or coffee temperature Very/burning hot Hot Warm Trend test *P* value, 0.03	 50 81 25	 1.00 0.75 (0.38–1.47) 0.34 (0.13–0.88)	Slimming diet, breakfast, salad, smoking, aspirin use, centre-aspirin interaction	Only female participants Strengths: Results for at least one specified histological subtype
Terry et al. (2001) Sweden 1995–1997 Case–control	Cases: 356 from Swedish population < 80 years of age; histologically confirmed Controls: 815 from Swedish population; frequency matched on age and gender Exposure assessment method: questionnaire	Oesophagus (adenocarcinoma)	Tea or coffee temperature None, cold, lukewarm Hot Very hot Trend test *P* value, 0.13	 NR NR NR	 1.00 0.7 (0.5–1.1) 0.6 (0.3–1.3)	Age, sex, BMI, smoking, gastro-oesophageal reflux symptoms, alcohol intake, fruit, vegetable, and energy consumption, frequency of hot beverages	Cases included 167 SCC and 189 adenocarcinoma of the oesophagus Strengths: nationwide study; results for at least one specified histological subtype Limitations: the question on temperature concerned hot beverages 20 years before interview
		Oesophagus (SCC)	Tea or coffee temperature None, cold, lukewarm Hot Very hot Trend test *P* value, 0.77	 NR NR NR	 1.00 1 (0.6–1.6) 0.8 (0.4–1.8)		
Zhang et al. (2001) Guangdong Province, China 1999 Case–control	Cases: 214 Controls: 214; matched for sex, age, and residential locations Exposure assessment method: questionnaire	Oesophagus	Tea temperature Did not drink hot tea regularly Regular hot tea drinking	 116 98	 1.00 2.28 (1.39–3.74)	Cooking oil from pork fat, drinking tap water, regular meat eating, eating quickly, eating hard foods	Ever-smoking did not show a statistically significant association with oesophageal cancer risk in unadjusted models, and it was not included in multivariate analysis

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Onuk et al. (2002) Turkey, Erzurum 1999–2000 Case–control	Cases: 44 from one hospital; histologically confirmed Controls: 100 hospital patients with no dyspeptic symptoms Exposure assessment method: questionnaire	Oesophagus	Tea temperature Other Hot (Kitlama) Trend test *P* value, 0.001	 3 41	 1.0 8.7 (2.5–30.2)	Unclear in the article	Results may have been adjusted for tobacco use, fruit, vegetable, coffee, and pickle intake, and type of bread Limitations: small sample size; information on adjustments is unclear, no information on subtypes
Hung et al. (2004) Taiwan, China 1996–2002 Case–control	Cases: 365 histologically confirmed Controls: 532 individually matched for age and hospitalization date Exposure assessment method: questionnaire	Oesophagus (SCC)	Hot drink or soup consumption (at age 20–40 years) < 3 times/day ≥ 3 Hot drink or soup consumption (at age ≥ 40 years) < 3 times/day ≥ 3	 181 86 179 93	 1.0 1.8 (1.1–3.0) 1.0 1.3 (0.8–2.1)	Age, education, ethnicity, source of hospital, smoking, alcohol drinking, and areca nut chewing	Only male participants; Chen et al. (2009) may provide results from this population with an extended recruitment period Strengths: results for at least one specified histological subtype
Chen et al. (2009) Taiwan, China 1996–2005 Case–control	Cases: 343 from three medical centres; histologically confirmed Controls: 755 from same hospitals; matched for age Exposure assessment method: questionnaire	Oesophagus (SCC)	Hot drink or soup < 1 time/day ≥ 1	 48 226	 1.0 0.8 (0.5–1.4)	Age, education levels, ethnicity, source of hospital, smoking, alcohol drinking, and areca nut chewing	This study may provide results from an extended recruitment period of Hung et al. (2004) study Strengths: results for at least one specified histological subtype

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Yokoyama et al. (2006) Japan 2000–2004 Case–control	Cases: 52 from four hospitals; histologically confirmed Controls: 412 cancer-free women who visited clinics for health check-ups Exposure assessment method: questionnaire	Oesophagus (SCC)	Hot food or drink preference			Age	Only women Strengths: results for at least one specified histological subtype Limitations: small sample size; no adjustments for smoking or alcohol drinking
			Dislike very much	1	1.00		
			Dislike somewhat	1	0.21 (0.01–3.60)		
			Neither like or dislike	25	1.00 (0.12–8.17)		
			Like somewhat	15	1.53 (0.18–12.92)		
			Like very much	10	3.43 (0.39–30.46)		
			Trend test *P* value, 0.0011				
Islami et al. (2009a) Islamic Republic of Iran; Golestan Province 2003–2007 Case–control	Cases: 300 patients referring to the only gastrointestinal specialty clinic in the study area; histologically confirmed Controls: 571 population-based; individually matched or by neighbourhood of residence, age, and sex Exposure assessment method: questionnaire	Oesophagus (squamous cell carcinoma)	Tea temperature			Ethnicity, alcohol intake, vegetable intake, tobacco or opium use, rural residence, education, car ownership, and black and green tea consumption	Good agreement between questions Strengths: Information on temperature and the interval between pouring and drinking; results for at least one specified histological subtype; high participation
			Warm or lukewarm	127	1		
			Hot	108	2.07 (1.28–3.35)		
			Very hot	63	8.16 (3.93–16.91)		
			Trend test *P* value, < 0.001				
		Oesophagus (squamous cell carcinoma)	Interval between tea being poured and drunk (minutes)				
			≥ 4	132	1		
			2–3	112	2.49 (1.62–3.83)		
			< 2	54	5.41 (2.63–11.14)		
			Trend test *P* value, < 0.001				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Joshi et al. (2009) Uttarakhand, India 2005–2006 Case–control	Cases: 94 endoscopy patients in one hospital; histologically confirmed Controls: 94 healthy individuals accompanying or visiting patients, matched for age, sex, and socioeconomic status Exposure assessment method: questionnaire	Oesophagus	Tea or coffee temperature Warm Hot Too hot Trend test *P* value, < 0.01	 20 50 24	 1 0.26 (0.29–1.09) 0.27 (0.25–1.28)	None	Limitations: small sample size; participation rates were not reported
Lagiou et al. (2009) 13 European centres 2002–2005 Case–control	Cases: 235, a subanalysis of the ARCAGE study (on upper aerodigestive tract cancer) Controls: 2227 from population (UK) and hospital (other centres); frequency-matched with centres by sex, age, and area Exposure assessment method: questionnaire	Oesophagus	Tea or coffee temperature Warm Hot Very hot	 NR NR NR	 1 – 0.89 (0.51–1.55)	Matching variables, BMI, height, education, alcohol consumption, smoking	Strengths: using the same protocol across study centres Limitations: number of cases by category of exposure not reported; results for "hot" tea drinking not reported

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wu et al. (2009) China, Jiangsu Province 2003–2007 Case–control	Cases: 1520 local cancer registries, confirmed by endoscopy, X-ray, or histology Controls: 3879 from population, from the same county as cases; frequency matched by age and sex Exposure assessment method: questionnaire	Oesophagus	Green tea temperature (Dafeng County)			Age, sex, education level, income 10 years before, family history of cancer, body mass index, pack-year of smoking, and alcohol drinking	Strengths: large sample size Limitations: not all cases were histologically confirmed
			Never green tea drinking	467	1		
			Normal temperature	118	1 (0.7–1.3)		
			High temperature	51	1.9 (1.2–2.9)		
		Oesophagus	Green tea temperature (Ganyu County)				
			Never green tea drinking	384	1		
			Normal temperature	244	1.3 (0.9–1.7)		
			High temperature	252	3.1 (2.2–4.3)		
Ibiebele et al. (2010) Australia 2001–2005 Case–control	Cases: 524 (238 SCC, 286 adenocarcinoma) from major treatment centres and state cancer registries; histologically confirmed Controls: 1472 from electoral rolls, by strata of age, sex, and state Exposure assessment method: questionnaire	Oesophagus (adenocarcinoma)	Tea or coffee temperature			Age, sex, alcohol intake, smoking, heartburn and reflux symptoms, BMI, education, aspirin use, and fruit, vegetable, and energy intake	Female controls were intentionally over-sampled Strengths: nationwide study; results for at least one specified histological subtype Limitations: relatively low participation among controls.
			Room temperature to lukewarm	15	1		
			Warm	28	1.56 (0.67–3.61)		
			Warm to hot	111	0.91 (0.44–1.86)		
			Hot	113	0.75 (0.37–1.54)		
			Very hot	18	0.51 (0.21–1.22)		
			Trend test *P* value, 0.02				
		Oesophagus (squamous cell carcinoma)	Tea or coffee temperature				
			Room temperature to lukewarm	8	1		
			Warm	20	1.72 (0.64–4.60)		
			Warm to hot	92	0.99 (0.42–2.32)		
			Hot	73	0.70 (0.30–1.65)		
			Very hot	35	1.28 (0.51–3.19)		
			Trend test *P* value, 0.32				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chen et al. (2011) China, Guangdong Province 2004–2010 Case–control	Cases: 150 from one hospital Controls: 300 healthy individuals visiting the hospital for routine examination, matched for sex and age Exposure assessment method: questionnaire; researchers also measured drinking temperature of tea	Oesophagus (SCC)	Tea temperature (questionnaire)			Age, sex, education level, annual income, family history of cancer, and smoking and drinking status	Strengths: results for at least one specified histological subtype Limitations: participation rates were not reported; drinking temperature measured after diagnosis in cases
			Never drinker	63	1.00		
			Warm	33	0.76 (0.36–1.32)		
			Hot	24	2.41 (1.53–4.17)		
			Very hot	30	3.69 (2.56–6.73)		
			Trend test *P* value, < 0.001				
			Tea temperature (measured, °C)				
			Never drinker	63	1.00		
			< 50	12	0.75 (0.48–1.39)		
			50–59	15	0.87 (0.54–1.55)		
			60–69	30	1.53 (0.91–2.14)		
			70–79	18	2.21 (1.57–5.53)		
			≥ 80	12	4.74 (2.67–10.51)		
			Trend test *P* value, 0.024				
Jessri et al. (2011a) Islamic Republic of Iran, Kurdistan Province NR Case–control	Cases: 50 from hospital; incident histologically confirmed oesophageal SCC diagnosed within 6 months of interview Controls: 100 patients admitted to the same hospital with acute, non-neoplastic diseases; frequency matched for sex and age Exposure assessment method: questionnaire	Oesophagus (SCC)	High temperature food/beverage consumption			Age, sex, gastro-oesophageal reflux disease, body mass index, education level, smoking status, physical activity, medication use, and total energy intake	Strengths: results for at least one specified histological subtype Limitations: participation rates and number of cases in each category of exposure not reported; small sample size
			No	NR	1.00		
			Yes	NR	3.68 (1.20–8.99)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lin et al. (2011) China, Sichuan, Guangdong Provinces 2007–2010 Case–control	Cases: 213 (175 SCC, 38 adenocarcinoma) from two hospitals Controls: 213 healthy individuals visiting the same hospital for routine examinations Exposure assessment method: questionnaire; beverage temperature included the temperature of tea, coffee, or other hot beverages	Oesophagus	Beverage temperature			Age, sex, education, smoking, alcohol drinking, body mass index, and vegetable and fruit intake	Strengths: results for at least one specified histological subtype Limitations: participation rate among controls not reported
			Luke-warm	23	1.00		
			Warm	58	1.17 (0.62–2.87)		
			Hot	92	4.13 (2.13–8.05)		
			Very hot	40	8.55 (3.67–20.90)		
			Trend test *P* value, < 0.001				
		Oesophagus (SCC)	Beverage temperature				
			Luke-warm	17	1.00		
			Warm	44	1.53 (0.82–3.24)		
			Hot	84	5.61 (2.91–11.80)		
			Very hot	30	9.12 (4.03–24.70)		
			Trend test *P* value, 0.001				
Tang et al. (2013) China, Xinjiang Uyghur Autonomous Region, 2008–2009 Case–control	Cases: 359 from four hospitals; histologically confirmed within 12 months Controls: 380 inpatient wards at the same hospitals Exposure assessment method: questionnaire	Oesophagus	Tea temperature			Age, sex, education, BMI, smoking, alcohol drinking, family history, and fruit and vegetable intake	Limitations: some cases might have been interviewed up to one year after diagnosis; no information on whether or not any cases died before the interview
			Low or mild	294	1.00		
			High temperature	65	2.86 (1.73–4.72)		
			Water temperature (drinking)				
			Low or mild	283	1.00		
			High temperature	76	2.82 (1.78–4.47)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Dar et al. (2015) Kashmir, India 2008–2012 Case–control	Cases: 703 from referral hospital; histologically confirmed Controls: 1664 from same hospital as cases or another hospital in the same city or district hospitals; individually matched for sex, age, and district Exposure assessment method: questionnaire	Oesophagus (SCC)	Salt tea temperature			Age, sex, ethnicity, residence, income, wealth score, fruit and vegetable intake, use of bidi, gutka, hookah, cigarettes, nass, and alcohol	Strengths: large sample size; results for at least one specified histological subtype
			Warm	265	1.00		
			Hot	428	1.27 (1.00–1.68)		
			Salt tea temperature			As above plus several factors related to salt tea drinking, including the amount of tea, use of milk, vessel used, roti and cereal paste consumption, adding baking soda to tea, and the way the alkaline tea was consumed	
			Warm	265	1.00		
			Hot	428	0.98 (0.73–1.30)		

[a] The Working Group noted that the description of cases and enrolment period was unclear in the translated paper
[b] The full text of this article was not available to the Working Group
BMI, body mass index; CI, confidence interval; NR, not reported; SCC, squamous cell carcinoma

a scoring system for drinking hot tea, coffee, or barley drinks defined as 0, 1, 2, or 3 for no beverages or one, two, or three types of beverage consumed burning hot, respectively. This score was associated with increased risk of cancer of the oesophagus. [The adjusted odds ratio per unit temperature score calculated by the Working Group was 2.10 (95% CI, 1.83–2.40) in men and 2.47 (95% CI, 1.87–3.26) in women ($P < 0.01$ for both sexes).]

Cook-Mozaffari et al. (1979) studied 344 cases of cancer of the oesophagus identified by the Caspian Cancer Registry in northern parts of the Islamic Republic of Iran in 1975 and 1976. The study area included Mazandaran [which later divided to Mazandaran and Golestan] and Gilan Provinces and the district of Ardabil. For each case, two population controls ($n = 688$) matched for village of residence, age, sex, and language group were selected. Approximately 20% of interviews for cancer cases were by proxy. The odds ratio (95% CI) for the association between drinking hot tea and risk of cancer of the oesophagus, versus not drinking hot tea, was 1.72 ($P < 0.01$) in men and 2.17 ($P < 0.001$) in women. The results were not adjusted for smoking and alcohol drinking, but alcohol drinking in both sexes and smoking in women were uncommon habits in that study. [The Working Group noted that it was unclear whether or not the reference groups in this study included those who did not drink the beverage of interest. However, based on the published information from related studies, drinking tea was a very common habit in this region, and adults consumed an average of 25 cups of tea per day (Ghadirian, 1987). It is therefore likely that the reference group included no or only a small number of people who did not drink tea.]

Castellsagué et al. (2000) reported results of a pooled analysis of five hospital-based case–control studies in Argentina, Brazil, Paraguay, and Uruguay (two studies). The study methods and results for mate drinking are described in Section 2.1.1. In the analysis of tea drinking, 183 cases and 333 controls were ever drinkers of tea; drinking very hot (vs cold/warm) tea was associated with an increased risk of cancer of the oesophagus (OR, 3.73; 95% CI: 1.41–9.89) in analyses adjusted for risk factors including average number of cigarettes/day, and average amount of pure ethanol/day. No association was observed between drinking very hot coffee and the risk of cancer of the oesophagus (OR, 1.01; 95% CI, 0.52–1.98). [The Working Group excluded from this review the articles published from individual studies included in the pooled analysis, including Victora et al. (1987), which was reviewed in Volume 51.]

Nayar et al. (2000) conducted a hospital-based case–control study of 150 cases and 150 controls in New Delhi, India, during 1994–1997. Controls were randomly selected from apparently healthy individuals attending with patients the same hospitals as cases. In unadjusted analysis, the researchers did not find a significant association between drinking temperature of tea and the risk of cancer of the oesophagus (OR, 1.27; 95% CI, 0.60–2.69 for "burning hot"). [Adjusted odds ratios were not reported.] The Working Group identified two earlier papers (Srivastava et al., 1995, 1997) with the possibility of overlap with the Nayar et al. (2000) study. The later, larger study (Srivastava et al., 1997) reported a crude odds ratio of 1.74 (95% CI, 1.65–2.89) for drinking "very hot" tea.

Zhang et al. (2001) reported results of a study of 214 cases of cancer of the oesophagus and 214 controls conducted in Guangdong Province, China, in 1999. In this study, those who regularly drank hot tea experienced a higher risk of cancer of the oesophagus than those who did not (OR, 2.28; 95% CI, 1.39–3.74). [The Working Group noted that the odds ratio was adjusted for several risk factors, but not for smoking or drinking alcohol. Further, it was unclear whether or not the reference groups in this study included those who did not drink the beverage of interest.]

