IARC HANDBOOKS

ABSENCE OF EXCESS BODY FATNESS

VOLUME 16

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

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This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met in Lyon, 5–12 April 2016

LYON, FRANCE - 2018

IARC HANDBOOKS OF CANCER PREVENTION

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

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 Handbooks* are published online at http://publications.iarc.fr/.

To report an error, please contact editimo@iarc.fr.

How to cite this publication:
IARC (2018). Absence of excess body fatness. IARC Handb Cancer Prev. 16:1–646. Available from: http://publications.iarc.fr/570.

IARC Library Cataloguing in Publication Data

Absence of excess body fatness / IARC Working Group on the Evaluation of Cancer-Preventive Interventions, 2016.

(IARC Handbooks of Cancer Prevention ; Volume 16)

1. Neoplasms – prevention & control 2. Overweight 3. Body Mass Index 4. Prevalence 5. Risk Factors

ISBN 978-92-832-3020-5 (NLM Classification: W1)
ISSN 1027-5622

International Agency for Research on Cancer

The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly, as an independently funded organization within the framework of the World Health Organization. The headquarters of the Agency are in Lyon, France.

The Agency has as its mission to reduce the cancer burden worldwide through promoting international collaboration in research. The Agency addresses this mission through conducting cancer research for cancer prevention in three main areas: describing the occurrence of cancer; identifying the causes of cancer, and evaluating preventive interventions and their implementation. Each of these areas is a vital contribution to the spectrum of cancer prevention.

The publications of the Agency contribute to the dissemination of authoritative information on different aspects of cancer research. Information about IARC publications, and how to order them, is available at http://publications.iarc.fr/.

IARC Handbooks of Cancer Prevention

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 monographs of critical reviews and evaluations of individual chemicals.

The *IARC Handbooks of Cancer Prevention* complement the *IARC Monographs*' evaluations of carcinogenic hazards. The objective of the programme is to coordinate and publish critical reviews of data on the cancer-preventive effects of primary or secondary interventions, and to evaluate these data in terms of cancer prevention with the help of international working groups of experts in prevention and related fields. The lists of evaluations are regularly updated and are available at http://handbooks.iarc.fr/.

This *IARC Handbook of Cancer Prevention* is partly funded by the American Cancer Society (contract ACS #26531) and by the Grant or Cooperative Agreement Number DP004954-05, funded by the United States Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

Cover image: Overweight people sitting on a bench.

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NOTE TO THE READER

The *IARC Handbooks of Cancer Prevention* series was launched in 1995 to complement the *IARC Monographs*' evaluations of carcinogenic hazards. The *IARC Handbooks of Cancer Prevention* evaluate the published scientific evidence of cancer-preventive interventions.

Inclusion of an intervention in the *Handbooks* does not imply that it is cancer-preventive, only that the published data have been examined. Equally, the fact that an intervention has not yet been evaluated in a *Handbook* does not mean that it may not prevent cancer. Similarly, identification of organ sites with *sufficient evidence* or *limited evidence* of cancer-preventive activity in humans should not be viewed as precluding the possibility that an intervention may prevent cancer at other sites.

The evaluations of cancer-preventive interventions 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 cancer-preventive interventions is encouraged to make this information available to the IARC Handbooks Group, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, or by email to ihb@iarc.fr, in order that these data may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Handbooks* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the IARC Handbooks Group at ihb@iarc.fr.

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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.

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[3] Each Observer agreed to respect the Guidelines for Observers at *IARC Handbooks* meetings. Observers did not serve as Meeting Chair or Subgroup Chair, draft or revise any part of the *Handbook*, or participate in the evaluations. They also agreed not to contact participants before or after 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.

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WORKING PROCEDURES

The Working Procedures of the *IARC Handbooks of Cancer Prevention* describe the objective and scope of the programme, the scientific principles and procedures used in developing a *Handbook*, the types of evidence considered, and the scientific criteria that guide the evaluations. The Working Procedures should be consulted when reading a *Handbook* or a summary of evaluations made by the *IARC Handbooks*. These Working Procedures apply to the review and evaluation of primary prevention.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Prevention of cancer is one of the key objectives of the International Agency for Research on Cancer (IARC). The aim of the *IARC Handbooks of Cancer Prevention* series is to review and evaluate scientific information on interventions that may reduce the incidence of or mortality from cancer. As a result of the *IARC Handbooks* evaluations, national and international health agencies have been able, on scientific grounds, to take measures to develop interventions or recommendations that will reduce the risk of developing cancer.

The criteria guiding the evaluations were first established in 1995 at the inception of the *IARC Handbooks* series, and were revised in subsequent volumes.

2. Objective and scope

The objective of the *IARC Handbooks* programme is the preparation of critical reviews and evaluations of the evidence that a particular intervention can prevent cancer. The evaluations, which are prepared by a Working Group of international experts, are scientific judgements about the available evidence on efficacy, effectiveness, and safety of a wide range of cancer-preventive interventions. No recommendation is given with regard to national or international regulations or legislation, which are the responsibility of individual governments and/or other international authorities. The *IARC Handbooks* may assist national and international authorities in devising programmes of health promotion and cancer prevention, and in making benefit–risk assessments.

In this document, the term "intervention" refers to any chemical, activity, or strategy that is subject to evaluation in a *Handbook*. Cancer-preventive interventions encompass pharmacological, immunological, dietary, and behavioural interventions that may delay, block, or reverse carcinogenic processes, or reduce underlying risk factors.

Preventive interventions can be applied across a continuum of: (1) the general population; (2) subgroups with particular predisposing host or environmental risk factors, including genetic susceptibility to cancer; (3) persons with precancerous lesions; and (4) cancer patients at risk of

developing second primary tumours. Use of the same interventions in the treatment of cancer patients to control the growth, metastasis, and recurrence of tumours is considered to be patient management and not prevention, although data from clinical trials of such interventions may be pertinent when reaching an evaluation.

3. Selection of interventions for review

Interventions to be evaluated in the *IARC Handbooks* series are selected on the basis of one or more of the following criteria:

- The available evidence suggests potential for significantly reducing the incidence of cancer.
- There is a substantial body of human, experimental, clinical and/or mechanistic data suitable for evaluation.
- The intervention is in widespread use and of putative protective value, but of uncertain efficacy and safety.

If significant new data become available on an intervention for which a *Handbook* exists, a re-evaluation may be made at a subsequent meeting of the Working Group.

4. Data for the *IARC Handbooks*

Each *Handbook* considers all pertinent intervention trials and observational epidemiological studies, and all relevant cancer bioassays in experimental animals. Those studies that are judged by the Working Group to be uninformative for the evaluation (e.g. because of methodological limitations or small numbers) may be cited but not summarized. When such studies are not reviewed, the reasons are indicated.

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

With regard to intervention trials, epidemiological studies, cancer bioassays, and mechanistic and other relevant data, in the interests of transparency, only reports that have been published or accepted for publication in the openly available peer-reviewed 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 in final form are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Data on exposure and other information on an intervention under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use, and on occurrence and exposure, the Working Group may consider published and unpublished sources of information.

In some cases it may be appropriate to review only the data published subsequent to a previous evaluation; this can be useful for updating a database, to resolve a previously open question, or to identify new organ sites associated with a protective effect of the intervention. Major changes (e.g. a large body of additional data that may lead to a new classification; see Part B, Section 6) are more appropriately addressed by a full review and re-evaluation of the entire body of data.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the authors' analysis and interpretation of the results; any limitations noted by the Working Group 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 meetings of the *IARC Handbooks*:

(a) Member of the Working Group

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of members of the Working Group 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-preventive effects; (v) to evaluate data relevant to the understanding of mechanisms of cancer prevention; and (vi) to make an overall evaluation of the cancer-preventive effect of the intervention in humans. Members of the Working Group are selected on the basis of (a) knowledge and experience; and (b) absence of real or perceived conflicts of interests. Members of the Working Group generally have published significant research related to the cancer-preventive effects of the interventions being reviewed, and have in most cases been identified as experts by IARC on the basis of literature searches. Consideration is also given to demographic diversity and balance of scientific findings and views. Each member of the Working Group serves as an individual scientist and not as a representative of any organization, government, or industry.

(b) Invited Specialist

Invited Specialists are experts who have knowledge and experience that is critical to consideration of the intervention being evaluated, but who also have a real or perceived conflict of interests. These experts are invited when necessary to assist the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues, for example for the general description of the intervention or for the exposure (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, do not draft text that pertains to the description or interpretation of data directly relevant to the evaluations, and do not participate in the evaluations.

(c) Representative

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

(d) Observer

Observers with relevant scientific credentials are admitted to an *IARC Handbook* meeting 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, do not draft any part of a *Handbook*, and do not participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after a discussion has been completed by the Working Group. Observers agree to respect the Guidelines for Observers at *IARC Handbooks* meetings (available from http://handbooks.iarc.fr).

(e) The IARC Secretariat

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

and analyses. Members of the Secretariat do not participate in the evaluations.

(f) Declaration of Interests

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 or any tobacco-related interests. 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 published on the website of the *IARC Handbooks* programme (http://handbooks.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). The names and principal affiliations of all meeting participants are also listed at the beginning of the corresponding volume of the *Handbooks*.

B. SCIENTIFIC REVIEW AND EVALUATION

A wide range of findings must be taken into account before a particular intervention can be recognized as preventing cancer, and a systematic approach to data presentation has been adopted for *Handbooks* evaluations.

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 *IARC Handbooks* evaluate a wide range of interventions for primary prevention, including those involving chemical or pharmacological agents (e.g. drugs, vitamins, minerals, other nutritional supplements), immunological agents (vaccination), foods, behaviour changes (e.g. weight control, physical activity), and public-health policies (e.g. smoking restrictions). The structure of a *Handbook* typically comprises the following sections:

1. Exposure data
2. Studies of cancer prevention in humans
3. Studies of cancer prevention in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

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

The following part of the Working Procedures discusses the types of evidence considered and summarized in each section of a *Handbook*, followed by the scientific criteria that guide the evaluations.

1. Characteristics and occurrence of the intervention

Each *Handbook* includes general information identifying and describing the intervention. As preventive interventions can range from community-based interventions to measures targeted to individuals (e.g. behavioural, dietary, pharmacological measures), this information may vary substantially between interventions. Depending on the intervention, this section may include information on production and use, occurrence and exposure, prevalence, risk factors, and regulations and guidelines.

Given the wide variety of preventive interventions, this section will have an outline specific to each *Handbook*.

2. Studies of cancer prevention in humans

This section includes all pertinent experimental and observational epidemiological studies of cancer prevention in humans, with cancer as an outcome (see Part A, Section 4). Studies of biomarkers as indicators of the intervention are included in Section 4 when they are relevant to an evaluation of the cancer-preventive effect in humans.

(a) Types of study considered

This section focuses on studies that assess the prevention of cancer as an outcome in humans. Relevant evidence is normally provided by experimental studies (for example, randomized clinical trials and community intervention trials), and analytical observational studies, primarily cohort studies and case–control studies. For certain interventions applied at the population level, well-designed ecological studies (studies measuring both outcome and exposure on the aggregate, or population, level) or interrupted time-series studies may also be informative. Cross-sectional studies, descriptive epidemiological studies, case-series, and case reports are usually not reviewed. The uncertainties that surround the interpretation of such studies make them inadequate, except in exceptional circumstances, to form the basis for inferring a preventive relationship. However, when considered together with experimental and analytical observational studies, these types of study can sometimes contribute to the decision of the Working Group as to whether or not a causal relationship exists.

Intervention studies are experimental in design – that is, the use of, or exposure to, the intervention is assigned by the investigator. Experimental studies can provide the strongest and most direct evidence of a protective or preventive effect; however, the use of such studies is limited for practical and ethical reasons and the subjects are often drawn from select groups that may not represent the population at large.

In exceptional cases, epidemiological studies on advanced pre-neoplastic lesions and other end-points thought to be relevant to cancer are also reviewed in this section. The results of such studies may strengthen inferences drawn from other studies.

(b) Quality of studies considered

In considering whether a particular study should contribute to the evaluation of an intervention, the Working Group considers the following aspects:

- The relevance of the study;
- The appropriateness of the design and analysis to the question being asked;
- The adequacy and completeness of the presentation of the data; and
- The degree to which chance, bias, and confounding may have affected the results; for drugs or other marketed products, this bias assessment should include review of the funding source.

Aspects that are particularly important in evaluating randomized controlled trials are: the selection of participants, the nature and adequacy of the randomization procedure, evidence that randomization achieved an adequate balance between the groups, exclusion criteria used before and after randomization, compliance with the intervention in the intervention group, and "contamination" of the control group with the intervention. Other considerations are the means by which the end-point was determined and validated (either by screening or by other means of detection of the disease), the length and completeness of follow-up of the groups, and the adequacy of the analysis.

It is necessary to take into account the possible roles of bias, confounding, and chance in the interpretation of cohort and case–control studies. Bias is the effect of factors in study design or execution that leads erroneously to a stronger or weaker association than in fact exists between an intervention and outcome. Confounding is a form of bias that occurs when the relationship with the outcome is made to appear stronger or weaker than it is in reality, due to an association between the apparent causal factor and another factor that is associated with either an increase or a 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 a number of aspects of design and analysis as described in the report of the study. Most of these considerations apply equally to all types of study. Lack of clarity regarding any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation.

Firstly, the study population, target organ, and exposure should have been well defined by the authors. Cancer occurrence in the study population should have been identified in a way that was independent of the intervention of interest, and exposure to the intervention should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken into account – in the study design and analysis – other variables that could 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 (e.g. by matching) or in the analysis (by statistical adjustment). Internal comparisons of frequency of disease among individuals with different levels of exposure are 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.

Thirdly, 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 duration of exposure 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) Quantitative aspects

The Working Group gives special attention to quantitative assessment of the preventive effect of the intervention under study, by assessing data from studies investigating different doses or levels of exposure. The Working Group also addresses issues of timing and duration of use or exposure. Such quantitative assessment is important to clarify the circumstances under which a preventive effect can be achieved, as well as the dose or level of exposure at which a toxic effect has been shown.

(d) Criteria for preventive effects

After summarizing and assessing the individual studies, the Working Group makes a judgement concerning the strength of the evidence that the intervention in question prevents cancer in humans. In making its judgement, the Working Group considers several criteria for each relevant cancer site.

Evidence is frequently available from different types of study and is evaluated as a whole. Findings that are replicated in several studies of the same design or in studies using different approaches are more likely to provide evidence of a true protective effect than are isolated observations from single studies.

Evidence of protection derived from intervention studies of good quality is particularly informative. Evidence of a substantial and significant reduction in risk, including a "dose"–response relationship, is more likely to indicate a true effect. Nevertheless, a small effect, or an effect without a dose–response relationship, does not imply lack of real benefit and may be important for public health if the cancer is common.

The Working Group evaluates possible explanations for inconsistencies across studies, including differences in use of, or exposure to, the intervention, differences in the underlying risk of cancer, and metabolism and genetic differences in the population, as well as differences in study methodology. The results of studies judged to be of high quality are given more weight. Note is taken both of the applicability of preventive action to several cancers and of possible differences in activity, including the possibility of different findings between cancer sites.

3. Studies of cancer prevention in experimental animals

(a) Types of study considered

Animal models are an important component of research into cancer prevention. Models that permit evaluation of the effects of cancer-preventive interventions on the occurrence of cancer in most major organ sites are available. Animal models for such studies include: those in which cancer is produced by the administration of a chemical or physical carcinogen; those involving genetically engineered animals; and those in which tumours develop spontaneously. Most cancer-preventive interventions investigated in such studies can be placed into one of three categories: interventions that prevent molecules from reaching or reacting with critical target sites (blocking agents); interventions that decrease the sensitivity of target tissues to carcinogenic stimuli; and interventions that prevent evolution of the neoplastic process (suppressing agents). There is increasing interest in the use of combinations of interventions as a means of improving efficacy and minimizing toxicity; animal models are useful in evaluating such combinations. The development of optimal strategies for intervention trials in humans can be facilitated by the use of animal models that mimic the neoplastic process in humans.

Specific factors to be considered in such experiments are: (1) the temporal requirements of administration of the cancer-preventive interventions; (2) dose–response effects; (3) the site specificity of cancer-preventive activity; and (4) the number and structural diversity of

carcinogens whose activity can be reduced by the intervention being evaluated.

An important variable in the evaluation of the cancer-preventive response is the time and duration of administration of the intervention in relation to any carcinogenic treatment, or in transgenic or other experimental models in which no carcinogen is administered. Furthermore, concurrent administration of an intervention may result in a decreased incidence of tumours in a given organ and an increase in incidence in another organ of the same animal. Thus, in these experiments it is important that multiple organs be examined.

For all these studies, the nature and extent of impurities or contaminants present in the cancer-preventive intervention or interventions being evaluated are given when available. Also, consideration is given to the possibility of changes in the physicochemical properties of the test substance during collection, storage, extraction, concentration, and delivery. Chemical and toxicological interactions of the components of mixtures may result in non-linear dose–response relationships.

As certain components of commonly used diets of experimental animals are themselves known to have cancer-preventive activity, particular consideration should be given to the interaction between the diet and the apparent effect of the intervention being studied. Likewise, restriction of diet may be important. The appropriateness of the diet given relative to the composition of human diets may be commented on by the Working Group.

(b) Quality of studies considered

An assessment of the experimental prevention of cancer involves several considerations of qualitative importance, including: (1) the experimental conditions under which the test was performed (route and schedule of exposure, species, strain, sex and age of the animals studied, duration of the exposure, and duration of the study); (2) the consistency of the results, for example across species and target organ(s); (3) the stage or stages of the neoplastic process studied, from pre-neoplastic lesions and benign tumours to malignant tumours; and (4) the possible role of modifying factors.

In the interpretation and evaluation of a particular study, the Working Group takes into consideration: (1) how clearly the intervention was defined and, in the case of mixtures, how adequately the sample composition was reported; (2) the composition of the diet and the stability of the intervention in the diet; (3) whether the source, strain, and quality of the animals was reported; (4) whether there were adequate numbers of animals, of appropriate age, per group; (5) whether males and females were used, if appropriate; (6) whether animals were allocated randomly to groups; (7) whether appropriate respective controls were used; (8) whether the dose and schedule of treatment with the known carcinogen were appropriate in assays of combined treatment; (9) whether the doses of the cancer-preventive intervention were adequately monitored; (10) whether the agent(s) was absorbed, as shown by blood concentrations; (11) whether the survival of treated animals was similar to that of controls; (12) whether the body and organ weights of treated animals were similar to those of controls; (13) whether the duration of the experiment was adequate; (14) whether there was adequate statistical analysis; and (15) whether the data were adequately reported.

(c) Quantitative aspects

The incidence of tumours may depend on the species, sex, strain, and age of the animals, the dose of carcinogen (if any), the dose of the agent, and the route and duration of exposure. A decreased incidence and/or decreased multiplicity of tumours in adequately designed studies provide evidence of a cancer-preventive effect. A dose-related decrease in incidence and/or multiplicity further strengthens this association.

The nature of the dose–response relationship can vary widely, depending on the agent and the target organ. Saturation of steps such as absorption, activation, inactivation, and elimination may produce non-linearity in the dose–response relationship (Hoel et al., 1983; Gart et al., 1986), as could saturation of the detoxication processes. The dose–response relationship can also be affected by differences in survival between the treatment groups.

(d) Statistical analyses

Factors considered in the statistical analysis by the Working Group include: (1) the adequacy of the data for each treatment group; (2) the initial and final effective numbers of animals studied and the survival rate; (3) body weights; and (4) tumour incidence and multiplicity.

The statistical methods used should be clearly stated and should be the generally accepted techniques defined for this purpose. In particular, the statistical methods should be appropriate for the characteristics of the expected data distribution and should account for interactions in multifactorial studies. Consideration is given as to whether the appropriate adjustment was made for differences in survival.

If available, recent data on the incidence of specific tumours in historical controls, as well as in concurrent controls, are taken into account in the evaluation of tumour response.

4. Mechanistic and other relevant data

In evaluating an intervention, effects other than cancer are described and weighed. Furthermore, information that facilitates an understanding of the applicability of findings to different species, or to different human populations is particularly important; this includes metabolic, kinetic, and genetic data. Whenever possible, quantitative data, including information on dose, duration, and potency, are considered.

The focus of this section is on studies in humans, including intervention trials and epidemiological studies with cancer-relevant molecular biomarkers or intermediate end-points as an outcome. Studies in experimental systems can strengthen the evidence for the potential cancer-preventive effect of an intervention observed in humans, and can elucidate the mechanism(s) of cancer prevention. A brief summary of important findings in experimental systems is therefore included.

Evaluation of the results of intervention studies in humans includes consideration of quality, as described above. Study quality factors generally consider the adequacy of the methods and the reporting of results, addressing: (1) the description of the methods; (2) the appropriateness of control populations; (3) whether toxic effects were considered in the outcome; (4) whether the data were appropriately compiled and analysed; (5) whether appropriate quality controls were used; (6) whether appropriate concentration ranges were used; (7) whether adequate numbers of independent measurements were made per group; and (8) the relevance of the end-points.

The observation of effects on the occurrence of lesions presumed to be pre-neoplastic, or the emergence of benign or malignant tumours, may aid in assessing the mode of action of the intervention being considered. Particular attention is given to assessing the reversibility of these lesions and their predictive value in relation to cancer development.

(a) Toxicokinetics

Information is given on absorption, distribution (including placental transfer), metabolism, and excretion in humans. If human data are sparse, evidence from experimental animals may be summarized. Studies in humans that indicate the metabolic pathways and fate of an intervention are summarized. Data indicating long-term accumulation in human tissues are included.

Observations are made on inter-individual variations and relevant metabolic polymorphisms. Physiologically based pharmacokinetic models and their parameter values are relevant and are included whenever they are available.

Information from experimental systems, including on the fate of the compound within tissues and cells (transport, role of cellular receptors, compartmentalization, binding to macromolecules) may be briefly summarized.

The metabolic consequences of interventions are described.

(b) Mechanisms of cancer prevention

For a rational implementation of cancer-preventive measures, it is essential not only to assess protective end-points but also to understand the mechanisms by which the intervention exerts its anticarcinogenic action. Data on mechanisms will be primarily from studies in humans. Data from relevant experimental models can also be summarized, including studies of the inhibition of tumorigenesis in vivo, studies of intermediate biomarkers in vivo, analyses of interactions between agents and specific molecular targets, and studies of specific end-points in vitro. Information on the mechanisms of cancer-preventive activity inferred from relationships between chemical structure and biological activity can also be included.

Cancer-preventive interventions may act at different levels: (1) extracellular, for example inhibiting the uptake or endogenous formation of carcinogens, or forming complexes with, diluting, and/or deactivating carcinogens; (2) intracellular, for example trapping carcinogens in nontarget cells, modifying transmembrane transport, modulating metabolism, blocking reactive molecules, inhibiting cell replication, or modulating gene expression or DNA metabolism; or (3) at the level of the cell, tissue, or organism, for example affecting cell differentiation, intercellular communication, proteases, signal transduction, growth factors, cell adhesion molecules, angiogenesis, interactions with the extracellular matrix, hormonal status, and the immune system.

Many cancer-preventive interventions are known or suspected to act by several mechanisms, which may operate in a coordinated manner and allow them a broader spectrum of anticarcinogenic activity. Therefore, a range of possible mechanisms of action are taken into account in the evaluation of cancer prevention. These can be conceptually organized to encompass impacts on one or more related key characteristics of carcinogens (Smith et al., 2016), particularly interference with: (1) metabolic activation of carcinogens; (2) mutagenesis; (3) DNA repair or genomic instability; (4) epigenetic effects; (5) oxidative stress; (6) inflammation; (7) immune function; (8) receptor-mediated effects; (9) immortalization; or (10) cell proliferation, cell death, or nutrient supply.

(c) Susceptible populations

This section summarizes studies of cancer in humans that have addressed differential susceptibility due to toxicokinetics, mechanisms of cancer prevention, and other factors. Such studies may identify individuals, populations, and life-stages with greater or lesser susceptibility. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the intervention, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for alteration of metabolic capacity by medications or other chemical exposures, a 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). Genotyping is being used increasingly, not only to identify subpopulations at increased or decreased risk for cancers but also

to characterize variation in the biotransformation of and response to cancer-preventive interventions. 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.

(d) Adverse effects

Relevant clinical or other evidence that would impact any recommendations may be summarized as appropriate.

5. Summary of data

This section is a summary of data presented in the preceding sections.

(a) Exposure data

Data are summarized, as appropriate, on elements such as characteristics and production or implementation of the intervention, and patterns of use or exposure in human populations. Quantitative data and time trends are given to compare exposure, use, or implementation in different regions and settings.

(b) Cancer prevention in humans

Results of epidemiological studies pertinent to an assessment of the cancer-preventive effect in humans are summarized. The target organ(s) or tissue(s) in which a decrease in cancer occurrence 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 a cancer-preventive effect in animals are summarized. For each animal species, study design, and route of administration, it is stated whether decreased incidence, increased latency, or decreased severity or multiplicity of tumours or preneoplastic lesions were observed, and the tumour sites are indicated. Negative findings, positive relationships, dose–response, and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Human data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of cancer prevention are summarized. In addition, human studies on cancer susceptibility including on genetic polymorphisms, susceptible populations and life-stages are summarized. This section also reports briefly on adverse effects as well as any additional relevant data from experimental systems that are considered to be influential for the evaluation of a cancer-preventive effect.

6. Evaluation and rationale

Evaluations of the strength of the evidence for cancer-preventive effects from studies in humans and experimental animals are made using standard terms. Similarly, an evaluation of the strength of the mechanistic evidence is given.

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

The evaluation categories refer only to the strength of the evidence that an intervention prevents cancer, and not to the extent of its cancer-preventive effects (potency). The evaluations may change as new information becomes available.

Evaluations are inevitably limited to the intervention as actually implemented and observed, for example to the cancer sites, conditions, and duration of observation covered by the available studies.

(a) Cancer-preventive effects in humans

The evidence relevant to cancer prevention in humans is classified into one of the following categories:

Sufficient evidence of cancer-preventive effects: The Working Group considers that a preventive relationship has been established between the intervention and the risk of cancer in humans. That is, a preventive association has been observed in studies in which chance, bias, and confounding could be ruled out with confidence. A statement that there is sufficient evidence is followed by a sentence identifying the organ(s) or tissue(s) for which a preventive effect has been observed in humans. Identification of preventive effects in a specific organ or tissue does not preclude the possibility that the intervention may prevent cancer at other sites.

Limited evidence of cancer-preventive effects: A reduced risk of cancer is associated with the intervention for which a preventive effect is considered credible by the Working Group, but chance, bias, or confounding could not be ruled out with confidence.

Inadequate evidence of cancer-preventive effects: The available studies are not of sufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a cancer-preventive effect of the intervention, or no data on the prevention of cancer by this intervention in humans are available.

Evidence suggesting lack of cancer-preventive effects: When several epidemiological studies show little or no indication of an association between an intervention and a reduced risk of cancer, a judgement may be made that the studies, taken together, show evidence of lack of a preventive effect. Such a judgement requires that the studies meet the standards of design and analysis described above. Specifically, the possibility that bias, confounding, or misclassification of the intervention or the outcome could explain the observed results should be considered and excluded with confidence.

(b) Cancer-preventive effects in experimental animals

Cancer-preventive effects 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.

Evidence for cancer prevention in experimental animals is classified into one of the following categories:

Sufficient evidence of cancer-preventive effects: The Working Group considers that a causal relationship has been established between the intervention and a decreased incidence and/or multiplicity of spontaneous or chemically induced malignant neoplasms, or of an appropriate combination of benign and malignant neoplasms in an adequate number (four or more) of independent studies carried out at different times, or in different laboratories, or under different protocols.

Limited evidence of cancer-preventive effects: The data indicate a cancer-preventive effect, but are limited for making a definitive evaluation because, for example: (a) the evidence of a cancer-preventive effect is restricted to a small number (fewer than four) of experiments; or (b) the intervention decreases the incidence and/or multiplicity of benign neoplasms only.

Inadequate evidence of cancer-preventive effects: The studies cannot be interpreted as showing either the presence or absence of a preventive effect because of major methodological or quantitative limitations: unresolved questions regarding the adequacy of the design, conduct, or interpretation of the study, or few or no data on cancer prevention in experimental animals are available.

Evidence suggesting lack of cancer-preventive activity: Adequate evidence from conclusive studies in several models shows that, within the limits of the tests used, the intervention has no cancer-preventive effects.

(c) Mechanistic data on cancer-preventive effects

Mechanistic and other evidence judged to be relevant to an evaluation of a cancer-preventive effect and of sufficient importance to affect the overall evaluation is brought forward to the evaluation.

The strength of mechanistic evidence supporting the cancer-preventive effect is evaluated, using terms such as 'weak', 'moderate', or 'strong'. Indications that a particular mechanism operates in humans are strongest. The data may be considered to be especially relevant if they show in humans that the intervention in question has caused suppression of effects that are on the pathway to cancer. The mechanistic evidence can be strengthened by findings of consistent results in different experimental designs, by the demonstration of biological plausibility, and by coherence of the overall database.

The Working Group considers whether multiple mechanisms might contribute to cancer prevention, whether different mechanisms might operate in different dose ranges or at different sites, or whether separate mechanisms might operate in a susceptible group.

For complex interventions, such as food categories, the chemical composition and the potential contribution of different nutrients known to be present may be considered by the Working Group in its overall evaluation of cancer prevention.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, and summary statements are made that encompass the effects of the intervention with regard to cancer-preventive effects in humans. The overall evaluation is described according to the wording of one of the following standard categories. The categorization of an intervention 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.

(i) The intervention prevents cancer (Group A)

This category is used for interventions for which there is *sufficient evidence* of a cancer-preventive effect in humans.

The sites on which the evidence in humans is based are given.

(ii) The intervention probably prevents cancer (Group B1)

This category is used for interventions for which there is *limited evidence* of a cancer-preventive effect in humans and *sufficient evidence* in animals. An intervention may also be classified in this category when there is *limited evidence* in humans, less than *sufficient evidence* in experimental animals, and strong supporting evidence from mechanistic and other relevant data that the mechanism(s) of prevention also operates in humans.

The sites on which the evidence in humans is based are given.

(iii) The intervention possibly prevents cancer (Group B2)

This category is used for interventions for which there is *inadequate evidence* in humans and *sufficient evidence* in experimental animals. An intervention may also be classified in this category when there is *inadequate evidence* in humans, *limited evidence* in experimental animals, and strong supporting evidence from mechanistic and other relevant data that the mechanism(s) of prevention also operates in humans.

(iv) The intervention is unclassifiable as to its cancer-preventive effects (Group C)

This category is used for interventions for which the evidence is *inadequate* in humans and less than *sufficient* in experimental animals. Interventions that do not fall into any other group are also placed in this category.

(v) The intervention probably does not prevent cancer (Group D)

This category is used for interventions for which there is *evidence suggesting lack of a cancer-preventive effect* both in humans and in experimental animals.

(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 in humans, studies 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, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. The human populations that were the subject of study should be identified. Additionally, important health concerns identified – such as adverse effects, including cancer-causing properties – should be clearly addressed.

When there are significant differences in 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.

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GENERAL REMARKS

This sixteenth Volume of the *IARC Handbooks of Cancer Prevention* series evaluates the cancer-preventive effects of absence of excess body fatness. It is the second Volume since the relaunch of the *IARC Handbooks* series in 2014, and the first Volume on primary prevention in the new series.

The *IARC Handbooks* provide the same rigorous evaluation process as the *IARC Monographs*. They serve national health agencies to inform their preventive strategies for cancer control. To support the World Health Organization Global Action Plan for the prevention and control of noncommunicable diseases, the availability of an international consensus from an independent, specialized agency within the United Nations family provides an authoritative basis for national decision-making, and should facilitate national recommendations and communication with the population at risk.

For this Volume, the Working Procedures of the *IARC Handbooks* have been updated in accordance with the current Preamble of the *IARC Monographs* (IARC, 2006), with definitions of the different types of participants and guidelines for selection of experts and literature searches. In addition, more detailed instructions are given for the scientific review and evaluation criteria. (See the Working Procedures in this Volume.)

Previous evaluations

In 2001, a Working Group of international experts developed Volume 6 of the *IARC Handbooks*, on weight control and physical activity (IARC, 2002). The resulting consensus evaluations are presented in Table 1.

Rationale for a re-evaluation

A re-evaluation of the cancer-preventive effects of avoidance of weight gain was highly desired. The mean body mass index (BMI) of the population has increased dramatically worldwide during the past 40 years (NCD Risk Factor Collaboration (NCD-RisC), 2016). The United Nations High-Level Meeting on Noncommunicable Diseases in September 2011 identified obesity as one of the leading risk factors for chronic diseases, including coronary heart disease, diabetes, and cancer (Beaglehole et al., 2011). Overweight and obesity have been estimated to have accounted for 4.0 million deaths (95% uncertainty interval, 2.7–5.3 million) worldwide in 2015, representing 7.1% (95% uncertainty interval, 4.9–9.6%) of total global mortality (Afshin et al., 2017). In 2014, the overall socioeconomic cost associated with obesity was estimated at US$ 2 trillion globally (Dobbs et al., 2014).

Table 1 Evaluations of *IARC Handbooks* Volume 6 (2002)

Intervention	Humans		Experimental animals		Overall evaluation
	Strength of evidence	Organ site	Strength of evidence	Organ site	
Avoidance of weight gain	*Sufficient*	Colon Breast (postmenopausal) Endometrium Kidney (renal cell) Oesophagus (adenocarcinoma)			Limiting weight gain during adult life, thereby avoiding overweight and obesity, **reduces** the risk of postmenopausal breast cancer and cancers of the colon, uterus (endometrium), kidney (renal cell), and oesophagus (adenocarcinoma).
	ESLE	Breast (premenopausal)			
Intentional weight loss	*Inadequate*		*Sufficient*	(Calorie/dietary restriction) Mammary gland Liver Pituitary gland (adenoma) Colon Skin (non-melanoma) Lymphoma	Weight loss among overweight or obese persons **possibly reduces** risks of these cancers, but no firm conclusion can be drawn because of the sparsity of the epidemiological evidence.
			Limited	Prostate Pancreas	

ESLE, evidence suggesting a lack of effect

Worldwide, it has been estimated that 481 000 new cancer cases (3.6% of all new cases) in adults in 2012 could be attributed to high BMI; the attributable fraction was as high as 9% in women in North America, Europe, and the Middle East (Arnold et al., 2015). This estimation was based on evidence for an association of high BMI with oesophageal adenocarcinoma and cancers of the colon, rectum, pancreas, gall bladder, kidney, postmenopausal breast, corpus uteri, and ovary (Arnold et al., 2015). Taking into account the evaluations of this Volume, which indicate that excess body fatness increases cancer risk at additional sites (a total of 13 cancer sites or subtypes), the fraction of cancer cases worldwide that are attributable to overweight and obesity is even higher than previously estimated.

Content of this *Handbook*

In this Volume, in addition to the identification of target organs for excess body fatness, the following topics have been reviewed when available:

- Sex specificity
- Anthropometric measures of body fatness other than BMI: weight, waist circumference, and waist-to-hip ratio
- Effect of change in BMI or weight over the life-course
- Risk reduction after intentional weight loss
- Effect of excess body fatness on cancer survival in cancer patients, and on recurrence in cancer survivors
- Excess body fatness in children, adolescents, and young adults (age ≤ 25 years) and subsequent cancer risk.

Weight loss

Few data are available on intentional weight loss in humans. Therefore, data in experimental animals provide important information to assess the effect of intentional weight loss. Studies in animals use dietary or calorie restriction to induce a lower weight gain compared with animals fed ad libitum, or to induce weight reduction in obese animals.

For humans, the Working Group considered the data on bariatric surgery as a proxy for the evidence on intentional weight loss. The clinical effectiveness of bariatric surgery for weight loss and improved health has been established (Picot et al., 2009), although risks of complications, reoperation, and death exist.

Impact of physical activity on the assessment of the cancer-preventive effects of absence of excess body fatness

The major contributors to weight gain are excess energy intake and insufficient levels of physical activity, which both lead to chronic positive energy balance. In recent years, new evidence has accumulated on the different types of physical inactivity and on sedentary behaviour as risk factors for cancer. In this *Handbook*, the cancer-preventive effects of absence of excess body fatness were evaluated taking into account potential confounding and/or effect modification by physical activity. Physical activity will be evaluated separately in a future *Handbook*.

A summary of the findings of this Volume has appeared in *The New England Journal of Medicine* (Lauby-Secretan et al., 2016).

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LIST OF ABBREVIATIONS

AKT	protein kinase B
AL	ad libitum
AML	acute myeloid leukaemia
AMP	adenosine monophosphate
AMPK	AMP-activated protein kinase
AOM	azoxymethane
ATP	adenosine triphosphate
BIA	bioelectrical impedance analysis
BMI	body mass index
BOP	*N*-nitrosobis(2-oxopropyl)amine
CDK	cyclin-dependent kinase
cDNA	complementary DNA
CDR	chronic dietary restriction
CI	confidence interval
CIMP	CpG island methylator phenotype
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia
COX-2	cyclooxygenase-2
CR	calorie restriction
CRC	colorectal cancer
CRP	C-reactive protein
CT	computed tomography
DEN	diethylnitrosamine
DHEA	dehydroepiandrosterone
DIO	diet-induced obesity
DLBCL	diffuse large B-cell lymphoma
DMBA	7,12-dimethylbenz[*a*]anthracene
DR	dietary restriction
DXA	dual-energy X-ray absorptiometry
EDC	endocrine-disrupting chemical
8-epi-$PGF_{2\alpha}$	8-epi-prostaglandin F2α
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	estrogen receptor
F344	Fischer 344

GIANT	Genetic Investigation of Anthropometric Traits
GRS	genetic risk score
GTG	gold thioglucose
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HFD	high-fat diet
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone replacement therapy
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IDR	intermittent dietary restriction
IGF-1	insulin-like growth factor 1
IGF-1R	IGF-1 receptor
IGFBP	IGF binding protein
IL	interleukin
IWL	intentional weight loss
LFD	low-fat diet
MAPK	mitogen-activated protein kinase
METs	metabolic equivalents
MMTV	mouse mammary tumour virus
MNU	*N*-methyl-*N*-nitrosourea
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSS	microsatellite-stable
mTOR	mammalian target of rapamycin
NAFLD	non-alcoholic fatty liver disease
NAFPD	non-alcoholic fatty pancreatic disease
NASH	non-alcoholic steatohepatitis
NCDs	noncommunicable diseases
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin lymphoma
NIH-AARP	National Institutes of Health–AARP Diet and Health Study
NOS	not otherwise specified
25(OH)D	25-hydroxyvitamin D
OR	odds ratio
8-oxo-dG	8-hydroxydeoxyguanosine
PAI-1	plasminogen activator inhibitor-1
PanIN	pancreatic intraepithelial neoplasia
PCR	polymerase chain reaction
PDAC	pancreatic ductal adenocarcinoma
PI3K	phosphoinositide 3-kinase
PIN	prostatic intraepithelial neoplasia
PPAR	peroxisome proliferator-activated receptor
PR	progesterone receptor
PSA	prostate-specific antigen
RCC	renal cell carcinoma

RCT	randomized controlled trial
ROS	reactive oxygen species
RR	relative risk
SASP	salicylazosulfapyridine
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results
sGC	soluble guanylyl cyclase
SHBG	sex hormone-binding globulin
SHT	scopolamine hydrobromide trihydrate
SLL	small lymphocytic lymphoma
SNP	single nucleotide polymorphism
STAT	signal transducer and activator of transcription
TDR	total dietary restriction
TGF	transforming growth factor
TNF-α	tumour necrosis factor alpha
TPA	12-*O*-tetradecanoylphorbol-13-acetate
TRAMP	transgenic adenocarcinoma of the mouse prostate
VEGF	vascular endothelial growth factor
Vo_{2max}	maximal oxygen uptake
WC	waist circumference
WCRF	World Cancer Research Fund
WHO	World Health Organization
WHR	waist-to-hip ratio

1. BODY FATNESS

1.1 Background and definitions

1.1.1 Scientific definitions of obesity

Obesity is the abnormal or excessive accumulation of body fat that results from energy imbalance, i.e. energy intake exceeding energy expenditure, and presents a risk to health. Obesity is both a condition and an important risk factor for other noncommunicable diseases, including diabetes, cardiovascular disease, and many types of cancer.

Overweight and obesity in humans are often classified by the body mass index (BMI), which is obtained by dividing the body weight (in kilograms) by the square of the height (in metres).

In adults, overweight is defined as BMI ≥ 25 kg/m^2 and obesity as BMI ≥ 30 kg/m^2 (WHO, 2000). Obesity can be further classified, by level of severity and the corresponding different medical approaches for treatment, into class I (30–34.9 kg/m^2), class II (35–39.9 kg/m^2), and class III (≥ 40 kg/m^2) obesity (Table 1.1). In children younger than 5 years, overweight is defined as a weight-for-height more than 2 standard deviations (SD) above the WHO Child Growth Standards median, and obesity is often defined as a weight-for-height more than 3 SD above the WHO Child Growth Standards median. In children and adolescents from age 5 years to younger than 19 years, overweight and obesity are defined as a BMI-for-age more than 1 SD and more than 2 SD, respectively, above the WHO Growth Reference median (WHO, 2016, 2017a, b).

1.1.2 Cultural definitions of obesity

Perceptions of overweight and obesity can vary across different settings and populations. People who are overweight or obese may be admired or may be stigmatized, depending on contextual, cultural, spiritual, and other relevant factors.

It is well documented that in many populations, overweight and obese people are discriminated against and stigmatized because of their physical appearance – in interpersonal settings, in the workplace, and in health-care settings (Link & Phelan, 2001; Puhl & Brownell, 2001; Sikorski et al., 2011; Spahlholz et al., 2016). Stigmatization of children is also common, leading to rejection and harassment, especially in educational settings (Puhl & Brownell, 2001).

In contrast, in cultures where overweight and obesity in children are viewed favourably, an obese child may be seen as having a healthy body status (Peña et al., 2012) and as a reflection of good parenting (Brown, 1991). Favourable perceptions of increased body weight can also lead to inaccurate interpretations of a "healthy" body weight when parents assess the weight of their children. In a systematic review based on 13 studies, 13% to 100% of the parents interviewed underestimated the obesity status of their child, and in six studies 70% or more of the parents were unable to identify their child as overweight (Tompkins et al., 2015). In cultures that favour larger body size, women of reproductive age who are overweight may be perceived as having

Table 1.1 Overweight and obesity cut-off values

Population	Measure	Overweight	Obese	Obese I	Obese II	Obese III
Adults	BMI (kg/m^2)	≥ 25.0	≥ 30.0	30.0–34.9	35.0–39.9	≥ 40.0
Children						
< 5 years	Weight-for-height	> 2 SD[a]	> 3 SD[a]	–	–	–
5–19 years	BMI-for-age	> 1 SD[b]	> 2 SD[b]	–	–	–

[a] Above the WHO Child Growth Standards median
[b] Above the WHO Growth Reference median
BMI, body mass index; SD, standard deviation.
Sources: WHO (2000, 2016, 2017a, b)

been well cared for and, by extension, will care for their children in a similar manner. In such cultures, increased body weight can be linked to favourable qualities such as self-worth, health, prosperity, and maternity. For men, overweight and obesity can symbolize (in addition to good health) economic success, political power, or social status, and in some societies the power of the elders or leaders (Brown, 1991).

Positive perceptions of large body size in cancer survivors have been reported among cancer care clinicians. Until the past few decades, cancer was frequently diagnosed at a late stage of the disease, in which weight loss was a major diagnostic sign. However, with early detection programmes, many cancer survivors are overweight and obese and suffer obesity-related comorbidities (e.g. diabetes). In a weight-loss feasibility trial in overweight patients with colorectal cancer, Anderson et al. (2010) reported that clinicians describe avoidance of weight loss as desirable and express concern about reported weight loss (even intentional weight loss). In a study of colorectal clinicians in the United Kingdom and Ireland, Anderson et al. (2013) reported that current opinion and practice are influenced by the lack of evidence for the impact of weight management on health, and by a belief that weight gain is good and weight loss is bad in the cancer setting.

1.1.3 Body fatness as a public health problem

Until recently, obesity was perceived as being an issue of an individual's behaviour. As a result, interventions for the prevention and treatment of obesity were focused on the individual level (Caballero, 2007). This perception has changed with the increasing awareness of the influence of external environmental factors on obesity (e.g. the built environment, the marketing of food and beverages), and obesity is now seen as a health problem that demands a social response (Opalinski, 2013); this is recognized both by the public and by health-care professionals (Obesity Society, 2014; see Sections 1.3.6 and 1.3.7).

1.2 Prevalence and trends

1.2.1 Prevalence and trends in adults

Worldwide, in 2014 more than 640 million adults (14% of adults) were obese, 6 times the number in 1975; of those, more than 18% lived in high-income English-speaking countries, and 13.9% lived in the Middle East and North Africa (NCD Risk Factor Collaboration, 2016).

From 1975 to 2014, the average weight of the population increased in all world regions; during those four decades, the global prevalence of underweight decreased and the global prevalence of obesity increased, so that the number of obese adults surpassed the number of underweight adults (NCD Risk Factor Collaboration,

2016). The global average BMI in the adult population (≥ 18 years) in 1975 was 21.7 kg/m² in men and 22.1 kg/m² in women, and by 2014 these averages had increased to 24.2 kg/m² in men and 24.4 kg/m² in women, according to the latest available estimates (NCD Risk Factor Collaboration, 2016). This means that between 1975 and 2014, the average weight of a man with a height of 170 cm increased by about 7 kg, and that of a woman with a height of 160 cm increased by about 6 kg. This general increase in the average BMI affected both high-income countries and low- and middle-income countries.

The overall increase in the average BMI corresponded to a general increase in the prevalence of obesity. In 2014, the global prevalence of obesity in the adult population was 10.8% in men and 14.9% in women, ranging from less than 1% (Burundi) to almost 50% (Cook Islands and French Polynesia) in men, and from less than 3% (Timor-Leste and Japan) to more than 58% (American Samoa) in women (NCD Risk Factor Collaboration, 2016; Fig. 1.1). In 2014, the prevalence of obesity was lowest in low-income countries, whereas lower-middle-, upper-middle-, and high-income countries were characterized by a high level of heterogeneity; in countries in any of these three income categories, the highest prevalence of obesity was more than 40% in men and about 55% in women. In general, the prevalence of obesity was higher in women than in men, but trends over the four decades suggested a greater increase in the prevalence of obesity in men. However, it should be noted that despite the worldwide increase in the prevalence of obesity and the fact that the number of obese adults is now higher that the number of underweight adults, the proportion of the population that is underweight is still very high (> 20%) in some countries (India and Bangladesh) (NCD Risk Factor Collaboration, 2016).

In light of the obesity epidemic, there is an increasing interest in understanding weight-loss strategies in the population. A study of university students in 22 countries in different regions of the world suggested that the prevalence of trying to lose weight increases with levels of BMI, and is higher in women than in men at any given BMI level (Wardle et al., 2006). Similarly, figures from a survey of European Union citizens aged 15 years and older showed that 34% of people reported changing their eating and drinking behaviour to lose weight, a percentage that increased to 48% among those who perceived their weight as being too high (European Commission, 2006).

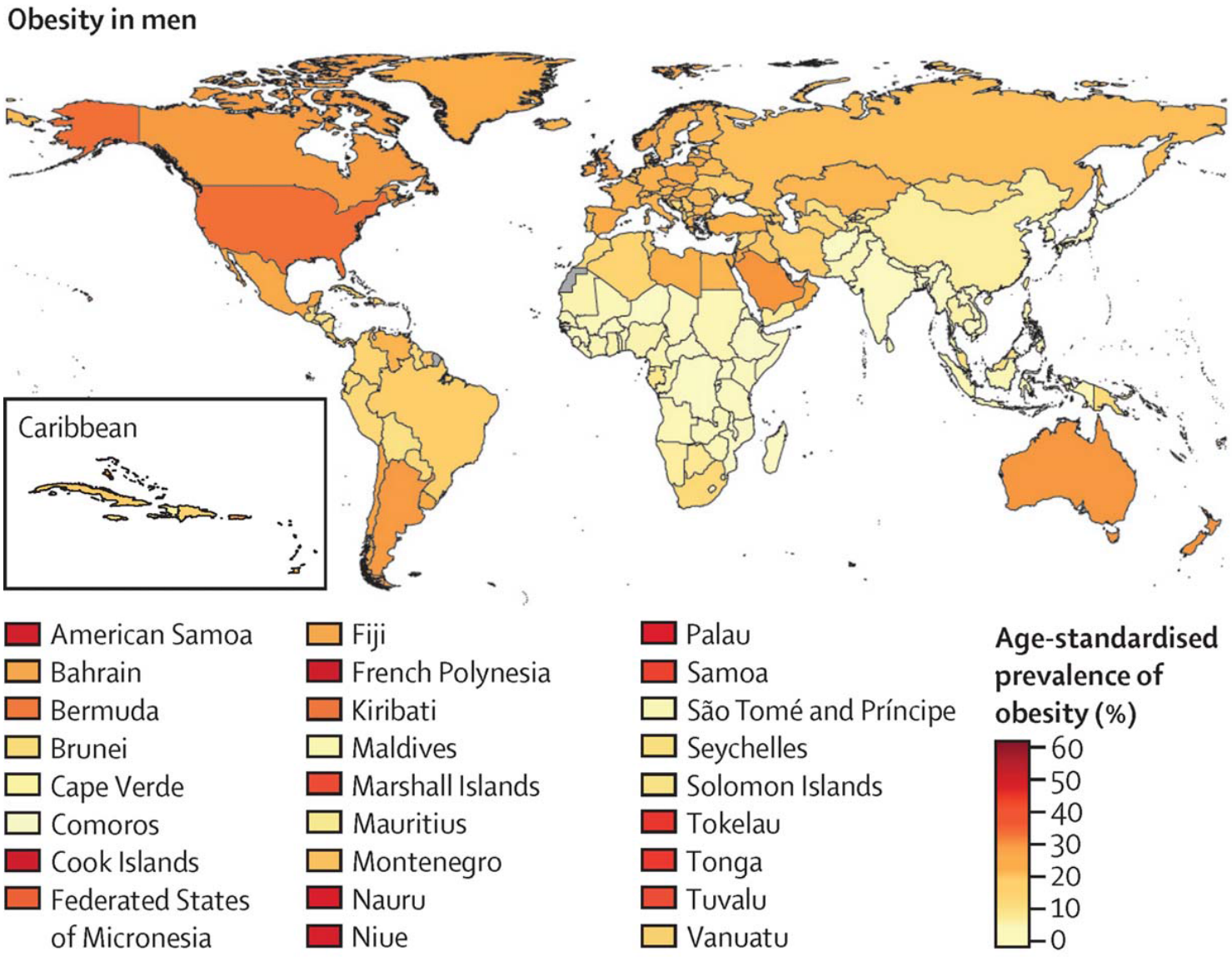
With earlier diagnosis and improved cancer treatments, many cancer survivors have similar BMI levels to those of the general population; in addition, some cancer treatments may induce weight gain. Data on BMI distribution by cancer diagnosis are not routinely reported. It was found that 47.3% of patients with breast cancer had a BMI greater than 25 kg/m² (Nichols et al., 2009), and in a cohort of colorectal cancer survivors, 29.1% were obese (Rohan et al., 2015). Gross et al. (2015) reported that breast cancer survivors gained weight at a higher rate than their cancer-free peers. The implications of high body mass for treatment dosing, subsequent morbidity, and recurrence are not fully understood (see Section 2.4).

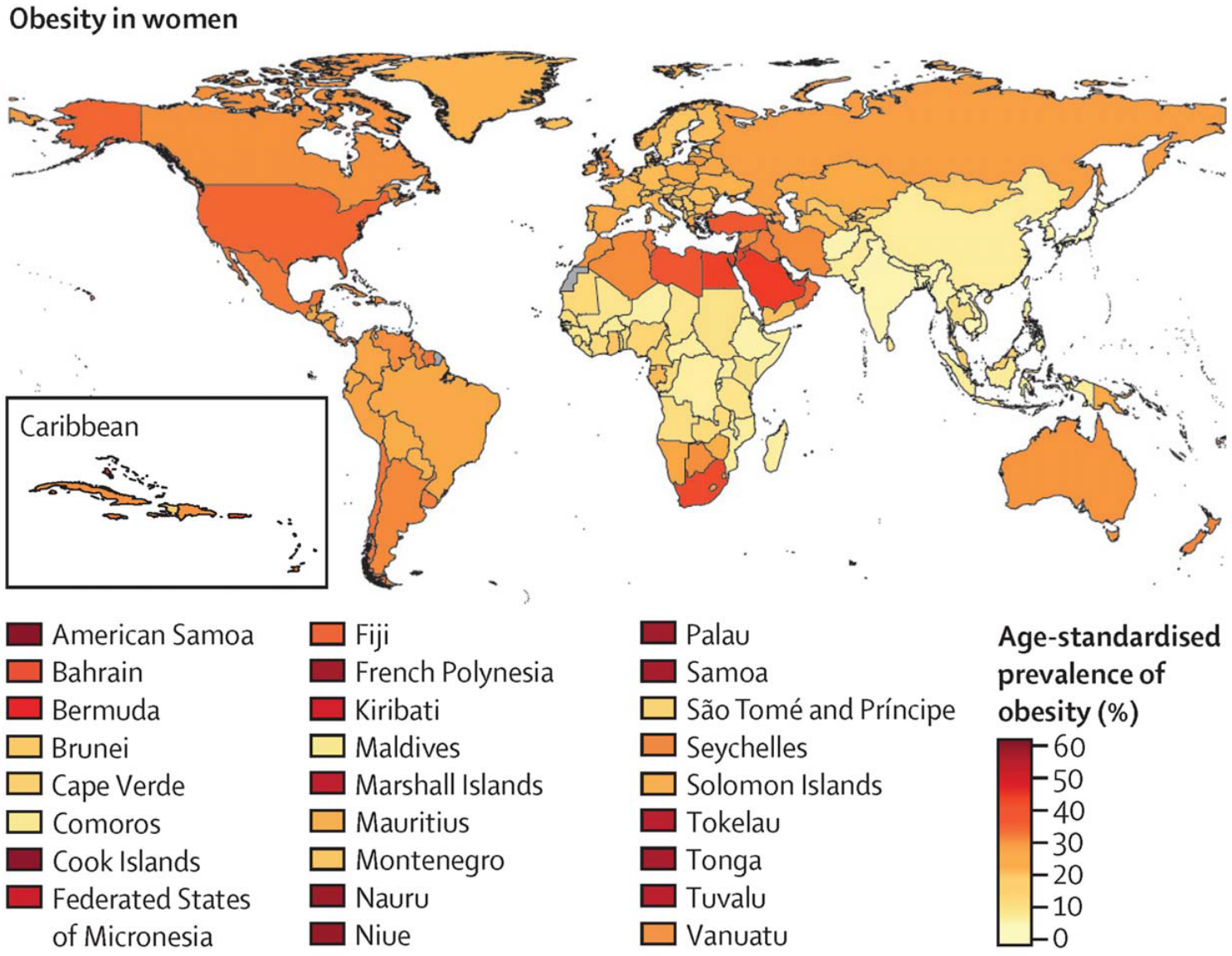
1.2.2 Prevalence and trends in children and adolescents

Recent estimates have shown a rapid rise in the prevalence of overweight and obesity in children and adolescents worldwide; however, trend analyses in developed countries have shown a tendency for the prevalence to stabilize starting from mid-2000 (Ng et al., 2014; UNICEF, WHO, and World Bank Group, 2015). The long-term impact of obesity during childhood and adolescence is a higher risk of obesity during adulthood (Guo & Chumlea, 1999; Freedman et al., 2005; Singh et al., 2008).

The WHO European Childhood Obesity Surveillance Initiative (COSI), established in

Fig. 1.1 Prevalence of obesity (BMI ≥ 30 kg/m²) by sex and country in 2014





2007 to monitor changes in the prevalence of overweight (including obesity) in primary schoolchildren, reported that in 2009–2010 the prevalence of overweight ranged from 18% to 57% in boys and from 18% to 50% in girls; 6–31% of boys and 5–21% of girls were obese (Wijnhoven et al., 2014). A recent position statement from the European Association for the Study of Obesity (EASO) Childhood Obesity Task Force (COTF) classified obesity as a chronic disease in children and adolescents (Farpour-Lambert et al., 2015).

In 2013, about 110 million children and adolescents worldwide aged 2–19 years (prevalence of 4.7%) were obese (IHME, 2014), almost twice the number in 1980. In 2013, 24% of boys and 22% of girls living in high-income countries were overweight or obese, whereas the corresponding percentages observed in low- and middle-income countries were about 13% for boys and girls (Ng et al., 2014). The highest prevalence of obesity in children and adolescents was observed in North America (Canada and the USA) for both boys (12.1%) and girls (13.0%). The next-highest prevalences were seen in southern Latin America for boys (~10%) and in North Africa and the Middle East for girls (~10%). The lowest prevalence was observed in South Asia for both sexes. In 2013, the two countries with the highest prevalence of obesity for both boys and girls were Kiribati and Samoa, where 20% of boys and 33% of girls were obese; similar prevalences were observed in Qatar for boys and in the Federated States of Micronesia for girls, whereas prevalences were less than 1.5% for boys and girls in Bangladesh and the Republic of Korea.

Independently of the level of income, sex differences in the prevalence and trends of overweight and obesity were small (Ng et al., 2014). Nevertheless, the prevalence of obesity was higher in boys than in girls in 70% of low-income countries and in 63% of high-income countries; the corresponding percentage in lower-middle- and upper-middle-income countries was 33% (IHME, 2014; Ng et al., 2014).

According to estimates from the United Nations Children's Fund (UNICEF), WHO, and the World Bank Group, the number of overweight children younger than 5 years has been increasing steadily everywhere in the world; in 2014, almost 50% of all overweight children younger than 5 years lived in Asia, and about 25% lived in Africa (UNICEF, WHO, and World Bank Group, 2015).

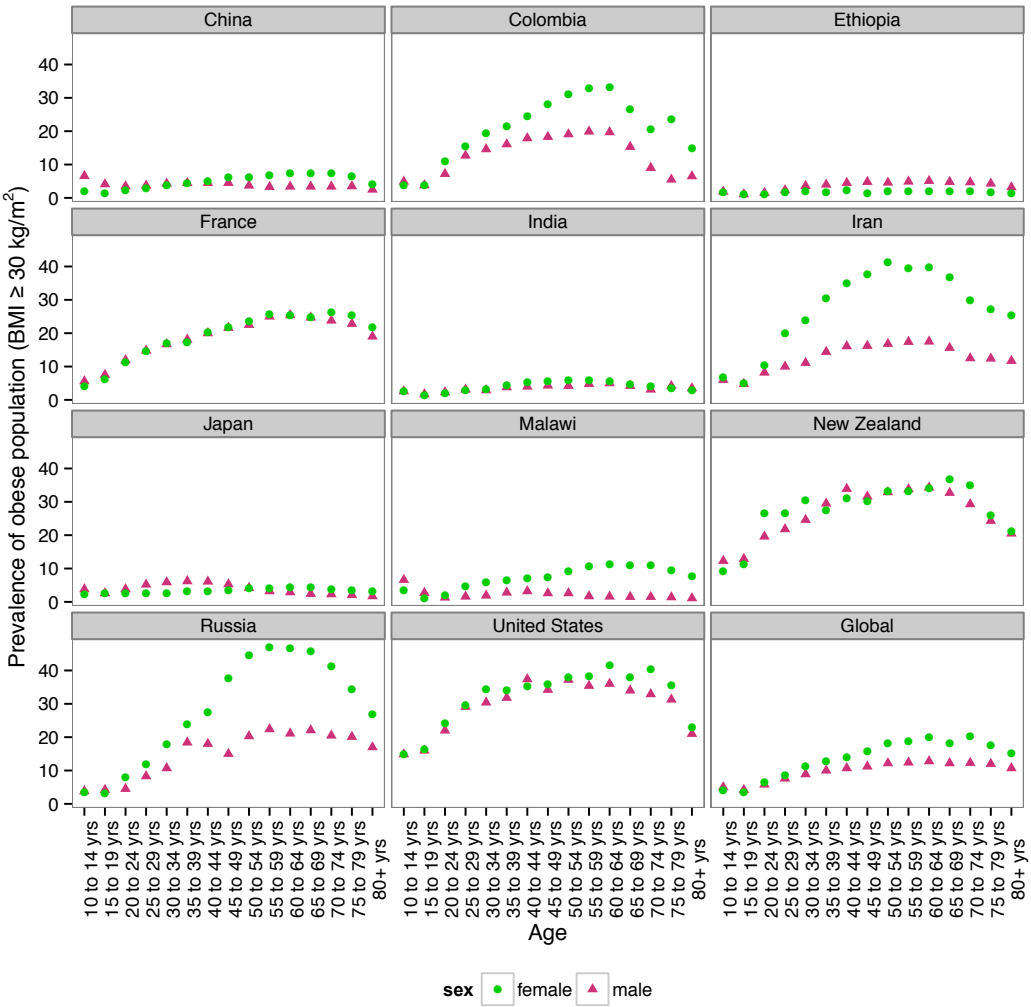
Similarly to findings for adult cancer survivors, a study of paediatric cancer survivors reported that boys aged 6–11 years were more likely to be overweight than the general population (Nathan et al., 2006).

1.2.3 Prevalence by age and sex

Several studies in the USA and Europe, using cross-sectional data, have shown that BMI increases with age up to the sixth decade of life and then starts to decrease (Flegal et al., 2002; Vasan et al., 2005; Ogden et al., 2006). However, results from cohort studies suggest a more modest decline in BMI at older ages (Grinker et al., 1995). This difference in findings may be due to higher mortality rates at younger ages in the obese population, leading to a lower prevalence of obesity in the surviving older population. Ageing is also associated with a change in body composition, with a decline in fat-free mass, which may cause a decrease in weight, and therefore in the measured obesity (Villareal et al., 2005). [The validity of assessing obesity by BMI is limited in elderly people (see Section 1.4.2).]

The prevalence of obesity and its association with age vary widely across countries, showing both similarities and differences regardless of the socioeconomic level of the country (IHME, 2014). For example, low prevalences of obesity are observed at all ages in China, Ethiopia, India, and Japan (Fig. 1.2), whereas in Colombia, France, the Islamic Republic of Iran, New Zealand, the Russian Federation, and the USA the prevalence

Fig. 1.2 Prevalence of obese population by age and sex in selected countries



From IHME (2014). Overweight and Obesity Viz. Seattle (WA), USA: Institute for Health Metrics and Evaluation. © 2017 University of Washington. Available from: http://www.healthdata.org/data-visualization/overweight-and-obesity-viz.

increases with age, followed by a decrease later in life.

The difference between the prevalence of obesity in men and in women is only weakly associated with the level of socioeconomic development of the country. The prevalence of obesity is markedly higher in women than in men in Colombia, the Islamic Republic of Iran, and the Russian Federation, whereas a smaller difference or no difference is observed, for example, in China, Ethiopia, France, India, Japan, New Zealand, and the USA.

1.2.4 Prevalence by ethnicity

Several studies have examined the association between ethnicity and obesity, mainly in high-income countries with high levels of immigration (e.g. the United Kingdom and the USA), but very little evidence is available for low- and middle-income countries.

Studies in the USA have clearly shown differences in health between different ethnic groups (Murray et al., 2005; Caprio et al., 2008; Ogden et al., 2014). The prevalence of obesity in the adult population (≥ 20 years) was almost 50% in non-Hispanic Blacks (37.1% in men and 56.6% in women), more than 42% in Hispanics (40.1% in men and 44.4% in women), about 32% in non-Hispanic Whites, and almost 11% in non-Hispanic Asians (Ogden et al., 2014). The prevalence of obesity in children and adolescents (2–19 years) was 22.4% in Hispanics, 20.2% in non-Hispanic Blacks, 14.1% in non-Hispanic Whites, and 8.6% in non-Hispanic Asians (Ogden et al., 2014). Similarly, important ethnic differences have been observed in England (National Obesity Observatory, 2011). According to data from the Health Survey for England 2004, in women the prevalence of obesity was highest for Black African women (38%), followed by Black Caribbean (32%) and Pakistani (28%) women, and lowest in Chinese women (6%). The largest gap between the sexes was observed among the Black African, Pakistani, and Bangladeshi groups, in which the prevalence of obesity in women was 1.9–2.8 times that in men. In addition, data from the National Child Measurement Programme in England in the 2012–2013 school year compared the prevalence of obesity in children aged 4–5 years and 10–11 years. The prevalence of obesity was highest among "Asian or Asian British", "Black or Black British", and "Other than White, Chinese, and Mixed" children, with levels of 20–30% (Health and Social Care Information Centre, 2013). [These differences may be partly due to differences in socioeconomic status.]

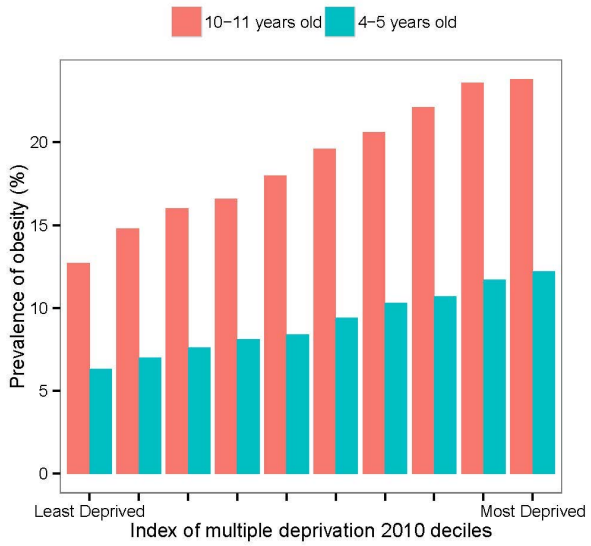
A study of the ethnic differences in obesity among immigrants to Norway from low- and middle-income countries showed large variability in general adiposity among different ethnicities (Kumar et al., 2006). Whereas 50% of Turkish women were obese, the levels of other anthropometric indicators, such as waist circumference, were higher among the Pakistani and Sri Lankan groups, and these differences persisted after adjustment for sociodemographic, biological, and lifestyle factors.

As a way of avoiding biases when comparing data, it has been suggested to define different obesity cut-off values when comparison between ethnicities is performed (see Section 1.4.2(ii)).

1.2.5 Prevalence by social class and education

The association between socioeconomic status and prevalence of overweight and obesity changes according to the level of economic development of the country (Dinsa et al., 2012). Lower socioeconomic status is protective against obesity in low-income countries, whereas it is a risk factor for obesity in middle- and high-income countries, mostly in women (Monteiro et al., 2004a, b; Dinsa et al., 2012). Similar patterns have been observed in children. Studies in high-income countries have shown an inverse association between socioeconomic status and child obesity (Lamerz et al., 2005; Shrewsbury & Wardle, 2008; Due et al., 2009). For example, data from the National Child Measurement Programme in England in the 2012–2013 school year showed a positive association [increasing deprivation leads to increasing prevalence] between level of deprivation and prevalence of obesity in children aged 4–5 years and 10–11 years (Fig. 1.3). Using the deciles of the Index of Multiple Deprivation 2010 (Department for Communities and Local Government, 2011), children in the most deprived decile had a prevalence of obesity twice that observed in the least deprived decile, with a prevalence of about 10% in children aged 4–5 years and about 20% in children aged 10–11 years (National Obesity Observatory, 2012; Health and Social Care Information Centre, 2013). In contrast, in low-income countries the association is inverted, and children in affluent groups

Fig. 1.3 Prevalence of obesity by age and decile of Index of Multiple Deprivation in England



Adapted from National Obesity Observatory (2012). NOO data factsheet: child obesity and socioeconomic status. Available from: http://webarchive.nationalarchives.gov.uk/20160805121933/http://www.noo.org.uk/uploads/doc/vid_16967_ChildSocioeconSep2012.pdf.

are more likely to be obese (Dinsa et al., 2012; Lissner et al., 2016).

As is the case for the socioeconomic level, BMI has been shown to be positively associated with education in lower-middle-income countries in women, and for men also in middle-income countries, whereas in high-income countries an inverse association was observed between level of education and BMI in women and no association was seen in men (Di Cesare et al., 2013; Fig. 1.4; see also Section 1.3.7).

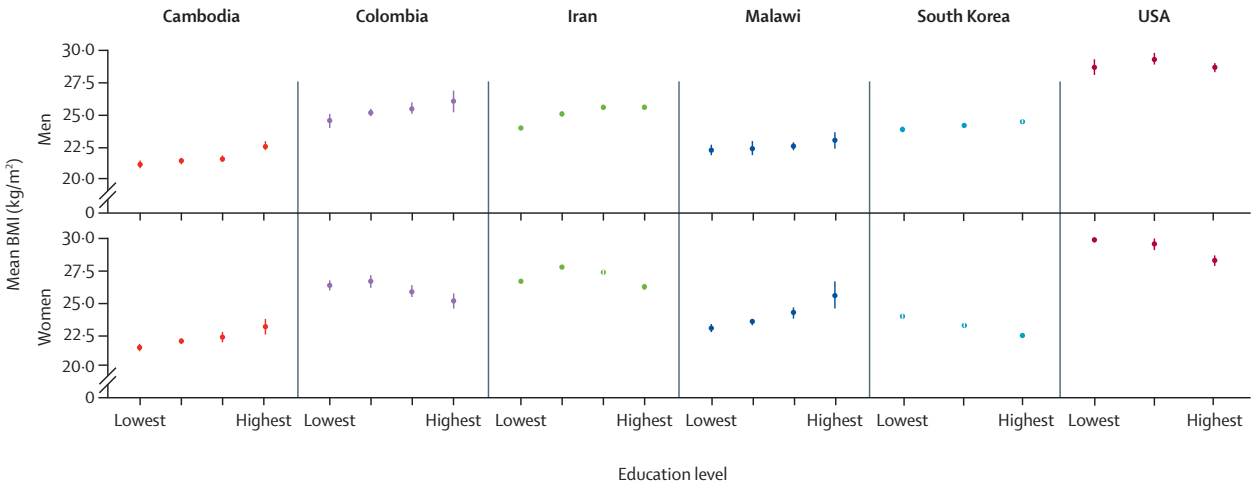
1.3 Risk factors

1.3.1 Regulation of hunger and satiety

The current epidemic of obesity suggests that the processes of satiety and body weight control are not tightly regulated, and physiological systems appear to permit fat storage when humans are exposed to sensory stimulation (e.g. palatability and taste) and opportunities for high energy intakes (hedonic response) (Blundell & Finlayson, 2004). In addition, a range of psychological factors can affect appetite control, including stress, mood, and guilt. Polymorphisms in the fat mass and obesity-associated gene (*FTO*) are associated with increased food intake, which is thought to be due to the effect of the gene on ghrelin and its role in appetite control (Eissing, 2013; Benedict et al., 2014). Thus, it seems that alterations in appetite control and subsequent food intake (rather than metabolic effects) are important factors for positive energy balance in humans.

The hypothalamus is the main regulatory organ for human appetite; peripheral signals from adipose tissue and the gastrointestinal system are delivered to the hypothalamus to influence short-term food intake (Lean & Malkova, 2015) (see also Sections 4.3.4a and 4.3.6b). Of the several adipokines produced by white adipose tissue, only leptin appears to have a significant effect on appetite suppression (Blundell et al., 2015a, b); in contrast, more than 30 gut-derived peptides, including hormones and neuropeptides, are known to affect appetite (Lean & Malkova, 2015). Meal ingestion results in production of hormones from enteroendocrine cells found at multiple sites in the digestive system (stomach, proximal/distal small intestine, pancreas, and colon). Gut hormones inhibit or stimulate food intake (anorexigenic or orexigenic effects). Key anorexigenic gut peptides include glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), whereas ghrelin is a gut hormone with potent orexigenic effects. Interest in the effect of bariatric surgery on long-term appetite control has highlighted the role of gut hormones (Chakravartty et al., 2015). Lean & Malkova (2015) reported that diet-induced weight loss affects gut hormones and favours increased appetite (and therefore weight regain), whereas physical exercise favours enhanced satiety (supporting maintenance of weight loss). They postulated that the sustained

Fig. 1.4 Mean BMI by education level in adults aged 25–64 years in selected countries



Reprinted from Di Cesare et al. (2013). Inequalities in non-communicable diseases and effective responses. *Lancet*, 381(9866):585–97. Copyright 2013, with permission from Elsevier.

weight loss achieved by bariatric surgery may in part be mediated via favourable changes to gut hormones.

There has been much speculation about the concept of a physiological "set point" that is automatically adjusted to maintain weight. Recent evidence suggests that structural changes in the hypothalamus may lead to a "reset", and thus maintain an increased body weight.

1.3.2 Weight gain throughout the life-course

The association of noncommunicable diseases in adulthood with nutrient status during pregnancy was proposed in 1990 (Barker, 1990), and there is substantial evidence supporting an early-life origin of susceptibility to obesity in later life (Scientific Advisory Committee on Nutrition, 2011). Both prenatal and postnatal factors, influencing fetal and infant growth, development, birth weight, and programming of metabolism, have been implicated in the later development of obesity. Overall, it is difficult to disentangle the impact of single early-life risk factors in the development of adult obesity.

Maternal obesity is associated with both large-for-gestational-age babies and macrosomia (birth weight > 90th percentile). It has been reported that in women with a pre-pregnancy BMI greater than 30 kg/m², the likelihood of having a large-for-gestational-age baby is 3.75 times that in women with a BMI less than 30 kg/m², and that large-for-gestational-age babies have both higher insulin resistance and higher free fatty acid levels (Liu et al., 2013). There is global concern about the number of women in developing countries who enter pregnancy with excess body weight (WHO, 2011; Torloni et al., 2012).

Systematic reviews of studies mainly in developed countries have demonstrated a positive association between birth weight and BMI in later life. The association has been described as strongest in children and young adults and weaker in middle-aged adults. It has been estimated that a 1 kg increment in birth weight is associated with a rise of 0.5–0.7 kg/m² in the BMI of young adults (Scientific Advisory Committee on Nutrition, 2011). Some studies suggest that both low and high birth weight are associated with subsequent risk of obesity in children and young

adults; however, a meta-analysis of 66 studies from 26 countries shows that low birth weight (< 2500 g) is followed by a decreasing long-term risk of overweight, whereas high birth weight predisposes to being overweight in later life (Schellong et al., 2012).

The role of maternal diet (both quantity and quality) during pregnancy is of particular interest with respect to fetal developmental programming (Liu et al., 2013), and it is plausible that epigenetic mechanisms are responsible for the associations between birth weight and risk of overweight later in life (Dominguez-Salas et al., 2014; Tobi et al., 2014).

Weight trajectories during infancy are influenced by breastfeeding and complementary feeding practices, which in turn influence body fatness in childhood and growth patterns (Poskitt & Breda, 2012; Bagci Bosi et al., 2016). There is growing evidence from recent reviews of observational studies that breastfeeding is associated with a decreased risk of becoming overweight later in life (Weng et al., 2012; Horta et al., 2015). Horta et al. (2015) reported an odds ratio (OR) of 0.74 (95% confidence interval [CI], 0.70–0.78) that people who were breastfed as babies were less likely to be classified as overweight or obese at ages 1–9 years, 10–19 years, and 20 years and older.

Feeding choices during infancy and childhood are influenced by parental factors, food availability, and other socioeconomic factors, including cultural norms, peer effects, and the marketing of food and beverages (Boyland et al., 2016). However, current research findings on the type of complementary foods and the age at which complementary foods are introduced into the infant diet and subsequent body fatness are inconsistent (Langley-Evans, 2015).

The development of overweight during childhood appears to track into adult life (Brisbois et al., 2012); however, a systematic review showed that childhood BMI is not a good predictor of the incidence of adult obesity or overweight, because most obese adults were not obese in childhood (Simmonds et al., 2015). Observational studies in industrialized countries have shown a consistent association of poor early growth followed by rapid catch-up in infancy with later obesity in childhood and adulthood (Monasta et al., 2010). An early adiposity rebound (a period of increasing BMI after the early childhood nadir), which usually occurs at ages 4–8 years, is associated with high body weight in later life (Williams & Goulding, 2009; Brisbois et al., 2012). Nutritional stunting (usually caused by chronic undernutrition) during childhood is also positively associated with overweight and obesity in later life (Popkin et al., 1996; Black et al., 2013).

Several studies have reported an association between parental smoking and later obesity in the offspring, with the greatest effect from maternal smoking (Power et al., 2010; Dior et al., 2014; Wang et al., 2014; Han et al., 2015). Prenatal maternal exposure to smoking (including secondhand tobacco smoke) was associated with increased risk of obesity in adolescents, independent of birth weight (Wang et al., 2014).

Throughout adult life, there are further periods or key life events associated with weight gain, including student life, the transition from single status to marriage or cohabitation, diet and activity behaviours during pregnancy, postpartum weight retention, the demands of employment, unemployment and job loss, the demands of parenting, and physiological changes associated with the ageing process (including menopause) (WHO Regional Office for Europe, 2016). Maternal weight gained during pregnancy is also associated with the likelihood of weight retention in the mother in the postpartum period and beyond. It is estimated that in the USA 50–67% of women gain more weight during pregnancy than is considered desirable by the United States Institute of Medicine (now known as the National Academy of Medicine) (Liu et al., 2013). It is likely that the metabolic load of exclusive breastfeeding (~500 kcal per day) can help

women in losing the weight gained during pregnancy, although results have been inconsistent (Bobrow et al., 2013; Jarlenski et al., 2014; Neville et al., 2014; Palmer et al., 2015).

Physiological changes associated with the ageing process influence weight gain (see Section 1.2.3). Comorbidities also have the potential to increase weight gain, for example through the action of different treatment modalities (Leslie et al., 2007; Rummel-Kluge et al., 2010; McPheeters et al., 2011; Almandil et al., 2013). Unintentional weight loss has also been reported as a side-effect of several therapeutic agents, and this is usually dose-dependent (Leslie et al., 2007).

1.3.3 Excessive energy intake

(a) Total energy intake

Obesity is determined primarily by increased total energy intake (Vandevijvere et al., 2015), which itself is influenced by portion size, the frequency of consumption, and the energy density of food and drinks consumed (Ello-Martin et al., 2005). Assessing total energy intake is challenging in epidemiological studies, because of measurement error, including selective underreporting by overweight and obese people (Livingstone & Black, 2003) and the inability to quantify energy provided by the colonic microbiome (Rahat-Rozenbloom et al., 2014). Because objective measures of energy intake do not exist (de Jonge et al., 2007), the best long-term indicator (or life-course indicator) of positive energy balance is weight gain (Hill et al., 2012). Weight gain cannot differentiate between the proportions of fat and lean tissues gained, but in most adults it is primarily determined by gain in adipose tissue (Okorodudu et al., 2010). The amount of adipose tissue gained over time depends on the degree of positive energy balance, the duration of the energy surplus, and the body composition before weight gain (Schutz et al., 2014).

(b) Macronutrient composition of diet

(i) Total fat

There has been a lack of consensus about whether the macronutrient composition of the diet is a significant determinant of body fatness (Bray & Popkin, 1998; Willett, 2002). Two systematic reviews of observational studies found no significant evidence for an association between percentage of energy from fat and body weight (Fogelholm et al., 2012; Hooper et al., 2015), whereas two systematic reviews with meta-analyses of randomized controlled trials (RCTs) in people with no intention of losing weight suggest that the percentage of energy from fat is positively associated with body weight (Hooper et al., 2015; Tobias et al., 2015). However, in weight-loss trials, no difference in weight loss was observed between diets with different percentages of energy from fat, whereas diets with a low percentage of energy from carbohydrates led to greater weight loss than those with a low percentage of energy from fat (Tobias et al., 2015). A third meta-analysis of RCTs reported that diets with a low percentage of energy from fat and those with a low percentage of energy from carbohydrates resulted in comparable reductions in body weight (Hu et al., 2012). [It is recognized that the success of any dietary restriction regimen in achieving weight loss is dependent on compliance with that regimen.]

(ii) Sugars

Two systematic reviews and meta-analyses of RCTs in adults found a significant positive association between intake of free sugars (defined as monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook, or consumer, and sugars naturally present in honey, syrups, fruit juices, and fruit juice concentrates; WHO, 2015) and weight gain (Te Morenga et al., 2012) and energy intake (Scientific Advisory Committee on Nutrition, 2015), respectively.

Overconsumption of sugar-sweetened beverages in particular has been linked to weight

gain and obesity. Reviews and meta-analyses of prospective cohort studies and RCTs indicate that consumption of sugar-sweetened beverages promotes weight gain and obesity (Hu & Malik, 2010; Te Morenga et al., 2012; Malik et al., 2013; Fardet & Boirie, 2014; Scientific Advisory Committee on Nutrition, 2015). In contrast, there are investigations that consistently show weak or null results for the association between consumption of sugar-sweetened beverages and obesity (Forshee et al., 2008; Gibson, 2008; Kaiser et al., 2013; Trumbo & Rivers, 2014). [Concern has been expressed about potential bias of these studies, because of sources of funding.]