Onuk et al. (2002) studied 44 cases of cancer of the oesophagus and 100 controls in a population-based case–control study conducted in Turkey during 1999–2000. Controls were patients with no dyspeptic symptoms and were matched to cases for age and sex. In this study, drinking hot tea (vs not drinking hot tea) was associated with an increased risk of cancer of the oesophagus (OR, 8.7; 95% CI, 2.5–30.2). [Based on the description of the study methods, the Working Group was not able to determine whether or not the results were adjusted for smoking. Further, the Working Group noted that it was unclear whether or not the reference groups in this study included those who did not drink the beverage of interest.]

Islami et al. (2009a) reported results of a population-based case–control study conducted in Golestan Province, the Islamic Republic of Iran, in 2003–2007. A total of 300 cases of squamous cell carcinoma of the oesophagus and 571 controls were recruited. Controls with no history of any cancer were selected from the same neighbourhood as that of cases and were additionally matched to cases for age and sex. Compared with drinking warm or lukewarm tea, drinking hot (OR, 2.07; 95% CI, 1.28–3.35) and very hot (OR, 8.16; 95% CI, 3.93–16.91) tea was associated with an increased risk of oesophageal squamous cell carcinoma (P for trend, < 0.001). In addition, compared with a time interval of ≥ 4 minutes between tea being poured and drunk (suggesting lower drinking temperatures of tea), shorter intervals were associated with an increased risk; the odds ratio was 2.49 (95% CI, 1.62–3.83) for an interval of 2–3 minutes and 5.41 (95% CI, 2.63–11.14) for < 2 minutes (P for trend, < 0.001). The correlation between these two variables (tea temperature and interval between tea being poured and drunk) was also examined and a weighted kappa statistic of 0.68 and Spearmans' rank correlation coefficient of 0.69 were reported. In addition to this case–control study, the actual temperature at which tea was drunk was measured for 48 582 healthy individuals in the same region. In this cross-sectional analysis, 39.0% of participants drank their tea at temperatures < 60 °C, 38.9% at 60–64 °C, and 22.0% at ≥ 65 °C. There was a moderate agreement between reported drinking temperature of tea and actual temperature measurements (weighted kappa = 0.49). [The Working Group noted that the attempt to validate drinking temperature of tea for nearly 50 000 individuals was a strength of this study. This study also used two indicators to assess tea temperature (the description of drinking temperature of tea and the duration between tea being poured and drunk), which showed a good correlation.]

Wu et al. (2009) conducted a population-based case–control study of 1520 cases of cancer of the oesophagus and 3879 controls in the counties of Dafeng and Ganyu in Jiangsu Province, China, in 2003–2007. Controls with no history of cancer were selected from the same county as cases, and were frequency-matched for age and sex. The researchers found an association between drinking high-temperature green tea and risk of cancer of the oesophagus in both Dafeng (OR, 1.9; 95% CI, 1.2–2.9) and Ganyu (OR, 3.1; 95% CI, 2.2–4.3) compared with those who did not drink tea. The odds ratio (95% CI) for the association between tea of "normal" temperature and risk of cancer of the oesophagus was 1.0 (95% CI, 0.7–1.3) in Dafeng and 1.3 (95% CI, 0.9–1.7) in Ganyu. [The Working Group noted that the reference groups in this study included those who did not drink tea. However, the risk estimates for those who drank tea of "normal" temperature was not statistically different from the reference groups, and the risk associated with drinking high-temperature tea was higher than that for drinking tea of normal temperature in both counties. Although not all cases were histologically confirmed, based on the pattern of cancers of the oesophagus in the region, most cases were likely to be squamous cell carcinoma of the oesophagus.]

Chen et al. (2011) reported results of a hospital-based case–control study conducted in Guangdong Province, China, in 2004–2010. They recruited 150 cases of squamous cell carcinoma of the oesophagus and 300 controls. Controls were matched to cases for sex and age. Compared with never drinkers of tea, those who drank hot (OR, 2.41; 95% CI, 1.53–4.17) or very hot (OR, 3.69; 95% CI, 2.56–6.73) tea had a higher risk of oesophageal squamous cell carcinoma (*P* for trend, < 0.001). The researchers also measured the actual temperature at which tea was drunk among cases and controls. The correlation coefficient between self-reported and measured drinking temperature of tea was 0.62 ($P < 0.001$). Compared with never drinkers of tea, those who drank their tea at 70–79 °C (OR, 2.21; 95% CI, 1.57–5.53) or ≥ 80 °C (OR, 4.74; 95% CI, 2.67–10.51) had a higher risk of oesophageal squamous cell carcinoma. [The Working Group noted that the reference groups in this study included those who did not drink tea. However, the risk estimates for those who drank warm tea were not statistically different from the reference groups (OR, 0.76; 95% CI, 0.36–1.32).] Those who drank hot or very hot tea were at a higher risk of cancer of the oesophagus compared with drinkers of warm tea. Similarly, the risk for those who drank their tea at temperatures of < 50 °C (OR, 0.75; 95% CI, 0.48–1.39) or 50–59 °C (OR, 0.87; 95% CI, 0.54–1.55) was not different from never drinkers of tea. Compared with these two groups who drank low-temperature tea, those who drank their tea at 70–79 °C or ≥ 80 °C were at a higher risk of cancer of the oesophagus. The measurement of drinking temperature of tea in cases was made after the development of cancer. [The Working Group noted that the correlation between measured and actual tea drinking temperatures before the development of cancer was unknown; measurements were only made after the development of cancer in cases. Patients with cancer of the oesophagus may present after dysphagia, which leads to changes in dietary habits (particularly in more advanced cases). This could cause dehydration or other changes in the mucosa, and possibly affect the temperature preference for beverages.]

Tang et al. (2013) conducted a hospital-based case–control study in Xinjiang Uyghur Autonomous Region, China, in 2008–2009. They recruited 359 cases of cancer of the oesophagus and 380 controls. Controls were recruited from inpatient wards at the same hospitals from the departments of ophthalmology, orthopaedics, respiratory disease, and physiotherapy. In this study, drinking tea at a high temperature compared with a low or mild temperature was associated with risk of cancer of the oesophagus (OR, 2.86; 95% CI, 1.73–4.72) in logistic regression analyses adjusted for age, sex, education, smoking status, alcohol drinking, family history of cancer, and daily intake of fruits and vegetables.

Dar et al. (2015) reported results of a hospital-based case–control study conducted in Kashmir, India, in 2008–2012. They recruited 703 cases of squamous cell carcinoma of the oesophagus and 1664 matched controls. In the analysis adjusted for the use of various tobacco products and alcohol and several sociodemographic characteristics, compared with drinking warm salt tea, the odds ratio for the association between drinking hot salt tea and risk of oesophageal squamous cell carcinoma was 1.27 (95% CI, 1.00–1.68). [The Working Group noted that the odds ratio is not the geometric mean of the upper and lower bounds.] This association disappeared following further adjustments for factors related to salt tea drinking habits, including the amount of tea, use of milk, the vessel used, roti and cereal paste consumption with salt tea, adding baking soda to tea, and the way in which the alkaline tea was consumed (OR, 0.98; 95% CI, 0.73–1.30).

Two studies from the USA (Brown et al., 1988 with 207 cases and 422 controls; and Yu et al. 1988 with 275 cases and 275 controls) reported finding no association between the drinking

temperature of tea and the risk of cancer of the oesophagus, but did not provide the actual results.

(b) Very hot coffee and cancer of the oesophagus

Only one case–control study and a pooled analysis of multiple case–control studies exclusively investigated the association between drinking very hot coffee and cancer of the oesophagus. Several other studies reported results for coffee and other beverages combined, for example tea and/or coffee; these studies are discussed in Section 2.2.1 (c).

In a study in Singapore, De Jong et al. (1974) reported an approximately 4-fold increase in the risk of cancer of the oesophagus associated with drinking "burning hot" coffee (compared with not drinking burning hot coffee) in models adjusted for dialect group. In multivariate models, the researchers created a scoring system for drinking hot tea, coffee, or barley drinks combined, which showed a statistically significant association with risk of cancer of the oesophagus. [For more information about study design and this composite score, see Section 2.2.1 (a).]

In a pooled analysis of five hospital-based case–control studies in South America, Castellsagué et al. (2000) did not find any association between coffee and risk of squamous cell carcinoma of the oesophagus. However, those who drank their coffee with milk at very hot temperatures were at a higher risk of oesophageal squamous cell carcinoma (OR, 2.29; 95% CI, 1.37–3.81) in logistic regression models that adjusted for age group, hospital, residency, years of education, average number of cigarettes/day, and average amount of pure ethanol/day. [For more information about this study, see Section 2.2.1 (a).]

(c) Combinations of very hot beverages and cancer of the oesophagus

One cohort study, 14 case–control studies, and one pooled analysis of five case–control studies investigated the association between drinking several types of very hot beverages combined and cancer of the oesophagus. The majority of these studies examined the effect of tea and/or coffee and sometimes included other hot liquids or foods. The studies that reported results exclusively for drinking tea or for drinking coffee are discussed in Sections 2.2.1 (a) and 2.2.1 (b), respectively.

(i) Cohort study

Tran et al. (2005) reported results of a prospective cohort study conducted in Linxian, China. A total of 29 584 individuals with no history of cancer or debilitating disease were recruited from the general population and interviewed in 1984. Participants were randomly assigned to treatment with vitamins and minerals. They received supplements for 5.25 years and were followed up until 2001. Cancer diagnoses were ascertained through local contacts and monthly visits by village health workers. Study subjects were then contacted monthly by either village health workers or interviewers. During the follow-up period, 1958 cases of squamous cell carcinoma of the oesophagus were identified. Drinking hot liquids was not associated with the risk of oesophageal squamous cell carcinoma. [The Working Group noted a possible systematic error in the reporting of some dietary factors in this study. The incidence rate for cancer of the oesophagus in Linxian was one of the highest reported rates worldwide. When this study was conducted there were health campaigns in the region highlighting possible risk factors of cancer of the oesophagus, including drinking hot tea or consuming pickled vegetables. It is possible that participants in this study had temporarily changed their dietary habits or felt uncomfortable about reporting their habits during the

campaigns. As an example, the proportion of participants in this study who reported pickled vegetable consumption was 0%, and there was no difference between cases of cancer of the oesophagus and controls in this regard. On the other hand, studies conducted in this region a few years later (after the campaigns had subsided) revealed a much higher prevalence of pickled vegetable consumption (Islami et al., 2009c); 38% of cases of cancer of the oesophagus diagnosed in 1998–1999 in a case–control study (Xibib et al., 2003) reported regular consumption of pickled vegetables 10 years before the interview (i.e. the late 1980s).]

(ii) Case–control studies

Gao et al. (1994) reported a subanalysis of a larger study of cancers of the oesophagus, pancreas, colon, and rectum conducted in Shanghai, China. For this analysis, 902 cases of cancer of the oesophagus diagnosed from 1990 to 1993 were identified from the Shanghai Cancer Registry. Using the Shanghai Resident Registry, 1552 controls frequency-matched for age and sex were randomly selected. Compared with the consumption of cold/neither cold nor hot soup/porridge, the consumption of burning hot soup/porridge [porridge is not a liquid but soup is] was associated with increased risk of cancer of the oesophagus in men (OR, 4.75; 95% CI, 3.33–6.79) and women (OR, 6.77; 95% CI, 4.09–11.20) in analyses controlling for age, education, birthplace, tea drinking, smoking, alcohol drinking, and consumption of preserved foods, vegetables, and fruit.

Garidou et al. (1996) reported results of a hospital-based case–control study conducted in Athens, Greece, in 1989–1991. The case group consisted of 43 cases of squamous cell carcinoma of the oesophagus and 56 cases of adenocarcinoma of the oesophagus; 200 controls were recruited from patients hospitalized as a result of injuries in an accident hospital. Those with alcohol-related accidents were not eligible as controls. Controls were individually matched to cases for age (± 5 years) and sex. The odds ratio for the association between the consumption of hot or very hot, compared with cold, beverages and foods and cancer risk was 1.89 (95% CI, 0.80–4.49) for oesophageal squamous cell carcinoma and 1.82 (95% CI, 0.85–3.91) for oesophageal adenocarcinoma in analyses that controlled for age, sex, birthplace, education, height, analgesics, coffee drinking, tobacco and alcohol use, and energy intake.

In a study of 208 cases of squamous cell carcinoma of the oesophagus and 399 controls in France, Launoy et al. (1997) reported an association between drinking hot calvados (an apple-based distilled alcoholic beverage) mixed with coffee and the risk of squamous cell carcinoma of the oesophagus. This study did not find a statistically significant association for cold calvados, cold spirits, and hot spirits. However, the total number of cases of cancer of the oesophagus who drank cold calvados was 13. [The Working Group noted that it would be difficult to separate the effect of temperature from that of the alcoholic beverages on the development of cancer of the oesophagus. This study also found a statistically significant inverse association between drinking whisky and the risk of oesophageal squamous cell carcinoma based on a modest number of whisky drinkers. This may suggest the presence of some other causal factors that could have distorted the association between consumption of certain types of alcoholic beverages and risk of cancer of the oesophagus in this study.]

In a pooled analysis of five hospital-based case–control studies in South America, Castellsagué et al. (2000) reported an association between drinking any combination of very hot beverages excluding and including mate, compared with never drinking the corresponding beverages at a high temperature, and cancer of the oesophagus. Odd ratios of 2.45 (95% CI, 1.72–3.49) and 2.07 (95% CI, 1.55–2.76) were reported for the groups drinking a combination

of hot beverages which excluded and included mate, respectively. [For more information about this study, see Section 2.2.1 (a)].

Cheng et al. (2000) conducted a population-based case–control study in four regions in England and Scotland in 1993–1996. The case group included 74 women with oesophageal adenocarcinoma aged < 75 years of age (< 80 years in one region), resident in the study areas at the time of their diagnosis. They recruited 74 controls that were randomly selected using the Family Health Service Authority or Health Board primary care registers. Controls were matched to cases by age (within 5 years) and general practice. There was no association between the drinking temperature of tea or coffee and the risk of adenocarcinoma of the oesophagus.

Sharp et al. (2001) reported the results of a population-based case–control study conducted in three regions in England and eastern Scotland in 1993–1996 on women. They recruited 159 women with squamous cell carcinoma of the oesophagus and 159 controls. One control was matched to each case by age and general practice. An approximately 3-fold increased risk of oesophageal squamous cell carcinoma was associated with drinking very hot or burning hot, compared with warm, tea or coffee. [The Working Group noted that results were reported by considering the reference group to be those who drunk very hot or burning hot tea or coffee. The odds ratio (95% CI) for drinking warm tea or coffee was 0.34 (95% CI, 0.13–0.88).]

Terry et al. (2001) studied 356 cases of cancer of the oesophagus (167 squamous cell carcinomas and 189 adenocarcinomas) and 815 controls selected from the entire population in Sweden. Cases were of cancer of the oesophagus identified through a nationwide cancer registry of the entire Swedish population < 80 years of age in 1995–1997. Controls were randomly selected from the Swedish population to approximate the age and sex distribution among cases. The question of tea or coffee temperature was about hot beverages consumed 20 years before interview. The researchers did not find any association between tea or coffee drinking temperature 20 years before the interview and either squamous cell carcinoma or adenocarcinoma of the oesophagus. [The Working Group noted that, in addition to those who drank cold or lukewarm tea or coffee, the reference group in this study also included those who did not drink tea or coffee.]

Hung et al. (2004) reported results of a hospital-based case–control study conducted in Taiwan, China, in 1996–2002 on men. They recruited 365 men with squamous cell carcinoma of the oesophagus and 532 controls. Controls were individually matched to cases for age and hospitalization date. Those who consumed hot drinks or soup three times or more per day at the age of 20–40 years were at a higher risk of oesophageal squamous cell carcinoma (OR, 1.8; 95% CI, 1.1–3.0) than those who did not. There was no such association for patients of age ≥ 40 years in this study (OR, 1.3; 95% CI, 0.8–2.1). [The Working Group noted that data from this study may be included in a later study by Chen et al. (2009). Further, the reference group included those who consumed hot drinks or soups fewer than three times per day and might have included those who did not drink hot liquids.]

Yokoyama et al. (2006) reported results of a hospital-based case–control study conducted among women in Japan in 2000–2004. Cases were 52 women with squamous cell carcinoma of the oesophagus treated at four hospitals (in Chiba, Kanagawa, Osaka, and Tokyo). Controls consisted of 412 cancer-free women who visited two clinics in Tokyo for annual health check-ups. The researchers categorized preference for hot foods or drinks to one of five groups. Compared with the group "dislike very much", the category of "like very much" was associated with a higher risk of oesophageal squamous cell carcinoma (OR, 3.43; 95% CI, 0.39–30.46; adjusted for age only). The reference category, however,

consisted of only one case subject. [The Working Group combined the three categories of "dislike very much", "dislike somewhat", and "neither like or dislike" using frequencies of cases and controls provided in the article, and considered this combined group as the reference group. Compared with this group, the category of "like very much" was associated with oesophageal squamous cell carcinoma (unadjusted OR, 3.24; 95% CI, 1.27–7.68).]

Joshi et al. (2009) reported results of a hospital-based case–control study conducted in Uttarakhand, India, in 2005–2006. They recruited 94 cases of cancer of the oesophagus and 94 controls. Cases were selected from those who underwent upper gastrointestinal endoscopy in one hospital. Controls were healthy individuals who accompanied the cases or other patients who attended the hospital, matched to cases for age, sex, and socioeconomic status. Compared with drinking warm tea or coffee, drinking hot or "too hot" tea or coffee was not associated with an increased risk of cancer of the oesophagus. There was evidence of an inverse exposure–response trend of risk of cancer of the oesophagus with tea or coffee temperature ($P < 0.01$).

Lagiou et al. (2009) reported results of the Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) study, a multicentre case–control study on cancers of the upper aerodigestive tract in 13 centres in nine countries across Europe (Croatia, Czech Republic, Germany, Greece, Ireland, Italy, Norway, Spain, and the United Kingdom). For this analysis, 235 cases of cancer of the oesophagus (from 10 centres) and 2227 controls were included. Controls were frequency-matched to cases for sex, age (5-year groups), and referral (or residence) area within each study centre. There was no association between drinking temperature of tea or coffee and risk of cancer of the oesophagus.

Ibiebele et al. (2010) reported results of a nationwide population-based case–control study conducted in Australia in 2001–2005. They recruited 524 cases of cancer of the oesophagus and 1472 controls. Cases included 524 patients aged 18–79 years with cancer of the oesophagus (238 squamous cell carcinomas and 286 adenocarcinomas) identified through major treatment centres throughout Australia or by state-based cancer registries. Controls were randomly selected from the Australian electoral roll and sampled from within strata of sex and age and state of residence. The researchers did not find an association between tea or coffee temperature and either squamous cell carcinoma or adenocarcinoma of the oesophagus. The trend analysis, however, suggested a trend for an inverse association between tea or coffee temperature and oesophageal adenocarcinoma risk (P for trend = 0.02).

Jessri et al. (2011a) conducted a hospital-based case–control study of 50 cases of squamous cell carcinoma of the oesophagus and 100 controls in the Islamic Republic of Iran. Controls were individuals admitted to the same hospital as cases for a wide spectrum of acute non-neoplastic diseases that were not related to smoking, alcohol abuse, or long-term modification of the diet. The consumption of high-temperature foods or beverages was associated with an increased risk of oesophageal squamous cell carcinoma (OR, 3.68; 95% CI, 1.20–8.99). [Based on another publication from this study, which provided the frequency distribution but not odds ratio for food or beverage temperature, the Working Group noted that the reference group included those who consumed warm/cold foods or beverages (Jessri et al., 2011b).]

Lin et al. (2011) reported results of a hospital-based case–control conducted in Sichuan and Guangdong Provinces, China, in 2007–2010. They recruited 213 cases of cancer of the oesophagus (175 squamous cell carcinoma) and 213 controls selected from healthy individuals visiting the same hospital during the same period as cases for routine physical examination. Compared

with drinking lukewarm beverages, drinking hot (OR, 4.13; 95% CI, 2.13–8.05) and very hot (OR, 8.55; 95% CI, 3.67–20.90) beverages was associated with an increased risk of cancer of the oesophagus (*P* for trend, < 0.001). The respective odds ratios for oesophageal squamous cell carcinoma were 5.61 (95% CI, 2.91–11.8) and 9.12 (95% CI, 4.03–24.7) (*P* for trend, < 0.001).

Tang et al. (2013) conducted a hospital-based case–control study in Xinjiang Uyghur Autonomous Region, China. A total of 359 newly diagnosed cases of cancer of the oesophagus (in 2008–2009) were identified by retrospective reviewing of medical records and pathology in four hospitals. A total of 380 controls were recruited from inpatient wards at the same hospitals Drinking water of high temperature (OR, 2.82; 95% CI, 1.78–4.47) and tea of high temperature (OR, 2.86; 95% CI, 1.73–4.72), compared with water or tea of low or mild temperature, was associated with increased risk of cancer of the oesophagus.

(d) Systematic reviews and meta-analyses

At least three systematic reviews have examined the association between drinking hot beverages and risk of cancer of the oesophagus (Islami et al., 2009c; Andrici & Eslick, 2015; Chen et al., 2015b). Two of these reviews estimated a pooled odds ratio for the association. Andrici & Eslick (2015) reported an overall odds ratio of 2.28 (95% CI, 1.62–3.22) for the association between the consumption of hot beverages (other than mate) or food and risk of squamous cell carcinoma risk of the oesophagus. The odds ratio for 11 studies on all hot beverages (including mate) and food, with results adjusted for smoking and alcohol drinking, was 2.39 (95% CI, 1.71–3.22). [A meta-OR of adjusted results excluding mate was not reported.] There was no statistically significant association between hot beverage or food consumption and oesophageal adenocarcinoma based on the results of four studies (OR, 0.78; 95% CI, 0.45–1.35). Chen et al. (2015) reported an odds ratio of 1.82 (95% CI, 1.53–2.17) for the association between hot beverage and food consumption (including mate) and risk of cancer of the oesophagus (39 studies), 1.60 (95% CI, 1.29–2.00) for squamous cell carcinoma of the oesophagus (26 studies), and 0.79 (95% CI, 0.53–1.16) for adenocarcinoma of the oesophagus (4 studies). The corresponding odds ratio was 2.06 (95% CI, 1.62–2.61) in Asia (28 studies), 1.52 (95% CI, 1.25–1.85) in South America (13 studies), and 0.95 (95% CI, 0.68–1.34) in European populations (5 studies). The pooled odds ratios were comparable for hot tea, mate, and other beverages (ranging from 1.72 to 1.88). There was high heterogeneity in most analyses performed in these two meta-analyses. [The Working Group noted that the systematic reviews are informative for synthesis of the information but, given the high heterogeneity in the meta-analyses, regional differences in incidence, and the subjective nature of the exposure (preference for hot beverages), meta odds ratios for the association between hot beverages and cancer of the oesophagus and should be interpreted with caution. The Working Group also noted the inclusion of several overlapping studies in the meta-analysis of Chen et al. (2015), notably original reports from studies included in the pooled analysis of Castellsagué et al. (2000), as well as the pooled analysis.]

2.2.2 Other cancers

See Table 2.2.2 (web only; available at: http://publications.iarc.fr/566).

(a) Cancer of the upper aerodigestive tract

Martinez (1969) studied 179 cases of cancer of the oesophagus, 153 cases of cancer of the mouth, and 68 cases of cancer of the pharynx, all histologically confirmed cases of squamous cell carcinoma reported to the Puerto Rico Cancer Registry in 1966. As controls, one non-cancer patient from the same hospital and two

individuals from the community were matched to each case for age and sex. The results were shown for cancer of the mouth, pharynx, and oesophagus combined. There was a significant association between drinking hot coffee [OR, 2.14; 95% CI, 1.36–3.35] or hot coffee with milk [OR, 1.47; 95% CI, 1.01–2.12], versus drinking cold or warm coffee, and cancer at these three sites. The results were not adjusted for major causes of upper aerodigestive tract cancers, notably smoking.

Franco et al. (1989) reported results of a study of the association between drinking hot coffee and cancer of the oral cavity (tongue, gum, floor of the mouth, and other parts of the oral cavity) conducted in Brazil in 1986–1988. Cases ($n = 232$) were selected from patients referred to three head and neck surgery services in three cities. Two control subjects for each case were selected from patients in the same hospital as cases or from neighbouring general hospitals. Controls were matched to cases for sex, age, and trimester of hospital admission. The researchers did not show the results, but they reported that they did not find any association between drinking "burning hot" coffee, compared with drinking coffee at lower temperatures, and the risk of cancer of the oral cavity.

Gridley et al. (1990) conducted a population-based case–control study of cancer of the oral cavity and pharynx among African Americans in the USA. Cases (n = 190) were histologically confirmed incident cases of cancer of the tongue, pharynx, and other oral cancers excluding cancers of the lip, salivary gland, or nasopharynx, and were identified from the population-based cancer registries of New Jersey, Atlanta, Los Angeles, and counties of Santa Clara and San Mateo in California. A total of 201 controls matched for sex and age were selected using random-digit dialling and Health Care Financing Administration rosters. Proxy interviews were conducted for 29% of cases, but only and 1% of controls. The data were not reported, but the researchers stated that there was no association between drinking hot beverages and risk of cancer of the oral cavity or pharynx.

In the the ARCAGE study, described previously (Lagiou et al., 2009), there were 2304 cases with cancer of the oral cavity, pharynx (excluding nasopharynx), larynx, or oesophagus, and 2227 controls. Compared with drinking warm tea or coffee, the researchers found an inverse association between drinking hot (OR, 0.78; 95% CI, 0.65–0.92) or very hot (OR, 0.67; 95% CI, 0.52–0.86) tea or coffee and the risk of cancers of the upper aerodigestive tract (P for trend < 0.001). [For more details of this study, see Section 2.2.1 (c).]

Chen et al. (2015) conducted a population-based case–control study of 203 cases with cancer of the oral cavity and 572 controls in Fujian Province, China, in 2011–2015. All cases and controls were non-smokers and non-drinkers of alcohol. This study reported an inverse association between drinking tea at moderate temperatures (OR, 0.55; 95% CI, 0.31–0.98; based on 17 cases) or high temperatures (OR, 0.50; 95% CI, 0.28–0.88; based on 18 cases) and the risk of cancer of the oral cavity, compared with never drinkers of tea. [The Working Group noted that the inverse associations were observed when never drinkers of tea were the reference group. There was no difference between the reported risk associated with drinking tea at moderate temperatures and drinking tea at high temperatures, and 95% confidence intervals for these two risk estimates were fully overlapping.]

(b) Cancer of the stomach

Pourfarzi et al. (2009) conducted a population-based case–control study of cancer of the stomach in Ardabil Province, the Islamic Republic of Iran, in 2004–2005. Cases (n = 217) were identified from the Ardabil Cancer Registry, which listed cancer surveillance data from doctors and pathology services making a cancer diagnosis in Ardabil, as well as from an active surveillance for cancer of the stomach conducted

by the Cancer Registry through all hospitals and clinics in the province. A total of 394 controls were randomly selected from the community using a sampling frame created for the annual household survey by the health department. Drinking hot tea versus non-hot tea was associated with an increased risk of cancer of the stomach (OR, 2.85; 95% CI, 1.65–4.91) in models adjusted for gender, age group, education, family history of gastric cancer, *Helicobacter pylori*, and dietary factors.

Deandrea et al. (2010) conducted a hospital-based case–control study of the association between drinking green tea and cancer of the stomach in Heilongjiang Province, China, in 1987–1989. Cases ($n = 266$) were newly diagnosed cancer of the stomach cases admitted to six hospitals. Controls ($n = 533$) were patients admitted for non-neoplastic and non-gastric diseases to surgical departments at the same hospitals. The researchers reported results based on exposure at three time points, which were usual green tea drinking temperatures in 1961 (around the time of the Great Chinese Famine), 1966 (the beginning of the cultural revolution), and the 1980s (close to the time of interview). However, the results for 1961 and 1966 were based on only 10 and 20 drinkers of green tea, respectively. The researchers did not find any statistically significant evidence of an association between the risk of cancer of the stomach and drinking hot green tea in any quantity. [The Working Group noted that the reference group in this study consisted of those who did not drink green tea. Compared with not drinking green tea, the pooled odds ratio for drinking either < 750 g/year or ≥ 750 g/year lukewarm green tea calculated by the Working Group was 0.31 (95% CI, 0.16–0.60). This risk estimate suggests that drinking hot green tea was associated with an increased risk of cancer of the oesophagus when compared with drinking lukewarm tea in this study. However, the risk estimate for lukewarm tea was based on only 11 cancer cases in the exposed group.]

Mao et al. (2011) reported results of a hospital-based case–control study of the association between drinking green tea and cancer of the stomach conducted in Yunnan Province, China, in 2010–2011. They recruited 200 cases from two hospitals and 200 age- and sex-matched controls who were healthy individuals visiting a different hospital for routine physical examination. Compared with never drinkers of green tea, drinkers of hot (OR, 1.82; 95% CI, 1.03–3.52) or very hot (OR, 3.07; 95% CI, 1.78–7.36) green tea experienced a higher risk of cancer of the stomach. No statistically significant association between risk of cancer of the stomach and tea temperature combined with either smoking ($P = 0.24$) or drinking alcohol ($P = 0.37$) was found. [The Working Group noted that the reference group in this analysis consisted of those who did not drink tea. However, the reported risk associated with drinking cool (OR, 0.85; 95% CI, 0.54–1.72) or warm (OR, 0.81; 95% CI, 0.58–0.97) green tea was not different from the reference group. Based on the reported odds ratios and 95% confidence intervals, this study indicates an association between drinking hot or very hot green tea, compared with drinking green tea at lower temperatures, and cancer of the stomach.]

Wang et al. (2015) conducted a hospital-based case–control study of the association between drinking temperature of green tea and risk of cancer of the stomach in Shenyang and Zhengzhou, China, in 2005–2010. They recruited 160 cases from two hospitals and 320 randomly selected controls matched for sex from outpatients without a diagnosis of cancer at the same hospitals. Compared with drinking lukewarm or cool green tea, drinking warm (OR, 1.64; 95% CI, 1.16–2.41) or hot (OR, 3.13; 95% CI, 1.85–5.11) green tea was associated with an increased risk of cancer of the stomach. [The researchers reported adjusted results, but the covariates were unclear to the Working Group.] The analysis was repeated among men and

women separately to examine the potential confounding effects of smoking [which in China is generally much less common in women], and found similar results [data were not shown].

(c) Cancer of the skin

Hakim et al. (2000) reported results of a population-based case–control study conducted in Arizona, USA. Participants in the baseline study were recruited in 1993–1996, and were contacted again by telephone in 1998 to complete a tea consumption questionnaire. For this analysis, 234 cases of squamous cell carcinoma of the skin were randomly selected from people identified via the Southeastern Arizona Skin Cancer Registry as a first occurrence of squamous cell carcinoma of the skin; 216 controls were selected using the method of random-digit dialling. Compared with not drinking tea, there was no association between drinking warm (OR, 1.51; 95% CI, 0.37–6.12) or hot (OR, 0.76; 95% CI, 0.56–1.01) tea and squamous cell carcinoma of the skin in this study. [The Working Group noted that the reference group in this study included non-drinkers of tea. However, there was no difference between the risk associated with drinking warm tea and drinking hot tea, with fully overlapping 95% confidence intervals for the risk estimates.]

(d) Cancer at multiple sites combined

One of the Islamic Republic of Iran studies on cancer of the oesophagus (Cook-Mozaffari et al., 1979) also studied a second group of 181 patients with cancers of the lung, stomach, breast, large bowel, larynx, and pharynx (approximately 50% with cancer of the stomach) with 2 matched neighbourhood controls per case. Approximately 20% of interviews for cancer cases were by proxy. In this study, drinking hot tea was associated with a higher risk of cancers other than cancer of the oesophagus in men (OR, 3.23; $P < 0.001$), but not in women (OR, 0.86; $P > 0.05$). The results were not adjusted for smoking. The researchers stated that the increased risk mainly reflected the association with cancer of the stomach, but they did not report the results for cancer of the stomach (or any cancer other than that of the oesophagus) separately.

3. Cancer in Experimental Animals

There were no data in experimental animals regarding the carcinogenicity of mate in the previous *IARC Monographs* evaluation (Volume 51; IARC, 1991).

See Table 3.1.