(c) Dietary patterns

Studies using dietary patterns as derived by factor or cluster analysis to examine common eating behaviour in relation to weight control and obesity found that diets characterized by high intakes of sugar-sweetened beverages, refined grains, potatoes, and red and processed meat were related to greater gains in BMI and waist circumference, whereas diets typified by high intakes of fruit, vegetables, whole grains, fish, poultry, and reduced-fat dairy products were associated with smaller weight gains (Newby et al., 2003; Schulze et al., 2006). Similarly, the traditional Mediterranean diet – as characterized by high intakes of fruit, vegetables, legumes, nuts/seeds, and wholegrain cereals; regular consumption of fish and seafood; moderate intakes of dairy products, poultry, and eggs; low consumption of red and processed meat; use of olive oil as the main source of dietary fat; and moderate intake of wine – has been consistently found to be inversely related to the development of weight gain and obesity (Buckland et al., 2008; García-Fernández et al., 2014; Gotsis et al., 2015). It has been suggested that eating patterns, such as eating breakfast, frequency of eating, snacking, and timing of meals, may also modulate the risk of overweight and obesity (van der Heijden et al., 2007; McCrory, 2014; Jiang & Turek, 2017).

(d) Fast food

Fast foods are energy-dense, micronutrient-poor foods that are often high in fatty acids, processed starches, and added sugars (Jaworowska et al., 2013); they have more recently been termed "ultra-processed foods" (Martínez Steele et al., 2016). There is concern about the rising global trend in consumption of fast food and its potential impact on obesity (McCrory et al., 1999; Paeratakul et al., 2003; Louzada et al., 2015).

Most available studies are limited by their cross-sectional designs, non-standardized definitions of fast food, and potential confounding by unmeasured factors. A recent narrative review reported that frequent consumption of fast foods is accompanied by weight gain and obesity (Bahadoran et al., 2016). In one observational cohort study, frequency of consumption of fast food was positively related to changes in body weight. Specifically, more frequent consumers (more than twice per week) gained an extra 4.5 kg of body weight over a 15-year period compared with less frequent consumers (less than once per week) of fast-food products (Pereira et al., 2005).

(e) Alcoholic beverages

Findings on the association between consumption of alcoholic beverages and body weight have been inconsistent, with observational studies showing positive, inverse, or null associations (reviewed in Poppitt, 2015). In addition, evidence linking alcohol consumption to weight gain and obesity was ranked insufficient by international reports (WHO, 2003; WCRF/AICR, 2007).

(f) Sleep

The relationship of sleep duration to adiposity has been examined in numerous epidemiological studies. Results from studies in adults have been mixed, but most investigations support an association of short sleep duration with adiposity, with the association appearing to wane with

increasing age (Marshall et al., 2008; Patel & Hu, 2008). By comparison, studies in children showed a clear pattern, with short sleep duration being positively related to obesity (Chen et al., 2008; Marshall et al., 2008; Patel & Hu, 2008). Results from systematic reviews and meta-analyses are in line with these findings (Cappuccio et al., 2008; Magee & Hale, 2012; Capers et al., 2015). [One possible explanation for the divergent results between children and adults is that the association between short sleep duration and weight gain diminishes over time after the transition to chronic short sleep duration (Magee & Hale, 2012).]

Sleep deprivation can lead to enhanced energy intake, possibly through a mechanism involving greater propensity to overeat and altered levels of hormones involved in appetite regulation, such as ghrelin and leptin (Bayon et al., 2014; Kim et al., 2015). By comparison, there is little evidence to support that insufficient sleep leads to decreased energy expenditure (Chaput & Tremblay, 2012). Light exposure during the night decreases melatonin synthesis (Haus & Smolensky, 2013; McFadden et al., 2014), and melatonin deficiency has been shown to exert beneficial effects on obesity and to normalize the expression and secretion patterns of adipokines such as leptin and adiponectin (Szewczyk-Golec et al., 2015).

[Limitations of study designs in the area of short sleep duration and obesity include a failure to account for potential confounding, mediating, and moderating variables, such as sedentary behaviour, and measurement issues such as a paucity of objective measures of sleep duration, lack of repeated assessments of both sleep duration and body weight, and an insufficient number of experimental study designs that manipulate sleep.]

1.3.4 Endocrine disruptors

An endocrine-disrupting chemical (EDC) is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of the regulation of hormone action (Zoeller et al., 2012). EDCs act directly by binding or interfering with receptors, or indirectly by disrupting hormone levels or by altering hormonal transport mechanisms (Heindel et al., 2015). Because endocrine systems exhibit tissue-, cell-, and receptor-specific actions during the life-cycle, EDCs can produce a complex mosaic of effects across the life span (Zoeller et al., 2012).

Some EDCs, referred to as "obesogens" (Janesick & Blumberg, 2016), improperly interfere with lipid homeostasis, and promote adipogenesis by perturbing various endocrine axes (Burgio et al., 2015). The developmental age at which EDC exposures occur is a critical consideration in understanding their effects. Exposure to obesogenic EDCs during fetal life and early childhood appears to have an impact on obesity during childhood and adulthood (Grün & Blumberg, 2009; Heindel et al., 2015).

The EDCs with obesogenic properties that are most prevalently used are presented in Table 1.2 (adapted from Heindel et al., 2015), and the available data are summarized below. [The overall limitations of the data from humans lie in the cross-sectional nature of the majority of the studies and in the use of a single measure of exposure. The inconsistences in results in the small number of birth cohort studies is likely to be related to the small sample size, differences in population characteristics, and differences in levels of exposure and timing of exposure.]

(a) Bisphenol A

Studies in animals have shown that exposure to bisphenol A can disrupt many metabolic pathways and could alter the hypothalamic energy balance circuitry, resulting in increased susceptibility to developing diet-induced obesity

Table 1.2 Endocrine-disrupting chemicals with obesogenic properties

Chemical	Source	Potential mechanism
Bisphenol A	Plastic and epoxy resins	Estrogenic Inhibition of proliferation of neural progenitor cells
Phthalates	Plasticizers, adhesives, and personal care products	Increase the rate of adipocyte differentiation
Tributyltin	Fungicide in paints and component of polyvinyl chlorides	Activation of peroxisome proliferator-activated receptor-γ and increased fat cell differentiation
Polychlorinated biphenyls	Coolants, plasticizers, and flame retardants	Altered thyroid function Altered metabolism Bioaccumulation in fat cells
Polycyclic aromatic hydrocarbons	Incomplete combustion of fossil fuels	Accumulation of visceral fat Inflammation
Perfluorinated chemicals	Components of lubricants, non-stick coatings, and stain-resistant compounds	Increase serum levels of insulin Increase serum level of leptin
Flame retardants	Chemicals applied to furniture and electronics	Increase rate of adipogenesis Increase glucose intolerance

Adapted from Heindel et al. (2015) by permission from Springer Nature.

and metabolic impairment (Heindel et al., 2015). Some studies reported an association between urinary concentrations of bisphenol A and increased obesity in children (OR, 2.53; 95% CI, 1.72–3.74, between the highest and lowest quartile of bisphenol A concentration; Trasande et al., 2012) and in adults (OR, 1.50; 95% CI, 1.15–1.97, between the highest and lowest quartile) (Wang et al., 2012), whereas other studies reported no association (Lakind et al., 2014). Also, exposure to bisphenol A during fetal life increased adipokine levels in childhood (Volberg et al., 2013; Ashley-Martin et al., 2014).

(b) Phthalates

In animal models, prenatal exposure to phthalates led to increased body weight, increased number and size of adipocytes, and activation of peroxisome proliferator-activated receptor gamma in male offspring (Heindel et al., 2015). Also, cross-sectional studies suggest an association between exposure to phthalates and weight gain (Kim & Park, 2014). However, data from human birth cohorts are inconsistent (Ashley-Martin et al., 2014; Maresca et al., 2015).

(c) Tributyltin

In animals, prenatal exposure to tributyltin causes lipid accumulation in adipose tissue, with effects persisting into adulthood and into future generations (Heindel et al., 2015). A recent study showed a positive association between placenta tributyltin levels and weight gain in male infants at age 3 months (Rantakokko et al., 2014).

(d) Polychlorinated biphenyls and other persistent organic pollutants

Data from the National Health and Nutrition Examination Survey 1999–2002, in adults and children, showed an association of detectable levels of persistent organic pollutants with waist circumference and BMI (Elobeid et al., 2010). Cohort studies in children have not confirmed the association with weight gain (Cupul-Uicab et al., 2013; Tang-Péronard et al., 2015). However, in a birth cohort in the Faroe Islands, higher prenatal exposure to polychlorinated biphenyls was associated with increased BMI at age 7 years in daughters of overweight mothers (Tang-Péronard et al., 2014). In addition, higher levels of persistent organic pollutants have been observed

in visceral fat of obese subjects with larger metabolic dysfunction compared with those without metabolic dysfunction (Pestana et al., 2014).

(e) Polycyclic aromatic hydrocarbons

Studies in animals have shown that the combination of exposure to diesel exhaust in utero and a high-fat diet as an adult increases susceptibility to diet-induced obesity and neuroinflammation in females but not in males (Bolton et al., 2012). In a birth cohort of women who were exposed to air pollutants during pregnancy, higher exposure levels were associated with higher obesity in their children at ages 5 years and 7 years (Rundle et al., 2012).

(f) Other compounds

Very limited data in humans are available for perfluorinated chemicals and flame retardants, and the results are inconclusive (Erkin-Cakmak et al., 2015; Heindel et al., 2015).

1.3.5 Physical activity and sedentary behaviour

Physical activity is considered "any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen et al., 1985). The intensity of physical activity refers to the rate of energy expenditure brought about by physical activity; in epidemiological studies, it is commonly expressed in metabolic equivalents (METs) of tasks. Specifically, activities are grouped according to light (1.6–2.9 METs), moderate (3.0–5.9 METs), and vigorous (≥ 6 METs) levels of activity (Ainsworth et al., 2011). Several methods for measuring physical activity are available and have been used in epidemiological studies (Ndahimana & Kim, 2017).

Globally, there have been declines in levels of physical activity and increases in time spent sedentary in adults over the past decades (Ng et al., 2012; Dearth-Wesley et al., 2014). However, experimental evidence from repeated cross-sectional studies since the 1980s with measurements of energy expenditure by the doubly labelled water method indicate that levels of physical activity have not declined over the time period in which the prevalence of obesity has risen (Westerterp & Speakman, 2008). Thus, it seems likely that the recent rise in the average body weight of the population globally is determined largely by increased energy intake rather than by decreased energy expenditure (Swinburn et al., 2009).

(a) Physical activity and prevention of weight gain

Evidence from long-term observational studies (Williamson et al., 1993; Di Pietro et al., 2004; Gordon-Larsen et al., 2009; Lee et al., 2010; Mozaffarian et al., 2011) suggests a positive relationship between self-reported physical activity and prevention of weight gain. Data from RCTs are sparse and are based on short-term interventions and follow-up (Simkin-Silverman et al., 2003). Expert consensus has estimated that the amount of moderate-intensity physical activity associated with prevention of weight gain is 150–250 minutes per week (Donnelly et al., 2009), or 45–60 minutes per day (Saris et al., 2003).

(b) Physical activity and weight loss

In adults, moderate physical activity shows a dose–response association with weight loss. Based on evidence from observational studies of varying durations (spanning time periods of several months to several years), the American College of Sports Medicine concluded that less than 150 minutes per week results in minimal weight loss, more than 150 minutes per week yields weight loss of 2–3 kg, and 225–420 minutes per week leads to weight loss of 5–7.5 kg (Donnelly et al., 2009). Moreover, a positive relationship was reported, for a similar duration, between the intensity of the physical activity and the amount of weight lost (Shaw et al., 2006). A meta-analysis of trials with durations of 12 weeks to 12 months reported that moderate-intensity physical activity

is only modestly effective in producing weight loss in overweight and obese adults, showing a small weighted mean difference in body weight of –1.6 kg (Thorogood et al., 2011).

Physical activity may generate a more pronounced effect on weight loss in children and adolescents, as suggested by a meta-analysis of 20 intervention studies reporting that an exercise programme involving approximately 150 minutes per week of physical activity for 13 weeks led to a 3.6% decrease in BMI in overweight and obese children and adolescents (Kelley et al., 2015).

A meta-analysis of 15 RCTs compared the effects of 2.5–6 months of aerobic and resistance exercise on weight loss in overweight and obese subjects and concluded that the combination of aerobic and resistance training may be the most efficacious physical activity regimen for weight loss (Schwingshackl et al., 2013).

Physical activity and energy restriction should yield similar amounts of weight loss if they provide comparable degrees of negative energy balance, and they are both important for achieving optimal weight loss. However, energy restriction combined with physical activity results in the combination of loss of fat mass and maintenance of lean mass, thereby leading to a more desirable effect on body composition (Miller et al., 2013).

(c) Physical activity and prevention of weight regain after weight loss

An early systematic review of RCTs and observational studies reported that people who engaged in physical activity experienced less weight regain than their sedentary counterparts, but confounding by a healthy lifestyle or reverse causation by better exercise adherence among those with less weight regain could not be ruled out (Fogelholm & Kukkonen-Harjula, 2000). In contrast, a more recent meta-analysis of RCTs on long-term maintenance of weight loss found no evidence of effectiveness for interventions involving physical activity only. However, the combination of physical activity and dietary energy restriction resulted in a difference of –1.56 kg in weight regain compared with controls at 12 months (Dombrowski et al., 2014). Taken together, findings from observational studies and RCTs show inconsistent results, and the volume of physical activity needed to prevent weight regain after weight loss remains poorly defined.

Data about the influence of resistance training on prevention of weight gain and weight regain after weight loss are sparse.

(d) Sedentary behaviour

Sedentary behaviour is a behaviour with reduced light activity and is distinct from lack of moderate to vigorous activity (Lynch et al., 2010). Time spent in sedentary activities reduces energy expenditure, potentially promoting weight gain over time (Owen et al., 2010). Long-term observational epidemiological studies in adults reported that sedentary behaviour, such as television viewing and computer gaming, is associated with enhanced risk of adiposity (Hu et al., 2003; Thomée et al., 2015). Also, television viewing is associated with enhanced intake of sugar-sweetened beverages and sweets (Lipsky & Iannotti, 2012). Moreover, a meta-analysis of 25 RCTs showed a small but significant decrease in BMI with reducing sedentary behaviour in children and adolescents (Liao et al., 2014). [Potential confounding by energy intake could not be ruled out.] Data on sedentary behaviour and prevention of weight regain after weight loss are sparse.

1.3.6 Built environment

The human body has evolved to transform excess energy into body fat during exceptional times of food abundance for protection during periods of low food availability, but has not adapted to meet the challenge of the supply

provided by current food systems (Hill et al., 1998).

The built environment refers to aspects of a person's surroundings that are human-made (or modified), compared with naturally occurring features (Caballero, 2007; Papas et al., 2007). It is one part of the so-called obesogenic environment, which includes sociocultural, economic, and marketing barriers to the achievement of healthy ways of life.

Food availability has undergone many changes in recent decades, as a result of economic, social, and demographic changes (the nutrition transition) (Brown, 1991; Popkin, 1993), resulting in an increased dependence on processed foods, a strong emphasis on the marketing and promotion of energy-dense foods and beverages, a decreased intake of fruit and vegetables, and an increased intake of foods that are high in fat and sugar (Caballero, 2007). The food environment has changed as the opportunities for consumption have increased through increased diversification of food outlets (e.g. vending and fast-food restaurants) and intensive and creative marketing strategies. In addition, changes in the built environment, including shifts in transportation patterns, labour-saving devices, limited public space for recreational physical activity, and increased public safety concerns, have promoted sedentary lifestyles (Caballero, 2007; Parizkova et al., 2007) (see also Section 1.3.5).

It is important to note that although individual energy balance is strongly predicted by personal behaviours, the factors that influence these behaviours are a response to the stimulus of the obesogenic environment. Thus, societal change that will have an impact both on public health and on the health of the individual is required to counter the current obesity epidemic (Mackenbach et al., 2014).

The ecological approach to obesity research embraces the biological, behavioural, and environmental factors that have an impact on energy balance (Egger & Swinburn, 1997). The built environment is thought to play a key role in promoting both reductions in energy expenditure and increases in energy intake, but it also has the potential to promote and sustain healthy behaviours for significant periods of time throughout the life-course (Ludwig et al., 2011). The built environment affects a person's ability to comply with interventions, including educational interventions, that are focused on individual behaviour change (Sallis et al., 2012).

Most research has focused on the role of the built environment in providing opportunities for physical activity; with respect to the food environment, most work has focused on food availability within communities.

Several reviews have examined the relationship between the built environment and obesity, but they have had heterogeneous measurement approaches. The lack of valid and reliable measurement tools and analytical approaches may have contributed to inconsistent findings (Feng et al., 2010).

Metrics of the food environment (relevant for energy intake) include measures of the density, proximity, and diversity of and spatial access to food establishments (supermarkets, convenience stores, farmers' markets, and restaurants). It is difficult to compare studies, because of metrics used and the overall suboptimal quality of the studies (Ding & Gebel, 2012). A review (Cobb et al., 2015) that assessed the relationship of obesity to local food environments reported few significant findings, although a trend towards an inverse association between availability of supermarkets and obesity was noted. Metrics that are relevant for physical activity (and thus energy expenditure) include measures of population density, diversity, connectivity, design of and spatial access to physical activity facilities, walkability, and sprawl (Lopez & Hynes, 2003).

Although a consistent relationship has been seen between physical activity (in the form of active transport and recreational walking) and

neighbourhood walkability in adults, these studies have not always reported measures of obesity. Where obesity has been reported, there seems to be a lower than average BMI in neighbourhoods with higher perceived mixed land use, improved walkability, and better access to sports facilities (Black & Macinko, 2008). In a review by Papas et al. (2007), significant associations between some objectively measured aspects of the built environment (e.g. residential density, street connectivity, greenery, and access to destinations) and obesity were observed in 84% of the studies. In a study on environmental attributes and adult weight status in 12 countries, De Bourdeaudhuij et al. (2015) reported that safety from traffic had the most robust correlation with BMI.

Several studies have evaluated accessibility to recreation or exercise spaces and facilities (such as parks, playgrounds, cycle routes, and sports facilities) using adiposity as an outcome. In a review of cross-sectional studies that directly measured body weight in adults or children, two out of three studies in adults observed that shorter distance to (or greater density of) fitness facilities was associated with lower BMI and lower prevalence of overweight (Papas et al., 2007). In their review of population approaches to improving health behaviours, Mozaffarian et al. (2012) concluded that greater access to recreation and exercise spaces and facilities is relatively consistently linked to higher levels of physical activity and lower adiposity or other metabolic risk factors. However, they noted that nearly all the evidence is cross-sectional, which limits inferences about causality.

In a review by Dunton et al. (2009) of childhood obesity, associations between physical environmental variables and obesity differed by sex, age, socioeconomic status, population density, and whether reports were made by the parent or the child.

Research in the USA shows that children and adults living in rural areas are more likely to be obese than their urban counterparts (even after adjustment for individual-level behaviours). A review by Hansen et al. (2015) suggests that limited "active living" built environments are a contributory factor.

1.3.7 Social determinants

Socioeconomic status is an aggregate concept that consists of numerous indicators that reflect a person's position in society, including education level, occupation, income, wealth, poverty, and deprivation. Because levels of BMI vary according to levels of economic development, sociocultural factors, and characteristics of the health-care system of a country, the relationship between social determinants and obesity cannot be explained by any individual factor; rather, numerous interrelated factors are involved (WHO, 2008).

It has been widely shown that in high-income countries, the prevalence of obesity is higher among people with lower socioeconomic status (WHO, 2014); this inverse association is driven mainly by the fact that socially disadvantaged people experience a more obesogenic environment, which favours access to cheap, energy-dense foods, lower levels of physical activity, and poor education. In contrast, in low-income countries a positive association is seen between socioeconomic status and the prevalence of obesity (Monteiro et al., 2004a, b; Blakely et al., 2005; Dinsa et al., 2012; Pampel et al., 2012). Possible reasons for this are food scarcity among the poor in low-income countries, leading to low or moderate food intake, and greater engagement in manual labour, requiring higher energy expenditure. By comparison, the rich in low-income countries may be particularly susceptible to obesity because of easy access to excess food and lower levels of occupational physical activity. Also, in some low-income countries, a large body size may be perceived as an indicator of socioeconomic status (for additional cultural aspects,

see also Section 1.1). Inequalities in childhood obesity generally mirror those seen in adults (Due et al., 2009; Dinsa et al., 2012) (see also Section 1.2.5).

The relationship of socioeconomic status to obesity appears to be affected by the choice of socioeconomic indicator (income vs education level) in approximately 20–30% of studies conducted in low-income countries. This may be due to the weak correlation observed between wealth and education level in some low-income countries where educational investment has not yet translated into a higher income (Dinsa et al., 2012). One literature review of studies from high-income countries examined various indicators of socioeconomic status and found inverse relationships of education level and occupation to weight gain, with less consistent findings when income was used as the measure of socioeconomic status (Ball & Crawford, 2005). Another review of studies conducted in industrialized countries reported that women who changed social class after childhood took on the prevalence of adiposity of the class they joined, a relationship that was not evident in men (Parsons et al., 1999). Data about other social determinants, such as family size, number of parents at home, or availability of childcare and their relationship to obesity are sparse.

Education level has been one of the most frequently used measures of socioeconomic status (Krieger et al., 1997) and has been shown to be associated with obesity. This has led to an emphasis on nutrition education and practical food skills as a route to improving dietary habits. However, recent data from the United Kingdom (Adams & White, 2015) show an inconsistent relationship between sociodemographic variables and all markers of cooking skills, highlighting the need to explore the wider social factors that educational background reflects (see, for example, Lawrence & Barker, 2009).

It is recognized that numerous factors potentially influence food choice (and thus energy intake) across the population, which may have differential health effects according to socioeconomic status (McKinnon et al., 2014). Such factors include perception of sensory attributes, such as a liking for sweetness (Deglaire et al., 2015); psychological factors, such as mood (Singh, 2014); mental health and well-being, including stress (Moore & Cunningham, 2012); and the food marketing environment, notably with marketing of foods high in sugars, fats, and salt being targeted at children (Cairns et al., 2013).

1.3.8 Microbiota and gastrointestinal environment

The adult human gut hosts a complex community of microorganisms (microbiota), including about 1.5 kg of bacteria, most of which belong to four major phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. The amount, composition, and ratio of these vary according to diet and energy intake, and it is clear that variations in eating habits can lead to selective promotion of particular species. It is estimated that 57% of the bacterial variation in the gut is due to diet, and there are particular concerns that high-fat, high-sugar diets may alter the functionality of the microbiota (Harris et al., 2012). There is accumulating evidence to support a role for the microbiota in obesity and its downstream metabolic sequelae.

For example, the gut microbiota has been found to be significantly altered in animal models of obesity, with a reduction in bacterial diversity as well as a change in bacterial composition. It is generally agreed that a lower diversity of microorganisms and the presence of more tolerant bacteria are also observed in obese people. In many studies, the pattern associated with obesity is a relative decrease in Bacteroidetes (gram-negative) and a corresponding relative increase in Firmicutes (gram-positive), although

there is some inconsistency in results in relation to ratios of different phyla (Sanmiguel et al., 2015). Reduction in body weight results in a shift in the composition of the gut microbiota, with a significant relative increase in Bacteroidetes and relative decrease in Firmicutes as weight loss progresses. Exercise alone is also associated with an alteration in the ratio of the major bacteria, with a higher proportion of butyrate-producing bacteria (Bacteroidetes) (Harris et al., 2012).

Both animals and humans experience major changes in the gut microbiota after gastric bypass, when there is a restoration to a normal ratio of Firmicutes to Bacteroidetes. It is postulated that this occurs as a result of major changes in the composition of the diet after surgery, a decrease in production of bile acid, and a raised pH, which encourages the growth of bacteria associated with weight loss (Harris et al., 2012; Sanmiguel et al., 2015). The changes in the microbiota appear to be independent of energy intake, suggesting that weight loss may also be the result of an interplay between the microbiota and host biology.

It is recognized that along with an impact on metabolic state, obesity-associated changes in bacterial diversity, as well as specific shifts in gut bacteria such as *Faecalibacterium prausnitzii* (phylum Firmicutes), are associated with alterations in the inflammatory state (Le Chatelier, et al., 2013; Marchesi et al., 2016) (see also Section 4.4.1). In studies in rats, it has been demonstrated that inflammation alone can cause weight gain in normal rats and that the absence of inflammation protects rats against weight gain from a high-fat diet (Harris et al., 2012).

Studies in animal models have demonstrated that transfer of the gut microbiota (faecal microbiota transplantation) from obese mice to lean mice results in weight gain despite decreases in food intake. Similarly, the introduction of a "lean" microbiota will result in weight loss in obese animals. However, in humans similar changes in the gut microbiota created by probiotics and prebiotics have not been successful in demonstrating weight loss (Graham et al., 2015; Sanmiguel et al., 2015). It seems likely that in humans, differences in the gut microbiota accompany obesity rather than causing the problem. Further research in experimental systems and in humans is needed to understand the link between the microbiome and obesity and whether variation in the microbiome is a direct cause of obesity or is a consequence of it.

1.3.9 Genetic and epigenetic determinants of body fatness

There is growing evidence that gene–environment interactions play a major role in obesity (Reddon et al., 2016). A hereditary component to obesity has long been recognized, but the underlying genetic variants have only recently been identified. The first single nucleotide polymorphism robustly associated with increased BMI was identified in 2007 and mapped to a gene now known as *FTO* (Frayling et al., 2007). Since then, genome-wide association studies and meta-analyses conducted through large-scale consortium efforts (e.g. the Genetic Investigation of Anthropometric Traits [GIANT] consortium) have identified almost 100 gene variants robustly linked to BMI, including genes involved in appetite regulation, neural networking, glutamate receptor activity, insulin function, and energy metabolism (Speliotes et al., 2010; Locke et al., 2015). In addition, BMI-associated variants in genes linked to immune function, such as *TLR4*, may confer susceptibility to obesity through interactions with the microbiome. Genome-wide association studies for other anthropometric parameters, such as central adiposity (as determined by waist circumference), have identified additional variants (Heard-Costa et al., 2009). As even larger studies of common genetic variation and studies of rare variants are undertaken, and more sophisticated computational tools become available, it is likely that additional genetic variants associated with obesity will be identified.

Nevertheless, the variants identified to date, combined, explain only a modest fraction (~3%) of the variation in BMI (Locke et al., 2015).

Epigenetic mechanisms, such as DNA methylation and histone modifications, may also play a role in obesity and represent an integrated measure of both genetic and environmental factors (see also Section 4.2.3). Emerging data from population-based studies indicate that specific regions of the genome are differentially methylated in obese people compared with those of normal weight (Dick et al., 2014; Aslibekyan et al., 2015). These studies demonstrate that increased adiposity is associated with specific epigenetic changes and may provide clues about the biology of obesity. Maternal exposure to environmental risk factors during pregnancy can alter the metabolic phenotype of offspring (e.g. "body size") by means of epigenetic regulation of specific genes, and the epigenetic modifications could be passed on to future generations (Cutfield et al., 2007; Chamorro-García & Blumberg, 2014). Although developmental programming of body weight regulation occurs in humans, it is still unclear whether it occurs via epigenetic mechanisms (Institute of Medicine, 2015).

1.4 Assessment of anthropometric measures and body composition

The assessment of body composition is essential in obesity research, and several approaches have been proposed. The simpler and less expensive approach is to use weight and height – the most commonly used measures of nutritional status in epidemiological studies – and waist circumferences as a measure of abdominal obesity. More technologically advanced methods include bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). These methods provide more precise and accurate estimates of body composition and fat distribution, but their use is limited by the lack of practicality and the cost; they are mostly used to validate simpler methods or in small clinical and epidemiological studies (Willett & Hu, 2013).

1.4.1 Weight and height

Standardized methods are available to measure weight, height, and other anthropometric variables (Gibson, 2005). These are currently used in nutritional surveys (CDC, 2016) and analytical epidemiological studies. These measurements should be obtained by trained health technicians, with routine calibration of equipment and strict quality control. Body weight is measured in kilograms (to the second decimal place) using a self-zeroing digital scale, while the subject is wearing light clothing and without shoes, preferably in the fasting state. Height is measured to the nearest millimetre with a stadiometer, while the subject is without shoes, with the back square against a metal wall tape, and with the eyes looking straight ahead and a set square resting on the scalp (Willett & Hu, 2013).

Among various anthropometric variables, weight and height are measured with the highest precision (reproducibility) and accuracy (little deviance from the true value) and with the least amount of technical error (Ulijaszek & Kerr, 1999). In many large cohort studies, weight and height are based on self-reports. Self-reported measures are more feasible for large samples and are necessary when considering past weight (Ulijaszek & Kerr, 1999). When self-reported measures are validated with objective measures, it has been shown that subjects tend to understate weight and overstate height (Krul et al., 2011); in general, the achieved degree of accuracy is sufficient to rank individuals in epidemiological studies, but use of self-reported measures will lead to an underestimation of the prevalence of obesity (Willett & Hu, 2013). Self-reported weight

and height obtained by telephone interviews have been shown to be less reliable than those obtained by in-person interviews (Ezzati et al., 2006).

Adult height is a complex variable, determined primarily by genetics but also by nutritional factors, especially intakes of energy and proteins during the pre-adult period (Cole, 2000). Thus, height may reflect energy balance during childhood and adolescence (Willett & Hu, 2013).

Recalled weight from many years in the past appears to be valid, although the error is greater than for self-reported current weight. In women, the correlation between weight, height, and BMI measured at age 18 years and reported at ages 71–76 years was found to be 0.84, 0.92, and 0.83, respectively (Must et al., 1993).

In addition, useful information can be obtained by asking subjects to describe their **body profile (body silhouette)** currently and at different earlier ages using pictograms that range from very thin to massively obese (Sørensen et al., 1983). Recalled body silhouette at ages 20, 15, and 10 years has been found to correlate well with measured BMI at ages 71–76 years (Pearson correlation ranging from 0.53 to 0.75 in men and women) (Must et al., 1993). The use of these pictograms is particularly helpful in populations in which it is challenging to obtain accurate anthropometric measurements and to obtain information about body fatness at earlier ages (Romieu et al., 2012). Similar pictograms have been used to study personal perception of current body silhouette (Thompson & Gray, 1995) and perception of body silhouette in relation to age and health (Han et al., 1999).

Self-reported **birth weight** also appears to be reasonably valid. In the Nurses' Health Study II cohort, the correlation between recorded birth weight and self-reported birth weight was 0.74 (Troy et al., 1996).

1.4.2 Indexes of adiposity

(a) BMI

The most commonly used index of obesity is the BMI (see Section 1.1). The cut-off value for underweight (18.5 kg/m^2) is based largely on health-related problems associated with malnutrition in developing countries (IARC, 2002).

BMI is easy to assess and has high precision and accuracy. It has been shown to correlate strongly with both absolute body fat and body fat percentage in different age, sex, and racial groups when compared with more sophisticated measures of fat distribution (DXA) (Gallagher et al., 1996; Blew et al., 2002; Evans et al., 2006). BMI is a useful indicator of body fatness, but it is an imperfect measure of obesity, because it does not differentiate between lean mass and fat mass, the relative proportions of which vary between individuals and with age, sex, and race/ethnicity (Garn et al., 1986; Prentice & Jebb, 2001).

(i) Age and sex differences

For biological reasons, women have higher body fat percentages than men for the same BMI (Gallagher et al., 1996). For children, BMI centiles and Z-scores [measures of standard deviation] should be used to determine BMI status for ages up to 18 years, because these indicators are age- and sex-specific in children and adolescents (Cole, 2002; WHO 2016, 2017a, b). Among elderly people, the validity of BMI as a measure of body fatness appears to be reduced because of changes in body composition, such as loss of lean mass (sarcopenia) and increase in abdominal fat mass associated with ageing (Gallagher et al., 1996: Hu, 2008). This lower validity of BMI in elderly people may explain why the relationship of BMI with mortality is less pronounced in elderly people than in younger adults; in elderly people, waist circumference is a better marker of adiposity, in particular of abdominal fatness (Seidell & Visscher, 2000, Janssen et al., 2005).

(ii) Ethnic differences

The interpretation of BMI in epidemiological studies is further complicated by the ethnic variation in body composition (Hu, 2008). For the same BMI, Blacks have a lower adiposity and body fat percentage than Whites, on average, whereas Asians have a higher body fat percentage than Whites (Wagner & Heyward, 2000; Rush et al., 2009; Liu et al., 2011). On the basis of these observations, lower cut-off values have been proposed for overweight (23 kg/m^2 to 27.4 kg/m^2) and obesity (≥ 27.5 kg/m^2) in Asian populations (WHO Expert Consultation, 2004). However, the available data do not allow a clear cut-off value to be established for all Asians, given the heterogeneity in the observed risks related to BMI in different Asian populations (WHO Expert Consultation, 2004).

(b) Waist circumference and hip circumference

There is increasing recognition that body fat distribution contributes to obesity-related disease risk, independently of overall adiposity (Eckel et al., 2005). Distribution of body fat has been used to delineate two body shapes: gynecoid (or pear shape), with fat accumulation in the lower part of the body, such as the hips and the thighs), and android (or apple shape), with fat accumulation in the upper part of the body, such as in the abdomen. Consistent evidence has linked android obesity with more metabolic alterations than gynecoid obesity (Hu, 2008).

Waist circumference is widely used as an indirect measure of abdominal and central obesity in epidemiological studies. Waist circumference is measured at the natural waist (midway between the lowest rib margin and the iliac crest) at the level of the umbilicus (Hu, 2008). Because a "natural waist" may be difficult to locate for obese subjects, the umbilicus site is preferred, although it may introduce substantial variations in defining the measurement site for very obese patients. Therefore, waist circumference is a less standardized metric than BMI. Correlation of waist circumference with predicted total abdominal fat and abdominal visceral fat using CT scan was 0.87–0.93 and 0.84–0.93, respectively, in men and women, and waist circumference performed as well as DXA (Clasey et al., 1999). However, in non-obese women, DXA appears to be superior to waist circumference (Kamel et al., 1999). Despite the fact that waist circumference has greater accuracy than BMI for measuring abdominal fat, it still does not differentiate the subcutaneous fat from the visceral fat.

Hip circumference is typically measured at the maximal circumference over the buttocks (Hu, 2008). Hip circumference is more difficult to interpret than waist circumference, because it can reflect more accumulation of subcutaneous fat, greater gluteal muscle mass, or larger bone structure (pelvic width) (Willett, 1998).

Waist-to-hip ratio is used as an indirect measure of abdominal and central obesity, but there is some evidence that waist circumference may be superior to waist-to-hip ratio as a surrogate marker of central obesity, in particular among elderly people, for whom waist-to-hip ratio may be an indicator of visceral obesity combined with muscle loss (Clasey et al., 1999; Snijder et al., 2006).

Waist circumference-to-height ratio has been used as an alternative to waist-to-hip ratio as a measure of central obesity, but it does not seem to be a better predictor of total mortality than waist circumference or waist-to-hip ratio (Hu, 2008).

Other more complex measures, such as sagittal abdominal diameter (i.e. the horizontal distance between the anterior and the posterior of the abdomen), waist-to-thigh ratio, or conicity index (waist circumference (m)/{0.109 × square root of weight (kg)/height (m)}) have been proposed; however, the difference with other measures is small (IARC, 2002).

Waist circumference has been recommended as a measure of central obesity over waist-to-hip ratio (NHLBI Obesity Education Initiative,

Table 1.3 Recommendations of body mass index and waist circumference cut-off values made for overweight or obesity

Category	Body mass index (kg/m²)	Obesity class	Waist circumference (cm)
Overweight	25.0–29.9		
Obesity	30.0–34.9	Class I	Men: > 102
	35.0–39.9	Class II	Women: > 88
	≥ 40.0	Class III	

Adapted from WHO (2000).

2000). Recommended cut-off values for waist circumference were 102 cm for men and 88 cm for women (Table 1.3), and for waist-to-hip ratio were 0.95 for men and 0.88 for women (Hu, 2008). However, as for BMI, these cut-off values are arbitrary, given that metabolic risk appears to increase linearly. In addition, the association of central obesity with chronic disease varies across different ages, sexes, and ethnicities. Recently, the International Diabetes Federation proposed a new definition of metabolic syndrome diagnosis that includes central obesity measured by waist circumference (Zimmet et al., 2005; IDF, 2006). Table 1.4 presents the recommended waist circumference cut-off values for Caucasian and Asian populations.

In large cohort studies, waist circumference and hip circumference are self-reported. Although obese participants tend to underestimate waist circumference, validation studies have shown high correlations between self-reported and technician-measured waist circumferences (r = 0.95 for men and 0.89 for women), whereas for waist-to-hip ratio the correlation was slightly lower (r = 0.69 for men and 0.70 for women) (Hu, 2008). [It is important to note that the validation studies on self-reported height, weight, waist circumference, and hip circumference have been done in educated populations in the USA and that, depending on the cultural and social context, self-reported anthropometric measures may have less validity.]

1.4.3 Other measures of adiposity or body composition

(a) Skinfold thickness

Skinfold thickness measurements are used as an indirect assessment of body fat distribution using a special caliper (skinfold caliper) to measure the thickness of a double layer of skin and the fat beneath it at predetermined sites, such as the triceps, the biceps, the subscapular region, the abdomen, and the thigh. The measurements are repeated most commonly at four body sites that are high in fat mass (usually the chest, arm, abdomen, and thigh), and in some cases at seven body sites. Skinfold measurement requires great expertise, is prone to inter-observer variations, and is less reproducible than other anthropometric methods. Skinfold thickness measurements and the use of standardized equations have been validated as a good measure of body fat percentage in adults and in children, but this is highly dependent on the validity of the prediction equation, which is population-specific (Hu, 2008; Horan et al., 2015). However, because skinfold thickness measurements are measures of subcutaneous fat, they are unable to quantify intra-abdominal or visceral fat (Steinberger et al., 2005).

(b) Bioelectrical impedance (BIA)

BIA estimates body composition by measuring the impedance or resistance to a small electrical current (typically 800 μA; 50 kHz) passing across the body tissues. A simple version is foot-to-foot BIA assessment, where an individual steps onto scales with electrode foot plates; this is particularly advantageous for children. The BIA method is based on the principle that resistance to an applied alternating electrical current is a function of tissue composition; because fat is a non-conductor of electricity, the greater the lean mass or water content of a person, the faster the current will pass through, and the greater the fatty tissue content, the greater the resistance to

Table 1.4 International Diabetes Federation criteria for waist circumference cut-off by ethnicity

Ethnicity	Sex	Waist circumference (cm)
Caucasian	Men	≥ 94
	Women	≥ 80
Asian (including South Asian, Chinese, and Japanese)	Men	≥ 90
	Women	≥ 80

Adapted from IDF (2006) with permission.

the current (Hu, 2008). BIA measures total body water content and enables the calculation of lean mass and fat mass (Kyle et al., 2004). Numerous prediction equations have been used to determine fat-free mass and body fat percentage. Models typically involved height, age, sex, race, weight, and other anthropometric measures. As with other prediction equations for body fat, those for BIA tend to be population-specific. [The limitations of this method include the hydration levels of the individual, the composition of the latest meal, whether a workout took place before the measurement, and the time of the day when the measurement took place.]

Comparison of estimates of body fat percentage has shown a good correlation between BIA and DXA in subjects within a normal range of body fat (r = 0.88 for the whole population; 0.78 for men and 0.85 for women). However, BIA tended to overestimate body fat percentage in lean subjects and to underestimate it in overweight and obese subjects (by 3–4%) (Sun et al., 2005).

Because BIA equipment is portable, it can be used in large surveys or epidemiological studies (Kyle et al., 2003).

(c) Ultrasound

Ultrasound, or ultrasonography, involves exposure of the body to high-frequency sound waves which reflect off the structures and tissues of the body and are detected by transducers. This method is non-invasive, portable, and quick, and ultrasound is a readily available technique in the clinical setting. It can also distinguish between visceral and subcutaneous fat (Wagner, 2013). However, interpretation of ultrasound images requires technical skill and practice. Ultrasound measures subcutaneous and pre-peritoneal fat, which give a good approximation of visceral fat in adults. Among children, results are conflicting (Horan et al., 2015).