3.1 Mate

In the study by Silva et al. (2009), three groups of male Wistar rats (age, 6 weeks) were given *N*-nitrosodiethylamine (NDEA) at a dose of 80 mg/kg body weight (bw) intraperitoneally in saline once per week for 8 weeks, with (two groups of 20 rats) or without (5 rats) concomitant treatment with 1 mL of water at 65 °C instilled in the oesophagus by a metal probe twice per week for 8 weeks. The rats were given a single source of drinking-water with or without mate (2% w/v; 20 g of dried and minced leaves of *I. paraguariensis* was added to 1 L of hot water at 70 °C for 20 minutes, then filtered and allowed to cool down to room temperature), for 8 weeks. Two groups of five rats served as additional controls and were given intraperitoneal injections of 1 mL of saline (vehicle) once per week and a single source of drinking-water at 25 °C, with or without mate (2% w/v), twice per week for 8 consecutive weeks. The rats were killed 20 weeks after the start of treatment. There was a body-weight loss in rats treated with NDEA either alone (266.8 ± 27.8 g) or together with hot water (260.8 ± 29.5 g) ($P < 0.001$) when compared with rats treated with NDEA, hot water, and mate (296.8 ± 32.8 g). Five rats were found dead during

Table 3.1 Studies of carcinogenity in experimental animals exposed to mate or very hot water

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dosing regimum Animals per group at start	Results for each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Co-carcinogenicity Rat, Wistar (M) Age, 6 wk 20 wk Silva et al. (2009)	Mate given as drinking fluid in distilled water (2% w/v) NDEA (80 mg/kg bw) intraperitoneally 1×/ wk for 8 wk + water at 65 °C by gavage (1 mL, 2×/ wk for 8 wk) + water (control) or mate for 8 wk 20 mice/group	*Liver* Incidence of adenoma: 8/12, 1/13 *Oesophagus* Incidence of papilloma: 7/12, 2/13	$P < 0.001$ (reduction) $P < 0.05$ (reduction)	Survival, 12/20, 13/20
Co-carcinogenicity Mouse, BALB/c (F) Age, 2 mo Up to 32 wk Rapozo et al., (2016)	Oesophageal installation of hot water (70 °C) NDEA (> 99%) at 10 ppm in the drinking-water with or without (control) 0.3 mL hot water, 3×/wk 10, 11 mice/group	*Oesophagus* Squamous cell papilloma or carcinoma (combined), at 8 wk Tumour incidence: 0/10, 1/11 Total tumours: 0, 1	 NS NS	Principal strengths: dose–response design experiment; hot water at 50 °C and 60 °C also tested Treatment with 10 ppm NDEA alone induced focal hyperplasia in only 1 mouse out of 7 at 16 wk of treatment. Treatment with water at 70 °C and 10 ppm NDEA (combined) produced oesophageal lesions at all time intervals: Hyperplasia: 3/5 at 2 wk; 3/5 at 4 wk; 5/11 at 8 wk; and 1/8 at 16 wk High-grade dysplasia – 1/11 at 8 wk; focal hyperplasia – 1/5 at 4 wk, 3/11 at 8 wk; and 5/8 at 16 wk
Initiation–promotion (tested as promoter) Rat, F344 M Age, 12 wk 20 wk Li et al. (2003)	Gavage (hot water) Hot water (55 °C or 65 °C) at 1 mL/kg bw + NMBzA (purity, 99%) at 1 mg/kg bw subcutaneously 0.9% NaCl 65 °C + NMBzA, 55 °C + NMBzA, NMBzA (control) 5 × /wk for 5 wk then 1 × /wk for 10 wk 11, 9, 9 mice/group	*Oesophagus* Squamous cell papilloma or carcinoma (combined) Tumour multiplicity: 8.0 ± 2.1*[a], 5.7 ± 2.1, 5.5 ± 1.5[b] Total tumours: 89, NR, 47	*$P < 0.05$; [a] 18 papillomas, 44 papillomas with atypia, and 27 carcinomas (increase in the number of carcinomas, $P < 0.05$); [b] 19 papillomas, 20 papillomas with atypia, and 8 carcinomas	Principal strengths: good histopathological analysis, dose–response design of experiment, adequate number of tumours produced Principal limitations: small number of rats, loss of weight, and animal death caused by hot water Survival, 9/11, 9/9, 9/9

bw, body weight; mo, month; NA, not applicable; NDEA, *N*-nitrosodiethylamine; NMBzA, *N*-nitrosomethylbenzylamine; NR, not reported; NS, not significant; wk, week

the experiment: three from the group treated with NDEA and hot water; and two from the group treated with NDEA, hot water, plus mate. There was no induction of malignant tumours of the oesophagus, but treatment with mate reduced the incidence of oesophageal neoplastic lesions when compared with treatment with NDEA plus water at 65 °C. There were 2 out of 13 rats with papilloma of the oesophagus in the group treated with mate plus hot water and NDEA, versus 7 out of 12 rats in the group treated with hot water and NDEA ($P < 0.05$, decrease). There was also a significant ($P < 0.001$, decrease) reduction in the incidence of adenoma of the liver (1 out of 13 rats in the group treated with NDEA, hot water, and mate, vs 8 out of 12 rats in the group treated with NDEA and hot water). [The Working Group noted that there were no tumour data on rats given NDEA only.]

3.2 Very hot water

3.2.1 Mouse

In the study by Rapozo et al. (2016), female BALB/c mice (age, 2 months) were given drinking-water containing NDEA at a concentration of 10 ppm and/or water at different temperatures (25, 50, 60, or 70 °C, instilled by a metal straw into the oesophagus) three times per week for up to 32 weeks. Cohorts of [presumably up to 11] mice were killed periodically between 24 hours and 32 weeks, and a histopathological examination was conducted for diagnosis of oesophageal preneoplastic lesions. There was approximately 15% mortality in the cohorts that were given water at 70 °C during the first 2 weeks of treatment. There was body-weight loss in the group of mice treated with 70 °C hot water (mean body-weight loss, from 19 g to 16 g) during the second week of treatment, but the mice recovered at the third week (mean body weight, 22 g). The study clearly showed a coagulation necrosis of the oesophagus produced by hot water at 70 °C, and that this damage healed when NDEA was not given together with water at 70 °C. Treatment of mice with hot water at either 50 °C or 60 °C did not produce weight loss, death, or coagulation necrosis of the oesophagus. Mice treated with water at 70 °C for up to 32 weeks did not develop hyperplasia, dysplasia, or tumours of the oesophagus. Treatment with NDEA at 10 ppm alone induced focal hyperplasia of the oesophagus in only 1 mouse out of 7 at 16 weeks of treatment. Treatment with water at 70 °C and NDEA at 10 ppm (combined) produced oesophageal lesions – including preneoplastic lesions – at all time intervals: hyperplasia – 3 out of 5 at 2 weeks, 3 out of 5 at 4 weeks, 5 out of 11 at 8 weeks, and 1 out of 8 at 16 weeks; high-grade dysplasia – 1 out of 11 at 8 weeks; focal hyperplasia – 1 out of 5 at 4 weeks, 3 out of 11 at 8 weeks; and 5 out of 8 at 16 weeks. In addition, 1 out of 11 mice treated with water at 70 °C and 10 ppm NDEA (combined) had a squamous cell papilloma at 8 weeks. Mice that were given NDEA plus 70 °C water treatment had an almost nine times higher chance of developing oesophageal lesions when compared with mice given NDEA only ($P = 0.0042$). [Regarding data from Rapozo et al. (2016), the Working Group observed that several lesions originally presented as preneoplastic lesions should be considered as squamous cell papillomas.]

3.2.2 Rat

In a study by Yioris et al. (1984), four groups of 30 male and 30 female Wistar rats (age, 3 months) were given either 65 °C water (3 mL, instilled with a metal probe 2 cm above the cardia, twice per week for a total of 50 treatments) or *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG, 5.0 mg/kg bw by gavage five times per week for a total dose of 900 mg/kg bw), or the combined treatment (in this case the total dose of MNNG was 700 mg/kg bw because of the interruption of treatment) for 37 weeks. Treatment with hot water produced a considerable deterioration of

the rats, leading to a brief interruption of treatment at 4 and 20 weeks [additional details on the interruption not provided]. Rats were allowed to live their lifespan. There was a reduction in mean survival among rats treated with hot water (420 days) and with MNNG (370 days), a reduction that was even more pronounced with the combined treatment (280 days) when compared with controls (580 days). Water at 65 °C alone or MNNG alone did not produce tumours of the oesophagus, whereas the combined treatment produced malignant polymorphocellular sarcomas of the oesophagus in 4 out of 30 rats [not statistically significant] at the location where hot water was instilled. [The Working Group noted that different groups were not given the same total dose of MNNG, and that the 3 mL volume of hot water instilled was very large for the oesophagus of the rat. This study was therefore considered inadequate for evaluation.]

Groups of male F344 rats (age, 12 weeks) were given *N*-nitrosomethylbenzylamine (NMBzA) subcutaneously at a dose of 1 mg/kg bw, or hot water (1 mL/kg bw at 55 °C or 65 °C by oesophageal intubation), or a combination of these (Li et al. (2003)). Groups sizes were 5 rats (groups receiving only saline or only hot water at either temperature), 9 rats (groups receiving NMBzA alone or with hot water at 55 °C), or 11 rats (group receiving NMBzA and hot water at 65 °C). Both agents were given five times per week for 5 weeks and then once per week for 10 weeks. The experiment was concluded at 20 weeks due to the rapid progression of tumours caused by NMBzA plus hot water. Rats that received NMBzA and hot water at 65 °C presented a statistically significant ($P < 0.05$) reduction in their body weight as compared with rats in the control group. None of the 5 rats that received only saline or only hot water at either temperature developed tumours of the oesophagus. There was a statistically significant increase in the mean number of squamous cell papillomas or carcinomas (combined) per rat (11 rats) that received NMBzA and 65 °C hot water (8.0 ± 2.1, $P < 0.05$) compared with those treated with NMBzA alone (9 rats) (5.5 ± 1.5). Treatment with NMBzA and 55 °C hot water (9 rats) did not produce an increase in tumour multiplicity (5.7 ± 2.1) when compared with NMBzA alone. Hot water at 65 °C increased NMBzA-induced carcinogenesis: rats that received NMBzA developed 47 tumours (19 squamous cell papillomas, 20 squamous cell papillomas with atypia, and 8 squamous cell carcinomas), whereas rats that received the combined treatment of NMBzA and hot water at 65 °C developed 89 tumours (18 squamous cell papillomas, 44 squamous cell papillomas with atypia, and 27 squamous cell carcinomas; increase in the number of carcinomas, $P < 0.05$). [The Working Group considered that the study was well designed and well conducted, with an exposure–response relationship regarding hot water temperature. There was, however, a small number of rats per group, particularly in the group treated with hot water only.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion of mate

4.1.1 Absorption and distribution

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

The only study available evaluated 5-caffeoylquinic acid (5-CQA), caffeic acid (CA), and caffeine absorption and distribution in male Wistar rats given single or multiple (during a 30-day period) oral dose(s) of mate infusion extract, either hydrolysed or unhydrolysed

(Rivelli et al., 2011). [Hydrolysis was performed using chlorogenate esterase in a process that is not involved in traditional mate preparation.] The extract contained 7.93% 5-CQA, 1.48% CA, and 162 ± 5 µmol equiv quercetin/g. Maximum plasma concentrations (C_{max}) of 5-CQA and CA were achieved 10 and 20 minutes after extracts were administered, respectively. Hydrolysis increased the CA plasma concentration, whereas caffeine reached a higher C_{max} after ingestion of nonhydrolysed extract. 5-CQA was only evaluated after the unhydrolysed extract was administered, and was below the detection limit.

Distribution of 5-CQA, CA, and caffeine was assessed at the time of highest plasma concentration by high-pressure liquid chromatography analysis of liver, brain, and skin samples. In liver, only CA was found in rats treated with hydrolysed extract. None of the compounds was detected in brain or skin.

4.1.2 Metabolism

(a) Humans

No data were available to the Working Group in exposed humans.

However, two studies examined the effect of the mate plant on human metabolic enzyme activities in vitro. In human placental microsomes, ursolic acid was an efficient and dose-dependent aromatase inhibitor, with the half-maximal inhibitory concentration (IC_{50}) of 32 µM (Gnoatto et al., 2008). Martins et al. (2010) reported dose-dependent inhibition of human pancreatic lipase at 37 °C, with the maximal inhibition observed at mate tea concentration of 3.0 mg/mL, i.e. 9 mg of tea per gram of substrate (79 ± 1.3% inhibition). The IC_{50} value was estimated to be 1.5 mg/L or 4.5 mg of mate tea per gram of substrate.

(b) Experimental systems

No data in vivo were available to the Working Group.

One study in vitro explored modulation of pancreatic lipase (Martins et al., 2010), reporting dose-dependent, competitive inhibition with the maximal inhibition observed at a mate-preparation concentration of 3.0 mg/mL, corresponding to 9 mg of preparation per gram of substrate (83 ± 2.1% inhibition). The IC_{50} was determined to be 1.5 mg/L or 4.5 mg of mate preparation per gram of substrate.

4.1.3 Excretion

No data were available to the Working Group.

4.2 Mechanisms of carcinogenesis

For the experiments discussed below, the temperature of mate at which the experiments were conducted was not specified unless otherwise indicated.

4.2.1 Genetic and related effects

(a) Mate

(i) Humans

See Tables 4.1 and 4.2.

Only two studies in exposed humans were available, and neither evaluated the recommended number of cells (2000) according to a recently published micronucleus protocol (Thomas et al., 2009). A study of 145 mate drinkers and 99 non-drinkers reported induction of micronuclei (MN) in oesophageal cells by mate (Dietz et al., 2000). In the overall group of mate consumers, no effect was observed in comparison to the controls, and neither smoking nor alcohol influenced the MN levels. No increase in MN frequencies was observed in a small intervention trial without controls (Bortoluzzi et al., 2014), in which 10 volunteers consumed mate at 1 L/day over a week (4 drinks/day for 7 days). Buccal cells were collected 14–16 days after the intervention. [The Working Group noted that

Table 4.1 Genetic and related effects of drinking mate in humans

Cell type	End-point	Test	Description of exposure and controls	Result/ significance	Comments	Reference
Oesophageal cells	Chromosomal damage	Micronucleus formation	Healthy subjects (145 consumers and 99 non-consumers)	(–)	Only 500 cells were evaluated; no increase of micronuclei due to alcohol consumption or smoking	Dietz et al. (2000)
Buccal cells	Chromosomal damage	Micronucleus formation	Intervention trial with 10 healthy subjects who consumed 4 drinks/ day for 7 days	(–)	Only 1000 cells were evaluated	Bortoluzzi et al. (2014)

(–), negative in a study of limited quality

cells were stained with Giemsa, which is not suitable for this test (Nersesyan et al., 2006).]

In cells collected from patients with squamous cell carcinoma of the oesophagus from an area in Brazil of high risk where mate is consumed at high temperatures, Pütz et al. (2002) reported increased levels of *TP53* gene mutations. Information concerning demographic data and lifestyle factors, including alcohol, mate consumption, and smoking, were collected with questionnaires. The type of alterations found differed from that detected in cancer of the oesophagus in other geographic areas, i.e. a relatively high number of transition mutations was reported (G > A, C > T, and A > G). [The Working Group noted that this conclusion was based on comparisons with results from other studies.]

In an in vitro study of human lymphocytes, Fonseca et al. (2000) reported a significant increase of chromosomal aberrations after treatment with mate at concentrations of 50–750 µg/mL, while higher concentrations were not clastogenic. In the presence of metabolic activation mix (S9), only the highest test concentration (750 µg/mL) was clastogenic while lower amounts (100, 250, and 500 µg/mL) were ineffective.

Two groups reported on the formation of MN with the cytokinesis-block method in cultured human lymphocytes. While Alves et al. (2008) found no evidence for mutagenic and cytotoxic activities, a clear positive result was reported by Wnuk et al. (2009). The latter authors also used fluorescence in situ hybridization (FISH) probes and found that aneugenic effects contribute to the formation of MN.

(ii) Experimental systems

See Tables 4.3 and 4.4.

Two studies using the comet assay in laboratory rodents yielded negative results. The first examined genotoxic effects in rats of nitrosamines in combination with high temperatures (Silva et al., 2009). Mate (2.0% in drinking-water) did not induce DNA strand breaks in leukocytes, whereas protective effects of mate (given over 8 weeks) were found in combination experiments with diethylnitrosamine (Silva et al., 2009). In mice, mate solutions (60 days) did not induce strand breaks in cells from the liver, kidneys, and bladder (Miranda et al., 2008). At the highest dose (2.0 g/kg), a small but significant reduction of comet formation was observed (Miranda et al., 2008). In parallel experiments, a protective effect of mate ingestion on DNA strand breaks was seen

Table 4.2 Genetic and related effects of mate in human lymphocytes in vitro

End-point	Test	Results[a]		Dose (LED or HID)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Chromosomal damage	Chromosomal aberrations	+	+	50 µg/mL without S9; 750 µg/mL S9		Fonseca et al. (2000)
Chromosomal damage	Micronucleus	–	NT	1400 µg/mL		Alves et al. (2008)
Chromosomal damage	Micronucleus	+	NT	10.0 µg/mL	100 and 1000 µg/mL were ineffective	Wnuk et al. (2009)

+, positive; –, negative; HID, highest ineffective dose; LED, lowest effective dose; NT, not tested; S9, 9000 × *g* supernatant from rat liver

when isolated liver cells were exposed to reactive oxygen species (ROS) (H_2O_2) (see also Section 4.2.2). No increase in chromosomal aberrations in bone marrow cells was seen in male and female Wistar rats treated once intragastrically with mate (1.0 and 2.0 g/kg), or with the same doses divided over 4 consecutive days Fonseca et al. (2000).

In non-mammalian systems, Fonseca et al. (2000) mate was positive in *Salmonella* strains TA100 and TA102 (but not in TA97 and TA98 strains) and in assays for phage induction with *E. coli* (strains WP2sλ and RJF013). In *E. coli*, results were negative when exogenous activation mix (S9) was added. [The Working Group noted that no positive controls were used in the experiments and no standard deviations (SDs) are shown in the results.] In *Saccharomyces cerevisiae* (Candreva et al., 1993), hot (but not cold) mate was mutagenic.