(d) Dual-energy X-ray absorptiometry (DXA)

DXA involves the use of X-ray beams with different photon energies to determine body composition. High-density material (i.e. bone) attenuates the X-ray beam the most, whereas lower-density material allows more photons to pass through. DXA enables the determination of three components of the whole body (fat-free mass, fat mass, and bone mineral density) as well as of specific regions, such as the arms, legs, and trunk (Hu, 2008). The procedure is relatively simple, and the measurements are highly reproducible and accurate for lean mass and fat mass. DXA has the inconvenience of involving ionizing radiation, but the exposure is very low.

DXA measures of body composition have shown high reproducibility over several months (Cordero-MacIntyre et al., 2002) and high validity (Lohman & Chen, 2005). DXA estimates of trunk and abdominal fat mass were strongly correlated with CT scan estimates of total abdominal fat (correlations, 0.94–0.97) and abdominal visceral fat (correlations, 0.86–0.90) (Clasey et al., 1999; Glickman et al., 2004).

Although the DXA instrument is expensive and immobile, it has been used in several epidemiological studies either as a references method or in an association study with metabolic disorders or chronic outcomes. DXA has been used as a reference method to determine the body fat percentage corresponding to BMI cut-off values stratified by age, sex, and race/ethnicity

in a large sample from the United States population (n = 12 906) (Heo et al., 2012). The oldest age group had the highest cut-off values of body fat percentage. Non-Hispanic Blacks had lower cut-off values, whereas Mexicans had the highest. Cut-off values of body fat percentage were higher in women than in men.

DXA is becoming a frequent measure of human body composition in small clinical and epidemiological studies to obtain a reliable estimate of total body fat mass and fat distribution, alone or together with ultrasound.

(e) Computed tomography (CT) and magnetic resonance imaging (MRI)

CT and MRI are considered to be the most accurate methods for assessing body composition and ascertaining fat distribution at the levels of tissues and organs. Both CT and MRI provide high-resolution cross-sectional scans of selected tissues or organs and can be used to measure the volume and distribution of subcutaneous versus visceral fat, muscle mass, and organ composition. Unlike CT, MRI does not expose subjects to ionizing radiation and can be used in children and pregnant women (Hu, 2008). The measurements are highly reproducible and accurate (Ross & Janssen, 2005). These methods are expensive and not readily accessible and are used mostly for calibrating or validating simpler and less expensive methods for measuring body fat distribution. CT and MRI have been used in small clinical and epidemiological studies to measure total adipose tissue, subcutaneous adipose tissue, visceral adipose tissue, and hepatic and intramuscular triglyceride content. Significant correlations have been found between visceral adipose tissue (but not subcutaneous adipose tissue), insulin resistance, and metabolic syndrome (Lebovitz & Banerji, 2005).

Recent epidemiological studies have implemented CT or MRI measurements on large subsamples to investigate biomarkers of fat distribution (Shah et al., 2016) or to validate simpler anthropometric indices (Neamat-Allah et al., 2014). Measured BMI, waist circumference, and hip circumference correlated well with MRI measures of total body volume, total adipose tissue, and subcutaneous adipose tissue in a cohort of German men (n = 598) and women (n = 594) aged 51–81 years (see Table 1.5).

1.4.4 Change in weight

Change in weight is also of interest when considering the association between weight and risk of cancer, and change in weight has been widely used in epidemiological studies as both exposure and outcome. Several definitions have been used across studies, such as the highest attained weight or current weight, weight gain, weight loss, weight cycling (repeated loss and regain of body weight over time), or body weight variability. Body weight gain during the period from young adulthood (18–20 years) to middle age (30–55 years) is of great interest.

Change in weight may rely on recall of previous weights by participants. The Nurses' Health Study found a high correlation between recalled weight at age 18 years and measured weight from medical records, and this finding has been confirmed in additional studies (Troy et al., 1995). When considering weight loss, it is important to distinguish between intentional and unintentional weight loss, because unintentional weight loss is associated with increased morbidity and mortality (Wannamethee et al., 2005).

When epidemiological evidence is evaluated for a relationship between weight change and risk of cancer, the timing of weight change measurements must be considered, because evaluation of weight change at certain life stages may not be adequate to fully address potential associations.

Analysis to relate weight change to cancer risk should control for baseline BMI. As demonstrated in cardiovascular disease, to assess the contribution of waist circumference and

Table 1.5 Prediction of body compartments by anthropometric indices in multiple linear regression analysis (partial correlation coefficient adjusted for age and height) in a cohort of German men (*n* = 598) and women (*n* = 594) aged 51–81 years

Anthropometric variable	Total body volume	Total adipose tissue	Subcutaneous adipose tissue	Visceral adipose tissue
Men				
BMI (kg/m²)	0.72	0.25	0.21	0.15
Waist circumference (cm)	0.32	0.48	0.32	0.44
Hip circumference (m)	0.28	0.27	0.39	−0.13
Women				
BMI (kg/m²)	0.80	0.49	0.46	0.22
Waist circumference (cm)	0.14	0.20	0.0	0.42
Hip circumference (m)	0.34	0.45	0.52	−0.13

BMI, body mass index.
Adapted from Neamat-Allah et al. (2014).

waist-to-hip ratio separately from BMI, it is helpful to present results in strata of baseline BMI (Wormser et al., 2011). In particular, the initial value of BMI before the weight gain should be included in the model to directly assess the independent effect of the subsequent weight gain on risk; then, the subsequent weight change is predominantly change in adiposity. At present, analysis and reporting of weight gain is inconsistent in the cancer epidemiology literature.

1.4.5 Assessment of paediatric adiposity

The main anthropometric indicators of adiposity in children are BMI and waist circumference, which provide sufficient information to enable classification of overweight or obesity when growth centile charts and ratios are used (Horan et al., 2015). There is little evidence that alternative measures, including skinfold thickness and foot-to-foot BIA assessment, provide better estimates than BMI when measurements of weight and height are taken accurately and compared with appropriate growth charts and/or cut-off values. Indirect proxy reporting, such as parental reports, should only be used with caution (Himes, 2009; Van Cauwenberghe et al., 2014). In adolescents, self-reported height and weight have been shown to underestimate the prevalence of overweight, with a 25–50% underdiagnosis of overweight (Sherry et al., 2007).

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2. CANCER-PREVENTIVE EFFECTS IN HUMANS

2.1 Methodological considerations

Randomized trials addressing body fatness and risk of cancer are rare and are often not feasible. Hence, observational epidemiological studies on various weight parameters are relied on to provide evidence. Body fatness can be a reflection of genetic, metabolic, lifestyle, dietary, environmental, and psychosocial factors. Therefore, it is important that epidemiological studies are designed appropriately to control for the many potential confounders. This section reviews some of the methodological issues in epidemiological studies that must be carefully considered when evaluating the body of evidence on the association between body fatness and risk of cancer.

2.1.1 Bias

(a) Recall bias

Retrospective studies addressing body fatness and risk of cancer may rely on participants' recollections of their past weight or other measures. If there is differential recall between cases and controls, or between overweight people and lean people, this is considered recall bias. This imbalance can have an impact on estimates of effect, particularly in case–control studies.

(b) Selection bias

Non-randomized studies are at risk of selection bias, because subjects are not allocated to groups at random, and instead are generally selected based on their disease or exposure status. Therefore, if cases and controls, or exposed and unexposed individuals, are selected systematically in a different way, estimation of the association between exposure and risk can be affected, depending on the study design.

For example, in case–control studies, those who agree to participate as controls may be more likely to have a history of being at a healthy weight, and may be more likely to engage in other healthy behaviours, than those who do not agree to participate. They may not be representative of the larger population from which they are selected, and this can result in an overestimation or underestimation of the association between body fatness and risk of cancer.

(c) Detection bias

Detection bias refers to systematic differences between groups in the detection of outcomes of interest. Studies of cancers that can be detected by screening are at higher risk of this bias, affecting their estimate of effect. Individuals who are likely to engage in healthy behaviours, such as behaviours that lead to maintaining a healthy weight, may also be more likely to seek the recommended screening tests. They may

therefore be more likely to receive early diagnosis and to have access to early treatment, which can affect their prognosis. If the outcome of interest is mortality, individuals who receive early diagnosis may be less likely to die from the disease, because of earlier treatment. If these individuals are also more likely to have a lower weight, this could result in an overestimation of the impact of these behaviours.

Similarly, individuals who are less likely to engage in healthy behaviours, and may be less likely to be at a healthy weight, may also be less likely to participate in screening and therefore will be less likely to receive early diagnosis and to have access to early treatment. The estimated effect of body fatness on the poorer outcomes in such individuals can be affected by their behaviour. This type of bias is of less concern for cancers that are more likely to be fatal, because early detection or screening may not have as large an effect if the outcome of interest is death.

2.1.2 Confounding

Confounding is the result of an association between exposures, resulting in the conclusion that the effect on the risk of disease is due to one variable rather than another. Although the exposure and the risk of disease are linked, this is due to their joint relationship with the confounding variable, rather than due to a direct relationship.

Potential confounders can be addressed either in the design of studies or in the analysis of the data. In case–control studies, suspected confounders can be controlled for by matching on those variables. Similarly, in cohort studies, unexposed and exposed groups can be selected to be as similar as possible with respect to the potential confounders. In the analysis of the data, stratification or statistical adjustment can be used to control for potential confounders.

Individuals who maintain a healthy weight may be more likely to engage in other healthy behaviours, so these associations should be explored as potential confounders when investigating the association of body fatness with risk of cancer. In high-income countries, people with lower socioeconomic status are more likely to be overweight or obese. Race and other factors may also be related to body fatness and to risk of cancer, and when the results of epidemiological studies are evaluated, it is important to consider whether such confounders have been adjusted for appropriately.

Tobacco use is strongly associated with a higher risk of many cancers. However, smoking is more common among lean individuals than among overweight or obese individuals; one mechanism that could explain this association is that smoking can have an anorectic effect. Smoking must therefore be properly adjusted for to ensure that it is not confounding the relationship between body fatness and risk of cancer. Current smoking modifies weight gain trajectory; therefore, among former smokers, time since quitting must be considered when stratifying by smoking status.

2.1.3 Reverse causation

Reverse causation occurs when the exposure is affected by the outcome, whereas it is usually assumed that the outcome is affected by the exposure. The direction of causality must be considered when evaluating associations between body fatness and risk of cancer. Weight may affect risk of cancer, but preclinical cancer can also cause weight loss. Additional chronic diseases that may affect risk of cancer may also result in weight loss. The timing of measurement must also be considered, because closer to the time of diagnosis, body fatness is more likely to be affected by disease.

2.1.4 Mendelian randomization

In the absence of large-scale and long-term randomized controlled trials (RCTs) on body fatness and risk of cancer, the concept of Mendelian randomization can provide insights into whether observed associations are causal, by leveraging the properties of genetic variation to overcome limitations present in observational epidemiological studies. Mendelian randomization exploits the random allocation of alleles between parents and offspring at conception as the basis of natural experiment to strengthen causal inference within the association between a modifiable exposure and an outcome of interest (Smith & Ebrahim, 2003, 2004; Lawlor et al., 2008).

The method relies on three main assumptions: the genetic variant (i) is a valid instrument, in that it is reliably associated with the exposure of interest, (ii) is not independently associated with the outcome, except through the exposure (known as the exclusion restriction criterion), and (iii) is not associated with any of the confounding factors that would otherwise distort the observational association between the exposure and the outcome. There are several general limitations to this methodology (for reviews, see Smith & Ebrahim, 2003, 2004). Importantly, effects of common genetic variants on the exposure are small and prone to weak instrumentation if used alone, which can bias estimates (Smith & Ebrahim, 2003, 2004). Therefore, using a greater number of variants included within Mendelian randomization analyses increases the variance explained in a given trait and can thus improve the precision of the causal estimate (Locke et al., 2015).

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2.2 Cancer-preventive effects by organ site

2.2.1 Cancer of the colorectum

Colorectal cancer (CRC) accounts for about 10% of all cancer diagnoses and 8.5% of all cancer deaths worldwide (Ferlay et al., 2013). CRC is more common in high-income countries than in low- and middle-income countries and is more prevalent in men than in women. It is well established that the risk of CRC changes within one generation after migration from low-incidence areas to high-incidence areas and thus has a strong environmental component. Cancers of the colon and of the rectum, although similar in many ways, have important differences in their risk factor profiles. Cancers of the rectum seem to be less associated with dietary factors and more associated with consumption of alcohol (particularly beer). Cancers of the colon arise most often from colorectal adenomas, and cancers in the proximal colon tend to have a worse prognosis than cancers in the distal colon.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for cancer of the colon. The 2007 World Cancer Research Fund (WCRF) review concluded that there was convincing evidence that both body fatness and waist circumference were associated with increased risk of CRC (WCRF/AICR, 2007). The 2007 conclusions were reaffirmed in 2011 (WCRF/AICR, 2011). Results from studies published since 2001 are summarized here and in Table 2.2.1a, Table 2.2.1b, and Table 2.2.1c.

(a) Cohort studies

A total of 39 cohort studies have been published since 2001 (excluding analyses that were later updated and analyses based on fewer than 100 incident cases). Table 2.2.1a summarizes their results for body mass index (BMI) at baseline, with comments on findings according to other measures of body fatness, such as weight change over the life-course and waist circumference.

(i) Body mass index

Although findings vary across studies, there is a general observation of a positive association between BMI and colon cancer risk across most studies, and a much weaker (but still positive) association between BMI and rectal cancer risk. In the studies that included both colon cancer and rectal cancer, the association with BMI for colon cancer was almost always either stronger or of the same magnitude as that for rectal cancer. For both colon cancer and rectal cancer, the association with BMI is stronger in men than in women. The association between BMI and colon cancer is approximately linear with increasing BMI levels. In a meta-analysis of prospective studies (Table 2.2.1c), the relative risk per 5 kg/m^2 increase in BMI was estimated to be 1.24 in men and 1.09 in women for colon cancer, and 1.09 in men and 1.02 in women for rectal cancer (all $P < 0.05$, except for rectal cancer in women, with $P = 0.26$) (Renehan et al., 2008). Another meta-analysis reported a relative risk of CRC for obesity relative to normal weight of 1.53 (95% confidence interval [CI], 1.44–1.62) in men and 1.25 (95% CI, 1.14–1.37) in women, and an overall increase in CRC risk of 18% (95% CI, 14–21%) per 5 kg/m^2 increase in BMI (Ning et al., 2010). The most recent meta-analysis of CRC, by Ma et al. (2013), based on 43 cohorts, estimated the relative risk for obesity relative to normal weight to be 1.33 (95% CI, 1.25–1.42).

In women, an interaction between use of hormone replacement therapy (HRT) and the BMI–CRC association has not been found consistently in the identified cohort studies that have investigated this (Lin et al., 2004; Adams et al., 2007; Wang et al., 2007; Aleksandrova et al., 2013; Kabat et al., 2015). There is not a consistent

set of evidence pointing to a differential of the BMI association for proximal versus distal colon subsites (Lin et al., 2004; Larsson et al., 2006; Bassett et al., 2010; Laake et al., 2010; Oxentenko et al., 2010; Hughes et al., 2011; Matsuo et al., 2012; Kitahara et al., 2013). BMI is also associated with risk of colorectal adenomas (Keum et al., 2015). The BMI–CRC association is observed consistently in diverse parts of the world (Renehan et al., 2008; Ma et al., 2013).

Several investigators have assessed the association between BMI at different ages or weight gain over the life-course and later colon cancer risk and/or rectal cancer risk. BMI at earlier ages seems to also be related to colon cancer risk (see Section 2.3), but BMI closer to the time of diagnosis is more consistently and strongly associated with risk than is BMI earlier in life (Bassett et al., 2010; Hughes et al., 2011). Weight gain since age 18 years has been found to be associated with colon cancer risk in several studies (Thygesen et al., 2008; Bassett et al., 2010; Renehan et al., 2012), but it is difficult to separate the effects of long-term weight gain from those of the resultant excess adiposity.

(ii) Waist circumference

Several cohorts have included measurements of waist circumference. Waist circumference at baseline is about as strongly associated with risk as is BMI in those studies that used identical quantile cut-off points for both measures (Table 2.2.1a). The meta-analysis of CRC and waist circumference by Ma et al. (2013), based on 13 prospective cohort studies, estimated the relative risk for the highest versus lowest categories of waist circumference across studies to be 1.46 (95% CI, 1.33–1.60), and no heterogeneity among studies was found ($P = 0.323$).

(b) Case–control studies

Since 2002, a total of 11 case–control studies, in Australia, Canada, China, Europe, the Republic of Korea, Thailand, and the USA, have reported on the association of BMI with CRC risk (Table 2.2.1b). In most of the studies, BMI was calculated from body height and self-reported body weight for a recent period before cancer diagnosis; in some of the studies, body weight was measured after diagnosis. Most studies showed an increase in risk of cancers of both the colon and the rectum with increasing BMI, and in some studies the association of BMI with risk was stronger for colon cancer than for rectal cancer. Some, but not all, studies showed more pronounced BMI-associated increases in risk in men than in women, although globally the evidence indicated increases in risk in both sexes. A meta-analysis of 12 case–control studies (Ning et al., 2010) found a relative risk of 1.23 for colon and rectal cancers combined, per 5 kg/m^2 increase in BMI.

The frequent observation of stronger associations of BMI with colon cancer risk in men than in women has led to the hypothesis that high blood levels of estrogens might confer protection against colon cancer. To address this issue, a few studies provided results in women stratified by estrogen status (determined by menopausal status and use of HRT). In a study in Germany in postmenopausal women only, a stratified analysis by users and non-users of postmenopausal HRT showed a strong association between BMI and CRC risk in the non-users only (odds ratio [OR], 3.30; 95% CI, 1.25–8.72 for BMI ≥ 30 kg/m^2 compared with BMI < 23 kg/m^2, based on 31 cases in the highest BMI category) and no association in the ever-users (OR, 0.89; 95% CI, 0.29–2.75) (Hoffmeister et al., 2007). These findings were opposite to those from a previous large study in the USA, which showed an increase in colon cancer risk only in estrogen-positive women (i.e. women who were premenopausal or who were users of postmenopausal HRT; OR, 2.38; 95% CI, 1.50–3.77 for BMI > 30 kg/m^2 compared with BMI < 23 kg/m^2, based on 77 cases in the highest BMI category) compared with no association in estrogen-negative women (i.e. women

who were postmenopausal and were non-users of HRT; OR, 1.02; 95% CI, 0.71–1.46 for BMI > 30 kg/m^2 compared with BMI < 23 kg/m^2, based on 134 cases in the highest BMI category) (Slattery et al., 2003). Another study, conducted in Shanghai, China, in a relatively lean population, showed a direct association of BMI with colon cancer risk in premenopausal women (OR, 2.9; 95% CI, 1.7–8.6 for BMI > 23.6 kg/m^2 compared with BMI < 19.0 kg/m^2, based on 62 cases in the highest BMI category) and an inverse association in postmenopausal women (OR, 0.6; 95% CI, 0.3–0.9 for BMI > 23.6 kg/m^2 compared with BMI < 19.0 kg/m^2, based on 50 cases in the highest BMI category) (Hou et al., 2006). A fourth study, in Canada, found an absence of association both in "estrogen-positive" women and in "estrogen-negative" women (Campbell et al., 2007).

With regard to molecular tumour subtypes, Campbell et al. (2010) showed a BMI-associated increase in risk for tumours that have a microsatellite-stable phenotype (recent BMI, OR per 5 kg/m^2 increase, 1.38; 95% CI, 1.24–1.54), whereas no association was observed for tumours characterized by microsatellite instability (OR, 1.05; 95% CI, 0.84–1.31) (see Section 4.2.3c).

(c) Mendelian randomization studies

Two recent studies have applied Mendelian randomization to assess the association between BMI and CRC risk (Table 2.2.1d). In the first study, Thrift et al. (2015) used a genetic risk score (GRS) derived from 77 single nucleotide polymorphisms (SNPs) associated with higher BMI, identified by the Genetic Investigation of Anthropometric Traits (GIANT) consortium, which involved more than 300 000 individuals of European descent. In their analysis, higher BMI was associated with an increased risk of CRC (GRS-related OR per 5 kg/m^2 increase in BMI, 1.50; 95% CI, 1.13–2.01). The point estimate obtained using the Mendelian randomization approach was greater in magnitude than the point estimate obtained from conventional covariate-adjusted analysis (minimally adjusted OR per 5 kg/m^2 increase in BMI, 1.18; 95% CI, 1.15–1.22); however, the 95% confidence intervals overlapped and they were not statistically significantly different from one another ($P_{difference}$ = 0.10). In addition, there was a positive association between BMI and CRC risk in women (GRS-related OR per 5 kg/m^2 increase in BMI, 1.82; 95% CI, 1.26–2.61), and this estimate was much greater than that obtained from conventional observational analyses (OR, 1.14; 95% CI, 1.10–1.18; $P_{difference}$ = 0.01); although there was no strong evidence from Mendelian randomization analyses for an association in men (GRS-related OR per 5 kg/m^2 increase in BMI, 1.18 (95% CI, 0.73–1.92), the results were in the same direction as in the observational results in the same sample ($P_{difference}$ = 0.70). [This discrepancy between the sexes may be due to sex-specific residual confounding or measurement error in observational analyses. Alternatively, the distribution of body fat, rather than total body fatness (reflected by BMI), may be a more important predictor of CRC risk for men than for women.]

In the second study, Gao et al. used 15 SNPs reliably associated with childhood BMI (Felix et al., 2016) and 77 SNPs reliably associated with adult BMI (Locke et al., 2015) as Mendelian randomization instruments and assessed their association with CRC risk (Gao et al., 2016). Mendelian randomization analyses showed an 8% increase in risk of CRC with each increase of 1 kg/m^2 in adult BMI [assuming that a standard deviation was equivalent to 4.5 kg/m^2]. There was no evidence of an association with childhood BMI.

Table 2.2.1a Cohort studies of measures of body fatness and cancer of the colorectum

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Terry et al. (2001) Women in Swedish mammography programme (ages 40–76 yr) Sweden 1987–1998	61 463 Women Incidence	Colon	BMI < 22 22–24.2 24.2–26.7 > 26.7 [P_{trend}]	291 total	 1.0 1.05 (0.72–1.51) 1.09 (0.77–1.56) 1.21 (0.86–1.70) [0.25]	Age, education level, alcohol consumption, diet	Stronger risk within the women in age group 40–54 yr (P_{trend} = 0.06)
	61 463 Women Incidence	Rectum	BMI < 22 22–24.2 24.2–26.7 > 26.7 [P_{trend}]	159 total	 1.0 0.92 (0.56–1.54) 1.14 (0.71–1.83) 1.32 (0.83–2.08) [0.13]	Age, education level, alcohol consumption, diet	
Terry et al. (2002) Women in Canadian mammography programme (ages 40–59 yr) Canada 1980–1993	89 835 Women Incidence	Colon and rectum	BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	527 total	 1.0 1.03 (0.84–1.26) 1.08 (0.82–1.41) [0.57]	Age, smoking, education level, physical activity, OC use, HRT use, parity	Association stronger in premenopausal ages than postmenopausal ages ($P_{interaction}$ = 0.01)
Calle et al. (2003) Population-based cohort USA 1982–1998	404 576 Men Mortality	Colon and rectum	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 1292 1811 337 54	 1.00 1.20 (1.12–1.30) 1.47 (1.30–1.66) 1.84 (1.39–2.41) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat intake, vegetable intake	
	495 477 Women Mortality		BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 1706 906 312 67 21	 1.00 1.10 (1.01–1.19) 1.33 (1.17–1.51) 1.36 (1.06–1.74) 1.46 (0.94–2.24) [< 0.001]	Additionally adjusted for HRT use	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lin et al. (2004) Women's Health Study USA 1993–2002	39 876 Women Incidence	Colon and rectum	BMI < 23 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 44 45 31 40 42	 1.0 1.45 (0.96–2.20) 1.28 (0.81–2.04) 1.72 (1.12–2.66) 1.67 (1.08–2.59) [0.018]	Age, study group, family history, history polyps, physical activity, smoking, aspirin use, consumption of red meat, alcohol consumption, HRT use	Stronger association with proximal colon. Similar findings by HRT status in never-users of HRT. Proximal and distal subsites similar
MacInnis et al. (2004) Population-based cohort Australia 1990–2003	16 556 Men Incidence	Colon	BMI < 24.8 24.8–26.9 27–29.2 ≥ 29.2 [P_{trend}]	 26 37 39 51	 1.0 1.3 (0.8–2.2) 1.4 (0.8–2.3) 1.7 (1.1–2.8) [0.02]	Age, education level, country of birth	
	16 556 Men Incidence		WC < 87 87–93 93–99.3 ≥ 99.3 [P_{trend}]	 22 19 48 64	 1.0 10.8 (0.4–1.4) 1.7 (1.0–2.8) 2.1 (1.3–3.5) [< 0.001]	Age, education level, country of birth	
Moore et al. (2004) Framingham Study cohort USA 1948–1999	3764 Men and women aged 30–54 yr at baseline Incidence	Colon	BMI 18.5–24.9 25–29.9 ≥ 30	 67 69 21	 1.0 1.3 (0.91–1.8) 1.5 (0.92–2.5)	Age, sex, education level, height, alcohol consumption, smoking, physical activity	
			WC Small Medium Large Extra large	 17 61 46 33	 1.0 1.1 (0.66–2.0) 1.6 (0.91–2.9) 2.0 (1.1–3.7)	Age, sex, education level, height, alcohol consumption, smoking, physical activity	Additional adjustment for BMI has no effect on estimates

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Moore et al. (2004) (cont.)	3802 Men and women aged 55–79 yr at baseline Incidence	Colon	BMI 18.5–24.9 25–29.9 ≥ 30	 39 79 31	 1.0 1.8 (1.2–2.6) 2.4 (1.5–3.9)	Age, sex, education level, height, alcohol consumption, smoking, physical activity	Associations more evident in men than in women, and stronger in the proximal site
			WC Small Medium Large Extra large	 11 53 47 38	 1.0 1.4 (0.74–2.7) 2.1 (1.1–4.0) 2.6 (1.3–5.2)	Age, sex, education level, height, alcohol consumption, smoking, physical activity	Adjustment for BMI has no effect on estimates
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Colon	Obesity Non-obese Obese Non-obese Obese	 White men: 16 704 1420 Black men: 3830 262	 1.00 1.47 (1.39–1.55) 1.00 1.45 (1.28–1.64)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0 No significant differences in risk observed between White and Black veterans
	4 500 700 Men Incidence	Rectum	Obesity Non-obese Obese Non-obese Obese	 White men: 9849 719 Black men: 1773 93	 1.00 1.23 (1.14–1.33) 1.00 1.11 (0.90–1.37)	Age, calendar year	No significant differences in risk observed between White and Black veterans
Wei et al. (2004) Nurses' Health Study USA 1976–2000	46 632 Men Incidence	Colon	BMI < 23 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 57 119 225 51	 1.0 1.33 (0.97–1.83) 1.54 (1.15–2.07) 1.85 (1.26–2.72) [0.001]	Age, family history, physical activity, smoking, diet, screening history. alcohol consumption, height	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wei et al. (2004) (cont.)	87 733 Women Incidence		BMI < 23 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 210 141 207 113 	 1.0 1.10 (0.88–1.36) 1.11 (0.91–1.35) 1.28 (1.10–1.62) [0.05]		
	46 632 Men Incidence	Rectum	BMI < 23 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 24 42 55 11 	 1.0 1.16 (0.70–1.94) 0.93 (0.57–1.53) 1.03 (0.49–2.14) [0.70]	Age, family history, physical activity, smoking, diet, screening history, alcohol consumption, height	
	87 733 Women Incidence		BMI < 23 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 56 46 68 34 	 1.0 1.37 (0.92–2.02) 1.40 (0.98–2.01) 1.56 (1.01–2.42) [0.04]		
Engeland et al. (2005) Population-based cohort Norway 1963–2001	963 709 Men Incidence	Colon and rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 90 11 432 9953 1512 	 0.84 (0.68–1.03) 1.0 1.15 (1.12–1.18) 1.40 (1.32–1.48) [< 0.001]	Age at BMI measurement, birth cohort	Relationships similar for colon vs rectum
	1 038 010 Women Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 298 11 136 8780 3916 	 1.04 (0.93–1.17) 1.0 1.02 (0.99–1.05) 1.06 (1.02–1.10) [0.01]	Age at BMI measurement, birth cohort	Relationships similar for colon vs rectum. In women, associations stronger for colon
Kuriyama et al. (2005) Population-based prospective cohort Japan 1984–1992	12 485 Men Incidence	Colon and rectum	BMI < 18.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 114 25 11 5 	 1.00 1.04 (0.67–1.60) 1.58 (0.85–2.94) 1.78 (0.73–4.38) [0.3710]	Age, smoking, alcohol consumption, diet, health insurance	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kuriyama et al. (2005) (cont.)	15 052 Women Incidence		BMI < 18.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 73 22 11 9	 1.00 1.11 (0.69–1.80) 1.28 (0.68–2.43) 2.06 (1.03–4.13) [0.06]		
Oh et al. (2005) Civil servants and private school workers cohort Republic of Korea 1992–2001	781 283 Men Incidence	Colon (excluding rectosigmoid)	BMI < 18.5 18.5–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 [P_{trend}]	 14 359 316 190 63 11	 1.00 (0.62–1.63) 1.00 1.24 (1.07–1.43) 1.33 (1.13–1.57) 1.07 (0.83–1.38) 1.92 (1.15–3.22) [0.001]	Age, smoking, alcohol consumption, physical activity, family history, residence area	
	781 283 Men Incidence	Rectosigmoid	BMI < 18.5 18.5–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 [P_{trend}]	 20 606 480 326 117 14	 0.64 (0.36–1.13) 1.00 1.06 (0.92–1.22) 1.29 (1.10–1.52) 1.15 (0.91–1.46) 1.08 (0.56–2.10) [0.003]	Age, smoking, alcohol consumption, physical activity, family history, residence area	
Rapp et al. (2005) VHM&PP (population-based cohort) Austria 1985–2002	67 447 Men Incidence	Colon	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 86 128 39 7	 1.00 1.14 (0.86–1.50) 1.56 (1.06–2.30) 2.48 (1.15–5.39) [0.005]	Age, smoking status, occupational group	
	78 484 Women Incidence		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 122 106 35 8	 1.00 1.13 (0.86–1.47) 1.11 (0.76–1.62) 0.88 (0.43–1.81) [0.73]	Age, smoking status, occupational group	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Rapp et al. (2005) (cont.)	67 447 Men Incidence	Rectum	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 45 69 24 – 	 1.00 1.20 (0.82–1.75) 1.66 (1.01–2.73) – [0.05]	Age, smoking status, occupational group	All obese categories were merged (from BMI 30 kg/m^2 onwards) to ensure at least 5 cases
	78 484 Women Incidence		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 68 48 12 5 	 1.00 0.90 (0.62–1.31) 0.66 (0.36–1.23) 0.96 (0.38–2.39) [0.32]	Age, smoking status, occupational group	
Bowers et al. (2006) ATBC cohort Finland 1985–2002	29 133 Men Incidence	Colon	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 2 77 98 50	 1.47 (0.36–5.98) 1.00 1.07 (0.79–1.44) 1.78 (1.25–2.55)	Age, number of cigarettes smoked per day, total cholesterol, height, type 2 diabetes	Cohort of smokers
	29 133 Men Incidence	Rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 1 61 87 34	 0.96 (0.13–6.96) 1.0 1.18 (0.85–1.64) 1.51 (0.99–2.29)		
	29 133 Men Incidence	Colon and rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 3 138 185 84	 1.25 (0.40–3.93) 1.0 1.12 (0.90–1.39) 1.66 (1.27–2.18)		
Larsson et al. (2006) Population-based cohort Sweden 1997–2005	45 906 Men Incidence	Colon	BMI < 23 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 47 72 65 61 39 	 1.00 1.11 (0.77–1.61) 1.07 (0.73–1.56) 1.15 (0.78–1.70) 1.60 (1.03–2.48) [0.08]	Age, education level, family history, diabetes, smoking, aspirin use, physical activity	Proximal and distal subsites similar. WC also positively associated

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Larsson et al. (2006) (cont.)	45 906 Men Incidence	Rectum	BMI < 23 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 25 39 49 46 21	 1.00 1.08 (0.65–1.80) 1.35 (0.83–2.19) 1.53 (0.93–2.51) 1.44 (0.79–2.61) [0.06]	Age, education level, family history, diabetes, smoking, aspirin use, physical activity	
	45 906 Men Incidence	Colon and rectum	WC < 88 88–92 93–97 98–103 ≥ 104 [P_{trend}]	 47 67 95 96 102	 1.00 1.06 (0.73–1.55) 1.32 (0.92–1.88) 1.37 (0.96–1.96) 1.29 (0.90–1.85) [0.03]	Age, education level, family history, diabetes, smoking, aspirin use, physical activity	
Lukanova et al. (2006) Population-based cohort Sweden 1985–2003	33 424 Men Incidence	Colon and rectum	BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 45 69 22	 1.0 1.17 (0.80–1.71) 1.61 (0.95–2.65) [0.08]	Age, calendar year, smoking	Association with obesity significant only when excluding cases diagnosed within 1 yr of recruitment
	35 362 Women Incidence		BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 43 39 26	 1.0 1.27 (0.82–1.97) 2.01 (1.22–3.27) [0.005]	Age, calendar year, smoking	
MacInnis et al. (2006a) Melbourne Collaborative Cohort Study Australia 1990–2003	24 072 Women Incidence	Colon	BMI, tertiles T1 (< 25) T2 (25–29) T3 (≥ 30) [P_{trend}]	212 total	 1.0 0.8 (0.6–1.1) 1.0 (0.7–1.4) [0.59]	Age, education level, country of birth, HRT use	No differences between proximal and distal, or by disease stage (early vs late)
			WC, tertiles T1 (< 75) T2 (75–79) T3 (≥ 80) [P_{trend}]	212 total	 1.0 1.4 (1.0–1.9) 1.4 (1.0–1.9) [0.02]	Age, education level, country of birth, HRT use	No differences between proximal and distal, or by disease stage (early vs late)

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
MacInnis et al. (2006b) Population-based cohort Australia 1990–2003	16 867 Men Incidence	Rectum	BMI, tertiles			Age, country of birth, SES, height	Similar results in women (n = 24 247), no sex interaction
			< 25	24	1.0		
			25–29.9	86	1.7 (1.1–2.7)		
			≥ 30	24	1.3 (0.8–2.4)		
			[P_{trend}]		[0.48]		
			WC			Age, country of birth	Similar results in women (n = 24 247), no sex interaction
			< 94	57	1.0		
			94–101.9	43	1.3 (0.9–1.9)		
			≥ 102	34	1.4 (0.9–2.2)		
			[P_{trend}]		[0.11]		
Pischon et al. (2006) EPIC cohort Europe 1992–2003	129 731 Men Incidence	Colon	BMI			Age, centre, smoking, education level, alcohol consumption, physical activity, diet	
			< 23.6	64	1.0		
			23.6–25.3	85	1.18 (0.85–1.63)		
			25.4–27	74	1.00 (0.71–1.41)		
			27.1–29.3	88	1.19 (0.85–1.66)		
			≥ 29.4	110	1.55 (1.12–2.15)		
			[P_{trend}]		[0.006]		
			WC			Age, centre, smoking, education level, alcohol consumption, physical activity, diet, height	
			< 86	63	1.00		
			86–91.8	57	0.73 (0.50–1.04)		
			91.9–96.5	78	0.97 (0.69–1.36)		
			96.6–102.9	95	1.10 (0.79–1.53)		
			≥ 103	125	1.39 (1.01–1.93)		
			[P_{trend}]		[0.001]		

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pischon et al. (2006) (cont.)	238 546 Women Incidence	Colon	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}]	 87 96 120 137 135 123 	 1.0 0.92 (0.68–1.23) 1.02 (0.77–1.35) 1.09 (0.83–1.45) 1.06 (0.79–1.42) [0.40]	Age, centre, smoking, education level, alcohol consumption, physical activity, diet	
			WC < 70.2 70.2–75.8 75.9–80.9 81–88.9 ≥ 89 [P_{trend}]	 62 91 125 135 149 	 1.0 1.10 (0.80–1.52) 1.23 (0.90–1.68) 1.25 (0.91–1.70) 1.48 (1.08–2.03) [0.008]	Age, centre, smoking, education level, alcohol consumption, physical activity, diet, height	
	129 731 Men Incidence	Rectum	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}]	 52 52 58 69 64 	 1.0 0.88 (0.60–1.30) 0.96 (0.66–1.40) 1.11 (0.77–1.62) 1.05 (0.72–1.55) [0.47]	Age, centre, smoking, education level, alcohol consumption, physical activity, diet	WC, null association
	238 546 Women Incidence		BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}]	 47 44 72 63 65 	 1.0 0.78 (0.51–1.18) 1.14 (0.78–1.66) 0.95 (0.64–1.41) 1.06 (0.71–1.58) [0.51]	Age, centre, smoking, education level, alcohol consumption, physical activity, diet	WC, null association
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	Colon	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 763 842 190 	 1.00 1.24 (1.12–1.37) 1.74 (1.48–2.04) [< 0.001]	Age, year, smoking status	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Samanic et al. (2006) (cont.)	362 552 Men Incidence	Rectum	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 626 610 126	 1.00 1.08 (0.96–1.21) 1.36 (1.13–1.66) [< 0.01]	Age, year, smoking status	
Adams et al. (2007) NIH-AARP cohort USA 1995–2000	307 708 Men Incidence	Colon	BMI 18.5–22.9 23–24.9 25–27.4 27.5–29.9 30–32.5 32.5–34.9 35–39.9 ≥ 40 [P_{trend}]	 136 260 479 367 219 110 76 29	 1.0 1.11 (0.90–1.37) 1.22 (1.01–1.48) 1.44 (1.18–1.76) 1.53 (1.23–1.90) 1.57 (1.22–2.03) 1.71 (1.29–2.27) 2.39 (1.59–3.58) [< 0.0005]	Age, alcohol consumption, smoking, supplemental calcium intake, consumption of red meat	
	209 436 Women Incidence		BMI 18.5–22.9 23–24.9 25–27.4 27.5–29.9 30–32.5 32.5–34.9 35–39.9 ≥ 40 [P_{trend}]	 151 141 172 106 77 42 52 28	 1.0 1.20 (0.95–1.51) 1.29 (1.03–1.60) 1.31 (1.01–1.68) 1.28 (0.97–1.69) 1.13 (0.80–1.60) 1.46 (1.06–2.02) 1.49 (0.98–2.25) [0.02]	Additionally adjusted for HRT use	Similar findings by HRT status
	307 708 Men Incidence	Rectum	BMI 18.5–22.9 23–24.9 25–27.4 27.5–29.9 30–32.5 32.5–34.9 ≥ 35 [P_{trend}]	 74 101 218 135 74 42 33	 1.0 0.78 (0.58–1.06) 1.01 (0.77–1.31) 0.96 (0.72–1.28) 0.94 (0.68–1.30) 1.10 (0.75–1.61) 1.0 (0.68–1.58) [0.31]	Age, alcohol consumption, smoking, supplemental calcium intake, consumption of red meat	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Adams et al. (2007) (cont.)	209 436 Women Incidence		BMI 18.5–22.9 23–24.9 25–27.4 27.5–29.9 30–32.5 32.5–34.9 ≥ 35 [P_{trend}]	 60 49 60 37 26 14 32	 1.0 1.05 (0.72–1.53) 1.13 (0.79–1.63) 1.16 (0.76–1.76) 1.09 (0.68–1.75) 0.95 (0.52–1.71) 1.44 (0.92–2.25) [0.20]	Additionally adjusted for HRT use	Similar findings by HRT status
Driver et al. (2007) Physicians' Health Study USA 1982–2004	22 071 Men Incidence	Colon and rectum	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 190 171 20	 1.0 1.26 (1.05–1.52) 1.62 (1.09–2.42) [P_{trend}]	Age, smoking, alcohol consumption, diabetes, exercise	
Fujino et al. (2007) JACC cohort Japan 1988–1997	46 465 Men Incidence	Colon	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 12 155 36 1	 0.86 (0.48–1.57) 1.0 1.14 (0.79–1.65) 0.54 (0.07–3.90)	Age, study area	Weight at age 20 yr also positively associated with risk
	64 327 Women Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 14 128 42 8	 0.98 (0.56–1.71) 1.0 1.09 (0.77–1.56) 1.94 (0.94–3.98)	Age, study area	Weight at age 20 yr also positively associated with risk
	46 465 Men Incidence	Rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 6 128 21 2	 0.57 (0.25–1.30) 1.0 0.78 (0.49–1.24) 1.27 (0.31–5.17)	Age, study area	Weight at age 20 yr also positively associated with risk
	64 321 Women Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 2 58 19 2	 0.36 (0.08–1.48) 1.0 1.04 (0.62–1.76) 1.00 (0.24–4.12)	Age, study area	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lundqvist et al. (2007) Twin cohorts Sweden and Finland 1961–2004	24 821 older twins (mean baseline age, 56 yr) 10 804 men and 14 017 women Incidence	Colon and rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 7 274 196 36	 1.0 (0.5–2.1) 1.0 1.1 (0.9–1.3) 1.3 (0.9–1.8) [0.12]	Smoking, sex, country, physical activity, education level, diabetes	No association with rectal cancer
	43 328 younger twins (mean baseline age, 30 yr) 20 992 men and 22 336 women Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 146 47 7	 0.6 (0.2–1.7) 1.0 1.0 (0.7–1.4) 1.1 (0.5–2.5) [0.53]	Smoking, physical activity, education level, diabetes	No association with rectal cancer
Reeves et al. (2007) Population-based cohort United Kingdom 1996–2001	1.2 million Women Incidence	Colon and rectum	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	 789 1034 913 555 717	 1.02 (0.95–1.10) 1.00 1.04 (0.97–1.11) 1.01 (0.93–1.10) 1.01 (0.94–1.09) 1.00 (0.92–1.08)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, time since menopause, HRT use	
Wang et al. (2007) Cancer Prevention Study II (CPS II) Nutrition Cohort USA 1992–2003	73 842 Women	Colon and rectum	BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 399 274 141	 1.0 1.08 (0.93–1.27) 1.19 (0.97–1.45) [0.04]	Age, education level, endoscopy history, baseline HRT use, NSAID use, multivitamin use, smoking, physical activity, diabetes	Cohort of postmenopausal women Similar findings by HRT status (never, former, current use)
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1994–2003	107 481 Women Incidence	Colon (above rectosigmoid junction)	BMI < 18.5 18.5–20.9 21–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30 [risk per 1 kg/m²]	 11 46 86 141 129 64 32	 0.94 (0.37–2.39) 1.03 (0.63–1.70) 1.00 1.69 (1.17–2.44) 1.73 (1.18–2.53) 1.21 (0.77–1.90) 2.43 (1.40–4.23) [1.05 (1.02–1.09)]	Age, height, smoking, alcohol consumption, exercise, pay level at study entry	Cohort of postmenopausal women (age 40–64 yr) Results presented are those after excluding patients diagnosed within the first 5 yr of follow-up

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Song et al. (2008) (cont.)	107 481 Women Incidence	Rectum (below rectosigmoid junction)	BMI < 18.5 18.5–20.9 21–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30 [risk per 1 kg/m^2]	 10 69 110 140 102 85 20	 1.00 (0.43–2.33) 1.06 (0.67–1.67) 1.00 1.26 (0.88–1.81) 0.94 (0.63–1.40) 1.62 (1.10–2.38) 1.13 (0.57–2.24) [1.03 (0.99–1.06)]	Age, height, smoking, alcohol consumption, exercise, pay level at study entry	
Thygesen et al. (2008) Health Professionals Follow-Up Study USA 1986–2004	46 349 Men Incidence	Colon	BMI < 20 20.1–22.5 22.6–25 25.1–30 30.1–35 > 35	 9 50 205 341 75 13	 1.69 (0.83–3.44) 1.0 1.40 (1.03–1.92) 1.64 (1.21–2.22) 2.29 (1.58–3.31) 2.29 (1.23–4.26)	Age, physical activity, alcohol consumption, diet, smoking, aspirin use, family history, prior screening. All confounders were lagged 2 yr	Weight gain since age 21 yr positively associated with risk. The association became stronger when 2–4 yr of lag time for weight change was allowed
Wang et al. (2008) Cancer Prevention Study II (CPS II) Nutrition Cohort USA 1997–2005	44 068 Men Incidence	Colon	BMI < 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] WC < 95 95–105 105–120 ≥ 120 [P_{trend}]	 143 179 64 16 165 195 157 29 	 1.0 0.93 (0.75–1.17) 1.34 (0.99–1.82) 1.93 (1.14–3.28) [0.01] 1.0 0.95 (0.77–1.17) 1.21 (0.96–1.52) 1.68 (1.12–2.53) [< 0.006]	Height, education level, physical activity, smoking, alcohol consumption, NSAID use, multivitamin use, screening history	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wang et al. (2008) (cont.)	51 083 Women Incidence	Colon	BMI < 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 156 97 44 17	 1.0 0.92 (0.71–1.19) 1.25 (0.88–1.76) 1.40 (0.84–2.36) [0.18]	Height, education level, physical activity, smoking, alcohol consumption, NSAID use, multivitamin use, screening history, HRT use	
			WC < 85 85–95 95–110 ≥ 110 [P_{trend}]	 158 109 104 36	 1.0 1.01 (0.79–1.29) 1.27 (0.98–1.64) 1.75 (1.20–2.54) [0.003]	Height, education level, physical activity, smoking, alcohol consumption, NSAID use, multivitamin use, screening history, HRT use	
	44 068 Men Incidence	Rectum	BMI < 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 50 63 23 6	 1.0 0.80 (0.55–1.16) 1.01 (0.61–1.68) 1.38 (0.58–3.28) [0.70]	Height, education level, physical activity, smoking, alcohol consumption, NSAID use, multivitamin use, screening history; for women, also adjusted for HRT use	WC, also null association
	51 083 Women Incidence		BMI < 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 37 31 19 6	 1.0 1.34 (0.82–2.17) 2.62 (1.48–4.66) 2.67 (1.09–6.54) [0.001]		Similar association with WC
Andreotti et al. (2010) Agricultural workers USA 1993–2005	39 628 Men Incidence	Colon	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 per 1 kg/m^2	 1 44 112 58 15	 – 1.0 1.26 (0.86–1.86) 1.88 (1.23–2.91) 2.03 (1.05–3.93) 1.05 (1.02–1.09)	Race, education level, family history of colon cancer	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Andreotti et al. (2010) (cont.)	28 319 Women Incidence		BMI < 18.5 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 per 1 kg/m^2 [P_{trend}]	 1 40 49 19 4 	 – 1.0 1.48 (0.97–2.26) 1.36 (0.79–2.36) – 1.00 (0.96–1.04) [0.92]		
	39 628 Men Incidence	Rectum	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 per 1 kg/m^2 [P_{trend}]	 0 23 53 16 10 	 – 1.0 0.96 (0.51–1.82) 0.60 (0.24–1.50) 3.21 (1.34–7.71) 1.06 (1.00–1.12) [0.06]	Additionally adjusted for meat consumption	Results in women not presented due to too few incident cases
Bassett et al. (2010) Population-based cohort Australia 1990–2007	16 188 Men Incidence	Colon	BMI < 23 23–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 13 38 160 66 	 0.60 (0.32–1.13) 1.0 1.31 (0.91–1.87) 1.51 (1.00–2.28) [< 0.01]	Place of birth, education level, diet, smoking, alcohol consumption	BMI at age 18 yr, null association. Positive association with weight gain since age 18 yr. Association stronger for proximal colon
	23 438 Women Incidence		BMI < 23 23–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 64 59 102 67 	 0.95 (0.67–1.36) 1.0 0.84 (0.61–1.17) 1.00 (0.70–1.44) [0.90]		BMI at age 18 yr, null association. Weight gain since age 18 yr, also null association

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Laake et al. (2010) Population-based cohort Norway 1974–2005	38 822 Men Incidence	Colon	BMI < 18.5–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 695 112 140 75 54	 1.0 1.16 (0.86–1.56) 1.19 (0.89–1.60) 1.20 (0.86–1.68) 1.80 (1.25–2.59) [0.004]	Age, physical activity, height, energy intake, smoking, education level, county	Association stronger for distal colon than proximal
	37 357 Women Incidence		BMI < 18.5–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 115 95 81 57 71	 1.0 1.05 (0.80–1.38) 1.03 (0.77–1.38) 1.27 (0.92–1.76) 1.48 (1.09–2.02) [0.01]	Age, physical activity, height, energy intake, smoking, education level, county	Association stronger for distal colon
Oxentenko et al. (2010) Iowa Women's Health Study USA 1986–2005	36 941 Women Incidence after age 55 yr	Colon and rectum	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 19 495 548 272 93 37	 1.62 (0.98–2.66) 1.0 1.12 (0.99–1.28) 1.31 (1.12–1.54) 1.32 (1.03–1.68) 1.56 (1.10–2.22) [< 0.001]	Age, HRT use, OC use, smoking, physical activity, diabetes, alcohol consumption, diet, calcium intake, folate intake, vitamin E intake	Proximal and distal subsites similar. Association stronger for distal site
			WC, quartiles Q1 Q2 Q3 Q4 [P_{trend}]	 292 351 431 390	 1.0 1.18 (1.00–1.39) 1.34 (1.14–1.576) 1.32 (1.11–1.56) [< 0.001]	Age, HRT use, OC use, smoking, physical activity, diabetes, alcohol consumption, diet, calcium intake, folate intake, vitamin E intake	Proximal and distal subsites similar

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Parr et al. (2010) Pooled analysis of 39 cohort studies Asia, Australia, and New Zealand 1961–1999, median follow-up 4 yr	424 519 Men and women Incidence	Colon	BMI < 12–18.4 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	429 total	 0.63 (0.26–1.56) 1.0 1.13 (0.94–1.36) 1.50 (1.13–1.99) [0.02]	Age, sex, tobacco use	Stronger positive association in obese men
	424 519 Men and women Mortality	Rectum	BMI < 12–18.4 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	233 total	 0.86 (0.37–2.02) 1.0 1.44 (1.11–1.86) 1.68 (1.06–2.67) [0.03]	Age, sex, tobacco use	
Hughes et al. (2011) Population-based cohort The Netherlands 1986–2002	58 297 Men Incidence	Colon and rectum	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 232 238 240 247 254	 1.0 0.95 (0.74–1.24) 0.99 (0.77–1.28) 1.05 (0.81–1.36) 1.25 (0.96–1.62) [0.08]	Age, diet, occupation, physical activity, education level, family history, alcohol consumption, smoking	Rectal cancer not associated with BMI. Proximal and distal sites similar. Stronger associations with distal sites, P_{trend} significant. BMI at age 20 yr weakly associated
	62 573 Women Incidence		BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 228 211 223 222 222	 1.0 0.88 (0.69–1.13) 0.94 (0.73–1.20) 0.91 (0.71–1.16) 0.97 (0.76–1.24) [0.90]	Age, diet, occupation, physical activity, education level, family history, alcohol consumption, smoking	BMI at age 20 yr, null association Rectal cancer also not associated with BMI

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Odegaard et al. (2011) Singapore Chinese Health Study cohort Shanghai, China 1993–2007	51 251 Men and women Incidence	Colon	BMI < 18.5 18.5–21.4 21.5–24.4 24.5–27.4 ≥ 27.5 [P_{trend}]	 51 162 181 123 79	 1.23 (0.90–1.68) 1.17 (0.95–1.45) 1.0 1.12 (0.89–1.43) 1.48 (1.13–1.92) [0.44]	Age, sex, year enrolment, dialect, education level, diabetes, family history, smoking, alcohol consumption, diet, physical activity, sleep duration	Significant U-shaped quadratic association (P_{trend} = 0.014). Stronger association in older subjects (> 65 yr) and non-smokers
	51 251 Men and women Incidence	Rectum	BMI < 18.5 18.5–21.4 21.5–24.4 24.5–27.4 ≥ 27.5 [P_{trend}]	 25 111 137 76 35	 0.77 (0.50–1.19) 1.04 (0.81–1.34) 1.0 0.95 (0.71–1.25) 0.93 (0.64–1.36) [0.92]	Age, sex, year of enrolment, dialect, education level, diabetes, family history, smoking, alcohol consumption, diet, physical activity, sleep duration	
Matsuo et al. (2012) 8 population-based cohorts (pooled) Japan 1984–2006	157 927 Men Incidence	Colon	BMI < 19 19–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 98 317 473 512 319 168 32	 0.91 (0.70–1.17) 1.0 (0.85–1.16) 0.87 (0.75–1.00) 1.0 1.17 (1.01–1.36) 1.31 (1.09–1.58) 1.47 (0.99–2.18) [< 0.001]	Age, area, smoking, alcohol consumption, diet, physical activity	Association stronger for proximal colon
	183 457 Women Incidence		BMI < 19 19–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 76 215 330 512 217 136 48	 0.71 (0.52–0.97) 0.87 (0.71–1.07) 1.00 (0.84–1.19) 1.0 1.21 (1.02–1.44) 1.11 (0.88–1.39) 1.18 (0.83–1.68) [0.003]	Age, area, smoking, alcohol consumption, diet, physical activity	Association stronger for proximal colon

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Matsuo et al. (2012) (cont.)	157 927 Men Incidence	Rectum	BMI < 19 19–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 59 179 325 284 158 80 26	 0.91 (0.65–1.27) 0.98 (0.80–1.21) 1.12 (0.94–1.33) 1.0 1.12 (0.91–1.37) 1.20 (0.91–1.58) 1.57 (0.97–2.53) [0.20]	Age, area, smoking, alcohol consumption, diet, physical activity	
	183 457 Women Incidence		BMI < 19 19–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 53 97 147 284 80 54 20	 1.44 (0.99–2.08) 1.12 (0.84–1.50) 1.05 (0.81–1.35) 1.0 0.88 (0.64–1.20) 0.99 (0.70–1.39) 1.39 (0.81–2.39) [0.785]	Age, area, smoking, alcohol consumption, diet, physical activity	
Park et al. (2012) EPIC-Norfolk study cohort England 1993–2006	11 166 Men Incidence	Colon and rectum	BMI < 23.9 23.9–25.5 25.5–26.9 27–28.8 ≥ 28.9 [P_{trend}]	 67 41 30 32 27	 1.00 0.75 (0.50–1.12) 0.74 (0.48–1.14) 0.90 (0.58–1.38) 0.97 (0.61–1.54) [0.85]	Age, sex, smoking, alcohol consumption, education level, exercise, family history, diet	WC, also null association
	13 078 Women Incidence		BMI < 23.9 23.9–25.5 25.5–26.9 27–28.8 ≥ 28.9 [P_{trend}]	 34 31 44 21 30	 1.00 1.20 (0.72–1.98) 1.87 (1.17–2.99) 1.10 (0.62–1.93) 1.97 (1.18–3.30) [0.02]	Age, sex, smoking, alcohol consumption, education level, exercise, family history, diet	WC, null association

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Park et al. (2012) (cont.)	13 078 Women Incidence		WC < 73 73–78 78–83.3 83.4–90.4 ≥ 90.5 [P_{trend}]	 20 22 30 41 47	 1.00 0.86 (0.46–1.62) 1.16 (0.65–2.06) 1.52 (0.88–2.62) 1.65 (0.97–2.86) [0.001]	Age, sex, smoking, alcohol consumption, education level, exercise, family history, diet	
Renehan et al. (2012) NIH-AARP cohort USA 1995–2006	168 294 Men Incidence	Colon	BMI < 18.5 18.5–21.9 22.0–22.9 23.0–24.9 25.0–27.4 27.5–29.9 30.0–32.4 32.5–34.9 ≥ 35 [P_{trend}]	 6 98 93 349 600 438 249 124 113	 0.89 (0.39–2.02) 1.0 0.91 (0.68–1.22) 1.01 (0.80–1.27) 1.07 (0.86–1.34) 1.26 (1.01–1.58) 1.29 (1.01–1.64) 1.33 (1.01–1.75) 1.53 (1.16–2.03) [< 0.0001]	Age, race, education level, physical activity, smoking, alcohol consumption	BMI at ages 18, 35, and 50 yr shows similar associations as baseline BMI (mean baseline age, 62.8 yr)
	105 385 Women Incidence		BMI < 18.5 18.5–21.9 22.0–22.9 23.0–24.9 25.0–27.4 27.5–29.9 30.0–32.4 32.5–34.9 ≥ 35 [P_{trend}]	 14 148 68 176 207 127 82 54 86	 1.33 (0.76–2.30) 1.0 1.00 (0.75–1.34) 1.08 (0.87–1.35) 1.11 (0.89–1.38) 1.15 (0.90–1.47) 1.00 (0.76–1.32) 1.07 (0.78–1.48) 1.23 (0.93–1.64) [0.20]	Age, race, education level, physical activity, smoking, alcohol consumption, HRT use	BMI at ages 35 yr and 50 yr shows similar associations as baseline BMI, but BMI at age 18 yr null association

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Renehan et al. (2012) (cont.)	168 294 Men Incidence	Rectum	BMI < 18.5 18.5–21.9 22.0–22.9 23.0–24.9 25.0–27.4 27.5–29.9 30.0–32.4 32.5–34.9 ≥ 35 [P_{trend}]	 4 37 45 150 215 149 78 44 40	 1.63 (0.58–4.59) 1.0 1.22 (0.78–1.91) 1.20 (0.82–1.74) 1.06 (0.74–1.53) 1.15 (0.79–1.67) 0.99 (0.65–1.49) 1.22 (0.77–1.92) 1.43 (0.90–2.28) [0.51]	Age, race, education level, physical activity, smoking, alcohol consumption	BMI at ages 18, 35, and 50 yr shows similar associations as baseline BMI (mean baseline age, 62.8 yr)
	105 385 Women Incidence		BMI < 18.5 18.5–21.9 22.0–22.9 23.0–24.9 25.0–27.4 27.5–29.9 30.0–32.4 32.5–34.9 ≥ 35 [P_{trend}]	 6 43 22 50 64 32 20 20 25	 1.94 (0.82–4.58) 1.0 1.15 (0.68–1.93) 1.07 (0.71–1.63) 1.21 (0.82–1.81) 1.01 (0.63–1.61) 0.85 (0.49–1.47) 1.45 (0.84–2.51) 1.28 (0.76–2.16) [0.45]	Age, race, education level, physical activity, smoking, alcohol consumption, HRT use	BMI at ages 18, 35, and 50 yr also null association

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Aleksandrova et al. (2013) EPIC cohort (6 centres) Europe 1992–2010	74 091 Men Incidence	Colon	Weight change from age 20 yr			Age, weight at age 20 yr, smoking, education level, alcohol consumption, physical activity, consumption of red meat, fish and shellfish intake, intake of fruits and vegetables, fibre intake	
			Loss	37	0.84 (0.43–1.64)		
			Stable	67	1.0		
			2–5 kg gain	65	1.20 (0.67–2.14)		
			5–10 kg gain	122	0.97 (0.58–1.63)		
			10–15 kg gain	127	0.88 (0.53–1.48)		
			15–20 kg gain	114	1.09 (0.65–1.84)		
			≥ 20 kg gain	165	1.31 (0.78–2.19)		
			[P_{trend}]		[0.13]		
	127 605 Women Incidence		Weight change from age 20 yr				Similar findings by HRT status
			Loss	70	0.97 (0.56–1.68)		
			Stable	66	1.0		
			2–5 kg gain	87	1.34 (0.81–2.23)		
			5–10 kg gain	158	1.07 (0.68–1.69)		
			10–15 kg gain	139	1.05 (0.65–1.69)		
			15–20 kg gain	112	1.36 (0.83–2.23)		
			≥ 20 kg gain	141	1.49 (0.92–2.42)		
			[P_{trend}]		[0.05]		
	74 091 Men Incidence	Rectum	Weight change from age 20 yr				
			Loss	31	1.15 (0.53–2.49)		
			Stable	45	1.0		
			2–5 kg gain	48	0.64 (0.30–1.35)		
			5–10 kg gain	107	1.37 (0.74–2.52)		
			10–15 kg gain	103	1.28 (0.69–2.35)		
			15–20 kg gain	72	1.22 (0.65–2.30)		
			≥ 20 kg gain	91	1.36 (0.73–2.52)		
			[P_{trend}]		[0.16]		
	127 605 Women Incidence		Weight change from age 20 yr				
			Loss	32	1.77 (0.84–3.76)		
			Stable	39	1.0		
			2–5 kg gain	50	2.15 (1.12–4.11)		
			5–10 kg gain	84	1.34 (0.78–2.31)		
			10–15 kg gain	88	1.65 (0.93–2.93)		
			15–20 kg gain	53	1.82 (0.94–3.51)		
			≥ 20 kg gain	71	1.45 (0.79–2.66)		
			[P_{trend}]		[0.96]		

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kitahara et al. (2013) PLCO trial subjects (screening arm) USA 1993–2001	36 912 Men Incidence	Colon and rectum	BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 128 270 148	 1.0 1.19 (0.96–1.48) 1.48 (1.16–1.89) [0.002]	Age, study centre, screening history, race/ethnicity, tobacco use, HRT use	Proximal, distal, and rectal associations with BMI all similar, but only proximal significant
	37 562 Women Incidence		BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 156 154 106	 1.0 1.07 (0.86–1.34) 1.03 (0.80–1.33) [0.74]	Age, study centre, screening history, race/ethnicity, tobacco use, HRT use	All subsites null for BMI associations
Bhaskaran et al. (2014) Health system clinical database United Kingdom 1987–2012	5 243 978 Men and women Incidence	Colon	per 5 kg/m^2	13 465	1.10 (1.07–1.13)	Age, sex, year, diabetes, alcohol consumption, smoking, SES	Similar association in never-smokers. Significant sex interaction above 22 kg/m^2 (stronger association in men)
	5 243 978 Men and women Incidence	Rectum	per 5 kg/m^2	6123	1.04 (1.00–1.08)		Similar association in never-smokers

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kabat et al. (2015) Women's Health Initiative cohort USA 1992–2013	143 901 Women Incidence	Colon and rectum	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	1908 total	 1.0 1.18 (1.01–1.38) 1.15 (0.98–1.38) 1.27 (1.09–1.48) 1.44 (1.23–1.68) [< 0.0001]	Age, alcohol consumption, smoking, physical activity, age at menarche, age at first birth, parity, HRT use, family history, ethnicity, education level, aspirin use, diabetes, treatment allocation	Associations stronger in ever-users of HRT Similar findings by HRT status
			WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	1908 total	 1.0 1.49 (1.26–1.75) 1.36 (1.15–1.61) 1.67 (1.41–1.96) 1.90 (1.61–2.25) [< 0.0001]		

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index (in kg/m^2); CI, confidence interval; CRC, colorectal cancer; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NSAID, non-steroidal anti-inflammatory drug; OC, oral contraceptive; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SES, socioeconomic status; VHM&PP, Vorarlberg Health Monitoring and Prevention Program; WC, waist circumference (in cm); yr, year or years

Table 2.2.1b Case–control studies of measures of body fatness and cancer of the colorectum

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Boutron-Ruault et al. (2001) France (Burgundy) Period NR	CRC: Men: 109 Women: 62 Population	BMI, quintiles (sex-specific) Men: Women: < 22.9 < 20.3 23–24.4 20.4–22.6 25–25.9 22.7–23.9 26–28.7 24–26.1 > 28.7 > 26.1 [P_{trend}]	 29 45 23 40 34	 1.0 1.7 (0.9–3.0) 0.8 (0.4–1.6) 1.4 (0.8–2.6) 1.1 (0.6–2.1) [0.92]	Age	
Slattery et al. (2003) USA (Northern California, Utah, Minnesota) 1991–1994	Colon cancer: Men: 1095 Women: 1286 Population	BMI < 23 23–24 25–27 28–30 > 30 BMI < 23 23–24 25–27 28–30 > 30 BMI in estrogen-positive women < 23 23–24 25–27 28–30 > 30 BMI in estrogen-negative women < 23 23–24 25–27 28–30 > 30	Men: 56 119 320 305 295 Women: 144 146 224 152 211 56 60 59 49 77 88 86 165 103 134	 1.00 0.06 (0.64–1.44) 1.13 (0.79–1.63) 1.54 (1.06–2.23) 1.88 (1.29–2.74) 1.00 1.22 (0.90–1.65) 1.27 (0.96–1.67) 1.30 (0.96–1.76) 1.45 (1.09–1.92) 1.00 1.28 (0.81–2.02) 1.09 (0.69–1.73) 1.56 (0.95–2.56) 2.38 (1.50–3.77) 1.00 1.21 (0.80–1.82) 1.28 (0.90–1.82) 1.10 (0.75–1.62) 1.02 (0.71–1.46)	Age	Additional adjustment for dietary factors, NSAID use, physical activity level, and family history of CRC did not significantly alter associations

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Pan et al. (2004) Canada (eight Canadian provinces), NECSS study 1994–1997	Colon cancer: Men: 959 Women: 768 Population	BMI Men: < 25 25– < 30 ≥ 30 [P_{trend}] Women: < 25 25– < 30 ≥ 30 [P_{trend}]	 NR NR 	 1.00 1.54 (1.27–1.86) 2.16 (1.68–2.78) [< 0.0001] 1.00 1.22 (0.98–1.52) 1.77 (1.35–2.32) [< 0.0001]	5-yr age group, province, education level, smoking, alcohol consumption, total energy intake, diet, recreational physical activity Women only: menopausal status, number of live births, age at menarche, age at end of first pregnancy	
	Rectal cancer: Men: 858 Women: 589 Population	Men: < 25 25– < 30 ≥ 30 [P_{trend}] Women: < 25 25– < 30 ≥ 30 [P_{trend}]	NR NR 	1.00 1.41 (1.15–1.71) 1.75 (1.35–2.28) [0.0001] 1.00 1.28 (1.02–1.61) 1.50 (1.11–2.02) [0.0045]		
Chung et al. (2006) Republic of Korea 2002–2004	CRC: 105 Hospital	BMI < 22.9 23.0–24.9 ≥ 25.0	 37 32 36	 1.0 1.4 (0.6–3.3) 2.3 (0.9–5.8)	Age, sex, glucose, triglycerides, cholesterol	
Hou et al. (2006) China (Shanghai) 1990–1993	Colon cancer: Men: 461 Women: 465 Population	BMI, quintiles < 19.2 19.2–20.3 20.4–21.3 21.4–22.8 > 22.8 [P_{trend}]	Men: 80 85 68 109 119	 1.0 1.0 (0.7–1.4) 1.0 (0.7–1.4) 1.2 (0.9–1.8) 1.7 (1.1–2.4) [0.005]	Age, education level, family income, marital status, total energy intake, diet Women only: number of pregnancies, years of menstruation	In women, a significant interaction was observed by menopausal status ($P_{interaction}$ = 0.03)

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Hou et al. (2006) (cont.)		BMI, quintiles	Women:			
		< 19	86	1.0		
		19.1–20.5	91	1.2 (0.8–1.7)		
		20.6–21.9	80	0.9 (0.6–1.3)		
		22.0–23.6	92	1.1 (0.8–1.7)		
		> 23.6	116	1.4 (1.0–2.1)		
		[P_{trend}]		[0.08]		
		BMI in premenopausal women				
		< 19	15	1.0		
		19.1–20.5	19	1.2 (0.6–2.8)		
		20.6–21.9	20	1.2 (0.3–3.1)		
		22.0–23.6	24	1.3 (0.6–3.2)		
		> 23.6	62	2.9 (1.7–8.6)		
		[P_{trend}]		[0.01]		
		BMI in postmenopausal women				
		< 19	66	1.0		
		19.1–20.5	72	1.1 (0.6–1.5)		
		20.6–21.9	58	0.8 (0.5–1.2)		
		22.0–23.6	71	0.8 (0.6–1.4)		
		> 23.6	50	0.6 (0.3–0.9)		
		[P_{trend}]		[0.03]		
Campbell et al. (2007) Canada (Ontario and Newfoundland) 1997–2003	CRC: Men: 1292 Women: 1404 Population	BMI	Men:		Age, education level, consumption of red meat, physical activity, province of residence, CRC screening endoscopy, history of high cholesterol/ triglycerides Women only: menopausal status, use of postmenopausal HRT	Associations were moderately stronger for colon than rectum. Significant associations with weight gain since age 20 yr were observed in men only (≥ 20 kg vs reference 1–5 kg)
		18.5–24.99	298	1.0		
		25–29.99	627	1.29 (1.07–1.56)		
		≥ 30	322	1.80 (1.43–2.27)		
		BMI	Women:			
		18.5–24.99	616	1.0		
		25–29.99	443	0.99 (0.83–1.20)		
		≥ 30	260	0.94 (0.75–1.18)		
		BMI in estrogen-positive women				
		18.5–24.99	260	1.0		
		25–29.99	148	0.89 (0.66–1.21)		
		≥ 30	80	0.67 (0.45–0.98)		

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Campbell et al. (2007) (cont.)		BMI in estrogen-negative women				
		18.5–24.99	356	1.0		
		25–29.99	295	1.08 (0.85–1.37)		
		≥ 30	180	1.05 (0.79–1.40)		
Hoffmeister et al. (2007) Germany 2003–2004	CRC: Women: 208 Population	BMI			Age, county of residence, history of rheumatic disease, hyperlipidaemia, former health check-up, former colorectal endoscopy, smoking, alcohol consumption, regular NSAID use, use of statins, OC use	Cohort of postmenopausal women
		< 23	51	1.00		
		23– < 25	39	0.80 (0.42–1.53)		
		25– < 27	25	0.78 (0.39–1.58)		
		27– < 30	46	1.71 (0.89–3.31)		
		≥ 30	40	1.82 (0.92–3.62)		
		[P_{trend}]		[0.02]		
		BMI in never-users of HRT				
		< 23	24	1.00		
		23– < 25	31	1.31 (0.55–3.12)		
		25– < 27	18	1.60 (0.58–4.44)		
		27– < 30	33	2.76 (1.07–7.12)		
		≥ 30	31	3.30 (1.25–8.72)		
		[P_{trend}]		[0.01]		
		BMI in ever-users of HRT				
		< 23	27	1.00		
		23– < 25	8	0.49 (0.16–1.48)		
		25– < 27	7	0.36 (0.11–1.13)		
		27– < 30	13	1.18 (0.40–3.48)		
		≥ 30	9	0.89 (0.29–2.75)		
		[P_{trend}]		[0.96]		
Sriamporn et al. (2007) North-eastern Thailand 2002–2006	CRC: 253 Hospital	BMI			Age, sex, place of residence	
		< 25	34	1		
		≥ 25		0.5 (0.3–0.8)		
		[P_{trend}]		[< 0.5]		

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Campbell et al. (2010) Canada (Ontario and Newfoundland) 1997–2003	CRC: Men: 877 Women: 917 Sibling controls	BMI			Age, endoscopy screening, smoking Women only: postmenopausal HRT use	Only microsatellite stable tumours showed increased risk at higher BMI
			Women:			
		< 18.5	24	1.77 (0.91–3.45)		
		18.5–24.99	404	1.00		
		25–29.99	252	1.00 (0.80–1.25)		
		≥ 30	212	1.34 (1.03–1.75)		
		per 5 kg/m²		1.20 (1.10–1.32)		
		[P_{trend}]		[< 0.001]		
			Men:			
		< 18.5	2	0.51 (0.09–2.89)		
		18.5–24.99	223	1.00		
		25–29.99	408	1.33 (1.06–1.68)		
		≥ 30	222	1.79 (1.33–2.40)		
		per 5 kg/m²		1.30 (1.15–1.47)		
		[P_{trend}]		[< 0.001]		
		Adult weight change				
			Women:			
		Loss	94	0.70 (0.049–1.00)		
		0–5 kg gain	158	1.00		
		6–10 kg gain	155	0.88 (0.64–1.20)		
		11–20 kg gain	249	0.93 (0.70–1.23)		
		≥ 21 kg gain	229	1.08 (0.80–1.47)		
		per 5 kg		1.06 (1.01–1.12)		
		[P_{trend}]		[< 0.01]		
			Men:			
		Loss	104	1.40 (0.95–2.06)		
		0–5 kg gain	93	1.00		
		6–10 kg gain	143	1.47 (1.05–2.07)		
		11–20 kg gain	257	1.72 (1.25–2.36)		
		≥ 21 kg gain	233	2.23 (1.58–3.14)		
		per 5 kg		1.08 (1.03–1.14)		
		[P_{trend}]		[0.003]		

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Choe et al. (2013) Republic of Korea (Seoul) 2004–2008	CRC: 153 (stage I) Hospital	BMI, quartiles Q1 Q2 Q3 Q4	NR	 1.0 0.81 (0.48–1.38) 1.32 (0.80–2.19) 1.58 (0.95–2.63)	Current smoking status, alcohol consumption	No significant associations were observed when comparing CRC risk vs colorectal adenoma (554 cases in total) across quartiles of BMI
Boyle et al. (2014) Australia 2005–2007	CRC: 918 Population	BMI at age 20 yr Normal Overweight Obese [P_{trend}]	NR	 1.00 1.25 (0.92–1.71) 0.89 (0.44–1.77) [0.401]	Age group, sex, SES, energy intake, lifetime vigorous recreational physical activity, alcohol consumption, tobacco use, diabetes	No differences in associations were observed with BMI at age 40 yr

BMI, body mass index (in kg/m^2); CI, confidence interval; CRC, colorectal cancer; HRT, hormone replacement therapy; NECSS, National Enhanced Cancer Surveillance System; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; OC, oral contraceptive; SES, socioeconomic status; yr, year or years

Table 2.2.1c Meta-analyses of measures of body fatness and cancer of the colorectum

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding
Moghaddam et al. (2007)	31 studies (23 cohort studies, 8 case–control studies) 70 906 cases (49% women)	Colon and rectum	BMI ≥ 30 vs < 25	1.35 (1.24–1.46)	Age (all studies) and other factors (not in all studies): sex, diabetes, smoking, alcohol consumption, hypertension, hypercholesterolaemia, medication, race, family history, physical activity, diet, education level, SES, pregnancy (for women), menstruation (for women), study centre
	8 cohort studies N/A	Colon and rectum	WC Highest vs lowest category	1.50 (1.35–1.67)	
Renehan et al. (2008)	22 prospective studies in men 22 440 incident cases	Colon	BMI per 5 kg/m² increase	1.24 (1.20–1.28)	Age (all studies) and other factors (not in all studies): family history, inflammatory bowel disease, Western diet, increased weight, alcohol consumption, previous CRC, medical conditions (e.g. type 2 diabetes, acromegaly), intake of fruits and vegetables, fat intake, vitamin D and calcium intake, physical activity, aspirin use, HRT use
	19 prospective studies in women 20 975 incident cases	Colon	BMI per 5 kg/m² increase	1.09 (1.05–1.12)	
	18 prospective studies in men 14 894 incident cases	Rectum	BMI per 5 kg/m² increase	1.09 (1.06–1.12)	Age (all studies) and other factors (not in all studies): family history, inflammatory bowel disease, Western diet, increased weight, alcohol consumption, previous CRC, medical conditions (e.g. type 2 diabetes, acromegaly), intake of fruits and vegetables, fat intake, vitamin D and calcium intake, physical activity, aspirin use, HRT use
	14 prospective studies in women 9052 incident cases	Rectum	BMI per 5 kg/m² increase	1.02 (1.00–1.05)	
Ning et al. (2010)	51 studies (39 prospective and 12 retrospective) 93 812 cases	Colon and rectum	BMI per 5 kg/m² increase	1.18 (1.14–1.21)	Cancer site, sex, menopausal status (for women), directly measured BMI or self-reported BMI, and adjustment for physical activity
Ma et al. (2013)	41 prospective studies 85 935 cases	Colon and rectum	BMI ≥ 30 vs < 25	1.33 (1.25–1.42)	Age (36 studies), smoking (32 studies), physical activity (23 studies), alcohol consumption (23 studies). Fewer adjusted for energy intake (9 studies), NSAID/aspirin use (8 studies), folate intake (7 studies), calcium intake (6 studies), diabetes (6 studies)
	13 prospective studies 6546 cases	Colon and rectum	WC Highest vs lowest category	1.46 (1.33–1.60)	

BMI, body mass index (in kg/m²); CI, confidence interval; CRC, colorectal cancer; HRT, hormone replacement therapy; N/A, not applicable; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; WC, waist circumference

Table 2.2.1d Mendelian randomization studies of measures of body fatness and cancer of the colorectum

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI)	Adjustment for confounding	Comments
Thrift et al. (2015) Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)	11 studies of individuals of European descent (6 cohort and 5 case–control)	20 512 (10 226 cases and 10 286 controls)	Weighted genetic risk score representing an increase of 5 kg/m^2 in BMI	All: 1.50 (1.13–2.01) Men: 1.18 (0.73–1.92) Women: 1.82 (1.26–2.61)	Study, and the top three principal components of ancestry	
Gao et al. (2016) Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium	6 studies of individuals of European ancestry	9931 (5100 cases and 4831 controls)	Increase of 1 SD in genetically predicted childhood BMI or adult BMI	Childhood BMI: 1.20 (0.90–1.59) Adult BMI: 1.39 (1.06–1.82)	N/A	Waist-to-hip ratio, null association: 1.29 (0.75–2.22)

BMI, body mass index (in kg/m^2); CI, confidence interval; N/A, not applicable; SD, standard deviation

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2.2.2 Cancer of the oesophagus

There are two main histological subtypes of cancer of the oesophagus: adenocarcinoma and squamous cell carcinoma. Oesophageal squamous cell carcinoma arises from epithelial cells that line the oesophagus and typically occurs in the upper and middle parts of the oesophagus. Oesophageal adenocarcinoma originates from glandular cells; it occurs in the lower portion of the oesophagus and can spread into the gastric cardia.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for oesophageal adenocarcinoma. Although recent pathological classification recognizes the histological similarity between oesophageal adenocarcinoma and gastric cardia cancer, most epidemiological studies classify gastric cardia cancer with stomach cancer, and therefore these studies are considered in Section 2.2.3. Also, because evidence to date strongly suggests differences in etiological factors between oesophageal adenocarcinoma and squamous cell carcinoma, the results are presented separately for each histological subtype, and no results are presented for oesophageal cancer overall.

(a) Cohort studies

See Table 2.2.2a.

(i) Adenocarcinoma of the oesophagus

Several cohort studies (with at least 75 incident cases) have been published since the previous IARC evaluation (IARC, 2002). In all of those studies, BMI and/or weight were positively associated with risk (Engeland et al., 2004; Lindblad et al., 2005; Samanic et al., 2006; Merry et al., 2007; Reeves et al., 2007; Abnet et al., 2008; Corley et al., 2008; O'Doherty et al., 2012; Lindkvist et al., 2014; Steffen et al., 2015). Associations were similar across follow-up periods in one study (Engeland et al., 2004) and in another study that excluded the first 5 years of follow-up (Abnet et al., 2008). There did not appear to be any meaningful differences in associations when stratifying by smoking status (O'Doherty et al., 2012; Lindkvist et al., 2014) or when limiting results to non-smokers or never-smokers only (Reeves et al., 2007; Abnet et al., 2008).

In a meta-analysis including five prospective studies (Renehan et al., 2008), a relative risk of 1.5 for a 5 kg/m^2 increase in BMI at baseline was reported, with similar values in men and in women.

Few studies have examined the association between BMI measured at younger ages and subsequent risk of oesophageal adenocarcinoma. In the Netherlands Cohort Study, there was evidence of a positive association between high BMI at age 20 years and risk, although the relative risk estimate was not statistically significant (Merry et al., 2007).

The association between BMI change and incidence of oesophageal adenocarcinoma was examined in two prospective studies (Samanic et al., 2006; Merry et al., 2007). The first study, which considered BMI change during a period of 6 years, did not find evidence for a positive association [the analysis was based on only 28 incident cases] (Samanic et al., 2006). The second study, which included 113 cases, found that a 1 kg/m^2 increase in BMI from age 20 years to baseline was significantly associated with a 14% higher risk (95% CI, 1.06–1.23) (Merry et al., 2007).

There have been few prospective studies of abdominal fatness in relation to risk of oesophageal adenocarcinoma. A study nested within the Multiphasic Health Check-up cohort of Kaiser Permanente Northern California members observed a positive association between sagittal abdominal diameter [distance from the anterior to the posterior of the abdomen] and incidence

of oesophageal adenocarcinoma (Corley et al., 2008). Similarly, strong positive associations were reported of both waist circumference and waist-to-hip ratio with incidence of oesophageal adenocarcinoma in the National Institutes of Health–AARP Diet and Health Study (NIH-AARP) cohort ($P_{trend} \leq 0.01$ for both) (O'Doherty et al., 2012) and with oesophageal adenocarcinoma incidence/mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC) study ($P_{trend} \leq 0.0001$) (Steffen et al., 2015).