(b) Hot beverages

(i) Humans

A Canadian study (61 patients) reported an impact of hot beverage consumption (recorded with questionnaires) on the levels of *TP53* mutations in primary carcinomas of the oesophagus (Casson et al., 1998). The number of mutations increased as a function of the number of hot drinks consumed and with beverage temperature.

In a study of *TP53* mutation patterns in samples of squamous cell carcinomas of the oesophagus obtained from subjects in Golestan Province in the Islamic Republic of Iran, almost all samples were positive for mutations (Abedi-Ardekani et al., 2011). A total of 120 *TP53* mutations were detected in 107 out of 119 cases (89.9%), and a significant concordance in patterns of *TP53* mutations (G:C to A:T mutations at CpG sites) was found with respect to the self-reported temperature of tea consumption (measured in terms of the number of minutes the subject usually waited after pouring boiling water onto tea before drinking it).

[The Working Group noted the difficulty in assessing the relevance of these studies on *TP53* mutations to the etiological factors for cancer of the oesophagus.]

(ii) Experimental systems

No data were available to the Working Group.

4.2.2 Oxidative stress

(a) Mate

(i) Humans

No data were available to the Working Group.

Table 4.3 Genetic and related effects of mate in non-human mammals in vivo

Species, strain, sex	Tissue	End-point	Test system	Result	Dose (LED or HID) (mg/kg bw)	Route, duration, dosing regiment	Comments	Reference
Male Wistar rats, *n* = 5/group	Blood leukocytes	DNA damage	Comet assay	–	4500–5400	Mate 2%, 8 weeks with drinking-water	Hot mate decreased DNA strand breaks induced by diethylnitrosamine by 50%	Silva et al. (2009)
Male Swiss mice free of specific pathogens, *n* = 10/group	Liver, kidney, and bladder cells	DNA damage	Comet assay	–	2000	Aqueous extract of roasted mate, 500, 1000 and 2000 mg/kg for 60 days	Decrease of H_2O_2-induced DNA strand breaks and improved DNA repair after H_2O_2 challenge in liver cells after ingestion of mate infusion	Miranda et al. (2008)
Male and female Wistar rats (*n* = 5 single treatment, *n* = 10 in multiple treatment group)	Bone marrow cells	Chromosomal damage	Chromosomal aberrations	–	2000	1000 and 2000 mg/kg bw per day (single dose) 1000 × 4 and 2000 × 4 mg/kg bw per day; 1000 or 2000 mg/kg fractionated in multiple doses		Fonseca et al. (2000)

–, negative; bw, body weight; HID, highest ineffective dose; LED, lowest effective dose

Table 4.4 Genetic and related effects of mate in non-mammalian cells in vitro

Test system	Strain	End-point	Results[a]		Dose	Comments	References
			Without metabolic activation	With metabolic activation			
Bacteria	*Salmonella typhimurium*, *TA97*, *TA98*, *TA100*, *TA102*	Reverse mutation	+ +	– TA100 + TA102	10 mg/plate	Negative result in TA97 and TA98 (not shown); no positive control and no SD	Fonseca et al. (2000)
Bacteria	*Escherichia coli* WP2sλ and RJF013	Prophage induction	+	–	50 mg/plate	No positive control and no SD	Fonseca et al. (2000)
Yeast	*Saccharomyces cerevisiae*	Lys induction	–	NT	Mate at room temperature	Concentration not given	Candreva et al. (1993)
			+	NT	Hot mate		

[a] +, positive; –, negative
HID, highest ineffective dose; LED, lowest effective dose; NT, not tested; SD, standard deviation

(ii) Experimental systems

Miranda et al. (2008) demonstrated a reduction of damage induced by ROS (H_2O_2) as a result of mate consumption. The mice were given an aqueous extract of roasted mate (0.5, 1.0, and 2.0 g/kg) for 60 days. In isolated liver cells subsequently exposed to H_2O_2, significantly reduced DNA damage was seen in cells from the mice that had received mate. Additionally, mate consumption enhanced DNA repair capacity of the cells, as assessed by use of a modified single-cell gel electrophoresis (SCGE) protocol.

Catalase and radical scavenging compound (dipyridyl), but not superoxide dismutase, reduced the genotoxic effects of mate in a bacterial test system (phage induction experiments with *E. coli*) (Fonseca et al., 2000).

(b) Hot beverages

No data were available to the Working Group.

4.2.3 Inflammation

(a) Mate

(i) Humans

Muñoz et al. (1987) conducted an endoscopic examination of the oesophagus in 30 regular hot mate drinkers and 30 controls matched according to age, cigarette smoking, and alcohol intake who drank mate no more than once per week. There was little difference in the prevalence of endoscopically diagnosed oesophagitis between the two groups. However, histological oesophagitis was found in 43% of mate drinkers versus 20% of controls ($P = 0.046$). There was also a higher prevalence of gastritis in the mate drinkers (in 20% of mate drinkers vs 13% of controls), but no P value was reported for this comparison.

(ii) Experimental systems

In a study of murine RAW 264.7 macrophages in vitro, mate extracts containing caffeoylquinic acid inhibited lipopolysaccharides-induced inflammation via suppression of nitric oxide and prostaglandin E2/cyclooxygenase-2 pathways (Puangpraphant et al., 2011).

(b) Hot beverages

In a study of tissue from 90 patients with cancer of the oesophagus, consumption of hot beverages was associated with increased levels of extracellular signal-regulated kinase 1 and 2 but not cyclooxygenase 2 (Yang et al., 2013).

4.2.4 Alterations of cell profileration or death

(a) Mate

(i) Humans

No data on exposed humans were available to the Working Group.

In an in vitro study, mate extracts containing caffeoylquinic acid inhibited proliferation of CRL-2577 (RKO) and HT-29 human colon cancer cells through induction of apoptosis. The Bax:Bcl-2 ratio was increased in HT-29 but not RKO cells. Caspase-8 activation leading to caspase-3 cleavage was seen in both cell types (Puangpraphant et al., 2011).

Gonzalez de Mejia et al. (2005) reported that a mate extract induced dose-dependent cytotoxicity in human squamous cancer cell lines (SCC-61 and OSCC-3).

(ii) Experimental systems

Cell proliferation decreased in liver and oesophageal tissue when room-temperature drinking-water containing mate (2%) was given to rats that had previously been given diethylnitrosamine and hot water (65 °C, 1 mL per rat) (Silva et al., 2009) for 8 weeks ad libitum.

In a clone-forming assay using yeast (*Saccharomyces cerevisiae*), a mate extract inhibited topoisomerase II but not topoisomerase I (Gonzalez de Mejia et al., 2005).

(b) Hot beverages

(i) Humans

No data were available to the Working Group.

(ii) Experimental systems

Rapozo et al. (2016) reported that water at 70 °C induced oesophageal necrosis in mice that healed and became resistant to necrosis from further exposures. However, water at 70 °C given together with NDEA interfered with epithelial regeneration, resulting in recurrent thermal injury and inflammation. Lower temperatures were without effect. Immunohistochemical analyses revealed that recurrent thermal injury induced basal cell proliferation (Ki67-positive cells), resulting in the expansion of epithelial basal cells (increased number of cytokeratin 14-positive cells and decreased number of cytokeratin 5-positive cells).

4.3 Other adverse effects

Several case reports documented thermal injury of the oesophagus upon ingestion of very hot beverages and food (Javors et al., 1996; Dutta et al., 1998; Eliakim, 1999; Choi et al., 2005; Go et al., 2007). Most of these studies reported various clinical signs of acute (single ingestion or short-term repeated exposure to very hot liquids or foods) injury to the epithelial lining of the oesophagus as the outcome of consuming very hot food, and stated that the prognosis was favourable with respect to the eventual healing of the injury. [The Working Group noted that these case reports indicate clinical symptoms upon acute injury by very hot foods or beverages, and no long-term follow-up was conducted.]

Roshandel et al. (2014) performed a cross-sectional study of 302 adults who were participants of the Golestan Cohort Study, a population-based cohort of 50 000 adults in the Islamic Republic of Iran, to examine potential risk factors of oesophageal conditions in asymptomatic subjects. Randomly selected participants underwent an endoscopic examination of the oesophagus. Lifestyle factor data, including drinking cold or hot tea, were obtained from

dietary questionnaires. [The Working Group noted that while the drinking temperature of tea was not specified, a publication by Islami et al. (2009b) from the same region indicated that drinkers of hot tea consume the beverages at temperatures above 60 °C.] The diagnosis of oesophageal squamous dysplasia in asymptomatic adults was not associated with drinking hot tea. A significant association was observed for the diagnosis of oesophagitis with drinking hot tea in comparison with drinking cold tea (30.9% incidence in cold tea drinkers and 39.1% in hot tea drinkers) only in multivariate analysis adjusted for other variables (OR, 2.27; 95% CI, 1.15–4.47). [The Working Group noted that the strengths of the study were the design and the use of endoscopy to establish the appropriate diagnosis; however, the major limitation was the small size of the study and difficulty with establishing what temperature of the beverage was considered "hot" by each subject.]

Sajja et al. (2016) conducted a study of lifestyle factors and risk of Barrett oesophagus in a cross-sectional study of 310 patients with histologically confirmed disease with 1728 individuals with no endoscopic or histopathological features of Barrett oesophagus. While risk of Barrett oesophagus was increased for subjects drinking hot or extremely hot coffee (OR, 1.47; 95% CI, 1.10–1.96) or cold tea (OR, 1.45; 95% CI, 1.12–1.86), no associations were found for drinking warm, hot, or extremely hot tea.

5. Summary of Data Reported

5.1 Exposure data

5.1.1 Very hot beverages

Beverages that are prepared at high temperatures most commonly include coffee, tea, mate, and other infusions. Such beverages are typically served at temperatures of 71–85 °C but are consumed at lower temperatures, typically 50–70 °C. Drinking temperature can be considered "hot" between 50 °C and 65 °C, and "very hot" at temperatures above 65 °C. However, there is considerable variation in drinking temperature depending on geographical region or culture, type of drink, and other factors such as the sex and age of the consumer. Average drinking temperatures also vary with the type of beverage: coffee is typically consumed "hot", while mate is often drunk "very hot". A wide range of drinking temperatures, varying from below 60 °C to over 70 °C depending on region and method of preparation, has been reported for tea.

Most epidemiological studies on the relationship between hot beverage consumption and cancer have relied on questionnaires to assess participants' preferences for drinking temperature, often by subjective categories such as "cold", "warm", "hot", or "very hot". Available data suggest good correlation between these subjective assessments and measured temperature. Data on other aspects, such as the average quantity and frequency of drinking per day and the total duration of drinking, are considered useful, but have not been reported in many studies.

5.1.2 Mate

Mate is an aqueous infusion prepared from dried leaves of *Ilex paraguariensis* (both the leaves and the infusion are known as mate). The major producers of mate leaves are Brazil, Argentina, and Paraguay. About 800 000 tonnes of leaves are produced annually worldwide. The consumption of mate has expanded to millions of consumers in South America, and also to some countries in North America, Europe, and the Middle East. The main importers are Uruguay, Syrian Arab Republic, Chile, and Brazil. Mate is usually drunk very hot (above 65 °C); in Paraguay and some regions of Brazil, however, it may be drunk cold. Mate preparations can use unroasted or roasted mate. Although mate leaves are used

primarily to prepare beverages, mate also has traditional medicinal uses; mate extracts can be found as ingredients of dietary supplements and energy drinks.

Among the numerous constituents, caffeine, and several chlorogenic acids have been identified in mate. Polycyclic aromatic hydrocarbons, including benzo[*a*]pyrene, may be formed during high-temperature processes such as drying or roasting/toasting, and have been reported at trace levels in the mate beverage.

5.2 Human carcinogenicity data

5.2.1 Drinking mate

(a) Cancer of the oesophagus

Data on the association of mate drinking with cancer of the oesophagus were available from nine case–control studies, most hospital-based, in South America. Some publications had overlapping data, so it is difficult to count the number of independent studies. A particularly informative pooled analysis of data from six South American case-control studies included 1400 cases of cancer of the oesophagus and 3229 controls. Careful adjustment was made for the potential confounders, including tobacco smoking and alcohol drinking, and a statistically significant trend of increasing risk of cancer of the oesophagus with increasing amount of mate consumed was observed. However, the exposure–response trend was found to vary by temperature, and it was only statistically significant for mate consumed hot or very hot, but not warm. Data on cold mate drinking were reported in one study in Paraguay, which found no evidence of increased risk of cancer of the oesophagus.

An evaluation of the amount of mate drinking independent of temperature was challenging, because mate is often drunk hot. However, the Working Group noted that a large pooled analysis did not show a statistically significant association between cancer of the oesophagus and drinking warm mate or the quantity of warm mate consumed. Furthermore, the pooled analysis of five case–control studies in South America found a similar magnitude of increased risk with hot mate and with other hot drinks. Another study found no increase in risk from drinking cold mate.

(b) Other cancers

Hospital-based case–control studies of the association of mate drinking with other cancers, including cancers of the upper aerodigestive tract, lung, urinary bladder, kidney, cervix, prostate, stomach, colon and rectum, and breast have been conducted in South America, most by a single research group in Uruguay. The majority of these studies considered cancers of the upper aerodigestive tract; very few studies were available for other cancer sites. In some studies drinking mate was associated with a higher risk of cancer of the larynx, other parts of the upper aerodigestive tract, bladder, kidney, cervix, lung, prostate, and stomach. For several cancer sites, drinking mate at a higher versus lower temperature was associated with an increased risk in a few studies. Because of the small number of studies for each type of cancer and the limitations of hospital-based case-control studies, the Working Group was unable to reach a conclusion as to the association of mate drinking with these diverse cancers.

5.2.2. Very hot beverages

(a) Cancer of the oesophagus

Data on associations of drinking hot beverages other mate were available from one cohort study, more than a dozen case–control studies, and a separate pooled analysis of five case–control studies in South America (all included in the pooled analysis of six studies above). The cohort study and most of the case-control studies showed increased risk of cancer of the oesophagus

with drinking hot or very hot tea compared with drinking tea at lower temperatures.

One case–control study observed an increased risk of cancer of the oesophagus for drinking very hot coffee compared with those drinking lower-temperature coffee, while the pooled analysis of five case–control studies in South America observed an increased risk from drinking very hot coffee with milk, but not for very hot coffee alone.

One cohort study, the pooled analysis of five case–control studies, and more than a dozen individual case–control studies investigated the association of cancer of the oesophagus and consumption of various combinations of very hot beverages, including tea and coffee, alcoholic drinks, and soup. The pooled analysis and about half of the case–control studies showed statistically significant positive associations between drinking hot beverages and risk of cancer of the oesophagus, whereas the cohort study and the remaining case–control studies did not show an association. The Working Group noted there was potential for information bias in the drinking temperature of tea as reported in the cohort study, however.

Three relatively recent systematic reviews have examined the association between drinking hot beverages and risk of cancer of the oesophagus. When summary statistics were calculated, the meta-odds ratio for the association of squamous-cell carcinoma of the oesophagus with consumption of drinks at higher versus lower temperatures was approximately 2.0 for drinking both mate and other hot drinks. There was no significant association with adenocarcinoma of the oesophagus.

The Working Group concluded that studies have shown a largely consistent association between drinking beverages at higher temperatures, versus lower temperatures, and risk of squamous cell carcinoma of the oesophagus. However, only one of the studies reporting a positive association was a prospective cohort study. Exposure assessment has mainly been based on the subjective description of temperature preference. Furthermore, the quality of adjustment for potential confounding was inconsistent across studies and possibility of information bias and publication bias cannot be ruled out.

(b) Other cancers

The few studies available on the associations between drinking beverages other than mate at higher versus lower temperatures and cancers of the upper aerodigestive tract, stomach, and skin gave mixed results. The available studies also have important limitations: all had case–control designs that varied by selection of controls, types of hot drinks assessed, temperature categories, and quality of adjustment for confounding factors. As a result of these limitations and the small number of studies for each cancer site, the Working Group was unable to draw conclusions about the association of cancers other than cancer of the oesophagus with drinking very hot beverages.

5.3 Animal carcinogenicity data

5.3.1 Mate

One co-carcinogenicity study in rats showed that cold mate given as drinking fluid significantly reduced the incidences of papillomas of the oesophagus and adenomas of the liver induced by hot water (65 °C) and *N*-nitrosodiethylamine.

5.3.2 Very hot water

One co-carcinogenicity study in mice and two co-carcinogenicity studies in rats (with one study in rats being considered inadequate for the evaluation) tested oesophageal tumour induction by local instillation of hot water only (50–70 °C for up to 37 weeks), with all studies giving negative results.

However, in the study in mice, hot water (at 70 °C, but not at 60 °C) increased the incidences of benign tumours and preneoplastic lesions of the oesophagus induced by *N*-nitrosodiethylamine. In the study in rats, hot water (at 65 °C, but not at 55 °C) enhanced *N*-nitrosomethylbenzylamine-induced squamous cell papilloma or carcinoma of the oesophagus (combined).