(ii) Squamous cell carcinoma of the oesophagus

Since 2001, the association between BMI and/or weight assessed at baseline and the incidence and/or mortality of oesophageal squamous cell carcinoma has been examined in at least nine individual prospective studies (Engeland et al., 2004; Lindblad et al., 2005; Tran et al., 2005; Samanic et al., 2006; Merry et al., 2007; Reeves et al., 2007; Corley et al., 2008; Steffen et al., 2009; Lindkvist et al., 2014) and in one meta-analysis (Renehan et al., 2008). In all of the studies, BMI and/or weight were inversely associated with risk. Notably, higher risks were found in the lowest BMI categories (i.e. BMI < 20 kg/m^2) compared with categories within the normal range of BMI, whereas lower risks were observed in the overweight and obese categories. Although most studies adjusted for tobacco use, not all studies included alcohol consumption, another strong risk factor for oesophageal squamous cell carcinoma in their model. Furthermore, in two studies that stratified by smoking status, there was an inverse association in current smokers but no association in non-smokers [supporting a possible confounding effect of tobacco smoking] (Steffen et al., 2009; Lindkvist et al., 2014). In contrast, in the Million Women Study, an inverse association with both incidence and mortality of oesophageal squamous cell carcinoma was noted even in the never-smokers group (Reeves et al., 2007). An inverse association was also observed in the only study in Asia, which included 1958 incident cases in China (Tran et al., 2005). There was no evidence of differences in associations based on follow-up time (Engeland et al., 2004).

A meta-analysis of five prospective studies by Renehan et al. (2008) reported a relative risk per 5 kg/m^2 increase in BMI of 0.71 (95% CI, 0.60–0.85) in men and 0.57 (95% CI, 0.47–0.69) in women.

The association between BMI measured at age 20 years and risk of oesophageal squamous cell carcinoma was examined in the Netherlands Cohort Study (Merry et al., 2007). The relative risk for BMI ≥ 25 kg/m^2 compared with BMI 20–21.4 kg/m^2 was 2.49 (95% CI, 1.15–5.40), but there was no evidence of dose–response [$P_{trend} = 0.58$]. In that study, weight loss from age 20 years to baseline was associated with a statistically significant increased risk, with a relative risk of 2.57, but there was no evidence that weight gain was associated with risk.

Only two prospective studies examined measures of abdominal fatness in relation to risk of oesophageal squamous cell carcinoma. In the Kaiser Permanente Multiphasic Health Check-up nested case–control study, there was no association between sagittal abdominal diameter and risk (Corley et al., 2008), whereas in the EPIC study, there was some evidence of a weak inverse trend of waist circumference with incidence/mortality ($P_{trend} = 0.08$) (Steffen et al., 2009).

(b) Case–control studies

See Table 2.2.2b.

(i) Adenocarcinoma of the oesophagus

Of the case–control studies reporting on oesophageal adenocarcinoma, most studies showed increases of 2.5-fold and higher in risk of oesophageal adenocarcinoma when comparing the highest and lowest BMI categories, although in a few studies these associations were not statistically significant. When assessed, adjustments

for self-reported frequency or severity, or stratification by presence or absence of gastric reflux symptoms did not substantially alter the relative risk estimates (Chow et al., 1998; Lagergren et al., 1999; de Jonge et al., 2006; Anderson et al., 2007; Löfdahl et al., 2008; Whiteman et al., 2008; Olsen et al., 2011).

A pooled analysis of data from 10 case–control studies and 2 cohort studies (Hoyo et al., 2012), including a total of 3719 adenocarcinoma cases and 10 481 controls, showed significant trends of increasing adenocarcinoma risk with increasing BMI, up to odds ratios of 4.76 (95% CI, 2.96–7.66) for oesophageal adenocarcinoma and 3.07 (95% CI, 1.89–4.99) for oesophagogastric junction adenocarcinoma when comparing BMI ≥ 40 kg/m^2 with BMI < 25 kg/m^2. Subset analyses showed similar increases in risk of adenocarcinoma when stratifying by symptoms of gastro-oesophageal reflux disease. No differences in associations were observed by sex.

(ii) Squamous cell carcinoma of the oesophagus

For oesophageal squamous cell carcinoma, several case–control studies reported an inverse association between risk and recent BMI (Vaughan et al., 1995; Chow et al., 1998; Lahmann et al., 2012), and this inverse association was observed within both smokers and never-smokers (Lahmann et al., 2012). Of the two studies that investigated the association of risk of oesophageal squamous cell carcinoma with recalled BMI at age 20 years, one found a non-significant decrease in risk in relation to higher BMI (Lahmann et al., 2012), whereas the other study, based on a total of 167 cases in Sweden, showed an increase in risk with higher BMI (Lagergren et al., 1999).

(c) Mendelian randomization studies

See Table 2.2.2c.

One Mendelian randomization study estimated the causal association between BMI and risk of oesophageal adenocarcinoma (Thrift et al., 2014). Using a genetic risk score based on 29 SNPs previously shown to be associated with BMI (Speliotes et al., 2010), this Mendelian randomization study showed that each 1 kg/m^2 increase in BMI was associated with a 23% increase in risk (95% CI, 6–43%; P = 0.01), compared with a 6% increase in risk (95% CI, 5–8%; P < 0.001) observed in the same sample by conventional epidemiological analyses.

Table 2.2.2a Cohort studies of measures of body fatness and cancer of the oesophagus

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Adenocarcinoma							
Engeland et al. (2004) Population-based Norwegian cohort Norway 1963–2002	Men: 963 709 Women: 1 038 010 Incidence	Oesophageal adenocarcinoma ICD-7: 150	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	448 total	Men: – 1.00 1.80 (1.48–2.19) 2.58 (1.81–3.68) [< 0.001]	Age at measurement, height, birth cohort	
			BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	127 total	Women: 4.07 (1.44–11) 1.00 1.64 (1.08–2.49) 2.06 (1.25–3.39) [0.002]		
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 287 Men and women Incidence	Oesophageal adenocarcinoma	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	8 49 94 36	1.44 (0.67–3.10) 1.00 1.68 (1.18–2.40) 1.93 (1.24–3.01) [0.005]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Oesophageal adenocarcinoma	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	34 38 10	1.00 1.58 (0.98–2.53) 2.72 (1.33–5.55) [< 0.01]	Attained age (10-yr interval), calendar year, smoking	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Samanic et al. (2006) (cont.)			BMI, 6-yr change				
			−4% to +4.9%	19	1.00		
			5–9.9%	3	0.44 (0.13–1.49)		
			10–14.9%	5	2.24 (0.81–6.21)		
			> 15%	1	1.21 (0.16–9.45)		
			[P_{trend}]		[> 0.5]		
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 (case–cohort sample from 120 852 main cohort) Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15 Histology: 8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572	BMI at baseline			Age, sex For BMI change only: adjustment for BMI at age 20 yr	First year of follow-up excluded from the analyses
			< 20	3	1.29 (0.40–4.16)		
			20–24.9	51	1.00		
			25–29.9	60	1.40 (0.95–2.04)		
			≥ 30	19	3.96 (2.27–6.88)		
			[P_{trend}]		[0.001]		
			per 1 kg/m²		1.14 (1.08–1.21)		
			BMI at age 20 yr				
			< 20	21	1.07 (0.59–1.94)		
			20–21.4	24	1.00		
			21.5–22.9	37	1.61 (0.95–2.72)		
			23.0–24.9	18	1.02 (0.55–1.90)		
			≥ 25	13	1.97 (0.99–3.94)		
			[P_{trend}]		[0.17]		
			per 1 kg/m²		1.04 (0.95–1.14)		
			BMI change, age 20 yr to baseline				
			< 0	8	0.75 (0.34–1.64)		
			0–3.9	51	1.00		
			4–7.9	37	1.34 (0.86–2.08)		
			≥ 8	17	3.41 (1.88–6.18)		
			[P_{trend}]		[0.001]		
			per 1 kg/m²		1.14 (1.06–1.23)		
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence and mortality	Oesophageal adenocarcinoma ICD-10: C15	BMI	Incidence:		Age, geographical region, SES, reproductive history, smoking status, alcohol consumption, physical activity	Results remained significant after excluding never-smokers and excluding the first 2 yr of follow-up
			< 22.5	22	1.06 (0.70–1.62)		
			22.5–24.9	27	1.00 (0.68–1.46)		
			25–27.4	30	1.28 (0.90–1.83)		
			27.5–29.9	23	1.57 (1.04–2.36)		
			≥ 30	48	2.54 (1.89–3.41)		
			per 10 kg/m²		2.38 (1.59–3.56)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) (cont.)			BMI	Mortality:			
			< 22.5	20	1.35 (0.87–2.11)		
			22.5–24.9	19	1.00 (0.64–1.57)		
			25–27.4	20	1.21 (0.78–1.87)		
			27.5–29.9	15	1.44 (0.87–2.39)		
			≥ 30	37	2.75 (1.97–3.85)		
			per 10 kg/m²		2.24 (1.40–3.58)		
Abnet et al. (2008) NIH-AARP cohort USA 1995–2003	480 475 Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15.0–15.9 Histology: "adenocarcinoma"	BMI			Age, sex, cigarette smoking, alcohol consumption, education level, physical activity	Results were stable after excluding the first 5 yr of follow-up
			< 18.5	2	1.61 (0.39–6.55)		
			18.5–24.9	71	1.00		
			25–29.9	194	1.65 (1.26–2.18)		
			30–34.9	77	1.91 (1.38–2.66)		
			≥ 35	27	2.27 (1.44–3.59)		
Corley et al. (2008) Nested case–control of Kaiser Permanente Multiphasic Health Check-up cohort USA 1964–1973	3150 Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15.0–15.9 Histology: 8140–8573	BMI			Age, sex, year of health check-up BMI results also adjusted for ethnicity	
			< 18.5	1	1.36 (0.12–15.52)		
			18.5–24.9	28	1.00		
			25–29.9	51	2.20 (1.31–3.67)		
			≥ 30	14	3.17 (1.43–7.04)		
			per 1 kg/m² increase		1.10 (1.04–1.17)		
			Sagittal abdominal diameter (cm)				
			< 20	8	1.00		
			20–22.4	13	0.92 (0.31–2.74)		
			22.5–25	12	2.35 (0.78–7.12)		
			≥ 25	22	3.47 (1.29–9.33)		
			per 1 cm increase		1.10 (1.03–1.17)		
Renehan et al. (2008) Meta-analysis 1966–2007	4 673 213 Men and women Incidence	Oesophageal adenocarcinoma	BMI	Men:		Geographical region, age (all studies), and other factors (not in all studies) such as Western diet, alcohol consumption, medical conditions (e.g. type 2 diabetes, acromegaly), or physical activity	
			per 5 kg/m² increase	1315 total	1.52 (1.33–1.74)		
			BMI	Women:			
			per 5 kg/m² increase	735 total	1.51 (1.31–1.74)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
O'Doherty et al. (2012) NIH-AARP cohort USA 1995–2006	218 854 Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15.0–15.9 Histology: "adenocarcinoma"	BMI			Age, sex, total energy intake, antacid use, aspirin use, NSAID use, marital status, diabetes, cigarette smoking, education level, ethnicity, alcohol consumption, physical activity, intake of red and white meat, intake of fruits and vegetables; for weight, also adjusted for height	Waist-to-hip ratio also significantly associated with risk (Q3 and Q4)
			< 18.5	0	–		
			18.5–24.9	59	1.00		
			25–29.9	119	1.30 (0.94–1.78)		
			30–34.9	64	2.28 (1.57–3.30)		
			≥ 35	11	2.11 (1.09–4.09)		
			[P_{trend}]		[< 0.01]		
			Weight, quartiles (sex-specific)				
			Q1	41	1.00		
			Q2	58	1.49 (0.99–2.23)		
			Q3	53	1.37 (0.89–2.10)		
			Q4	101	2.66 (1.76–4.02)		
			[P_{trend}]		[< 0.01]		
			WC, quartiles (sex-specific)				
			Q1	37	1.00		
			Q2	49	1.36 (0.89–2.09)		
			Q3	79	1.51 (1.02–2.25)		
			Q4	88	2.01 (1.35–3.00)		
			[P_{trend}]		[< 0.01]		
Lindkvist et al. (2014) Me-Can cohort (prospective cohorts) Austria, Norway, and Sweden 1972–2006	587 700 Men and women Incidence	Oesophageal adenocarcinoma ICD-7: 150	BMI, quintiles			Sex, age, study cohort, smoking status	
			Q1	5	1.00		
			Q2	18	3.37 (1.25–9.10)		
			Q3	18	3.17 (1.17–8.57)		
			Q4	31	5.19 (2.00–13.42)		
			Q5	42	7.34 (2.88–18.68)		
			[P_{trend}]		[< 0.0001]		
			per 5 kg/m^2		1.78 (1.45–2.17)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2015) EPIC cohort 10 European countries 1992–2008	391 456 Men and women Incidence/ mortality	Oesophageal adenocarcinoma ICD-10: C15	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] Weight, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 15 22 24 30 33 17 25 23 26 33 7 22 20 26 39 	 1.00 1.30 (0.67–2.52) 1.36 (0.71–2.62) 1.76 (0.93–3.31) 2.15 (1.14–4.05) [0.004] 1.00 1.54 (0.82–2.88) 1.41 (0.74–2.70) 1.57 (0.82–3.01) 2.19 (1.14–4.21) [0.03] 1.00 2.78 (1.18–6.54) 2.47 (1.03–5.92) 3.19 (1.36–7.49) 5.08 (2.21–11.7) [< 0.0001]	Age at recruitment, centre, sex, education level, smoking, alcohol consumption, physical activity, diet, height	Sex-specific quintiles for weight, BMI, and WC. Cut-off points not provided, only the median values for each Positive associations with waist-to-hip ratio (Q4 and Q5)
Squamous cell carcinoma							
Engeland et al. (2004) Population-based Norwegian cohort Norway 1963–2002	Men: 963 709 Incidence	Oesophageal squamous cell carcinoma ICD-7: 150	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	1023 total 	 2.80 (1.73–4.54) 1.00 0.72 (0.63–0.82) 0.68 (0.50–0.93) [< 0.001]	Age at measurement, height, birth cohort	
	Women: 1 038 010 Incidence	Oesophageal squamous cell carcinoma ICD-7: 150	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	472 total 	 2.11 (1.23–3.62) 1.00 0.52 (0.42–0.65) 0.43 (0.32–0.59) [< 0.001]	Age at measurement, height, birth cohort	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 140 Men and women Incidence	Oesophageal squamous cell carcinoma	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	 9 34 39 4	 1.93 (0.90–4.11) 1.00 1.13 (0.71–1.80) 0.28 (0.10–0.79) [0.01]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Tran et al. (2005) Linxian General Population Trial China 1986–2001	29 584 Men and women Incidence	Oesophageal squamous cell carcinoma	BMI < 20 20–21 22 ≥ 23 [P_{trend}]	1958 total	 1.00 0.96 (0.85–1.08) 0.80 (0.71–0.91) 0.81 (0.72–0.92) [< 0.001]	Age, sex	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Oesophageal squamous cell carcinoma	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 134 57 13	 1.00 0.53 (0.39–0.72) 0.77 (0.43–1.36) [< 0.01]	Attained age, calendar year, smoking	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 (case–cohort sample from 120 852 main cohort) Men and women Incidence	Oesophageal squamous cell carcinoma ICD-10: C15 Histology: 8050–8076	BMI at baseline			Age, sex, current smoking, cigarettes per day, number of years of smoking For BMI change only: adjustment for BMI at age 20 yr	
			< 20	9	2.21 (0.99–4.92)		
			20–24.9	51	1.00		
			25–29.9	26	0.63 (0.39–1.02)		
			≥ 30	6	0.93 (0.38–2.26)		
			[P_{trend}]		[0.04]		
			per 1 kg/m^2		0.90 (0.82–0.98)		
			BMI at age 20 yr				
			< 20	22	1.35 (0.70–2.62)		
			20–21.4	16	1.00		
			21.5–22.9	11	0.72 (0.33–1.57)		
			23.0–24.9	13	1.03 (0.48–2.21)		
			≥ 25	12	2.49 (1.15–5.40)		
			[P_{trend}]		[0.58]		
			per 1 kg/m^2		1.07 (0.96–1.20)		
			BMI change, age 20 yr to baseline				
			< 0	18	2.57 (1.40–4.72)		
			0–3.9	32	1.00		
			4–7.9	16	0.73 (0.39–1.36)		
			≥ 8	8	1.39 (0.62–3.15)		
			[P_{trend}]		[0.10]		
			per 1 kg/m^2		0.90 (0.81–1.00)		
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence and mortality	Oesophageal squamous cell carcinoma ICD-10: C15	BMI	Incidence:		Age, geographical region, SES, reproductive history, smoking status, alcohol consumption, physical activity	Negative associations remained stable in non-smokers and excluding the first 2 yr of follow-up
			< 22.5	106	2.04 (1.67–2.48)		
			22.5–24.9	63	1.00 (0.78–1.28)		
			25–27.4	52	0.96 (0.73–1.26)		
			27.5–29.9	21	0.61 (0.40–0.94)		
			≥ 30	21	0.47 (0.31–0.73)		
			per 10 kg/m^2		0.26 (0.18–0.38)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) (cont.)			BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	Mortality: 75 44 39 11 13	 2.10 (1.66–2.65) 1.00 (0.74–1.35) 1.02 (0.75–1.40) 0.45 (0.25–0.82) 0.42 (0.24–0.73) 0.22 (0.14–0.35)		
Corley et al. (2008) Nested case–control of Kaiser Permanente Multiphasic Health Check-up cohort USA 1964–1973	3150 Men and women Incidence	Oesophageal squamous cell carcinoma ICD-10: C15.0–15.9 Histology 8050–8082	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 1 kg/m² increase Sagittal abdominal diameter (cm) < 20 20–22.4 22.5–25 ≥ 25 per 1 cm increase	 3 78 46 9 19 24 14 15	 0.91 (0.19–4.29) 1.00 0.66 (0.44–1.00) 0.30 (0.13–0.72) 0.89 (0.84–0.94) 1.00 0.91 (0.43–1.94) 0.89 (0.35–2.24) 0.78 (0.32–1.92) 1.00 (0.94–1.06)	Matched for age, sex, year of health check-up BMI results also adjusted for ethnicity	
Renehan et al. (2008) Meta-analysis 1966–2007	4 673 213 Men and women Incidence	Oesophageal squamous cell carcinoma	BMI per 5 kg/m² increase BMI per 5 kg/m² increase	Men: 6201 total Women: 1114 total	0.71 (0.60–0.85) 0.57 (0.47–0.69)	Geographical region, age (all studies), and other factors (not in all studies) such as Western diet, alcohol consumption, medical conditions (e.g. type 2 diabetes, acromegaly), or physical activity	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2009) EPIC cohort 10 European countries 1992–2007	346 554 Men and women Incidence/ mortality	Oesophageal squamous cell carcinoma ICD-10: C15	BMI, quintiles (sex-specific) Men: Women: < 23.4 < 21.7 23.4–25.2 21.7–23.6 25.2–26.9 23.6–25.6 26.9–29.1 25.6–28.7 ≥ 29.2 ≥ 28.8 [P_{trend}]	 42 22 15 14 17	 1.00 0.47 (0.27–0.79) 0.31 (0.17–0.57) 0.27 (0.14–0.51) 0.26 (0.14–0.51) [< 0.0001]	Age, study centre, education level, smoking, alcohol consumption, physical activity, consumption of fruits/vegetables/meat	BMI and WC were significantly inversely related to oesophageal squamous cell carcinoma only in smokers
			Weight, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 41 28 14 10 17	 1.00 0.61 (0.37–1.01) 0.30 (0.16–0.57) 0.19 (0.09–0.40) 0.33 (0.18–0.60) [< 0.0001]		
			WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 23 19 23 16 22	 1.00 0.76 (0.41–1.43) 0.78 (0.43–1.43) 0.51 (0.26–1.00) 0.62 (0.32–1.20) [0.08]		
Lindkvist et al. (2014) Me-Can cohort (prospective cohorts) Austria, Norway, and Sweden 1972–2006	587 700 Men and women Incidence	Oesophageal squamous cell carcinoma ICD-7: 150	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] per 5 kg/m^2	 55 29 46 30 24	 1.00 0.50 (0.32–0.79) 0.76 (0.51–1.12) 0.46 (0.30–0.72) 0.38 (0.23–0.62) [< 0.0001] 0.62 (0.50–0.79)	Sex, age, study cohort, smoking status	

BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.2b Case–control studies of measures of body fatness and cancer of the oesophagus

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Vaughan et al. (1995) USA (13 counties of Western Washington State) 1993–1990	EAC: Men and women: 133 Population	BMI, percentiles			Age, sex, education level, race, cigarette use, alcohol consumption	BMI percentiles based on sex-specific distribution in controls (1 yr before diagnosis in cases, 1 yr before interview in controls)
		1–10%	12	1.6 (0.7–3.6)		
		10–49%	43	1.0		
		50–89%	50	1.2 (0.7–2.1)		
		90–100%	26	2.5 (1.2–5.0)		
	ESCC: Men and women: 106 Population	BMI, percentiles				
		1–10%	34	3.2 (1.4–7.1)		
		10–49%	41	1.0		
		50–89%	24	0.7 (0.3–1.4)		
		90–100%	6	0.2 (0.1–1.0)		
Chow et al. (1998) USA 1993–1995	EAC: Men and women: 292 Population	BMI up to 1 yr before diagnosis (sex-specific)			Geographical location, age, sex, race, cigarette smoking, respondent status	No effect modification was observed by history of gastro-oesophageal reflux disease
		Men: / Women:				
		< 23.12 / < 21.95	45	1.0		
		23.12–25.08 / 21.95–24.12	63	1.3 (0.8–2.2)		
		25.09–27.31 / 24.13–27.43	85	2.0 (1.3–3.3)		
		≥ 27.32 / ≥ 27.44	99	2.9 (1.8–4.7)		
		[P_{trend}]		[< 0.0001]		
	ESCC: Men and women: 220 Population	BMI up to 1 yr before diagnosis (sex-specific)				
		Men: / Women:				
		< 23.12 / < 21.95	79	1.0		
		23.12–25.08 / 21.95–24.12	50	0.5 (0.3–0.9)		
		25.09–27.31 / 24.13–27.43	53	0.8 (0.5–1.3)		
		≥ 27.32 / ≥ 27.44	38	0.6 (0.3–1.0)		
		[P_{trend}]		[< 0.11]		
Lagergren et al. (1999) Sweden 1995–1997	EAC: Men and women: 189 Population	BMI 20 yr before interview			Age, sex, tobacco smoking, alcohol consumption, SES, reflux symptoms, intake of fruits and vegetables, energy intake, physical activity	No differences were observed in the associations for both cancer types when stratifying by presence of reflux symptoms
		< 22	10	1.0		
		22–24.9	68	3.2 (1.6–6.7)		
		25–30	89	6.9 (3.3–14.4)		
		> 30	22	16.2 (6.3–41.4)		
		[P_{trend}]		[< 0.001]		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories		Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Lagergren et al. (1999) (cont.)		BMI at age 20 yr, quartiles (sex-specific)					
		Men:	Women:				
		< 20.7	< 19.3	28	1.0		
		20.7–22.1	19.3–20.4	29	0.9 (0.5–1.6)		
		22.2–23.7	20.5–22.1	51	1.6 (0.9–2.8)		
		> 23.7	> 22.1	81	2.7 (1.6–4.6)		
		[P_{trend}]			[< 0.001]		
	ESCC: Men and women: 820 Population	BMI 20 yr before interview					
		< 22		48	1.0		
		22–24.9		67	1.0 (0.6–1.7)		
		25–30		42	1.3 (0.8–2.3)		
		> 30		10	2.0 (0.8–4.9)		
		[P_{trend}]			[0.12]		
		BMI at age 20 yr, quartiles (sex-specific)					
		Men:	Women:				
		< 20.7	< 19.3	36	1.0		
		20.7–22.1	19.3–20.4	38	1.2 (0.7–2.1)		
		22.2–23.7	20.5–22.1	40	1.4 (0.8–2.4)		
		> 23.7	> 22.1	53	1.8 (1.1–3.1)		
		[P_{trend}]			[0.03]		
Wu et al. (2001) USA 1992–1997	EAC: Men and women: 222 Population (proxy control)	BMI at age 40 yr, quartiles (sex-specific)				Smoking, sex, race, birthplace, education level	
		Men:	Women:	202 total			
		≤ 22	≤ 21		1.00		
		> 22–25	> 21–23		1.13 (0.7–1.7)		
		> 25– ≤ 27	> 23– ≤ 25		1.76 (1.1–2.9)		
		> 27	> 25		2.78 (1.7–4.4)		
		[P_{trend}]			[< 0.0001]		
		BMI at age 20 yr, quartiles (sex-specific)					
		Men:	Women:	207 total			
		≤ 20	≤ 18		1.00		
		> 20–22	> 18–20		1.23 (0.8–1.9)		
		> 22– ≤ 24	> 20– ≤ 22		1.34 (0.9–2.1)		
		> 24	> 22		1.77 (1.1–2.7)		
		[P_{trend}]			[0.011]		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
de Jonge et al. (2006) The Netherlands 2003–2005	EAC: Men and women: 91 Hospital	BMI 10 yr before questionnaire			Age, sex, education level, smoking status, alcohol consumption, reflux symptoms	Controls were patients with Barrett oesophagus
		< 25	29	1.0		
		> 25	58	1.8 (1.1–3.3)		
		BMI at age 20 yr				
		< 25	63	1.0		
		> 25	20	2.6 (1.2–5.5)		
Anderson et al. (2007) Ireland 2002–2004	EAC: 227 (192 men and 35 women) Population	Current BMI, tertiles			Sex, age at interview date, smoking status, alcohol consumption, years of full-time education, job type, gastro-oesophageal reflux	
		< 25.8	115	1.00		
		25.8–29.0	54	0.35 (0.21–0.58)		
		> 29.0	50	0.33 (0.20–0.56)		
		BMI 5 yr before, tertiles				
		< 25.0	51	1.00		
		25.0–28.1	55	1.74 (0.66–1.97)		
		> 28.1	120	2.69 (1.62–4.46)		
		BMI at age 21 yr				
		< 22.1	55	1.00		
		22.1–24.1	64	1.10 (0.65–1.25)		
		> 24.1	96	1.81 (1.08–3.02)		
Löfdahl et al. (2008) Sweden 1995–1997	EAC + EJAC: Men: 388 Women: 63 Population	BMI 20 yr before interview			Age, education level, alcohol consumption, cigarette smoking, intake of fruits and vegetables, *Helicobacter pylori* infection Maximum and minimum adult BMI, also adjusted for gastro-oesophageal reflux	The associations for maximum adult BMI and for minimum adult BMI were weaker, but also showed a stronger association in women than in men
			Men:			
		< 22	45	1.0		
		22–24.9	143	1.5 (1.0–2.3)		
		25–29.9	164	2.7 (1.8–4.1)		
		≥ 30	36	5.4 (2.6–10.8)		
			Women:			
		< 22	12	1.0		
		22–24.9	25	2.4 (0.9–6.0)		
		25–29.9	16	4.3 (1.4–13.1)		
		≥ 30	10	10.3 (2.6–42.3)		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Whiteman et al. (2008) Australia 2001–2005	EAC: Men and women: 367 Population	BMI in the last year			Age, sex, state, household income, cumulative smoking history, mean alcohol consumption, frequency of aspirin use in the 5 yr before diagnosis	Results did not significantly change when additionally adjusted for gastro-oesophageal reflux; significantly higher risk in men than in women; no significant associations or trend between change in BMI and risk of EAC or EJAC
		< 18.5	1	0.3 (0.0–2.6)		
		18.5–24.9	71	1.0		
		25.0–29.9	150	1.4 (1.0–1.9)		
		30.0–34.9	89	2.7 (1.8–3.9)		
		35.0–39.9	25	3.1 (1.8–5.5)		
		≥ 40	16	7.0 (3.3–15.0)		
		[P_{trend}]		[< 0.001]		
		Maximum BMI				
		< 18.5	1	0.9 (0.1–8.7)		
		18.5–24.9	39	1.0		
		25.0–29.9	136	1.4 (0.9–2.0)		
		30.0–34.9	114	2.5 (1.6–3.7)		
		35.0–39.9	43	4.1 (2.4–6.8)		
		≥ 40	24	5.2 (2.7–9.9)		
		[P_{trend}]		[< 0.001]		
		BMI at age 20 yr				
		< 18.5	14	0.8 (0.4–1.4)		
		18.5–24.9	227	1.0		
		25.0–29.9	81	1.7 (1.2–2.3)		
		30.0–34.9	13	2.6 (1.3–5.2)		
		35.0–39.9	5	3.6 (1.0–13.0)		
		[P_{trend}]		[< 0.001]		
	EJAC: Men and women: 426 Population	BMI in the last year				
		< 18.5	1	0.2 (0.0–1.7)		
		18.5–24.9	107	1.0		
		25.0–29.9	168	1.1 (0.8–1.4)		
		30.0–34.9	98	1.9 (1.3–2.6)		
		35.0–39.9	27	2.0 (1.2–3.4)		
		≥ 40	9	2.6 (1.1–6.2)		
		[P_{trend}]		[< 0.001]		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Whiteman et al. (2008) (cont.)		Maximum BMI				
		< 18.5	0	–		
		18.5–24.9	55	1.0		
		25.0–29.9	178	1.3 (0.9–1.8)		
		30.0–34.9	122	1.9 (1.3–2.7)		
		35.0–39.9	47	2.9 (1.8–4.6)		
		≥ 40	13	2.1 (1.1–4.2)		
		[P_{trend}]		[< 0.001]		
		BMI at age 20 yr				
		< 18.5	9	0.4 (0.2–0.8)		
		18.5–24.9	282	1.0		
		25.0–29.9	97	1.6 (1.2–2.1)		
		30.0–34.9	13	2.1 (1.0–4.1)		
		≥ 35.0	2	1.1 (0.2–5.9)		
		[P_{trend}]		[< 0.001]		
Olsen et al. (2011) Australia 2002–2005	EAC: Men and women: 364 Population	BMI 1 yr before			Age, sex, education level, NSAID use, smoking status, heartburn/acid reflux in the past 10 yr	
		18–24.9	71	1.0		
		25–29.9	149	1.4 (1.0–2.0)		
		30–34.9	89	2.5 (1.7–3.6)		
		≥ 35	40	3.7 (2.2–6.2)		
		Overweight or obese		1.8 (1.3–2.5)		
	EJAC: Men and women: 425 Population	BMI 1 yr before				
		18–24.9	107	1.0		
		25–29.9	168	1.1 (0.8–1.5)		
		30–34.9	98	2.0 (1.4–2.9)		
		≥ 35	36	2.5 (1.5–4.1)		
		Overweight or obese		1.8 (1.3–2.5)		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Hoyo et al. (2012) International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) Pooled analysis of 10 case–control and 2 cohort studies from Australia, Europe, and USA	EAC: Men and women: 1997 Population	BMI			Age, sex, smoking, education level, and other study-specific adjustment variables (e.g. study centre)	In stratified analyses, results were independent of the presence of symptoms of gastro-oesophageal reflux No differences in associations by sex
		< 25	577	1.00		
		25.0–29.9	862	1.54 (1.26–1.88)		
		30.0–34.9	331	2.39 (1.86–3.06)		
		35.0–39.9	86	2.79 (1.89–4.12)		
		≥ 40	41	4.76 (2.96–7.66)		
		continuous	1897	1.09 (1.06–1.12)		
	EJAC: Men and women: 1900 Population	BMI				
		< 25	663	1.00		
		25.0–29.9	742	1.28 (1.13–1.45)		
		30.0–34.9	304	2.08 (1.75–2.47)		
		35.0–39.9	85	2.36 (1.75–3.17)		
		≥ 40	28	3.07 (1.89–4.99)		
		continuous	1822	1.07 (1.05–1.09)		
Lahmann et al. (2012) Australia 2002–2005	ESCC: Men and women: 287 Population	BMI in the last year, quintiles (sex-specific)			Age, sex, education level, alcohol consumption, smoking status, NSAID/aspirin use, physical activity BMI at age 20 yr (only for BMI in the last year)	
		Men: / Women:				
		< 22.1 / < 23.7	108	1.00		
		22.1– ≤ 24.6 / 23.7– < 25.6	65	0.61 (0.42–0.90)		
		24.6– ≤ 27.0 / 25.6– ≤ 27.2	35	0.32 (0.20–0.50)		
		27.0– ≤ 31.9 / 27.2– ≤ 29.7	41	0.40 (0.26–0.61)		
		> 31.9 / > 29.7	38	0.36 (0.23–0.57)		
		[P_{trend}]		[< 0.001]		
		Maximum BMI, quintiles (sex-specific)				
		Men: / Women:				
		≤ 23.5 / < 25.1	90	1.00		
		23.5– ≤ 26.0 / 25.1– ≤ 27.0	73	0.78 (0.53–1.15)		
		26.0– ≤ 28.7 / 27.0– ≤ 28.9	42	0.49 (0.32–0.76)		
		28.7– ≤ 33.9 / 28.9– ≤ 31.7	43	0.45 (0.29–0.69)		
		> 33.9 / > 31.7	39	0.44 (0.28–0.69)		
		[P_{trend}]		[< 0.001]		
		BMI at age 20 yr				
		< 25	233	1.00		
		≥ 25	42	0.85 (0.57–1.25)		
		[P_{trend}]		[< 0.40]		

BMI, body mass index (in kg/m²); CI, confidence interval; EAC, oesophageal adenocarcinoma; EJAC, oesophagogastric junction adenocarcinoma; ESCC, oesophageal squamous cell carcinoma; GCAC, gastric cardia adenocarcinoma; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; yr, year or years

Table 2.2.2c Mendelian randomization studies of measures of body fatness and cancer of the oesophagus

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI)	Adjustment for confounding	Comments
Thrift et al. (2014) Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study (BEAGESS)	Subset of ethnically homogenous individuals from 14 studies in Australia, North America, and western Europe	5229 (999 EAC cases and 2169 controls)	1 kg/m^2 increase based on a genetic risk score of 29 SNPs	1.23 (1.06–1.43)	NR	Similar associations in men and women. Associations with the genetic instrument were stronger than those of conventional epidemiological analyses in the same sample

CI, confidence interval; EAC, oesophageal adenocarcinoma; NR, not reported; SNP, single nucleotide polymorphism

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2.2.3 Cancer of the stomach

In 2012, gastric cancer, or cancer of the stomach, was the fifth most commonly diagnosed cancer worldwide, with heterogeneous geographical distribution (Jemal et al., 2014). Gastric cancer can generally be classified into two subsites: cancer of the gastric cardia, which arises from the area of the stomach adjoining the gastro-oesophageal junction, and non-cardia gastric cancer, which develops in the distal stomach and represents about 73% of all gastric cancer cases globally (Colquhoun et al., 2015). Several risk factors for gastric cardia and non-cardia cancer have been identified. For example, infection with *Helicobacter pylori* has been strongly associated with non-cardia gastric cancer, whereas diets rich in smoked foods, salted foods (especially fish), or pickled foods, as well as cigarette smoking, appear to increase the risk of both types of gastric cancer (Kamangar et al., 2006; IARC, 2012).

In 2001, the *IARC Handbook* on weight control and physical activity (IARC, 2002) reviewed the studies of cancer of the gastric cardia together with studies of oesophageal adenocarcinoma, but did not provide a separate evaluation for stomach cancer (cardia or non-cardia). Since then, numerous individual and pooled cohort studies and meta-analyses, as well as several case–control studies of anthropometric measures and risk of stomach cancer have been published. Results from studies that examined this association for gastric cancer not otherwise specified (NOS) and separately for gastric cardia and non-cardia cancers are summarized here and in Tables 2.2.3a, 2.2.3b, and 2.2.3c. Studies that had fewer than 75 incident cases or that overlapped with a more recent study, as well as those that considered gastric cardia and oesophageal cancers together, were excluded.

(a) Cohort studies

(i) Gastric cancer NOS

Since 2000, at least 20 individual cohort studies (Table 2.2.3a) and six meta-analyses or pooled analyses (Table 2.2.3c) of prospective studies have examined associations of baseline BMI with gastric cancer incidence and/or mortality. Most of the individual prospective studies showed no associations with gastric cancer incidence or mortality (Table 2.2.3a). A few studies found inconsistent evidence of either positive or negative associations (Calle et al., 2003; Samanic et al., 2006; Jee et al., 2008; Persson et al., 2008; Camargo et al., 2014).

Although three pooled analyses and one meta-analysis also showed no association between high BMI and incidence of gastric cancer (Lindkvist et al., 2013) or incidence and/or mortality (Renehan et al., 2008; Whitlock et al., 2009; Parr et al., 2010), others were suggestive of a positive association (Yang et al., 2009; Chen et al., 2013; Lin et al., 2014). In the most recent meta-analysis of 12 prospective studies of gastric cancer incidence and mortality combined and more than 41 791 gastric cancer cases, strong associations with overweight and obesity were reported in men only, but there was no evidence of heterogeneity of results according to sex (Chen et al., 2013). The same study did not show heterogeneity in results between Asian and non-Asian populations.

No associations of weight or BMI in early adulthood, usually defined as age 18–21 years, with gastric cancer incidence or mortality were found in three studies (Fujino et al., 2007; Merry et al., 2007; Tanaka et al., 2007), or of BMI change during adulthood in relation to incidence of gastric cancer (Merry et al., 2007; Rapp et al., 2008). No prospective studies of waist circumference and total gastric cancer were identified.

(ii) Cancer of the gastric cardia

Most individual prospective studies of the association between baseline BMI (or weight) and cardia gastric cancer incidence (or incidence and mortality) showed a positive association (see Table 2.2.3a), except for four studies (Tran et al., 2005; Samanic et al., 2006; Corley et al., 2008; Steffen et al., 2015). In the large meta-analysis by Chen et al., overweight was associated with a 21% higher risk (based on six studies) and obesity was associated with an 82% higher risk (based on seven studies) compared with normal BMI (18.5–24.9 kg/m^2) (Chen et al., 2013). These findings were similar to those reported in an earlier meta-analysis of three prospective studies (Yang et al., 2009).

Associations of BMI in early adulthood and adult BMI change with incidence of cardia gastric cancer were examined in only one study of mortality (Merry et al., 2007). In that study, BMI at age 20 years was not associated with risk, whereas increasing BMI from age 20 years to baseline showed a positive association (P_{trend} = 0.02).

Although one study showed no association between sagittal abdominal diameter and risk of gastric cardia cancer (Corley et al., 2008), in the NIH-AARP cohort a 2.2-fold higher risk for the fourth versus the first quartile of waist circumference was reported, with a significant trend (O'Doherty et al., 2012). A similar positive trend of waist circumference and gastric cardia cancer risk (incidence and mortality) was also found in the EPIC study (Steffen et al., 2015).

(iii) Non-cardia gastric cancer

Findings from cohort studies and meta-analyses of excess body weight at baseline in relation to incidence of non-cardia gastric cancer are inconsistent. Neither BMI nor weight was associated with risk in most individual prospective studies (see Table 2.2.3a). Similarly, several meta-analyses did not show an association between BMI and risk either (Yang et al., 2009; Chen et al., 2013; Lin et al., 2014). However, in the Linxian General Population Trial, a significant inverse association was reported with a relative risk of 0.68 for BMI ≥ 23 kg/m^2 versus BMI < 20 kg/m^2 (Tran et al., 2005), and a significant inverse association was also reported in a Swedish cohort study (P_{trend} < 0.01) (Samanic et al., 2006). Conversely, one individual study suggested a positive association of BMI and/or weight and risk of non-cardia gastric cancer (O'Doherty et al., 2012).

No associations were reported in the only study of BMI in early adulthood and adult BMI change in relation to incidence of non-cardia gastric cancer (Merry et al., 2007), or in the three studies that examined waist circumference and risk of non-cardia gastric cancer (MacInnis et al., 2006; O'Doherty et al., 2012; Steffen et al., 2015).

(b) Case–control studies

See Table 2.2.3b.

There were a total of 11 independent reports from case–control studies on the association of BMI with risk of gastric cancer, in China, Europe, Japan, the Republic of Korea, the USA, and Venezuela. With the exception of one hospital-based study (Kim et al., 2015), in which BMI was measured at the time of initial endoscopic diagnosis, BMI was assessed through self-reports of height and body weight, referring to either a recent period (mostly 1 year) before disease diagnosis or a period in the more distant past (e.g. at age 18 years or 20 years), or both. In addition to standard adjustments for age and sex, studies were reported with variable adjustments for further confounding factors such as smoking, alcohol consumption, family history of gastric cancer, dietary variables, or *H. pylori* infection.

With regard to gastric cardia cancer, three out of four studies showed a positive association of BMI with risk. Three studies specifically addressing non-cardia cancer showed no association of recent BMI with risk, whereas two studies reported a positive association of risk

with BMI at age 20 years. With regard to overall gastric cancer – without specification by subsite – three studies showed an increase in risk with increasing BMI, one showed a decrease in risk, and two showed no significant association.