5.4 Mechanistic and other relevant data

5.4.1 Mate

Mate has many constituents; studies that used preparations or extracts from *Ilex paraguarensis*, rather than the individual components, were considered by the Working Group. Information on the pharmacokinetics and metabolism of individual components of mate is detailed in the monograph on Coffee Drinking in the present volume. No data from exposed humans on pharmacokinetics of these substances after oral ingestion of mate were available to the Working Group. In the only available study in rats of absorption and distribution, caffeine and caffeic acid, but not caffeoylquinic acid, were rapidly absorbed and distributed in systemic circulation after oral administration of an extract of mate constituents prepared differently from mate beverages. No information on the temperature of extract given or the concentration–time profiles was available. Only caffeic acid from hydrolysed mate extract was detected in liver, whereas no constituent was detected in brain or skin. In cell-free systems at 37 °C, mate preparations inhibited activity of human and porcine pancreatic lipase and human aromatase. No studies evaluated elimination kinetics of mate constituents.

The evidence is *weak* that mate is genotoxic. In two studies of mate drinkers that examined micronuclei induction in oesophagus and buccal swabs, no effect was reported. However, both studies had methodological limitations. Three studies in human cells in vitro did not provide consistent results for chromosomal alterations after direct exposure to mate. Three rodent in vivo studies of oral ingestion of mate solutions at room temperature for up to 60 days were negative for DNA strand breaks in lymphocytes, bone marrow, or other tissues. One study found a protective effect of mate on DNA strand breaks induced in the leukocytes in a study of diethylnitrosamine and hot water. One study in two bacterial test systems found a positive effect without, but not with, metabolic activation. In one study in yeast, no mutagenicity was detected with mate at room temperature, whereas hot mate was mutagenic.

Few data on other key characteristics of human carcinogens were available.

Few studies have reported other cancer-related adverse effects of drinking mate.

Overall, the mechanistic database on mate drinking is scant and only weak evidence for key characteristics of carcinogens or other effects is available.

5.4.2 Hot beverages

The evidence was *weak* that hot beverages are genotoxic. Hot beverage consumption (not otherwise specified) was associated with increased frequency of *TP53* mutation in primary oesophageal carcinomas in humans.

Few data on other key characteristics of human carcinogens were available for mate.

Several case reports have associated the consumption of hot beverages or foods with oesophageal injury. In addition, weak association has been found between consumption of very hot tea and oesophagitis in asymptomatic adults. One study of Barrett oesophagus found no association with drinking coffee or tea at any temperature, including hot or extremely hot.

Overall, the mechanistic data on hot beverages are scant.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of drinking very hot beverages. Positive associations have been observed between drinking very hot beverages and squamous cell carcinoma of the oesophagus.

There is *inadequate evidence* in humans for the carcinogenicity of drinking mate that is not very hot.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of very hot water at 65 °C or above.

There is *inadequate evidence* in experimental animals for the carcinogenicity of mate as a drinking fluid.

6.3 Overall evaluation

Drinking very hot beverages at temperatures above 65 °C is *probably carcinogenic to humans* (*Group 2A*).

Drinking mate that is not very hot is *not classifiable as to its carcinogenicity to humans* (*Group 3*).

6.4 Rationale

Rationale for the 2A evaluation of very hot beverages:

The epidemiological evidence for an association between drinking very hot beverages and human cancer has strengthened since Volume 51 with positive associations and trends in studies that considered various gradations of the temperature (e.g. cold, warm, hot, or very hot). Additionally, several experimental animal studies of initiation–promotion design conducted since 1991 demonstrate that hot water above 65 °C can act as a tumour promoter. While the mechanistic and other relevant evidence for very hot beverages is scant, there is biological plausibility of the association between drinking very hot beverages and cell injury, and the sequelae that may lead to cancer.

References

Abedi-Ardekani B, Kamangar F, Sotoudeh M, Villar S, Islami F, Aghcheli K, et al. (2011). Extremely high Tp53 mutation load in esophageal squamous cell carcinoma in Golestan Province, Iran. *PLoS One*, 6(12):e29488 doi:10.1371/journal.pone.0029488 PMID:22216294

Alves RJ, Jotz GP, do Amaral VS, Montes TM, Menezes HS, de Andrade HH (2008). The evaluation of maté (Ilex paraguariensis) genetic toxicity in human lymphocytes by the cytokinesis-block in the micronucleus assay. *Toxicol In Vitro*, 22(3):695–8. doi:10.1016/j.tiv.2007.11.005 PMID:18083001

Andrici J, Eslick GD (2015). Hot food and beverage consumption and the risk of esophageal cancer: a meta-analysis. *Am J Prev Med*, 49(6):952–60. doi:10.1016/j.amepre.2015.07.023 PMID:26590941

Bashirov MSh, Nugmanov SN, Kolycheva NI (1968). [On the epidemiology of cancer of the esophagus in the Aktiubinsk region of the Kazakhstan SSR.] *Vopr Onkol*, 14(8):3–7. [Russian] PMID:4235413

Bates MN, Hopenhayn C, Rey OA, Moore LE (2007). Bladder cancer and mate consumption in Argentina: a case-control study. *Cancer Lett*, 246(1–2):268–73. doi:10.1016/j.canlet.2006.03.005 PMID:16616809

Blum-Silva CH, Chaves VC, Schenkel EP, Coelho GC, Reginatto FH (2015). The influence of leaf age on methylxanthines, total phenolic content, and free radical scavenging capacity of Ilex paraguariensis aqueous extracts. *Rev Bras Farmacogn.*, 25(1):1–6. doi:10.1016/j.bjp.2015.01.002

Bortoluzzi MC, Campagnoli EB, Milan JR, Reinheimer A, Masson M, Capella DL (2014). Frequency of micronucleus in oral epithelial cells after exposure to mate-tea in healthy humans. *Med Oral Patol Oral Cir Bucal*, 19(4):e345–9. doi:10.4317/medoral.19570 PMID:24608213

Bracesco N, Sanchez AG, Contreras V, Menini T, Gugliucci A (2011). Recent advances on Ilex paraguariensis research: minireview. *J Ethnopharmacol*, 136(3):378–84. doi:10.1016/j.jep.2010.06.032 PMID:20599603

Brown F, Diller KR (2008). Calculating the optimum temperature for serving hot beverages. *Burns*, 34(5):648–54. doi:10.1016/j.burns.2007.09.012 PMID:18226454

Brown LM, Blot WJ, Schuman SH, Smith VM, Ershow AG, Marks RD, et al. (1988). Environmental factors and high risk of esophageal cancer among men in coastal South Carolina. *J Natl Cancer Inst*, 80(20):1620–5. doi:10.1093/jnci/80.20.1620 PMID:3193480

Candreva EC, Keszenman DJ, Barrios E, Gelós U, Nunes E (1993). Mutagenicity induced by hyperthermia, hot mate infusion, and hot caffeine in Saccharomyces cerevisiae. *Cancer Res*, 53(23):5750–3. PMID:8242632

Casson AG, Tammemagi M, Eskandarian S, Redston M, McLaughlin J, Ozcelik H (1998). p53 alterations in oesophageal cancer: association with clinicopathological features, risk factors, and survival. *Mol Pathol*, 51(2):71–9. doi:10.1136/mp.51.2.71 PMID:9713589

Castelletto R, Castellsague X, Muñoz N, Iscovich J, Chopita N, Jmelnitsky A (1994). Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. *Cancer Epidemiol Biomarkers Prev*, 3(7):557–64. PMID:7827585

Castellsagué X, Muñoz N, De Stefani E, Victora CG, Castelletto R, Rolón PA (2000). Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. *Int J Cancer*, 88(4):658–64. doi:10.1002/1097-0215(20001115)88:4<658::AID-IJC22>3.0.CO;2-T PMID:11058886

Chen F, He B, Huang J, Liu F, Yan L, Hu Z et al. (2015). [Effect of tea on oral cancer in nonsmokers and nondrinkers: a case-control study.] *Zhonghua Yu Fang Yi Xue Za Zhi*, 49(8):683–7. [Chinese] PMID:26733025

Chen Y, Tong Y, Yang C, Gan Y, Sun H, Bi H, et al. (2015b). Consumption of hot beverages and foods and the risk of esophageal cancer: a meta-analysis of observational studies. *BMC Cancer*, 15(1):449. doi:10.1186/s12885-015-1185-1 PMID:26031666

Chen YK, Lee C-H, Wu I-C, Liu J-S, Wu D-C, Lee J-M, et al. (2009). Food intake and the occurrence of squamous cell carcinoma in different sections of the esophagus in Taiwanese men. *Nutrition*, 25(7–8):753–61. doi:10.1016/j.nut.2009.02.002 PMID:19394796

Chen Z, Chen Q, Xia H, Lin J (2011). Green tea drinking habits and esophageal cancer in southern China: a case-control study. *Asian Pac J Cancer Prev*, 12(1):229–33. PMID:21517263

Cheng KK, Sharp L, McKinney PA, Logan RF, Chilvers CE, Cook-Mozaffari P, et al. (2000). A case-control study of oesophageal adenocarcinoma in women: a preventable disease. *Br J Cancer*, 83(1):127–32. doi:10.1054/bjoc.2000.1121 PMID:10883680

Choi EK, Lee GH, Jung HY, Hong WS, Kim JH, Kim JS, et al. (2005). The healing course of thermal esophageal injury: a case report. *Gastrointest Endosc*, 62(1):158–60. doi:10.1016/S0016-5107(05)00370-6 PMID:15990841

Cook-Mozaffari PJ, Azordegan F, Day NE, Ressicaud A, Sabai C, Aramesh B (1979). Oesophageal cancer studies in the Caspian Littoral of Iran: results of a case-control study. *Br J Cancer*, 39(3):293–309. doi:10.1038/bjc.1979.54 PMID:465299

Dar NA, Bhat GA, Shah IA, Iqbal B, Rafiq R, Nabi S, et al. (2015). Salt tea consumption and esophageal cancer: a possible role of alkaline beverages in esophageal carcinogenesis. *Int J Cancer*, 136(6):E704–10. doi:10.1002/ijc.29204 PMID:25209106

De Jong UW, Breslow N, Hong JG, Sridharan M, Shanmugaratnam K (1974). Aetiological factors in oesophageal cancer in Singapore Chinese. *Int J Cancer*, 13(3):291–303. doi:10.1002/ijc.2910130304 PMID:4822104

De Stefani E, Boffetta P, Deneo-Pellegrini H, Correa P, Ronco AL, Brennan P, et al. (2007). Non-alcoholic beverages and risk of bladder cancer in Uruguay. *BMC Cancer*, 7(1):57. doi:10.1186/1471-2407-7-57 PMID:17394632

De Stefani E, Correa P, Fierro L, Carzoglio J, Deneo-Pellegrini H, Zavala D (1990b). Alcohol drinking and tobacco smoking in gastric cancer. A case-control study. *Rev Epidemiol Sante Publique*, 38(4):297–307. PMID:2287798

De Stefani E, Correa P, Fierro L, Fontham E, Chen V, Zavala D (1991). Black tobacco, mate, and bladder cancer. A case-control study from Uruguay. *Cancer*, 67(2):536–40. doi:10.1002/1097-0142(19910115)67:2<536::AID-CNCR2820670236>3.0.CO;2-8 PMID:1985746

De Stefani E, Correa P, Oreggia F, Deneo-Pellegrini H, Fernandez G, Zavala D, et al. (1988). Black tobacco, wine and mate in oropharyngeal cancer. A case-control study from Uruguay. *Rev Epidemiol Sante Publique*, 36(6):389–94. PMID:3231843

De Stefani E, Correa P, Oreggia F, Leiva J, Rivero S, Fernandez G, et al. (1987). Risk factors for laryngeal cancer. *Cancer*, 60(12):3087–91. doi:10.1002/1097-0142(19871215)60:12<3087::AID-CNCR2820601238>3.0.CO;2-6 PMID:3677031

De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Correa P, Mendilaharsu M, et al. (2014). Diet patterns and risk of squamous cell oesophageal carcinoma: a case-control study in Uruguay. *Asian Pac J Cancer Prev*, 15(6):2765–9. doi:10.7314/APJCP.2014.15.6.2765 PMID:24761898

De Stefani E, Fierro L, Correa P, Fontham E, Ronco A, Larrinaga M, et al. (1996). Mate drinking and risk of lung cancer in males: a case-control study from Uruguay. *Cancer Epidemiol Biomarkers Prev*, 5(7):515–9. PMID:8827355

De Stefani E, Fierro L, Mendilaharsu M, Ronco A, Larrinaga MT, Balbi JC, et al. (1998). Meat intake, 'mate' drinking and renal cell cancer in Uruguay: a case-control study. *Br J Cancer*, 78(9):1239–43. doi:10.1038/bjc.1998.661 PMID:9820187

De Stefani E, Moore M, Aune D, Deneo-Pellegrini H, Ronco AL, Boffetta P, et al. (2011). Mate consumption and risk of cancer: a multi-site case-control study in Uruguay. *Asian Pac J Cancer Prev*, 12(4):1089–93. PMID:21790257

De Stefani E, Muñoz N, Estève J, Vasallo A, Victora CG, Teuchmann S (1990a). Mate drinking, alcohol, tobacco, diet, and esophageal cancer in Uruguay. *Cancer Res*, 50(2):426–31. PMID:2295081

Deandrea S, Foschi R, Galeone C, La Vecchia C, Negri E, Hu J (2010). Is temperature an effect modifier of the association between green tea intake and gastric cancer risk? *Eur J Cancer Prev*, 19(1):18–22. doi:10.1097/CEJ.0b013e328330eb1a PMID:19864955

Deneo-Pellegrini H, De Stefani E, Boffetta P, Ronco AL, Acosta G, Correa P, et al. (2013). Mate consumption and risk of oral cancer: case-control study in Uruguay. *Head Neck*, 35(8):1091–5. doi:10.1002/hed.23080 PMID:22915329

Deneo-Pellegrini H, Ronco AL, De Stefani E, Boffetta P, Correa P, Mendilaharsu M, et al. (2012). Food groups and risk of prostate cancer: a case-control study in Uruguay. *Cancer Causes Control*, 23(7):1031–8. doi:10.1007/s10552-012-9968-z PMID:22544454

Dietz J, Diehl AS, Prolla JC, Furtado CD, Furtado AD (2000). [Micronuclei research the esophageal mucosa and its relationship with risk factors with cancer of the esophagus.] *Rev Assoc Med Bras*, 46(3):207–11. [Portugese] doi:10.1590/S0104-42302000000300004 PMID:11070510

Dietz J, Pardo SH, Furtado CD, Harzheim E, Furtado AD (1998). Risk factors related to esophageal cancer in Rio Grande do Sul, Brazil [Fatores de risco relacionados ao câncer de esôfago no Rio Grande do Sul.] *Rev Assoc Med Bras*, 44(4):269–72. [Portugese] doi:10.1590/S0104-42301998000400003 PMID:9852644

Dutta SK, Chung KY, Bhagavan BS (1998). Thermal injury of the esophagus. *N Engl J Med*, 339(7):480–1. doi:10.1056/NEJM199808133390715 PMID:9705693

Edwards FC, Edwards JH (1956). Tea drinking and gastritis. *Lancet*, 271(6942):543–5. doi:10.1016/S0140-6736(56)92024-4 PMID:13368452

Eliakim R (1999). Thermal injury from a hamburger: a rare cause of odynophagia. *Gastrointest Endosc*, 50(2):282–3. doi:10.1016/S0016-5107(99)70243-9 PMID:10425431

EMA (2010). Assessment report on Ilex paraguariensis St. Hilaire, folium. London, United Kingdom: European Medicines Agency.

Fagundes RB, Abnet CC, Strickland PT, Kamangar F, Roth MJ, Taylor PR, et al. (2006). Higher urine 1-hydroxy pyrene glucuronide (1-OHPG) is associated with tobacco smoke exposure and drinking maté in healthy subjects from Rio Grande do Sul, Brazil. *BMC Cancer*, 6(1):139. doi:10.1186/1471-2407-6-139 PMID:16729889

FAO (2016) FAOSTAT. Food and agriculture data [online database]. Rome, Italy: Statistics Division, Food and Agriculture Organization of the United Nations. Available from: http://faostat3.fao.org/home/Eng, accessed 27 February 2016.

Fonseca CA, Otto SS, Paumgartten FJ, Leitão AC (2000). Nontoxic, mutagenic, and clastogenic activities of Mate-Chimarrão (Ilex paraguariensis). *J Environ Pathol Toxicol Oncol*, 19(4):333–46. PMID:11213015

Franco EL, Kowalski LP, Oliveira BV, Curado MP, Pereira RN, Silva ME, et al. (1989). Risk factors for oral cancer in Brazil: a case-control study. *Int J Cancer*, 43(6):992–1000. doi:10.1002/ijc.2910430607 PMID:2732011

Gao YT, McLaughlin JK, Gridley G, Blot WJ, Ji B-T, Dai Q, et al. (1994). Risk factors for esophageal cancer in Shanghai, China. II. Role of diet and nutrients. *Int J Cancer*, 58(2):197–202. doi:10.1002/ijc.2910580209 PMID:8026881

Garidou A, Tzonou A, Lipworth L, Signorello LB, Kalapothaki V, Trichopoulos D (1996). Life-style factors and medical conditions in relation to esophageal cancer by histologic type in a low-risk population. *Int J Cancer*, 68(3):295–9. doi:10.1002/(SICI)1097-0215(19961104)68:3<295::AID-IJC5>3.0.CO;2-X PMID:8903469

Ghadirian P (1987). Thermal irritation and esophageal cancer in northern Iran. *Cancer*, 60(8):1909–14. doi:10.1002/1097-0142(19871015)60:8<1909::AID-CNCR2820600840>3.0.CO;2-Y PMID:3652017

Giberti GC (1994). Mate (*Ilex paraguariensis*). In: Hernando BJE, Leon J, editors. Neglected crops: 1492 from a different perspective. Plant Production and Protection Series No. 26. Rome, Italy: Food and Agriculture Organization of the United Nations; pp. 252–4.

Gnoatto SC, Dassonville-Klimpt A, Da Nascimento S, Galéra P, Boumediene K, Gosmann G, et al. (2008). Evaluation of ursolic acid isolated from Ilex paraguariensis and derivatives on aromatase inhibition. *Eur J Med Chem*, 43(9):1865–77. doi:10.1016/j.ejmech.2007.11.021 PMID:18192087

Go H, Yang HW, Jung SH, Park YA, Lee JY, Kim SH, et al. (2007). Esophageal thermal injury by hot adlay tea. *Korean J Intern Med*, 22(1):59–62. doi:10.3904/kjim.2007.22.1.59 PMID:17427650

Golozar A, Fagundes RB, Etemadi A, Schantz MM, Kamangar F, Abnet CC, et al. (2012). Significant variation in the concentration of carcinogenic polycyclic aromatic hydrocarbons in yerba maté samples by brand, batch, and processing method. *Environ Sci Technol*, 46(24):13488–93. doi:10.1021/es303494s PMID:23101992

Gonzalez de Mejia E, Song YS, Ramirez-Mares MV, Kobayashi H (2005). Effect of yerba mate (Ilex paraguariensis) tea on topoisomerase inhibition and oral

carcinoma cell proliferation. *J Agric Food Chem*, 53(6):1966–73. doi:10.1021/jf048158g PMID:15769122

Graham H (1984). Mate. In: Spiller GA, editor. The methylxanthine beverages and foods: chemistry, consumption and health effects. New York (NY): Alan R. Liss; pp. 179–83.

Gridley G, McLaughlin JK, Block G, Blot WJ, Winn DM, Greenberg RS, et al. (1990). Diet and oral and pharyngeal cancer among blacks. *Nutr Cancer*, 14(3–4):219–25. doi:10.1080/01635589009514096 PMID:2084618

GRIN (2016). Germplasm Resources Information Network. Beltsville (MD), USA: United States Department of Agriculture. Available from: https://www.ars-grin.gov/, accessed 22 January 2016.

Hakim IA, Harris RB, Weisgerber UM (2000). Tea intake and squamous cell carcinoma of the skin: influence of type of tea beverages. *Cancer Epidemiol Biomarkers Prev*, 9(7):727–31. PMID:10919744

Heck CI, de Mejia EG (2007). Yerba mate tea (Ilex paraguariensis): a comprehensive review on chemistry, health implications, and technological considerations. *J Food Sci*, 72(9):R138–51. doi:10.1111/j.1750-3841.2007.00535.x PMID:18034743

Heckman MA, Sherry K, Gonzalezz de Mejia E (2010a). Energy drinks: an assessment of their market size, consumer demographics, ingredient profile, functionality, and regulations in the United States. *Compr Rev Food Sci Food Saf*, 9(3):303–17. doi:10.1111/j.1541-4337.2010.00111.x

Heckman MA, Weil J, Gonzalez de Mejia E, Gonzalez E (2010b). Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. *J Food Sci*, 75(3):R77–87. doi:10.1111/j.1750-3841.2010.01561.x PMID:20492310

Hung HC, Huang M-C, Lee J-M, Wu D-C, Hsu H-K, Wu M-T (2004). Association between diet and esophageal cancer in Taiwan. *J Gastroenterol Hepatol*, 19(6):632–7. doi:10.1111/j.1440-1746.2004.03346.x PMID:15151616

IARC (1991). Coffee, tea, mate, methylxanthines and methylglyoxal. *IARC Monogr Eval Carcinog Risks Hum*, 51:1–513. Available from: http://publications.iarc.fr/69 PMID:1674554

Ibiebele TI, Taylor AR, Whiteman DC, van der Pols JC; Australian Cancer Study (2010). Eating habits and risk of esophageal cancers: a population-based case-control study. *Cancer Causes Control*, 21(9):1475–84. doi:10.1007/s10552-010-9576-8 PMID:20467799

Iscovich J, Castelletto R, Estève J, Muñoz N, Colanzi R, Coronel A, et al. (1987). Tobacco smoking, occupational exposure and bladder cancer in Argentina. *Int J Cancer*, 40(6):734–40. doi:10.1002/ijc.2910400604 PMID:3692621

Islami F, Boffetta P, Ren JS, Pedoeim L, Khatib D, Kamangar F (2009b). High-temperature beverages and foods and esophageal cancer risk–a systematic review. *Int J Cancer*, 125(3):491–524. doi:10.1002/ijc.24445 PMID:19415743

Islami F, Pourshams A, Nasrollahzadeh D, Kamangar F, Fahimi S, Shakeri R, et al. (2009a). Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. *BMJ*, 338:b929. doi:10.1136/bmj.b929 PMID:19325180

Islami F, Ren JS, Taylor PR, Kamangar F (2009c). Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. *Br J Cancer*, 101(9):1641–7. doi:10.1038/sj.bjc.6605372 PMID:19862003

ISO (1980). ISO 3103. Tea — Preparation of liquor for use in sensory tests. Geneva, Switzerland: International Organization for Standardization. Available from: http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=8250.

ISO (2008). ISO 6668. Green coffee — Preparation of samples for use in sensory analysis. Geneva, Switzerland: International Organization for Standardization. Available from: http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=44609.

Javors BR, Panzer DE, Goldman IS (1996). Acute thermal injury of the esophagus. *Dysphagia*, 11(1):72–4. doi:10.1007/BF00385802 PMID:8556881

Jessri M, Rashidkhani B, Hajizadeh B, Jessri M, Gotay C (2011b). Macronutrients, vitamins and minerals intake and risk of esophageal squamous cell carcinoma: a case-control study in Iran. *Nutr J*, 10(1):137. doi:10.1186/1475-2891-10-137 PMID:22185224

Jessri M, Rashidkhani B, Hajizadeh B, Jessri M, Kreiger N, Bajdik CD (2011a). Adherence to dietary recommendations and risk of esophageal squamous cell carcinoma: a case-control study in Iran. *Ann Nutr Metab*, 59(2–4):166–75. doi:10.1159/000334334 PMID:22142938

Joshi SC, Saxena SR, Satyawali VN, Joshi A, Nigam P, Singh VK, et al. (2009). Oesophageal carcinoma–a study of risk factors (emphasis on nutrition) in a teaching hospital of Kumaon region of Uttarakhand. *J Assoc Physicians India*, 57:631–5. PMID:20213999

Kamangar F, Schantz MM, Abnet CC, Fagundes RB, Dawsey SM (2008). High levels of carcinogenic polycyclic aromatic hydrocarbons in mate drinks. *Cancer Epidemiol Biomarkers Prev*, 17(5):1262–8. doi:10.1158/1055-9965.EPI-08-0025 PMID:18483349

Kaufman BD, Liberman IS, Tyshetskiĭ VI (1965). [Data concerning the incidence of esophageal cancer in the Gurjev Region of the Kazakh S.S.R. (according to data of the 9th expedition of the A.M.S. Institute of Oncology).] *Vopr Onkol*, 11(12):78–85. [Russian] PMID:4225753 PMID:4225753

Kinjo Y, Cui Y, Akiba S, Watanabe S, Yamaguchi N, Sobue T, et al. (1998). Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *J Epidemiol*, 8(4):235–43. doi:10.2188/jea.8.235 PMID:9816815

Lachenmeier DW, Steffen C, el-Atma O, Maixner S, Löbell-Behrends S, Kohl-Himmelseher M (2012). What is a food and what is a medicinal product in the European Union? Use of the benchmark dose (BMD) methodology to define a threshold for "pharmacological action". *Regul Toxicol Pharmacol*, 64(2):286–95. doi:10.1016/j.yrtph.2012.08.017 PMID:22960033

Lagiou P, Talamini R, Samoli E, Lagiou A, Ahrens W, Pohlabeln H, et al. (2009). Diet and upper-aerodigestive tract cancer in Europe: the ARCAGE study. *Int J Cancer*, 124(11):2671–6. doi:10.1002/ijc.24246 PMID:19230023

Launoy G, Milan C, Day NE, Faivre J, Pienkowski P, Gignoux M (1997). Oesophageal cancer in France: potential importance of hot alcoholic drinks. *Int J Cancer*, 71(6):917–23. doi:10.1002/(SICI)1097-0215(19970611)71:6<917::AID-IJC1>3.0.CO;2-0 PMID:9185689

Lee HS, O'Mahony M (2002). At what temperatures do consumers like to drink coffee?: mixing methods. *J Food Sci*, 67(7):2774–7. doi:10.1111/j.1365-2621.2002.tb08814.x

Li ZG, Shimada Y, Sato F, Maeda M, Itami A, Kaganoi J, et al. (2003). Promotion effects of hot water on N-nitrosomethylbenzylamine-induced esophageal tumorigenesis in F344 rats. *Oncol Rep*, 10(2):421–6. PMID:12579283

Lin J, Zeng R, Cao W, Luo R, Chen J, Lin Y (2011). Hot beverage and food intake and esophageal cancer in southern China. *Asian Pac J Cancer Prev*, 12(9):2189–92. PMID:22296354

Lubin JH, De Stefani E, Abnet CC, Acosta G, Boffetta P, Victora C, et al. (2014). Mate drinking and esophageal squamous cell carcinoma in South America: pooled results from two large multicenter case-control studies. *Cancer Epidemiol Biomarkers Prev*, 23(1):107–16. doi:10.1158/1055-9965.EPI-13-0796 PMID:24130226

Mao XQ, Jia XF, Zhou G, Li L, Niu H, Li FL, et al. (2011). Green tea drinking habits and gastric cancer in southwest China. *Asian Pac J Cancer Prev*, 12(9):2179–82. PMID:22296352

Marques V, Farah A (2009). Chlorogenic acids and related compounds in medicinal plants and infusions. *Food Chem*, 113(4):1370–6. doi:10.1016/j.foodchem.2008.08.086

Martinez I (1969). Factors associated with ccer of the esophagus, mouth, and pharynx in Puerto Rico. *J Natl Cancer Inst*, 42(6):1069–94. PMID:5793187

Martins F, Noso TM, Porto VB, Curiel A, Gambero A, Bastos DH, et al. (2010). Maté tea inhibits in vitro pancreatic lipase activity and has hypolipidemic effect on high-fat diet-induced obese mice. *Obesity*, 18(1):42–7. doi:10.1038/oby.2009.189 PMID:19543216

Miranda DD, Arçari DP, Pedrazzoli J Jr, Carvalho PO, Cerutti SM, Bastos DH, et al. (2008). Protective effects of mate tea (Ilex paraguariensis) on H2O2-induced DNA damage and DNA repair in mice. *Mutagenesis*, 23(4):261–5. doi:10.1093/mutage/gen011 PMID:18308716

Munishi MO, Hanisch R, Mapunda O, Ndyetabura T, Ndaro A, Schüz J, et al. (2015). Africa's oesophageal cancer corridor: do hot beverages contribute? *Cancer Causes Control*, 26(10):1477–86. doi:10.1007/s10552-015-0646-9 PMID:26245249

Muñoz N, Victora CG, Crespi M, Saul C, Braga NM, Correa P (1987). Hot maté drinking and precancerous lesions of the oesophagus: an endoscopic survey in southern Brazil. *Int J Cancer*, 39(6):708–9. doi:10.1002/ijc.2910390609 PMID:3583450

Nayar D, Kapil U, Joshi YK, Sundaram KR, Srivastava SP, Shukla NK, et al. (2000). Nutritional risk factors in esophageal cancer. *J Assoc Physicians India*, 48(8):781–7. PMID:11273469

Nersesyan A, Kundi M, Atefie K, Schulte-Hermann R, Knasmüller S (2006). Effect of staining procedures on the results of micronucleus assays with exfoliated oral mucosa cells. *Cancer Epidemiol Biomarkers Prev*, 15(10):1835–40. doi:10.1158/1055-9965.EPI-06-0248 PMID:17035390

NLM (2016). Dietary supplements labels database. Bethesda (MD), USA: National Institutes of Health, United States National Library of Medicine. Available from: https://www.dsld.nlm.nih.gov/dsld/rptQSearch.jsp?item=ilex+paraguariensis&db=adsld#label, accessed 28 March 2016.

Onuk MD, Oztopuz A, Memik F (2002). Risk factors for esophageal cancer in eastern Anatolia. *Hepatogastroenterology*, 49(47):1290–2. PMID:12239927

Oreggia F, De Stefani E, Correa P, Fierro L (1991). Risk factors for cancer of the tongue in Uruguay. *Cancer*, 67(1):180–3. PMID:1985715 doi:10.1002/1097-0142(19910101)67:1<180::AID-CNCR2820670130>3.0.CO;2-R PMID:1985715

Peralta JM, Schmalko ME (2007). Modelling heat and mass transfer in the heat treatment step of yerba maté processing. *Braz J Chem Eng*, 24(1):73–82. doi:10.1590/S0104-66322007000100007

Pintos J, Franco EL, Oliveira BV, Kowalski LP, Curado MP, Dewar R (1994). Mate, coffee, and tea consumption and risk of cancers of the upper aerodigestive tract in southern Brazil. *Epidemiology*, 5(6):583–90. doi:10.1097/00001648-199411000-00005 PMID:7841239

Pourfarzi F, Whelan A, Kaldor J, Malekzadeh R (2009). The role of diet and other environmental factors in the causation of gastric cancer in Iran–a population based study. *Int J Cancer*, 125(8):1953–60. doi:10.1002/ijc.24499 PMID:19569234

Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR, et al. (2010). Cohort Profile: The Golestan Cohort Study–a prospective study of

oesophageal cancer in northern Iran. *Int J Epidemiol*, 39(1):52–9. doi:10.1093/ije/dyp161 PMID:19332502

Prestes SLC, Thewes FR, Kaehler Sautter C, Brackmann A (2014). Storage of yerba maté in controlled atmosphere. *Cienc Rural*, 44(4):740–5. doi:10.1590/S0103-84782014000400028

Puangpraphant S, Berhow MA, Vermillion K, Potts G, Gonzalez de Mejia E (2011). Dicaffeoylquinic acids in Yerba mate (Ilex paraguariensis St. Hilaire) inhibit NF-κB nucleus translocation in macrophages and induce apoptosis by activating caspases-8 and -3 in human colon cancer cells. *Mol Nutr Food Res*, 55(10):1509–22. doi:10.1002/mnfr.201100128 PMID:21656672

Pütz A, Hartmann AA, Fontes PR, Alexandre CO, Silveira DA, Klug SJ, et al. (2002). TP53 mutation pattern of esophageal squamous cell carcinomas in a high risk area (Southern Brazil): role of life style factors. *Int J Cancer*, 98(1):99–105. doi:10.1002/ijc.10128 PMID:11857392

Rapozo DC, Blanco TC, Reis BB, Gonzaga IM, Valverde P, Canetti C, et al. (2016). Recurrent acute thermal lesion induces esophageal hyperproliferative premalignant lesions in mice esophagus. *Exp Mol Pathol*, 100(2):325–31. doi:10.1016/j.yexmp.2016.02.005 PMID:26899552

Rivelli DP, Almeida RL, Ropke CD, Barros SB (2011). Hydrolysis influence on phytochemical composition, antioxidant activity, plasma concentration, and tissue distribution of hydroethanolic Ilex paraguariensis extract components. *J Agric Food Chem*, 59(16):8901–7. doi:10.1021/jf201665t PMID:21790134

Rolón PA, Castellsagué X, Benz M, Muñoz N (1995). Hot and cold mate drinking and esophageal cancer in Paraguay. *Cancer Epidemiol Biomarkers Prev*, 4(6):595–605. PMID:8547825

Ronco AL, Stefani ED, Mendoza B, Deneo-Pellegrini H, Vazquez A, Abbona E (2016). Mate intake and risk of breast cancer in Uruguay: a case-control study. *Asian Pac J Cancer Prev*, 17(3):1453–61. doi:10.7314/APJCP.2016.17.3.1453 PMID:27039789

Roshandel G, Khoshnia M, Sotoudeh M, Merat S, Etemadi A, Nickmanesh A, et al. (2014). Endoscopic screening for precancerous lesions of the esophagus in a high risk area in Northern Iran. *Arch Iran Med*, 17(4):246–52. PMID:24724600

Royal Society of Chemistry (2003). How to make a perfect cup of tea. London, England: Royal Society of Chemistry. Available from: http://www.academiaobscura.com/wp-content/uploads/2014/10/RSC-tea-guidelines.pdf, accessed 20 August 2017.