Table 2.2.3a Cohort studies of measures of body fatness and cancer of the stomach

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stomach not otherwise specified							
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	404 576 Men Mortality	Stomach ICD-9: 151.0–151.9	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 388 455 84 18	 1.00 1.01 (0.88–1.16) 1.20 (0.94–1.52) 1.94 (1.21–3.13) [0.03]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, consumption of fat and vegetables; for women, also adjusted for HRT use	
	495 477 Women Mortality		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 304 134 57 13	 1.00 0.89 (0.72–1.09) 1.30 (0.97–1.74) 1.08 (0.61–1.89) [0.46]		
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Stomach ICD-9: 151	Obesity Non-obese Obese Non-obese Obese	 White men: 4989 309 Black men: 2089 99	 1.00 1.07 (0.95–1.20) 1.00 0.98 (0.79–1.20)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Batty et al. (2005) Whitehall study of London-based male government employees United Kingdom 1967–2002	18 403 Men Mortality	Stomach	BMI 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 100 81 9	 1.00 1.05 (0.76–1.44) 1.23 (0.59–2.58) [0.60]	Age, employment grade, physical activity, smoking, marital status, prevalent disease, weight loss in past year, BP medication, height, skinfold thickness, systolic BP, plasma cholesterol, glucose intolerance, diabetes	
Kuriyama et al. (2005) Population-based cohort Japan 1984–1992	12 485 Men Incidence	Stomach ICD-9: 151.0–151.9	BMI 18.5–24.9 25.0–27.4 27..5–29.9 ≥ 30 [P_{trend}]	 243 50 14 7	 1.00 1.01 (0.74–1.37) 0.96 (0.56–1.65) 1.13 (0.53–2.41) [0.91]	Age, smoking, alcohol consumption, diet, type of health insurance; for women, also adjusted for menopausal status, parity, age at menarche, age at first pregnancy	
	15 054 Women Incidence		BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 79 26 17 4	 1.00 1.19 (0.76–1.86) 1.80 (1.06–3.05) 0.79 (0.29–2.17) [0.25]		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	11 023 Men and women Incidence	Stomach	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	 29 217 254 98	 1.05 (0.69–1.58) 1.00 1.09 (0.90–1.32) 1.21 (0.94–1.56) [0.21]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Rapp et al. (2005) VHM&PP (population-based cohort) Austria 1985–2001	67 447 Men Incidence	Stomach ICD-9: 151	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 58 75 13	 1.00 1.04 (0.73–1.47) 0.72 (0.40–1.33) [0.44]	Age, smoking status, occupation	
			BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 56 36 20 6	 1.00 0.78 (0.51–1.20) 1.28 (0.76–2.15) 1.34 (0.57–3.13) [0.48]	Age, smoking status, occupation	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Stomach ICD-7: 151	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 666 531 84	 1.00 0.87 (0.77–0.97) 0.83 (0.66–1.05) [< 0.05]	Attained age, calendar year, smoking	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Fujino et al. (2007) JACC cohort Japan 1988–1997	46 465 Men Mortality	Stomach	BMI			Age, study area	
			< 18.5	54	1.00 (0.75–1.32)		
			18.5–24	569	1.00		
			25–29	89	0.78 (0.62–0.97)		
			≥ 30	7	1.04 (0.49–2.20)		
			Weight (kg)				
			< 55	280	1.00		
			55–62	260	0.88 (0.74–1.04)		
			≥ 63	198	0.83 (0.69–1.01)		
			Weight (kg) at age 20 yr				
			< 55	339	1.00		
			55–60	210	1.04 (0.84–1.30)		
			≥ 61	157	1.17 (0.93–1.48)		
	46 465 Women Mortality	Stomach	BMI			Age, study area	
			< 18.5	37	1.44 (1.01–2.05)		
			18.5–24	227	1.00		
			25–29	66	0.98 (0.74–1.30)		
			≥ 30	11	1.52 (0.82–2.80)		
			Weight (kg)				
			< 47	156	1.00		
			47–54	84	0.79 (0.60–1.03)		
			≥ 55	118	1.01 (0.78–1.29)		
			Weight (kg) at age 20 yr				
			< 47	167	1.00		
			47–52	72	0.97 (0.70–1.34)		
			≥ 53	95	1.25 (0.92–1.70)		
Máchová et al. (2007) National Cancer Registry Czech Republic 1987–2002	17 218 Men Incidence	Stomach ICD-10: C16	BMI	222 total		Age, smoking, hypertension, height	Nested case–control study, reporting odds ratios
			18.5–24.9		1.00		
			25–29.9		1.05 (0.74–1.47)		
			≥ 30		0.92 (0.57–1.50)		
	20 932 Women Incidence		BMI	156 total		Age, smoking, hypertension, height	
			18.5–24.9		1.00		
			25–29.9		0.81 (0.51–1.27)		
			≥ 30		0.97 (0.60–1.57)		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 Men and women Incidence	Stomach, unspecified location ICD-O-3: C16.6–16.9 Histology: 8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572	BMI at baseline			Age, sex, smoking, education level, history of gastric ulcer or bleeding	
			< 20	6	0.92 (0.38–2.25)		
			20–24.9	93	1.00		
			25–29.9	67	0.85 (0.61–1.19)		
			≥ 30	7	0.77 (0.35–1.68)		
			[P_{trend}]		[0.33]		
			BMI at age 20 yr				
			< 20	26	0.60 (0.37–0.99)		
			20–21.4	49	1.00		
			21.5–22.9	40	0.92 (0.59–1.44)		
			23.0–24.9	26	0.70 (0.42–1.18)		
			≥ 25	12	0.82 (0.42–1.60)		
			[P_{trend}]		[0.72]		
			BMI change, age 20 yr to baseline				
			< 0	16	0.85 (0.47–1.55)		
			0–3.9	82	1.00		
			4–7.9	45	0.85 (0.56–1.27)		
			≥ 8	10	0.86 (0.41–1.80)		
			[P_{trend}]		[0.70]		
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence and mortality	Stomach ICD-10: C16	BMI	Incidence:		Age, geographical region, SES, reproductive history, smoking status, alcohol consumption, physical activity, menopausal status, time since menopause, HRT use	
			< 22.5	117	1.26 (1.05–1.51)		
			22.5–24.9	121	1.00 (0.84–1.20)		
			25–27.4	111	1.04 (0.86–1.25)		
			27.5–29.9	76	1.10 (0.88–1.38)		
			≥ 30	96	1.04 (0.84–1.27)		
			BMI	Mortality:			
			< 22.5	92	1.47 (1.19–1.81)		
			22.5–24.9	82	1.00 (0.80–1.24)		
			25–27.4	85	1.16 (0.93–1.43)		
			27.5–29.9	64	1.34 (1.05–1.71)		
			≥ 30	80	1.24 (0.99–1.55)		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Tanaka et al. (2007) Population cohort from Takayama Japan 1992–2000	13 211 Men Mortality	Stomach ICD-9: 151 ICD-10: C16	BMI at baseline < 20.3 20.3–22.2 > 22.2 [P_{trend}] BMI at age 20 yr < 20.3 20.3–22.2 > 22.2 [P_{trend}]	 29 20 16 12 33 41 	 1.00 0.68 (0.34–1.33) 0.53 (0.24–1.20) [0.12] 1.00 2.53 (1.18–5.43) 1.72 (0.79–3.73) [0.76]	Age, smoking, alcohol consumption, education level, physical activity, marital status	Too few incident cases in women (results not shown)
Jee et al. (2008) Cohort from the National Health Insurance Corporation Republic of Korea 1992–2006	770 556 Men Incidence	Stomach	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 1808 5602 3839 3188 131 	 1.04 (0.97–1.13) 1.07 (1.01–1.13) 1.00 1.09 (1.02–1.16) 1.31 (1.05–1.64) [0.50]	Age, smoking	
	423 273 Women Incidence	Stomach	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 524 1314 1035 1132 111 	 0.86 (0.75–1.00) 0.90 (0.80–1.00) 1.00 0.94 (0.84–1.05) 0.84 (0.64–1.11) [0.25]	Age, smoking	
Rapp et al. (2008) VHM&PP (population-based cohort) Austria 1985–2002	28 711 Men Incidence	Stomach ICD-10: C16	BMI change per year < –0.1 –0.1– < 0.1 0.1– < 0.3 ≥ 0.3 [P_{trend}]	 11 25 20 10 	 0.75 (0.36–1.54) 1.00 1.18 (0.65–2.13) 1.22 (0.58–2.59) [0.49]	Age, smoking status, blood glucose, occupational group, baseline BMI	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Rapp et al. (2008) (cont.)	36 938 Women Incidence		BMI change per year < −0.1 −0.1– < 0.1 0.1– < 0.3 ≥ 0.3 [P_{trend}]	 19 12 19 9	 1.73 (0.82–3.63) 1.00 1.73 (0.84–3.57) 1.11 (0.46–2.65) [0.73]	Age, smoking status, blood glucose, occupational group, baseline BMI	
Sjödahl et al. (2008) Nord-Trondelag Health Study Norway 1984–2002	73 133 Men and women Incidence	Stomach, adenocarcinoma ICD-7: 151.0, 151.8, 151.9	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 3 104 110 32	 0.7 (0.1–5.2) 1.0 1.0 (0.7–1.4) 1.1 (0.7–1.8) [0.74]	Age, sex, physical activity, occupation, salt intake, smoking, alcohol consumption	
Whitlock et al. (2009) Pooled analysis of 57 cohort studies Europe and North America Follow-up varied by cohort	894 576 Men and women Mortality	Stomach ICD-9: 151	BMI, per 5 kg/m² For BMI 15–25 For BMI 25–50 For BMI 15–50	 934 651	 0.86 (0.70–1.05) 1.11 (0.94–1.32) 0.98 (0.90–1.07)	Study, sex, age, smoking	
Parr et al. (2010) Pooled analysis of 39 cohort studies Asia, Australia, and New Zealand 1961–1999, median follow-up 4 yr	326 387 Men and women Mortality	Stomach ICD-9: 151 ICD-10: C16	BMI 12–< 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	NR	 1.19 (0.87–1.62) 1.00 1.05 (0.88–1.25) 1.04 (0.67–1.63) [0.66]	Age, sex, smoking	
Chen et al. (2012) Population-based cohort of men China 1990–2006	142 214 Men Mortality	Stomach	BMI 15–23.5 23.5–35	 757 198	 0.74 (0.59–0.94) 0.96 (0.61–1.49)	Age, area, smoking, alcohol consumption, education level	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lindkvist et al. (2013) Metabolic Syndrome and Cancer Project (Me-Can) pooled analysis of prospective cohorts Austria, Norway, and Sweden 1972–2006, follow-up varied by cohort	289 866 Men Incidence	Stomach ICD-7: 151	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 157 134 154 197 186	 1.00 0.79 (0.62–0.99) 0.84 (0.67–1.05) 1.02 (0.83–1.26) 1.00 (0.80–1.24) [0.26]	Smoking, age, study cohort, year of birth	Ranges of BMI quintiles not specified
	288 834 Women Incidence	Stomach ICD-7: 151	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 59 65 63 104 91	 1.00 0.92 (0.65–1.31) 0.73 (0.51–1.05) 1.01 (0.72–1.40) 0.85 (0.61–1.20) [0.68]	Smoking, age, study cohort, year of birth	Ranges of BMI quintiles not specified
Bhaskaran et al. (2014) Population-based cohort: Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Incidence	Stomach ICD-10: C16	BMI per 5 kg/m^2 increase [P_{trend}]	3337 total	 1.03 (0.98–1.09) [0.16]	Age, sex, diabetes, smoking, alcohol consumption, SES, calendar year	Stronger association in non-smokers
Camargo et al. (2014) NIH-AARP cohort USA 1995–2006	483 700 Men and women Incidence	Stomach ICD-10: C16.0–16.9	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 Weight, tertiles T1 T2 T3	1000 total	 1.00 1.05 (0.90–1.22) 1.40 (1.16–1.68) 1.57 (1.21–2.04) 1.00 1.00 (0.86–1.17) 1.18 (1.01–1.38)	Age, sex, education level, cigarette smoking	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Gastric cardia							
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Gastric cardia ICD-9: 151.0	Obesity Non-obese Obese	White men: 841 72	 1.00 1.38 (1.09–1.77)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0 Only 5 cases were available among Black men
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 195 Men and women Incidence	Gastric cardia	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	 2 36 55 20	 0.50 (0.12–2.10) 1.00 1.37 (0.89–2.10) 1.46 (0.84–2.54) [0.04]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Tran et al. (2005) Linxian General Population Trial China 1986–2001	29 584 Men and women Incidence	Gastric cardia	BMI < 20 20–21 22 ≥ 23 [P_{trend}]	1089 total	 1.00 0.98 (0.84–1.16) 0.96 (0.81–1.13) 0.95 (0.80–1.13) [0.51]	Age, sex	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Gastric cardia ICD-7: 151.0	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 108 105 16	 1.00 1.16 (0.88–1.52) 1.09 (0.64–1.85) [0.40]	Attained age, calendar year, smoking	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 Men and women Incidence	Gastric cardia ICD-O-3: C16.0 Histology: 8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572	BMI at baseline < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}] BMI at age 20 yr < 20 20–21.4 21.5–22.9 23.0–24.9 ≥ 25 [P_{trend}] BMI change, age 20 yr to baseline < 0 0–3.9 4–7.9 ≥ 8 [P_{trend}]	 2 68 76 17 21 40 39 22 16 10 70 45 13 	 0.67 (0.16–2.80) 1.00 1.32 (0.94–1.85) 2.73 (1.56–4.79) [0.002] 0.66 (0.39–1.14) 1.00 1.02 (0.65–1.60) 0.75 (0.44–1.28) 1.47 (0.81–2.70) [0.17] 0.68 (0.34–1.35) 1.00 1.22 (0.82–1.82) 2.07 (1.08–3.97) [0.02]	Age, sex	
Abnet et al. (2008) NIH-AARP cohort USA 1995–2003	480 475 Men and women Incidence	Gastric cardia ICD-O-3: C16.0 Histology: “adenocarcinoma”	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35	 1 76 128 71 31	 0.70 (0.10–5.06) 1.00 1.06 (0.79–1.41) 1.70 (1.22–2.36) 2.46 (1.60–3.80)	Age, sex, cigarette smoking, alcohol consumption, education level, physical activity	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Corley et al. (2008) Nested case–control of Kaiser Permanente Multiphasic Health Check-up cohort USA 1964–1973	3150 Men and women Incidence	Gastric cardia ICD-10: C16.0 Histology: 8140–8573	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 1 kg/m² increase Sagittal abdominal diameter (cm) < 20 20–22.4 22.5–25 ≥ 25 per 1 cm increase	 0 43 40 16 16 12 12 14 	 – 1.00 0.91 (0.55–1.53) 2.04 (0.99–4.21) 1.04 (0.98–1.09) 1.00 0.69 (0.29–1.60) 1.17 (0.49–2.84) 1.28 (0.38–4.25) 1.03 (0.95–1.11)	Age, sex, year of health check-up BMI results also adjusted for ethnicity	
O'Doherty et al. (2012) NIH-AARP cohort USA 1995–2006	218 854 Men and women Incidence	Gastric cardia ICD-10: C16.0	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] Weight, quartiles (sex-specific) Q1 Q2 Q3 Q4 [P_{trend}]	 2 50 79 45 15 28 46 44 73 	 2.57 (0.62–10.65) 1.00 1.15 (0.80–1.65) 2.16 (1.41–3.29) 3.67 (2.00–6.71) [< 0.01] 1.00 1.66 (1.03–2.67) 1.53 (0.93–2.51) 2.52 (1.55–4.11) [< 0.01]	Age, sex, total energy intake, antacid use, aspirin use, NSAID use, marital status, diabetes, cigarette smoking, education level, ethnicity, alcohol consumption, physical activity, diet	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
O'Doherty et al. (2012) (cont.)			WC, quartiles (sex-specific)				
			Q1	30	1.00		
			Q2	38	1.32 (0.82–2.14)		
			Q3	51	1.29 (0.82–2.04)		
			Q4	72	2.22 (1.43–3.47)		
			[P_{trend}]		[< 0.01]		
Camargo et al. (2014) NIH-AARP cohort USA 1995–2006	483 700 Men and women Incidence	Gastric cardia ICD-10: C16.0	BMI	478 total		Age, sex, education level, cigarette smoking	
			18.5–24.9		1.00		
			25–29.9		1.10 (0.87–1.38)		
			30–34.9		1.64 (1.26–2.14)		
			≥ 35		2.24 (1.58–3.17)		
			Weight, tertiles				
			T1		1.00		
			T2		1.20 (0.94–1.52)		
			T3		1.53 (1.21–1.92)		
Steffen et al. (2015) EPIC cohort 10 European countries 1992–2008	391 456 Men and women Incidence/mortality	Gastric cardia ICD-10: C16.0	BMI, quintiles			Age, centre, sex, education level, smoking, alcohol consumption, physical activity, diet, height	Sex-specific quintiles for weight, BMI, and WC. Cut-off points not provided, only the median values for each
			Q1	31	1.00		
			Q2	37	1.09 (0.68–1.77)		
			Q3	48	1.37 (0.87–2.17)		
			Q4	41	1.20 (0.74–1.94)		
			Q5	36	1.17 (0.71–1.92)		
			[P_{trend}]		[0.53]		
			Weight, quintiles				
			Q1	33	1.00		
			Q2	37	1.14 (0.71–1.84)		
			Q3	43	1.29 (0.81–2.08)		
			Q4	38	1.11 (0.68–1.83)		
			Q5	42	1.26 (0.75–2.10)		
			[P_{trend}]		[0.48]		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2015) (cont.)			WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 22 31 40 42 45	 1.00 1.20 (0.69–2.09) 1.41 (0.83–2.40) 1.52 (0.89–2.58) 1.59 (0.93–2.73) [0.06]		
Gastric non-cardia							
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Gastric non-cardia ICD-9: 151.x	Obesity Non-obese Obese Non-obese Obese	White men: 4148 237 Black men: 1958 94	 1.00 1.00 (0.88–1.14) 1.00 0.99 (0.80–1.22)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 327 Men and women Incidence	Gastric non-cardia	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	 16 70 83 23	 1.75 (1.00–3.08) 1.00 1.11 (0.80–1.54) 0.87 (0.54–1.41) [0.18]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Tran et al. (2005) Linxian General Population Trial China 1986–2001	29 584 Men and women Incidence	Gastric non-cardia	BMI < 20 20–21 22 ≥ 23 [P_{trend}]	363 total	 1.00 1.00 (0.76–1.32) 0.91 (0.68–1.20) 0.68 (0.49–0.93) [0.017]	Age, sex	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
MacInnis et al. (2006) Melbourne Collaborative Cohort Study Australia 1990–2004	41 295 Men and women Incidence/mortality	Gastric non-cardia ICD-9: 151.1–151.9 ICD-10: C16.1–16.9	BMI < 25 25–29 ≥ 30 [P_{trend}] Weight (kg) Men: Women: < 75 < 62 75–83 62–70 ≥ 84 ≥ 71 [P_{trend}] WC (cm) Men: Women: < 94 < 80 94–101 80–87 ≥ 102 ≥ 88 [P_{trend}]	68 total	1.0 0.5 (0.3–1.0) 1.0 (0.5–1.8) [0.76] 1.0 0.6 (0.3–1.1) 1.1 (0.6–1.9) [0.62] 1.0 0.8 (0.4–1.4) 1.1 (0.6–2.0) [0.57]	Sex, country of birth, education level, physical activity	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Gastric non-cardia ICD-7: 151.x	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	558 426 68	1.00 0.81 (0.72–0.92) 0.78 (0.61–1.01) [< 0.01]	Attained age, calendar year, smoking	
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 Men and women Incidence	Gastric non-cardia ICD-10: C16.1–16.5 Histology: 8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572	BMI at baseline < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	12 115 99 9	1.80 (0.96–3.39) 1.00 0.97 (0.73–1.30) 0.68 (0.34–1.35) [0.13]	Age, sex, current smoking, number of cigarettes smoked per day, smoking duration, education level	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Merry et al. (2007) (cont.)			BMI at age 20 yr				
			< 20	53	1.40 (0.91–2.15)		
			20–21.4	40	1.00		
			21.5–22.9	49	1.24 (0.80–1.91)		
			23.0–24.9	36	1.12 (0.69–1.80)		
			≥ 25	20	1.60 (0.91–2.83)		
			[P_{trend}]		[0.93]		
			BMI change, age 20 yr to baseline				
			< 0	17	0.77 (0.44–1.36)		
			0–3.9	106	1.00		
			4–7.9	61	0.85 (0.60–1.21)		
			≥ 8	14	0.86 (0.46–1.59)		
			[P_{trend}]		[0.77]		
Abnet et al. (2008) NIH-AARP cohort USA 1995–2003	480 475 Men and women Incidence	Gastric non-cardia ICD-O-3: C16.1–16.9 Histology: "adenocarcinoma"	BMI			Age, sex, cigarette smoking, alcohol consumption, education level, physical activity	
			< 18.5	7	2.97 (1.38–6.39)		
			18.5–24.9	107	1.00		
			25–29.9	123	0.80 (0.61–1.04)		
			30–34.9	61	1.08 (0.78–1.50)		
			≥ 35	17	0.84 (0.50–1.42)		
Persson et al. (2008) Japan Public Health Center-based Prospective Study Japan 1990–2004	44 453 Women Incidence	Stomach, non-cardia ICD-10: C16.2-16.7	BMI			Age, family history of gastric cancer, study area	Similar results in postmenopausal women only
			< 20	53	1.00		
			20–24.9	225	0.82 (0.61–1.11)		
			≥ 25	90	0.74 (0.53–1.04)		
			[P_{trend}]		[0.10]		
		Stomach, non-cardia, differentiated cancer type ICD-10: C16.2-16.7	BMI				Similar results in postmenopausal women only
			< 20	12	1.00		
			20–24.9	56	0.93 (0.50–1.74)		
			≥ 25	29	1.12 (0.57–2.21)		
			[P_{trend}]		[0.59]		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Persson et al. (2008) (cont.)		Stomach, non-cardia, undifferentiated cancer type ICD-10: C16.2-16.7	BMI < 20 20–24.9 ≥ 25 [P_{trend}]	 37 153 52	 1.00 0.79 (0.55–1.14) 0.60 (0.39–0.91) [0.01]		Similar results in postmenopausal women only
Sjödahl et al. (2008) Nord-Trondelag Health Study Norway 1984–2002	73 133 Men and women Incidence	Gastric non-cardia ICD-7: 151.0, 151.8, 151.9	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 2 84 92 29	 0.9 (0.1–6.7) 1.0 1.1 (0.7–1.6) 1.2 (0.7–2.1) [0.42]	Age, sex, physical activity, occupation, salt intake, smoking, alcohol consumption	
O'Doherty et al. (2012) NIH-AARP cohort USA 1995–2006	218 854 Men and women Incidence	Gastric non-cardia ICD-10: C16.1–16.7	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] Weight, quartiles (sex-specific) Q1 Q2 Q3 Q4 [P_{trend}] WC, quartiles (sex-specific) Q1 Q2 Q3 Q4 [P_{trend}]	 1 37 60 23 4 20 35 32 38 21 26 40 38 	 1.34 (0.18–9.79) 1.00 1.32 (0.86–2.00) 1.46 (0.84–2.51) 0.99 (0.34–2.84) [0.38] 1.00 1.93 (1.10–3.38) 1.73 (0.96–3.10) 1.93 (1.05–3.54) [0.07] 1.00 1.27 (0.71–2.26) 1.41 (0.82–2.41) 1.46 (0.83–2.55) [0.19]	Age, sex, total energy intake, antacid use, aspirin use, NSAID use, marital status, diabetes, cigarette smoking, education level, ethnicity, alcohol consumption, physical activity, diet	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Camargo et al. (2014) NIH-AARP cohort USA 1995–2006	483 700 Men and women Incidence	Gastric non-cardia ICD-10: C16.1–16.6	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 Weight, tertiles T1 T2 T3	522 total	 1.00 1.09 (0.83–1.43) 1.38 (0.99–1.92) 1.05 (0.61–1.82) 1.00 1.00 (0.76–1.32) 1.02 (0.77–1.34)	Age, sex, education level, cigarette smoking	
Steffen et al. (2015) EPIC cohort 10 European countries 1992–2008	391 456 Men and women Incidence/mortality	Gastric non-cardia ICD-10: C16.1–16.9	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] Weight, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 36 36 33 49 70 50 35 36 57 46 25 25 33 66 55 	 1.00 0.77 (0.48–1.22) 0.61 (0.38–0.99) 0.78 (0.50–1.22) 0.99 (0.64–1.54) [0.41] 1.00 0.68 (0.44–1.06) 0.67 (0.43–1.06) 1.02 (0.68–1.55) 0.84 (0.53–1.32) [0.94] 1.00 0.81 (0.46–1.42) 0.89 (0.52–1.52) 1.58 (0.97–2.57) 1.14 (0.68–1.91) [0.12]	Sex, education level, smoking, alcohol consumption, physical activity, diet, height	Sex-specific quintiles for weight, BMI, and WC. Cut-off points not provided, only the median values for each

BMI, body mass index (in kg/m^2); BP, blood pressure; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; ICD, International Classification of Diseases; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; VHM&PP, Vorarlberg Health Monitoring and Prevention Program; WC, waist circumference; yr, year or years

Table 2.2.3b Case–control studies of measures of body fatness and cancer of the stomach

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Stomach							
Hansson et al. (1994) Sweden 1989–1992	338 Population	Stomach	BMI at age 20 yr			Age, height	No differences were observed in the associations by age at interview (age groups: < 59 yr, 60–69 yr, and ≥ 70 yr) No associations were found between BMI and GC 20 yr before the interview
				Men:			
			≤ 21.20	37	1.00		
			21.21–22.60	40	1.06 (0.63–1.86)		
			22.62–24.20	45	1.09 (0.66–1.82)		
			≥ 24.21	84	2.16 (1.35–3.46)		
			continuous		1.12 (1.05–1.20)		
				Women:			
			≤ 19.20	12	1.00		
			19.21–20.80	18	1.39 (0.60–3.23)		
			20.81–23.30	40	3.06 (1.43–6.58)		
			≥ 23.21	28	2.14 (0.96–4.78)		
			continuous		1.11 (1.02–1.21)		
Muñoz et al. (2001) Venezuela 1991–1997	292 Population	Stomach	BMI			Age, sex	Similar results for self-reported weight at current age. Increased risk in overweight cases with self-reported weight in childhood, adolescence, and early adulthood
			< 18.5	51	11.0 (4.8–27.0)		
			18.5–25.0	200	1.0		
			> 25.0	41	0.3 (0.2–0.4)		
Inoue et al. (2002) Japan 1988–1998	Women: 365 Population	Stomach	Current BMI			Age, year, season of interview, family history of GC, smoking status, intake of raw vegetables and fish	Postmenopausal women only. *P* values for trend were non-significant among all subsites, both for current BMI and for BMI at age 20 yr
		Upper third		72 total			
			< 21.08		1.00		
			21.08–23.56		1.69 (0.91–3.12)		
			> 23.56		1.07 (0.54–2.10)		
		Middle third		155 total			
			< 21.08		1.00		
			21.08–23.56		0.75 (0.49–1.16)		
			> 23.56		0.80 (0.52–1.22)		
		Lower third		127 total			
			< 21.08		1.00		
			21.08–23.56		1.02 (0.63–1.66)		
			> 23.56		1.16 (0.72–1.89)		

Table 2.2.3b (continued)

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Inoue et al. (2002) (cont.)			BMI at age 20 yr				
		Upper third		72 total			
			< 21.08		1.00		
			21.08–23.56		1.33 (0.69–2.55)		
			> 23.56		1.33 (0.69–2.58)		
		Middle third		155 total			
			< 21.08		1.00		
			21.08–23.56		1.83 (1.14–2.94)		
			> 23.56		1.81 (1.12–2.93)		
		Lower third		127 total			
			< 21.08		1.00		
			21.08–23.56		0.88 (0.52–1.50)		
			> 23.56		1.31 (0.81–2.12)		
Chung et al. (2010) Republic of Korea 1990–2008	Men: 374 Women: 270 Hospital	Stomach	Current BMI			Age	Study in young individuals (ages 18–45 yr)
			> 35 vs ≤ 35	Men: 374 total	1.94 (1.63–2.37)		
			> 35 vs ≤ 35	Women: 270 total	1.65 (1.34–2.04)		
Praud et al. (2014) Italy 1985–2007	Men: 612 Women: 387 Hospital	Stomach	BMI			Age, sex, study, year of interview, education level, tobacco smoking, family history, total energy intake	
			< 25 vs ≥ 25 [P_{trend}]	Men: 646 total	0.85 (0.79–0.90) [< 0.0001]		
			< 25 vs ≥ 25 [P_{trend}]	Women: 348 total	0.86 (0.79–0.93) [0.0009]		
Kim et al. (2015) Republic of Korea 2003–2013	Men: 663 Women: 335 Hospital	Stomach	BMI measured at endoscopy			Age, smoking status, drinking status, family history of GC, *Helicobacter pylori* infection, atrophic gastritis, intestinal metaplasia, serum pepsinogen I/II ratio	No significant associations were observed when stratifying by cardia and non-cardia GC
			< 23	Men: 286	1.00		
			23– < 25	193	1.25 (0.87–1.81)		
			≥ 25– < 30	175	1.33 (0.92–1.92)		
			≥ 30	9	1.27 (0.42–3.86)		
			[P_{trend}]		[0.43]		

Table 2.2.3b (continued)

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Kim et al. (2015) (cont.)				Women:			
			< 23	182	1.00		
			23– < 25	73	0.92 (0.6–1.43)		
			≥ 25– < 30	69	1.11 (0.70–1.77)		
			≥ 30	11	0.86 (0.33–2.26)		
			[P_{trend}]		[0.904]		
Song et al. (2015) Republic of Korea 2010–2014	1492 Population	Stomach	BMI at age 18 yr			Age, smoking status, alcohol drinking status, regular exercise, family history of GC, past medical history	
				Men:			
			21.75		1.00		
			≥ 25.3		1.13 (1.01–1.55)		
				Women:			
			21.75		1.00		
			≥ 25.3		1.25 (1.01–1.55)		
Gastric cardia							
Vaughan et al. (1995) USA (13 counties of Washington State) 1993–1990	165 Population	Gastric cardia, adenocarcinoma	BMI, percentiles			Age, sex, education level, race, cigarette smoking, alcohol consumption	BMI percentiles (derived from in- person interviews) based on distribution of controls for each sex separately
			1–10%	13	0.8 (0.4–1.8)		
			10–49%	52	1.0		
			50–89%	74	1.3 (0.8–2.1)		
			90–100%	25	1.6 (0.8–3.0)		
Chow et al. (1998) USA 1993–1995	365 Population	Gastric cardia	BMI (sex-specific)			Geographical location, age, sex, race, cigarette smoking, respondent status	BMI up to 1 yr before diagnosis for cases and date of interview for controls
			Men: Women:				
			< 23.12 < 21.95	54	1.0		
			23.12–25.08 21.95–24.12	51	0.9 (0.6–1.5)		
			25.09–27.31 24.13–27.43	70	1.4 (0.9–2.1)		
			≥ 27.32 ≥ 27.44	86	1.6 (1.1–2.6)		
			[P_{trend}]		[0.008]		

Table 2.2.3b (continued)

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Lagergren et al. (1999) Sweden 1995–1997	262 Population	Gastric cardia	BMI 20 yr before interview			Age, sex, tobacco smoking, alcohol consumption, SES, reflux symptoms, intake of fruits and vegetables, energy intake, physical activity	
			< 22	47	1.0		
			22–24.9	100	1.3 (0.8–1.9)		
			25–30	91	2.2 (1.4–3.4)		
			> 30	24	4.3 (2.1–8.7)		
			[P_{trend}]		[< 0.001]		
			BMI at age 20 yr, quartiles (sex-specific)				
			Men: Women:				
			< 20.7 < 19.3	52	1.0		
			20.7–22.1 19.3–20.4	46	0.8 (0.5–1.3)		
			22.2–23.7 20.5–22.1	65	1.2 (0.8–1.9)		
			> 23.7 > 22.1	99	1.9 (1.3–2.9)		
			[P_{trend}]		[< 0.001]		
Wu et al. (2001) USA 1992–1997	277 Population (proxy control)	Gastric cardia	BMI at age 40 yr, quartiles (sex-specific)			Smoking, age, sex, race, education level	
			Men: Women:	247 total			
			≤ 22 ≤ 21		1.00		
			> 22– ≤ 25 > 21– ≤ 23		1.49 (1.0–2.1)		
			> 25– ≤ 27 > 23– ≤ 25		1.45 (0.9–2.3)		
			> 27 > 25		2.08 (1.4–3.2)		
			[P_{trend}]		[0.016]		
			BMI at age 20 yr, quartiles (sex-specific)				
			Men: Women:	246 total			
			≤ 20 ≤ 18		1.00		
			> 20– ≤ 22 > 18– ≤ 20		1.13 (0.8–1.7)		
			> 22– ≤ 24 > 20– ≤ 22		1.36 (0.9–2.0)		
			> 24 > 22		1.71 (1.2–2.6)		
			[P_{trend}]		[0.006]		
Gastric non-cardia							
Chow et al. (1998) USA 1993–1995	365 Population	Gastric non-cardia	BMI up to 1 yr before diagnosis (sex-specific)			Geographical location, age, sex, race, cigarette smoking, respondent status	BMI up to 1 yr before diagnosis for cases and date of interview for controls
			Men: Women:				
			< 23.12 < 21.95	105	1.0		
			23.12–25.08 21.95–24.12	77	0.9 (0.6–1.4)		
			25.09–27.31 24.13–27.43	91	1.2 (0.8–1.8)		
			≥ 27.32 ≥ 27.44	92	1.2 (0.8–1.8)		
			[P_{trend}]		[2.14]		

Table 2.2.3b (continued)

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Wu et al. (2001) USA 1992–1997	443 Population	Gastric non-cardia	BMI at age 40 yr, quartiles (sex-specific) Men: Women: ≤ 22 ≤ 21 > 22– ≤ 25 > 21– ≤ 23 > 25– ≤ 27 > 23– ≤ 25 > 27 > 25 [P_{trend}]	352 total	 1.00 0.86 (0.6–1.2) 1.00 (0.7–1.5) 1.10 (0.8–1.6) [0.57]	Smoking, age, sex, race, education level	Results did not change when stratifying by Whites/non-Whites or by sex
			BMI at age 20 yr, quartiles (sex-specific) Men: Women: ≤ 20 ≤ 18 > 20– ≤ 22 > 18– ≤ 20 > 22– ≤ 24 > 20– ≤ 22 > 24 > 22 [P_{trend}]	352 total	 1.00 1.21 (0.9–1.7) 1.39 (1.0–2.0) 1.43 (1.0–2.1) [0.03]		

BMI, body mass index (in kg/m^2); CI, confidence interval; GC, gastric cancer; SES, socioeconomic status; yr, year or years

Table 2.2.3c Meta-analyses of measures of body fatness and cancer of the stomach

Reference Period	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Renehan et al. (2008) 1996–2007	Men: 8 prospective studies 817 incident cases	Stomach	BMI per 5 kg/m² increase	0.97 (0.88–1.06)	Age (all studies) and other factors (not in all studies)	
	Women: 5 prospective studies 325 incident cases	Stomach	BMI per 5 kg/m² increase	1.04 (0.90–1.20)		
Yang et al. (2009) 1950–2009	12 prospective studies 9492 incident cases	Stomach	BMI Overweight and obese vs normal Obese vs normal Overweight vs normal	 1.22 (1.06–1.41) 1.36 (1.21–1.54) 1.21 (1.08–1.36)	NR	No differences in risk by sex; normal, overweight, and obese are defined in most studies as BMI of 18.5–25, 25–29.9, and ≥ 30, respectively
	3 prospective studies	Cardia	BMI Overweight and obese vs normal Obese vs normal Overweight vs normal	 1.55 (1.31–1.84) 2.06 (1.63–2.61) 1.40 (1.16–1.68)	NR	
	4 prospective studies	Non-cardia	BMI Overweight and obese vs normal Obese vs normal Overweight vs normal	 1.18 (0.96–1.45) 1.26 (0.89–1.78) 1.16 (0.94–1.43)	NR	
Chen et al. (2013) 1994–2012	12 prospective studies 41 791 incident cases	Stomach	BMI 18.5– < 25 25–29.9 ≥ 30	 1.00 1.01 (0.96–1.07) 1.06 (0.99–1.12)		Stronger associations in men in both BMI groups
	7 prospective studies	Cardia	BMI 18.5– < 25 25–29.9 ≥ 30	 1.00 1.21 (1.03–1.42) 1.82 (1.32–2.49)		
	8 prospective studies	Non-cardia	BMI 18.5– < 25 25–29.9 ≥ 30	 1.00 0.93 (0.82–1.05) 1.00 (0.87–1.15)		

Table 2.2.3c (continued)

Reference Period	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Lin et al. (2014) NR	13 prospective studies and 3 case–controls NR	Stomach	BMI		Age and others (not specified)	Stronger association of obesity with risk in men (5 studies) and in non-Asian population (11 studies)
			18.5– < 25	1.00		
			25–29.9	1.13 (1.03–1.24)		
			≥ 30	1.04 (0.96–1.12)		
		Cardia	BMI		Age and others (not specified)	
			18.5– < 25	1.00		
			25–29.9	1.61 (1.15–2.24)		
			≥ 30	1.22 (1.05–1.42)		
		Non-cardia	BMI		Age and others (not specified)	
			18.5– < 25	1.00		
			25–29.9	0.83 (0.68–1.01)		
			≥ 30	0.94 (0.81–1.10)		

BMI, body mass index (in kg/m^2); CI, confidence interval; CRC, colorectal cancer; HRT, hormone replacement therapy; IBD, inflammatory bowel disease; NR, not reported

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2.2.4 Cancer of the liver (hepatocellular carcinoma)

Hepatocellular carcinoma (HCC) is the most frequent primary malignancy of the liver (> 80% of primary liver cancers) and occurs predominantly in patients with underlying chronic liver disease or cirrhosis. Worldwide, liver cancer is among the most common causes of cancer death; the highest rates of liver cancer incidence and mortality occur in some areas in Asia and sub-Saharan Africa, as a result of chronic hepatitis infection (Jemal et al., 2014).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and liver cancer was *inadequate*. Since then, numerous individual cohort studies with at least 100 cases (Table 2.2.4a), case–control studies (Table 2.2.4b), and pooled and meta-analyses of cohort studies and case–control studies (Table 2.2.4c) have been published examining the association of anthropometric factors with liver cancer incidence and/or mortality. Notably, because chronic liver disease is among the most common risk factors for cancer of the liver, results from cohort studies of anthropometric factors in relation to liver cancer incidence and/or mortality in patients with liver disease have also been included.

(a) Cohort studies

(i) Body weight and body mass index

Six cohort studies of BMI or weight in relation to risk of HCC specifically (Samanic et al., 2006; Joshi et al., 2008; Ohishi et al., 2008; Borena et al., 2012; Loomba et al., 2013; Schlesinger et al., 2013) have been published (Table 2.2.4a). Of these studies, four showed statistically significant positive associations and/or trends (Samanic et al., 2006; Ohishi et al., 2008; Borena et al., 2012; Schlesinger et al., 2013). In a large cohort of men in Sweden, a relative risk for BMI ≥ 30 kg/m^2 versus BMI < 25 kg/m^2 of 3.13 (95% CI, 2.04–4.79) was reported (Samanic et al., 2006).

At least eight other studies have examined the association between BMI and liver cancer (hepatocellular and intrahepatic bile duct combined, or NOS) incidence and/or mortality (Table 2.2.4a). One study of Japanese men and women showed no evidence of association with increased incidence (Kuriyama et al., 2005) [the number of liver cancer cases in the highest categories of BMI was small or zero in both sexes, and therefore power was limited to detect an association]. Conversely, in the large Korea National Health Insurance Corporation Study, risk of liver cancer increased significantly for BMI ≥ 30 kg/m^2 in men (relative risk [RR], 1.63; 95% CI, 1.27–2.10) and in women (RR, 1.39; 95% CI, 1.00–1.94), compared with the reference category of BMI of 23.0–24.9 kg/m^2. Significant P_{trend} values were found in both men and women (Jee et al., 2008). Strong positive associations were also observed in another prospective cohort study of BMI in relation to liver cancer incidence, a data linkage study in the United Kingdom where a 5 kg/m^2 increase in BMI was associated with a 19% increase in risk (95% CI, 1.12–1.27) (Bhaskaran et al., 2014).