Sajja KC, El-Serag HB, Thrift AP (2016). Coffee or tea, hot or cold, are not associated with risk of Barrett's esophagus. *Clin Gastroenterol Hepatol*, 14(5):769–72. doi:10.1016/j.cgh.2015.12.007 PMID:26681488

Schmalko ME, Alzamora SM (2001). Color, chlorophyll, caffeine, and water content variation during Yerba mate processing. *Dry Technol*, 19(3–4):599–610. doi:10.1081/DRT-100103937

Sewram V, De Stefani E, Brennan P, Boffetta P (2003). Maté consumption and the risk of squamous cell esophageal cancer in Uruguay. *Cancer Epidemiol Biomarkers Prev*, 12(6):508–13. PMID:12814995

Sharp L, Chilvers CE, Cheng KK, McKinney PA, Logan RF, Cook-Mozaffari P, et al. (2001). Risk factors for squamous cell carcinoma of the oesophagus in women: a case-control study. *Br J Cancer*, 85(11):1667–70. doi:10.1054/bjoc.2001.2147 PMID:11742485

Silva JF, Bidinotto LT, Furtado KS, Salvadori DM, Rivelli DP, Barros SB, et al. (2009). Maté attenuates DNA damage and carcinogenesis induced by diethylnitrosamine and thermal injury in rat esophagus. *Food Chem Toxicol*, 47(7):1521–9. doi:10.1016/j.fct.2009.03.040 PMID:19358871

Srivastava M, Kapil U, Chattopadhyay TK, Shukla NK, Sundaram KR, Sekaran G, et al. (1997). Nutritional factors in carcinoma oesophagus: a case-control study. *Asia Pac J Clin Nutr*, 6(2):96–8. PMID:24394709

Srivastava M, Kapil U, Chattopadhyaya TK, Shukla NK, Gnanasekaran N, Jain GL, et al. (1995). Nutritional risk factors in carcinoma esophagus. *Nutr Res*, 15(2):177–85. doi:10.1016/0271-5317(95)92583-6

Szymańska K, Matos E, Hung RJ, Wünsch-Filho V, Eluf-Neto J, Menezes A, et al. (2010). Drinking of mate and the risk of cancers of the upper aerodigestive tract in Latin America: a case-control study. *Cancer Causes Control*, 21(11):1799–806. doi:10.1007/s10552-010-9606-6 PMID:20623173

Tang L, Xu F, Zhang T, Lei J, Binns CW, Lee AH-W (2013). High temperature of food and beverage intake increases the risk of oesophageal cancer in Xinjiang, China. *Asian Pac J Cancer Prev*, 14(9):5085–8. doi:10.7314/APJCP.2013.14.9.5085 PMID:24175780

Terry P, Lagergren J, Wolk A, Nyrén O (2001). Drinking hot beverages is not associated with risk of oesophageal cancers in a Western population. *Br J Cancer*, 84(1):120–1. doi:10.1054/bjoc.2000.1561 PMID:11139325

Thomas P, Holland N, Bolognesi C, Kirsch-Volders M, Bonassi S, Zeiger E, et al. (2009). Buccal micronucleus cytome assay. *Nat Protoc*, 4(6):825–37. doi:10.1038/nprot.2009.53 PMID:19444240

Tran GD, Sun X-D, Abnet CC, Fan J-H, Dawsey SM, Dong Z-W, et al. (2005). Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer*, 113(3):456–63. doi:10.1002/ijc.20616 PMID:15455378

Vasconcelos de Oliveir S, Dabdab Waquil P (2015). Dynamics of production and commercialization of yerba mate in Rio Grande do Sul, Brazil. *Cienc Rural*, 45(4):750–6. doi:10.1590/0103-8478cr20140276

Vassallo A, Correa P, De Stéfani E, Cendán M, Zavala D, Chen V, et al. (1985). Esophageal cancer in Uruguay:

a case-control study. *J Natl Cancer Inst*, 75(6):1005–9. PMID:3865007

Vázquez A, Moyna P (1986). Studies on mate drinking. *J Ethnopharmacol*, 18(3):267–72. doi:10.1016/0378-8741(86)90005-X PMID:3821141

Victora CG, Muñoz N, Day NE, Barcelos LB, Peccin DA, Braga NM (1987). Hot beverages and oesophageal cancer in southern Brazil: a case-control study. *Int J Cancer*, 39(6):710–6. doi:10.1002/ijc.2910390610 PMID:3583451

Victora CG, Muñoz N, Horta BL, Ramos EO (1990). Patterns of maté drinking in a Brazilian city. *Cancer Res*, 50(22):7112–5. PMID:2224846

Vieira MA, Maraschin M, Rovaris AA, Amboni RD, Pagliosa CM, Xavier JJ, et al. (2010). Occurrence of polycyclic aromatic hydrocarbons throughout the processing stages of erva-mate (Ilex paraguariensis). *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*, 27(6):776–82. doi:10.1080/19440041003587310 PMID:20349373

Wang Y, Duan H, Yang H (2015). A case-control study of stomach cancer in relation to Camellia sinensis in China. *Surg Oncol*, 24(2):67–70. doi:10.1016/j.suronc.2015.02.002 PMID:25920351

Winkler G, El Damaty M, Schröder C, Lachenmeier DW (2014). Mate – a "new" caffeine-containing ingredient for the food and beverage industry. *Ernahr-Umsch*, 61(10):160–3.DOI doi:10.4455/eu.2014.027

Wnuk M, Lewinska A, Oklejewicz B, Bugno M, Slota E, Bartosz G (2009). Evaluation of the cyto- and genotoxic activity of yerba mate (Ilex paraguariensis) in human lymphocytes in vitro. *Mutat Res*, 679(1–2):18–23. doi:10.1016/j.mrgentox.2009.07.017 PMID:19733686

Wu M, Liu A-M, Kampman E, Zhang Z-F, Van't Veer P, Wu D-L, et al. (2009). Green tea drinking, high tea temperature and esophageal cancer in high- and low-risk areas of Jiangsu Province, China: a population-based case-control study. *Int J Cancer*, 124(8):1907–13. doi:10.1002/ijc.24142 PMID:19123468

Xibib S, Meilan H, Moller H, Evans HS, Dixin D, Wenjie D, et al. (2003). Risk factors for oesophageal cancer in Linzhou, China: a case-control study. *Asian Pac J Cancer Prev*, 4(2):119–24. PMID:12875624

Yang Z, Guan B, Men T, Fujimoto J, Xu X (2013). Comparable molecular alterations in 4-nitroquinoline 1-oxide-induced oral and esophageal cancer in mice and in human esophageal cancer, associated with poor prognosis of patients. *In Vivo*, 27(4):473–84. PMID:23812217

Yioris N, Ivankovic S, Lehnert T (1984). Effect of thermal injury and oral administration of N-methyl-N′-nitro-N-nitrosoguanidine on the development of esophageal tumors in Wistar rats. *Oncology*, 41(1):36–8. doi:10.1159/000225787 PMID:6700933

Yokoyama A, Kato H, Yokoyama T, Igaki H, Tsujinaka T, Muto M, et al. (2006). Esophageal squamous cell carcinoma and aldehyde dehydrogenase-2 genotypes in Japanese females. *Alcohol Clin Exp Res*, 30(3):491–500. doi:10.1111/j.1530-0277.2006.00053.x PMID:16499490

Yu MC, Garabrant DH, Peters JM, Mack TM (1988). Tobacco, alcohol, diet, occupation, and carcinoma of the esophagus. *Cancer Res*, 48(13):3843–8. PMID:3378219

Zaions I, Picolo AP, Gonçalves IL, Piovezan Borges AC, Valduga AT (2014). Physico-chemical characterization of Ilex paraguariensis St. Hil. during the maturation. *Braz Arch Biol Technol.*, 57(5):663–7. doi:10.1590/S1516-8913201402076

Zhang W, An F, Lin H (2001). [A case-control study on the risk factors of esophageal cancer in Jieyang City of Guangdong in China.] *Zhonghua Liu Xing Bing Xue Za Zhi*, 22(6):442–5. [Chinese] PMID:11851060

Zuin VG, Montero L, Bauer C, Popp P (2005). Stir bar sorptive extraction and high-performance liquid chromatography-fluorescence detection for the determination of polycyclic aromatic hydrocarbons in Mate teas. *J Chromatogr A*, 1091(1–2):2–10. doi:10.1016/j.chroma.2005.07.057 PMID:16395787

LIST OF ABBREVIATIONS

5-CQA	5-caffeoylquinic acid
γ-GCL	γ-glutamylcysteine ligase
11β-HSD1	11β-hydroxysteroid dehydrogenase 1
1-MU	1-methyluric acid
1-MX	1-methylxanthine
3-NT	nitrotyrosine
8-OHdG	8-hydroxydeoxyguanosine
1-OHPG	1-hydroxypyrene glucuronide
8-OxodG	8-oxodeoxyguanosine
AAF	2-acetylaminofluorene
Ab	antibody
ABTS	2,2′-azino-bis 3-ethylbenzothiazoline-6-sulfonic acid
AHA	aromatic and heterocyclic amines
AHH	aryl hydrocarbon hydroxylase
AHR	aryl hydrocarbon receptor
AL	acute leukaemia
ALL	acute lymphoblastic leukaemia
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ANLL	acute non-lymphoblastic leukaemia
AOPP	advanced protein oxidation product
ARCAGE	Alcohol-Related Cancers and Genetic Susceptibility in Europe
ARE	antioxidant response element
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention
ATM	ataxia telangiectasia mutated
AUC	area under the curve
BMI	body mass index
BOP	*N*-nitrosobis(2-oxopropyl) amine
BPH	benign prostatic hypertrophy
bw	body weight
CA	caffeic acid
CAT	catalase
CCl_4	carbon tetrachloride
CGA	chlorogenic acid

CH	chloric acid equivalent
CHL	Chinese hamster lung
CHO	Chinese hamster ovary
CHUM	Centre hospitalier de l'Université de Montréal
CI	confidence interval
CLD	chronic liver disease
CLL	chronic lympocytic leukaemia
C_{max}	maximum plasma concentration
COSM	Cohort of Swedish Men
CRP	C-reactive protein
CSI	cumulative smoking index
CTS	California Teachers Study
CX3CL1	fractalkine
DHCA	dihydrocaffeic acid
DHFA	dihydroferulic acid
diCQA	dicaffeoylquinic acid
DMBA	dimethylbenz[*a*]anthracene
DMN	dimethylnitrosamine
DPPH	2,2-diphenyl-1-picrylhydrazyl
d-ROM	derivative of reactive oxygen metabolite
EDGE	Estrogen, Diet, Genetics, and Endometrial Cancer
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EOR	excess odds ratio
EPIC	European Prospective Investigation into Cancer and Nutrition
EpRE	electrophile response element
ER	estrogen receptor
ERα	estrogen receptor α
ESCALE	Etude Sur les Cancers et les Leucémies de l'Enfant
FA	ferulic acid
FAO	Food and Agriculture Organization of the United Nations
FFQ	food frequency questionnaire
FGF-2	fibroblast growth factor-2
FISH	fluorescence in situ hybridization
FQA	feruloylquinic acid
FRAP	ferric ion-reducing antioxidant power
FXR	farnesoid X receptor
GGT	gamma-glutamyltransferase
GLP-1	glucagon-like peptide 1
GPx	glutathione peroxisidase
GSH	glutathione
GSSG	glutathione disulfide
GST	glutathione *S*-transferase
GWAS	genome-wide association study
HBeAg	hepatitis B virus e-antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCE	health-check examinees

HCL	hairy cell leukaemia
HCV	hepatitis C virus
HF	high-fat (diet)
HF+C	high-fat diet plus cancer
HHQ	hydroxyhydroquinone
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
HRT	hormone replacement therapy
HsCRP	high-sensitivity C-reactive protein
IARC	International Agency for Research on Cancer
IC_{50}	half-maximal inhibitory concentration
ICC	intrahepatic cholangiocarcinoma
iFA	isoferulic acid
IFNγ	interferon gamma
IGF-1R	insulin-like growth factor 1 receptor
IL	interleukin
INHANCE	International Head and Neck Cancer Epidemiology
IRR	incidence rate ratio
IRS-1	insulin-receptor substrate-1
ISO	International Organization for Standardization
IWHS	Iowa Women's Health Study
JACC	Japan Collaborative Cohort Study for Evaluation of Cancer Risk
JPHC	Japan Public Health Center-based
LCL	lymphoblastoid cell line
LDL	low-density lipoprotein
LEC	Long Evans Cinnamon
LPDY	litres consumed per day × years of drinking
LPS	lipopolysaccharide
LUTS	lower urinary tract symptom
LW	low-fat (diet)
MALOVA	Danish MALignant OVArian cancer
MARIE	Mamma Carcinoma Risk Factor Investigation
MCCS	Melbourne Collaborative Cohort Study
MEC	Multiethnic Cohort
MGMT	O^6-methylguanine-DNA methyltransferase
MIP-1β	microphage inflammatory protein-1β
MM	multiple myeloma
MN	micronuclei
MNNG	*N*-methyl-*N*′-nitro-*N*-nitrosoguanidine
NAFLD	non-alcoholic fatty liver disease
NAT2	*N*-acetyltransferase 2
NC	neighbourhood controls
NDEA	*N*-nitrosodiethylamine
NDMA	*N*-nitrosodimethylamine
NECSS	National Enhanced Cancer Surveillance System
NF-κB	nuclear factor κB
NHL	non-Hodgkin lymphoma
NHS	Nurses' Health Study
NIH-AARP	National Institutes of Health–American Association of Retired Persons
NLCS	Netherlands Cohort Study

NLM	National Library of Medicine
NMBzA	*N*-nitrosomethylbenzylamine
NMP	*N*-methylpyridinium
NMSC	non-melanoma skin cancer
NOMAS	Northern Manhattan Study
NOWAC	Norwegian Women and Cancer
NQO1	NAD(P)H:quinone oxidoreductase 1
NRCH	National Registry of Childhood Haematopoietic Malignancies
NRCL	National Registry of Childhood Blood Malignancies
Nrf2	nuclear factor-erythroid-2-related factor
NYSC	New York State Cohort
OAT	organic anion transporter
OR	odds ratio
ORAC	oxygen radical antioxidant capacity
oxLDL	oxidized low-density lipoprotein
PAH	polycyclic aromatic hydrocarbons
PAI-1	plasminogen-activator inhibitor type-1
PBL	peripheral blood lymphocyte
PCNA	proliferation cell nuclear antigen
PEDS	Patient Epidemiology Data System
PGF2α	8-epi-prostaglandin F2α
PH	partial hepatectomy
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine
PLCO	Prostate, Lung, Colorectal, and Ovarian
PPARγ	peroxisome proliferator-activated receptor γ
ppm	parts per million
PR	progesterone receptor
PSA	prostate-specific antigen
PX	paraxanthine
PXR	pregnane X receptor
RCT	randomized controlled trial
RDD	random-digit dialling
RH	resistant hepatocyte
ROS	reactive oxygen species
RPCI	Roswell Park Cancer Institute
RPMI	Roswell Park Memorial Institute
RR	relative risk
SC	surgical controls
SCC	squamous cell carcinoma
SCE	sister-chromatid exchange
SCGE	single-cell gel electrophoresis
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results
SHBG	sex hormone-binding globulin
SHR	subhazard ratio
SMC	Swedish Mammography Cohort
SNP	single nucleotide polymorphism
SOD	superoxide dismutase
sTNFRII	soluble tumour necrosis factor receptor II
SU.VI.MAX	Supplémentation en Vitamines et Minéraux Anti-oxydants

SULT	sulfotransferase
sVACM-1	soluble vascular cell adhesion molecule-1
TAC	total antioxidant capacity
TAS	total antioxidant status
TBARS	thiobarbituric acid-reactive substance
TCC	transitional cell carcinoma
tGSH	total glutathione
THLE	transformed liver epithelial cell line
T_{max}	time to peak concentration
TNF-α	tumour necrosis factor alpha
TRAP	total peroxyl radical-trapping antioxidant parameter
UGT	UDP-glucuronosyl transferase
VIP	Västerbotten Intervention Project
vs	versus
WABOHS	Western Australian Bowel Health Study
WLH	Women's Lifestyle and Health

IARC MONOGRAPHS

This volume of the *IARC Monographs* presents evaluations of the carcinogenic hazard to humans of drinking coffee and very hot beverages including, but not limited to, mate.

An *IARC Monographs* Working Group reviewed epidemiological evidence, animal bioassays and co-carcinogenicity studies, and mechanistic and other relevant data to reach conclusions as to the carcinogenic hazard to humans of drinking coffee, mate, and very hot beverages.

The Working Group assessed more than 1000 observational and experimental studies that investigated the association between cancer at more than 20 sites with drinking coffee, mate, and very hot beverages.