In general, studies of BMI in relation to liver cancer mortality (Calle et al., 2003) or liver cancer incidence and mortality combined (Borena et al., 2012) showed strong positive associations. For example, in the Cancer Prevention Study II in the USA, there was a strong positive association between liver cancer mortality in men (RR, 4.52; 95% CI, 2.94–6.94 for BMI ≥ 35 kg/m^2 vs 18.5–24.9 kg/m^2; P_{trend} < 0.001), and to a lesser extent in women (RR, 1.68; 95% CI, 0.93–3.05 for BMI ≥ 35 kg/m^2 vs 18.5–24.9 kg/m^2; P_{trend} < 0.04) (Calle et al., 2003). In the Japan Collaborative Cohort Study, there was evidence of an association between higher BMI and liver cancer

mortality when men with liver disease were excluded (Li et al., 2013).

Associations of measures of body weight and liver cancer have been examined in at least six cohort studies of patients with cirrhosis, hepatitis infections, or other liver conditions. Of these studies, four showed statistically significant positive associations or trends between BMI and risk of HCC (N'Kontchou et al., 2006; Ioannou et al., 2007; Yu et al., 2008; Ohki et al., 2008). In the study with the largest number of HCC cases, the relative risk for BMI ≥ 30 kg/m^2 versus BMI < 18.5 kg/m^2 was 3.10 (95% CI, 1.41–6.81) in Japanese men and women who were patients at a liver clinic (Ohki et al., 2008). Two studies of cirrhosis patients also showed statistically significant 2.5–2.8-fold higher risks of HCC for obese versus normal-weight patients (N'Kontchou et al., 2006; Ioannou et al., 2007). The association was approximately of the same magnitude in a prospective study in Taiwan, China, of carriers of hepatitis B virus (HBV) (RR, 1.96; 95% CI, 0.72–5.38 for BMI ≥ 30 kg/m^2 vs 18.5–24.9 kg/m^2; P_{trend} = 0.048) [only 4 obese men developed HCC during follow-up] (Yu et al., 2008). A Japanese study of patients with hepatitis C virus (HCV) infection also found evidence of a borderline positive association when BMI was modelled as a continuous measure in women (RR per 1 kg/m^2 increase in BMI, 1.09; 95% CI, 0.99–1.19) but not in men (RR per 1 kg/m^2 increase in BMI, 1.01; 95% CI, 0.93–1.09) (Arano et al., 2011).

There have been numerous meta-analyses (Larsson & Wolk, 2007; Renehan et al., 2008; Chen et al., 2012; Rui et al., 2012; Tanaka et al., 2012; Wang et al., 2012; WCRF/AICR, 2015; Table 2.2.4c) and a large pooled analysis of 57 cohorts (Whitlock et al., 2009) on BMI and (primary) liver cancer incidence or mortality. Overall, these meta-analyses showed an increased risk of liver cancer in individuals with higher BMI independently of sex, geographical region, duration of follow-up, and potential confounders such as alcohol consumption, cigarette smoking, or diabetes history. The largest meta-analysis, by Chen et al. (2012), which included 26 prospective cohorts from Asia, Europe, and the USA, found a stronger risk of primary liver cancer in relation to higher BMI in patients with liver cirrhosis or HBV or HCV infection (n = 9 cohorts, summary RR, 1.73; 95% CI, 1.28–2.35) compared with the BMI-associated risk observed in the general population (n = 17 cohorts, summary RR, 1.36; 95% CI, 1.20–1.53) [the P value for difference was 0.15]. In the recent meta-analysis of the WCRF Continuous Update Project, a 5 kg/m^2 increase in BMI was associated with a 43% (95% CI, 1.19–1.70) increase in liver cancer incidence and a 13% (95% CI, 1.00–1.28) increase in liver cancer mortality based on 8 and 4 cohort studies, respectively, and the association was stronger in studies in Europe (summary RR, 1.59; 95% CI, 1.35–1.87) than in studies in Asia (summary RR, 1.18; 95% CI, 1.04–1.34) (WCRF/AICR, 2015).

(ii) Weight at different ages and weight change

Only a few cohort studies examined associations of BMI and/or weight at earlier ages or change in BMI or weight with risk of liver cancer. In the EPIC study, BMI at age 20 years was overall not associated with liver cancer mortality (Schlesinger et al., 2013). However, in that study there was a positive dose–response relationship between the average annual weight change from age 20 years to age at reporting and increased risk; the relative risk for each kilogram per year increase in weight of HCC was 3.51 (95% CI, 1.93–6.41), after adjustment for weight at age 20 years and other confounding factors. In a large Swedish occupational cohort, 6-year BMI change during adulthood in relation to liver cancer incidence was examined (Samanic et al., 2006). Although the results were somewhat suggestive of an increasing risk with increasing BMI gain, there were only 55 cases in total [and therefore statistical power was limited

to detect associations]. Similarly, in the Japan Collaborative Cohort Study, change in weight between age 20 years and baseline was not associated with liver cancer mortality in men or women, although some evidence for a trend could be observed in women (Li et al., 2013).

(iii) Waist circumference

A positive association between waist circumference and incidence of HCC was shown in the EPIC study, which was the only study to examine this association (Schlesinger et al., 2013). In that study, each increase of 5 cm in waist circumference was associated on average with a 25% (95% CI, 1.17–1.33) increase in risk in men and women combined.

(b) Case–control studies

A total of five case–control studies have been published since 2001 on the association of BMI with HCC in Canada, China, France, Italy, and the USA (Table 2.2.4b).

In the USA, a study of 622 cases and 660 population control subjects showed an increased risk of HCC for men and women with early adulthood (mid-20s to mid-40s) obesity (BMI > 30 kg/m^2) compared with normal-weight individuals (men: OR, 2.3; 95% CI, 1.2–4.4; women: OR, 3.6; 95% CI, 1.5–8.9) (Hassan et al., 2015), but no association was found for recalled BMI in the mid-50s. A hospital-based case–control study in Italy also showed an increased risk for subjects with elevated recalled BMI at about age 30 years, but not for BMI 1 year before cancer diagnosis (or equivalent time frame for the controls) (Polesel et al., 2009), and a study in France also showed a direct association of HCC risk with recalled past obesity in patients with non-viral liver cirrhosis (Archambeaud et al., 2015). In contrast, a population-based case–control study in Canada showed no association between risk of liver cancer and self-reported BMI 1 year before diagnosis (Pan et al., 2004).

Finally, using waist circumference as a measure of adiposity, a large population-based case–control study with 3649 cases all aged 68 years or older identified through the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute, and with 195 953 population control subjects, showed a significantly increased risk of HCC in men with waist circumference greater than 40 inches (101 cm) and in women with waist circumference greater than 35 inches (89 cm), compared with men or women with a smaller waist circumference (OR, 1.93; 95% CI, 1.71–2.18) (Welzel et al., 2011).

Several of the above-mentioned studies considered HBV or HCV infection as a confounder or effect modifier for the association between BMI and risk of liver cancer. In the study in Italy (Polesel et al., 2009), HCC risk was significantly increased in obese subjects without HBV and HCV infection (OR, 3.5; 95% CI, 1.3–9.2; compared with BMI < 30 kg/m^2) but not in subjects with HBV or HCV infection. The study by Hassan et al. (2015) in the USA showed a synergistic interaction between obesity and hepatitis virus infection, with highly increased risk in obese subjects with HBV or HCV infection.

Table 2.2.4a Cohort studies of measures of body fatness and cancer of the liver

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Hepatocellular carcinoma							
N'Kontchou et al. (2006) Cohort of patients with cirrhosis France 1994–2004	771 Men and women Incidence	HCC	BMI < 25 25–30 ≥ 30	220 total	 1.0 2.0 (1.4–2.7) 2.8 (2.0–4.0)		Patients with alcohol- or hepatitis C-related cirrhosis
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	HCC	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 73 90 31	 1.00 1.45 (1.06–1.98) 3.13 (2.04–4.79) [< 0.001]	Attained age, calendar year, smoking	Based on fewer than 30 incident cases, no significant associations for cholangiocarcinoma or adenocarcinoma of the liver were found. No associations between BMI change and liver cancer overall observed (n = 469)
Ioannou et al. (2007) Cohort of cirrhosis patients in the Veterans Affairs facility USA 1994–2005	2126 Men and women Incidence	HCC ICD-9: 155.0	BMI 18.5–24.9 25–29 ≥ 30	 15 45 40	 1.00 2.8 (1.4–5.4) 2.5 (1.3–4.9)	Age, HCV infection, HBsAg, HBV core antibody, type 2 diabetes mellitus, platelet count	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Joshi et al. (2008) Korean male civil service workers cohort Republic of Korea 1999–2004	548 530 Men Mortality	HCC ICD-10: C22.0	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	989 total	 1.00 1.38 (0.90–2.11) 0.98 (0.85–1.12) 1.08 (0.67–1.72)	Age, serum glucose, alcohol consumption, tobacco use, HBsAg	
Ohishi et al. (2008) Nested case–control in the Adult Health Study (atomic bomb survivors) Japan 1970–2002	868 Men and women Incidence	HCC	BMI 10 yr before diagnosis < 19.6 19.6–21.2 21.3–22.9 23–25 > 25 per 1 kg/m^2 [P_{trend}]	 38 33 36 49 54	 1.31 (0.51–3.34) 1.24 (0.43–3.54) 1.00 2.51 (0.99–6.37) 4.57 (1.85–11.3) 1.12 (1.03–1.22) [0.01]	Hepatitis infection, alcohol consumption, smoking, coffee consumption, diabetes, radiation dose to liver	
Ohki et al. (2008) Hospital-based cohort of patients with chronic hepatitis C Tokyo, Japan 1994–2006	1431 Men and women Incidence	HCC	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	340 total	 1.00 1.52 (0.93–2.47) 1.86 (1.09–3.16) 3.10 (1.41–6.81)	Age, sex, heavy alcohol consumption, diabetes mellitus, serum albumin concentration, total bilirubin concentration, ALT levels, prothrombin time activity, platelet counts, AFP concentration	
Yu et al. (2008) Cohort of male government employees (HBV carriers) Taiwan, China 1989–2005	2903 Men Incidence	HCC	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 3 77 50 4	 1.55 (0.49–4.93) 1.00 1.48 (1.04–2.12) 1.96 (0.72–5.38) [0.048]	Age, number of clinic visits, smoking, alcohol consumption, diabetes	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Loomba et al. (2010) HBV-positive men part of the REVEAL-HBV cohort Taiwan, China 1991–2004	2260 Men Incidence	HCC	BMI per 1 kg/m² increase	136	1.00 (0.93–1.06)	Age, serum HBV DNA level, smoking, serum ALT level, HBeAg status, cirrhosis at baseline visit	Alcohol consumption–BMI interaction
Arano et al. (2011) Hospital-based cohort of patients with hepatitis C Japan 1994–2009	146 Men Incidence	HCC	BMI per 1 kg/m² increase	67	1.01 (0.93–1.09)	Age, alcohol consumption, serum biomarkers, platelet count, diabetes	
	179 Women Incidence	HCC	BMI per 1 kg/m² increase	55	1.09 (0.99–1.19)	Age, alcohol consumption, serum biomarkers, platelet count, diabetes	
Borena et al. (2012) Me-Can cohorts Austria, Norway, and Sweden 1972–2006, follow-up varied by cohort	578 700 Men and women Incidence and mortality	HCC	BMI, per unit SD	155 total	1.51 (1.29–1.77)	Age, cohort, year of birth, sex, smoking status	
Loomba et al. (2013) Population-based cohort of residents (7 townships) Taiwan, China 1991–2004	23 712 Men and women Incidence	HCC	BMI < 30 ≥ 30	 284 21	 1.00 1.47 (0.85–2.30)	Only univariate model available	A significant interaction was reported between alcohol drinkers (4 days per week for at least 1 yr) and BMI ≥ 30 kg/m², with a 7-fold increased risk of HCC

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schlesinger et al. (2013) EPIC cohort 10 European countries 1992–2010	Men and women Incidence	HCC ICD-10: C22.0	BMI, tertiles (sex-specific) Men: Women: < 24.93 < 23.04 24.93–27.8 23.04–26.64 ≥ 27.81 ≥ 26.65 [P_{trend}] per 5 kg/m^2 Weight, tertiles T1 T2 T3 [P_{trend}] per 5 kg Weight change from age 20 yr to age at reporting, tertiles T1 T2 T3 [P_{trend}] per kg/yr WC, tertiles T1 T2 T3 [P_{trend}] per 5 cm	33 49 95 46 50 81 30 32 46 27 50 100 	1.00 1.31 (0.84–2.05) 2.28 (1.50–3.45) [< 0.0001] 1.55 (1.31–1.83) 1.00 1.19 (0.78–1.80) 2.04 (1.36–3.06) [< 0.001] 1.18 (1.11–1.25) 1.00 1.30 (0.77–2.19) 2.48 (1.49–4.13) [< 0.001] 3.51 (1.93–6.41) 1.00 1.45 (0.90–2.34) 2.60 (1.66–4.07) [< 0.0001] 1.25 (1.17–1.33)	Age, sex, study centre, education level, smoking, alcohol consumption, height Analysis of weight change also adjusted for weight at age 20 yr	Associations were lost when BMI analyses were further adjusted for WC No significant associations were observed with weight at age 20 yr, when comparing extreme tertiles (P_{trend} = 0.95)
Liver NOS							
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	404 576 Men Mortality	Liver	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	222 296 78 24 	1.00 1.13 (0.94–1.34) 1.90 (1.46–2.47) 4.52 (2.94–6.94) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, consumption of fat and vegetables	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) (cont.)	495 477 Women Mortality	Liver	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 200 96 37 12	 1.00 1.02 (0.80–1.31) 1.40 (0.97–2.00) 1.68 (0.93–3.05) [0.04]	For women, also adjusted for HRT use	
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Liver ICD-9: 155	Obesity Non-obese Obese Non-obese Obese	 White men: 3612 322 Black men: 1168 38	 1.00 1.44 (1.28–1.61) 1.00 0.68 (0.49–0.94)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0 Significantly different risk in White men and Black men ($P < 0.001$)
Kuriyama et al. (2005) Population-based cohort in Miyagi Prefecture Japan 1984–1992	12 485 Men Incidence 15 054 Women Incidence	Liver ICD-9: 155.0–155.2 Liver ICD-9: 155.0–155.2	BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}] BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 55 9 5 – 220 7 4 –	 1.00 0.80 (0.40–1.63) 1.14 (0.46–2.87) – [0.92] 1.00 1.30 (0.54–3.16) 0.91 (0.30–2.80) – [0.94]	Age, smoking, alcohol consumption, consumption of red meat, fruits and vegetables, and bean paste, type of health insurance; for women, also adjusted for menopausal status, parity, age at menarche, age at first pregnancy	
Jee et al. (2008) Cohort from National Health Insurance Corporation Republic of Korea 1992–2006	770 556 Men Incidence	Liver	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 862 3260 2463 2062 112	 0.90 (0.81–1.00) 0.97 (0.90–1.04) 1.00 1.04 (0.96–1.13) 1.63 (1.27–2.10) [0.0002]	Age, smoking	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Jee et al. (2008) (cont.)	423 273 Women Incidence	Liver	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 195 505 411 587 63	 0.85 (0.67–1.06) 0.76 (0.64–0.91) 1.00 1.14 (1.97–1.35) 1.39 (1.00–1.94) [< 0.0001]	Age, smoking	
Whitlock et al. (2009) Pooled analysis of 57 cohort studies Europe, Japan, and USA Follow-up varied by cohort	894 576 Men and women Mortality	Liver ICD-9: 155	BMI For BMI 15–25 For BMI 25–50 For BMI 15–50	 201 221 422	 1.37 (0.87–2.15) 1.61 (1.26–2.05) 1.47 (1.26–1.71)	Study, sex, age, smoking	
Parr et al. (2010) Pooled analysis of 39 cohort studies Asia, Australia, and New Zealand 1961–1999, median follow-up 4 yr	326 387 Men and women Mortality	Liver ICD-9: 155 ICD-10: C22	BMI 12.0–18.4 18.5–24.9 25–29.99 ≥ 30 per 5 kg/m^2 [P_{trend}]	774	 1.13 (0.78–1.64) 1.00 (0.89–1.13) 1.06 (0.83–1.36) 1.10 (0.63–1.91) 1.11 (0.94–1.31) [0.58]	Age, sex, smoking status	
Borena et al. (2012) Me-Can cohorts Austria, Norway, and Sweden 1972–2006, follow-up varied by cohort	578 700 Incidence and mortality	Liver, primary cancer ICD-7: 155.0	BMI, quintiles (mean) Q1 (20.7) Q2 (23.0) Q3 (24.7) Q4 (26.8) Q5 (31.3) [P_{trend}]	 36 38 45 53 94	 1.00 0.91 (0.55–1.51) 0.97 (0.59–1.57) 1.02 (0.63–1.64) 1.92 (1.23–2.96) [0.001]	Age, smoking status, cohort, year of birth, sex	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Li et al. (2013) JACC cohort Japan 1988–2009	31 018 Men Mortality	Liver ICD-10: C22.0–22.9	BMI at baseline			Age, smoking status, alcohol consumption, physical activity, intake of coffee and fish, education level, area of residence, diabetes, gall bladder disease, blood transfusions, history of liver disease	In stratified analyses, significant associations were observed in men without liver disease (P_{trend} = 0.03)
			< 18.5	32	1.42 (0.93–2.15)		
			18.5–20.9	82	1.09 (0.81–1.48)		
			21–22.9	88	1.00		
			23–24.9	73	1.04 (0.76–1.42)		
			≥ 25	63	1.15 (0.83–1.60)		
			[P_{trend}]		[0.37]		
			BMI at age 20 yr				
			< 18.5	14	0.74 (0.42–1.29)		
			18.5–20.9	91	0.89 (0.68–1.18)		
			21–22.9	115	1.00		
			23–24.9	75	0.92 (0.69–1.24)		
			≥ 25	43	0.91 (0.64–1.31)		
			[P_{trend}]		[0.54]		
			Weight change (kg), age 20 yr to baseline				
			≤–10.0	27	0.68 (0.43–1.08)		
			–9.9 to –5.0	76	1.08 (0.80–1.46)		
			–4.9 to 4.9	124	1.00		
			5.0 to 9.9	55	1.06 (0.77–1.47)		
			≥ 10.0	56	0.98 (0.70–1.37)		
			[P_{trend}]		[0.88]		

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Li et al. (2013) (cont.)	41 455 Women Mortality	Liver ICD-10: C22.0–22.9	BMI at baseline			Age, smoking status, alcohol consumption, physical activity, intake of coffee and fish, education level, area of residence, diabetes, gall bladder disease, blood transfusions, history of liver disease	
			< 18.5	8	0.74 (0.35–1.60)		
			18.5–20.9	36	1.08 (0.69–1.68)		
			21–22.9	42	1.00		
			23–24.9	41	1.16 (0.75–1.79)		
			≥ 25	62	1.42 (0.95–2.13)		
			[P_{trend}]		[0.10]		
			BMI at age 20 yr				
			< 18.5	11	0.98 (0.58–1.64)		
			18.5–20.9	17	0.85 (0.58–1.25)		
			21–22.9	28	1.00		
			23–24.9	13	0.91 (0.60–1.38)		
			≥ 25	14	0.73 (0.45–1.18)		
			[P_{trend}]		[0.18]		
			Weight change (kg), age 20 yr to baseline				
			≤–10.0	10	0.68 (0.34–1.40)		
			–9.9 to –5.0	24	0.83 (0.51–1.35)		
			–4.9 to 4.9	62	1.00		
			5.0 to 9.9	46	1.31 (0.89–1.94)		
			≥ 10.0	47	1.41 (0.94–2.11)		
			[P_{trend}]		[0.08]		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Liver ICD-10: C22	BMI per 5 kg/m^2 [P_{trend}]	1859 total	1.19 (1.12–1.27) [< 0.0001]	Age, sex, diabetes, smoking, alcohol consumption, socioeconomic status, calendar year	Similar association in never-smokers only

AFP, α-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; Me-Can, Metabolic Syndrome and Cancer Project; NOS, not otherwise specified; SD, standard deviation; WC, waist circumference; yr, year or years

Table 2.2.4b Case–control studies of measures of body fatness and hepatocellular carcinoma

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Pan et al. (2004) Canada 1994–1997	Men: 225 Women: 84 Population	BMI 1 yr before diagnosis Men: < 25 25– < 30 ≥ 30 [P_{trend}] Women: < 25 25– < 30 ≥ 30 [P_{trend}]	225 total 85 total 	 1.00 0.99 (0.72–1.38) 1.30 (0.85–1.97) [0.31] 1.00 0.61 (0.35–1.07) 0.94 (0.48–1.84) [0.40]	Age, geographical region, education level, smoking, physical activity, total calorie intake, total vegetable consumption, dietary fibre intake, multivitamin intake; for women, also adjusted for menopausal status, parity, age at menarche, age at end of first pregnancy	Self-reported BMI
Polesel et al. (2009) Italy 1999–2003	185 Hospital	BMI 1 yr before interview < 25 25– < 30 ≥ 30 5 kg/m² increase BMI at age 30 yr < 25 ≥ 25 5 kg/m² increase BMI increase from age 30 yr < 1 1– < 4 ≥ 4	 71 76 38 109 69 73 53 52	 1.00 1.0 (0.5–1.9) 1.9 (0.9–3.9) 1.1 (0.8–1.5) 1.00 1.0 (0.6–1.7) 0.8 (0.6–1.2) 1.00 1.2 (0.6–2.4) 1.6 (0.8–3.2)	Centre, sex, age, education, drinking status, lifetime maximal alcohol consumption, smoking status, cigarettes smoked per day, HBsAg and/or anti-HCV positivity	BMI calculated from self-reported weights and heights
Welzel et al. (2011) USA 1993–2005	3649 Population	WC (≥ 40 inches [101 cm] in men, ≥ 35 inches [89 cm] in women)	308 total	1.93 (1.71–2.18)	Age, sex, race, geographical location, Medicare/Medicaid dual enrolment	
Archambeaud et al. (2015) France 2007–2010	200 Hospital	Maximum BMI < 30 ≥ 30	125 total 	 1.00 1.56 (1.02–2.37)	Sex, age, diabetes, smoking (past or present)	

Table 2.2.4b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Hassan et al. (2015) USA 2004–2013	Men: 473 Women: 149 Population	Normal weight (reference)			Sex, age, ethnicity, education level, HCV, HBV, alcohol consumption, cigarette smoking, history of diabetes, physical activity, family history of cancer	BMI calculated from self-reported weights and heights at different ages; overweight and obesity defined as BMI 24–29.9 and BMI ≥ 30, respectively
		Overweight at different ages				
			Men:			
		Mid-20s	124	1.5 (0.9–2.3)		
		Mid-30s	172	1.3 (0.9–2.1)		
		Mid-40s	174	0.9 (0.6–1.4)		
		Mid-50s	170	0.5 (0.3–0.9)		
			Women:			
		Mid-20s	11	2.4 (0.9–3.0)		
		Mid-30s	19	1.2 (0.5–2.6)		
		Mid-40s	29	0.8 (0.4–1.6)		
		Mid-50s	35	0.9 (0.5–1.7)		
		Obesity at different ages				
			Men:			
		Mid-20s	33	1.8 (0.8–4.1)		
		Mid-30s	58	3.1 (1.6–6)		
		Mid-40s	101	2.2 (1.2–4)		
		Mid-50s	104	0.8 (0.4–1.4)		
			Women:			
		Mid-20s	13	5.2 (1.6–7.2)		
		Mid-30s	15	3.3 (1.3–8.6)		
		Mid-40s	26	2.1 (1.1–4.5)		
		Mid-50s	30	1.2 (0.5–2.5)		
		Obesity in early adulthood (mid-20s to mid-40s)	Men: 192	2.3 (1.2–4.4)		
			Women: 54	3.6 (1.5–8.9)		

BMI, body mass index (in kg/m^2); CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; WC, waist circumference

Table 2.2.4c Meta-analyses of measures of body fatness and cancer of the liver

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Larsson & Wolk (2007)	11 cohort studies (7 on overweight with 5037 cases, and 10 on obesity with 6042 cases)	Liver	BMI Overweight vs normal Obese vs normal	 1.17 (1.02–1.34) 1.89 (1.51–2.36)	Age and other covariates depending on study (calendar year, sex, race, diabetes, education, marital status, smoking, physical activity, diet, family history of cancer, alcohol consumption, occupational group, aspirin use, estrogen replacement therapy in women)	The relative risk for obesity compared with normal BMI was stronger in men than in women
Renehan et al. (2008)	4 cohort studies in men and 1 in women 2070	Liver	BMI per 5 kg/m^2 increase	Men: 1.24 (0.95–1.62) Women: 1.07 (0.55–2.08)	NR	Results are from random-effects models. Substantial heterogeneity was observed (I^2 = 83.1% in men)
Chen et al. (2012)	26 prospective cohort studies 25 337	Liver (primary cancer)	BMI < 25 25–29.9 ≥ 30 BMI < 25 25–29.9 ≥ 30 BMI < 25 25–29.9 ≥ 30	All: 1.00 1.48 (1.31–1.67) 1.83 (1.59–2.11) Men: 1.00 1.42 (1.22–1.65) 1.91 (1.51–2.41) Women: 1.00 1.18 (1.08–1.30) 1.55 (1.30–1.85)	Age (all studies), and most of the studies included alcohol consumption, HBV and/or HCV infection, diabetes mellitus	Significant heterogeneity in the overall analyses, and in analyses in men; effects significantly different in men vs women; associations independent of geographical location, alcohol consumption, diabetes, or HBV/HCV infections
Rui et al. (2012)	8 cohort studies in men and women 11 616	Liver	BMI 18.5–24.9 25–30 ≥ 30	 1.00 1.13 (1.05–1.21) 2.09 (1.72–2.45)	NR	Associations remained significant after excluding 3 studies on cirrhosis cohorts

Table 2.2.4c (continued)

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Tanaka et al. (2012)	9 cohort studies and 3 case–control studies NR	Liver	BMI per 1 kg/m² increase	1.13 (1.07–1.20)	Different adjustment factors depending on study (hepatitis, alcohol consumption, diabetes, smoking)	Study restricted to Japanese populations Overweight/obese individuals showed a 74% increased risk compared with those with normal weight
Wang et al. (2012)	21 prospective cohort studies (11 in men and 5 in women) 17 624	Liver (primary cancer)	BMI per 5 kg/m² increase	All: 1.39 (1.25–1.55) Men: 1.26 (1.11–1.44) Women: 1.18 (1.08–1.29)	Age (all studies). Other covariates, depending on study	Significant heterogeneity among studies was observed. Non-linear association was reported, with a steeper increase in risk from BMI > 32 kg/m²
WCRF/AICR (2015)	12 studies Men and women Incidence and mortality 14 311	Liver	BMI per 5 kg/m²	1.30 (1.16–1.46)		Heterogeneity between studies; non-linear associations; similar risks in men and women; associations stronger for incidence than for mortality, and for European vs Asian studies
	8 studies Men and women Incidence 11 530	Liver	BMI per 5 kg/m²	1.43 (1.19–1.70)		
	4 studies Men and women Mortality 2543	Liver	BMI per 5 kg/m²	1.13 (1.00–1.28)		
	8 studies Men Incidence and mortality 11 180	Liver	BMI per 5 kg/m²	1.21 (1.02–1.44)		

Table 2.2.4c (continued)

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
WCRF/AICR (2015) (cont.)	4 studies Women Incidence and mortality 2337	Liver	BMI per 5 kg/m²	1.21 (1.10–1.33)		
	Meta-analysis of European studies: 4 studies Men and women Incidence and mortality 588	Liver	BMI per 5 kg/m²	1.59 (1.35–1.87)		
	Meta-analysis of Asian studies: 7 studies Men and women Incidence and mortality 12 520	Liver	BMI per 5 kg/m²	1.18 (1.04–1.34)		

BMI, body mass index (in kg/m²); CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; NR, not reported; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research

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2.2.5 Cancer of the gall bladder

Cancer of the gall bladder cancer is uncommon, and almost all gall bladder cancers are adenocarcinomas. In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and gall bladder cancer was *inadequate*. Since then, numberous individual studies and meta-analyses of anthropometric measures of body fatness and risk of gall bladder cancer have been published. Results are presented here for cohort studies with at least 50 cases (Table 2.2.5a) and for case–control studies (Table 2.2.5b) and meta-analyses (Table 2.2.5c).

(a) Cohort studies

There are at least 11 individual informative prospective studies of the associations of BMI or weight with gall bladder cancer incidence or mortality (Table 2.2.5a). No association was observed in three of these studies (Samanic et al., 2006; Ishiguro et al., 2008; Hemminki et al., 2011). Findings from the other eight prospective studies showed statistically significant positive association between BMI or weight and risk of gall bladder cancer (Calle et al., 2003; Samanic et al., 2004; Engeland et al., 2005; Kuriyama et al., 2005; Jee et al., 2008; Schlesinger et al., 2013; Bhaskaran et al., 2014; Borena et al., 2014), and in several of those studies there was a dose–response relationship. In a large study of nearly 1.2 million public servants in the Republic of Korea (Jee et al., 2008), the relative risk of gall bladder cancer incidence for BMI ≥ 30 kg/m^2 versus 23.0–24.9 kg/m^2 was 1.44 (95% CI, 0.98–2.12) in women (P_{trend} = 0.0007) and 1.65 (95% CI, 1.11–2.44) in men (P_{trend} = 0.0003). A large cohort study in the United Kingdom that included more than 5.2 million men and women also showed a statistically significant positive association between BMI and risk of gall bladder cancer (RR per 5 kg/m^2 increase, 1.31; 95% CI, 1.12–1.52; P_{trend} < 0.0001) (Bhaskaran et al., 2014). In a nationwide prospective study in the USA, there was evidence of a strong positive association between being obese (BMI ≥ 30 kg/m^2) and risk of gall bladder cancer mortality in both women (RR, 2.13; 95% CI, 1.56–2.90; P_{trend} < 0.001) and men (RR, 1.76; 95% CI, 1.06–2.95; P_{trend} = 0.02) (Calle et al., 2003).

In one study that assessed waist circumference in relation to risk of gall bladder cancer, each increase of 5 cm in waist circumference was associated with a 17% (95% CI, 1.06–1.30) higher risk in men and women combined (Schlesinger et al., 2013). [These results should be interpreted with caution because only 76 cases of gall bladder cancer were identified during follow-up in 359 156 men and women included in the analysis.]

The association between weight change and risk of gall bladder cancer was also examined in the EPIC cohort. Average annual weight change from age 20 years to the age at cohort enrolment was not associated with risk of gall bladder cancer (Schlesinger et al., 2013).

(b) Case–control studies

Of the case–control studies that examined the association between BMI and risk of gall bladder cancer (Table 2.2.5b), seven showed no association (Strom et al., 1995; Serra et al., 2002; Máchová et al., 2007; Grainge et al., 2009; Nakadaira et al., 2009; Alvi et al., 2011; Cha, 2015), whereas in three studies there was a statistically significant positive association between adult BMI and risk of gall bladder cancer, which appeared to be dose-related (Zatonski et al., 1997; Ahrens et al., 2007; Hsing et al., 2008).

(c) Pooled analyses and meta-analyses

There have been one pooled analysis (Whitlock et al., 2009; Table 2.2.5a) and several meta-analyses of cohort and case–control studies (Larsson & Wolk, 2007; Renehan et al., 2008; Tan et al., 2015; WCRF/AICR, 2015; Table 2.2.5c) that

examined the relationship between BMI and gall bladder cancer incidence or mortality.

All meta-results were significantly positive. In the largest and most recent meta-analysis (Tan et al., 2015), which included 12 prospective studies in Asia, Europe, and the USA, both overweight (RR, 1.15; 95% CI, 1.02–1.29) and obesity (RR, 1.62; 95% CI, 1.45–1.81) were statistically significantly positively associated with risk of gall bladder cancer. Similarly, results from the 2015 WCRF Continuous Update Project on BMI and risk of gall bladder cancer showed a statistically significant 25% (95% CI, 1.15–1.37) higher risk per 5 kg/m^2 increase reported in a dose–response analysis based on eight prospective studies (WCRF/AICR, 2015). In the WCRF analysis, associations were similar between cancer incidence and mortality, between men and women, and between studies in Asia and in Europe. In a meta-analysis of eight case–control studies, both overweight (RR, 1.16) and obesity (RR, 1.37) were associated with statistically significant higher risks of gall bladder cancer (Tan et al., 2015).

Table 2.2.5a Cohort studies of measures of body fatness and cancer of the gall bladder

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	495 477 Women Mortality	Gall bladder and extrahepatic bile ducts ICD-9: 156.0–156.9	BMI 18.5–24.9 25–29.9 30–34 [P_{trend}]	 159 86 59	 1.00 1.12 (0.86–1.47) 2.13 (1.56–2.90) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat consumption, vegetable consumption; for women, also adjusted for HRT use	
	404 576 Men Mortality		BMI 18.5–24.9 25–29.9 30–34 [P_{trend}]	 66 94 20	 1.00 1.34 (0.97–1.84) 1.76 (1.06–2.94) [0.02]		
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Gall bladder and extrahepatic bile ducts ICD-9: 156	Obesity Non-obese Obese Non-obese Obese	 White men: 265 26 Black men: 45 2	 1.00 1.70 (1.13–2.57) 1.00 0.93 (0.23–3.86)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0
Engeland et al. (2005) Norwegian men and women Norway 1963–2002	1 037 892 Women Incidence	Gall bladder ICD-7: 155.1	BMI < 18.5 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	1087 total	 1.02 (0.54–1.91) 1.00 1.27 (1.10–1.47) 1.88 (1.60–2.21) [< 0.001]	Age, birth cohort, height	
	963 619 Men Incidence		BMI < 18.5 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	628 total	 0.31 (0.04–2.24) 1.00 1.00 (0.84–1.17) 1.38 (1.01–1.89) [0.2]		

Table 2.2.5a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kuriyama et al. (2005) Japanese men and women Japan 1984–1992	15 054 Women Incidence	Gall bladder and extrahepatic bile ducts ICD-9: 156.0–156.9	BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 12 3 5 4	 1.00 0.83 (0.23–2.98) 3.43 (1.19–9.94) 4.45 (1.39–14.23) [0.004]	Age, smoking, alcohol consumption, consumption of red meat, fruits and vegetables, and bean paste, type of health insurance; for women, also adjusted for menopausal status, parity, age at menarche, age at first pregnancy	
	12 485 Men Incidence		BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 8 1 – – 	 1.00 0.46 (0.05–3.93) – – [0.48]		
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Gall bladder ICD-7: 155.1	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 53 45 11 	 1.00 0.93 (0.62–1.39) 1.40 (0.73–2.70) [> 0.5]	Attained age, calendar year, smoking	
Ishiguro et al. (2008) Japan Public Health Center Japan 1990–2004	53 187 Women Incidence	Gall bladder ICD-O-3: C23.9, C24.0	BMI < 23 23.0–24.9 25.0–26.9 ≥ 27.0 [P_{trend}]	 35 9 8 11 	 1.00 0.47 (0.22–0.98) 0.62 (0.29–1.34) 0.94 (0.48–1.88) [0.50]	Age, study area, cholelithiasis, diabetes, smoking, alcohol consumption	
	48 681 Men Incidence		BMI < 23 23.0–24.9 25.0–26.9 ≥ 27.0 [P_{trend}]	 14 6 6 4 	 1.00 0.74 (0.28–1.92) 1.26 (0.48–3.33) 1.39 (0.45–4.34) [0.52]		

Table 2.2.5a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Ishiguro et al. (2008) (cont.)	101 868 Men and women Incidence		BMI < 23 23.0–24.9 25.0–26.9 ≥ 27.0 [P_{trend}]	 49 15 14 15	 1.00 0.55 (0.31–0.98) 0.80 (0.44–1.46) 1.06 (0.59–1.90) [0.82]		
Jee et al. (2008) Cohort from the National Health Insurance Corporation Republic of Korea 1992–2006	443 273 Women Incidence	Gall bladder (NOS)	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 121 302 262 341 36	 0.97 (0.78–1.21) 1.12 (0.90–1.41) 1.00 1.27 (1.02–2.12) 1.44 (0.98–2.12) [0.0007]	Age, smoking	Excluded first 2 yr of follow-up Update of study by Oh et al. (2005)
	770 556 Men Incidence		BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 246 787 670 542 31	 0.80 (0.68–0.94) 0.86 (0.77–0.96) 1.00 0.97 (0.86–1.10) 1.65 (1.11–2.44) [0.0003]		
Whitlock et al. (2009) Pooled analysis of 57 cohort studies Europe, Japan, and USA Follow-up varied by cohort	894 576 Men and women Mortality	Gall bladder and extrahepatic bile ducts ICD-9: 156	BMI, per 5 kg/m^2	120	1.29 (0.90–1.85)	Age, sex, smoking status, study	
Hemminki et al. (2011) Swedish hospital patients Sweden 1964–2006	30 020 Men and women Incidence	Gall bladder ICD-7: 155.1	Obesity Observed vs expected rates	19	SIR 1.55 (0.93–2.43)	Age, sex, time period, region, SES	Overlap with study by Wolk et al. (2001) is unclear Obesity defined as hospital discharge diagnosis

Table 2.2.5a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schlesinger et al. (2013) EPIC cohort 10 European countries 1992–2010	359 156 (191 856 for weight change) Men and women Incidence	Gall bladder ICD-10: C23.9	BMI, per 5 kg/m²	76 total	1.28 (0.99–1.65) 0.70 (0.43–1.15)*	Age, sex, study centre, education level, smoking, alcohol consumption, height *additional adjustment for WC **additional adjustment for BMI	
			Baseline weight, per 5 kg	76 total	1.11 (1.00–1.22)		
			Weight change (kg/year)	37 total	1.76 (0.59–5.29)		
			WC, per 5 cm	76 total	1.17 (1.06–1.30) 1.33 (1.10–1.62)**		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Gall bladder ICD-10: C23	BMI per 5 kg/m² [P_{trend}]	303 total	HR (99% CI) 1.31 (1.12–1.52) [< 0.0001]	Age, sex, diabetes, smoking, alcohol consumption, SES, calendar year	
Borena et al. (2014) Metabolic Syndrome and Cancer Project (Me-Can) cohort Austria, Norway, and Sweden 1972–2006	578 700 Men and women Incidence	Gall bladder ICD-7: 155.1	BMI, quintiles (mean)			Smoking status, baseline age, cohort, sex, year of birth	
			Q1 (20.7)	20	1.00		
			Q2 (23.0)	26	1.12 (0.58–2.19)		
			Q3 (24.7)	38	1.49 (0.80–2.76)		
			Q4 (26.8)	47	1.70 (0.93–3.09)		
			Q5 (31.3)	53	1.94 (1.08–3.51)		
			[P_{trend}]		[0.08]		
			BMI				
			< 25	77	1.00		
			≥ 25	107	1.52 (1.12–2.10)		

BMI, body mass index (in kg/m²); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; HRT, hormone replacement therapy; SES, socioeconomic status; SIR, standardized incidence ratio; WC, waist circumference

Table 2.2.5b Case–control studies of measures of body fatness and cancer of the gall bladder

Reference Study location Period	Total number of cases Total number of controls Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Strom et al. (1995) Bolivia and Mexico 1984–1988	84 126 Men and women Hospital		BMI, most of adult life < 24 24–25.9 26–28 > 28 BMI, maximum ever < 24 24–25.9 26–28 > 28	 33 17 12 3 12 15 22 19	 1.0 1.5 (0.5–4.6) 2.2 (0.7–8.4) 1.6 (0.4–6.1) 1.0 1.6 (0.4–7.6) 1.3 (0.3–5.6) 2.6 (0.5–18.6)	Age, sex, country
Zatonski et al. (1997) Australia, Canada, The Netherlands, and Poland 1983–1988	Men: 44 815 Population Women: 152 700 Population		BMI, quartiles Q1 Q2 Q3 Q4 [P_{trend}] BMI, quatiles Q1 Q2 Q3 Q4 [P_{trend}]	Men: 9 11 13 11 Women: 30 37 22 56	 1.0 1.0 (0.3–3.0) 0.7 (0.3–2.0) 1.0 (0.3–2.8) [0.74] 1.0 1.7 (0.9–3.1) 1.5 (0.3–3.0) 2.1 (1.2–3.8) [0.02]	
Serra et al. (2002) Chile 1992–1995	114 114 Hospital		BMI < 25 25–29.9 ≥ 30	 53 42 19	 1.0 0.8 (0.4–1.4) 0.9 (0.4–1.8)	Age, sex
Ahrens et al. (2007) Europe 1995–1997	104 1401 (men only) Population	Gall bladder ICD-O: C23.9	BMI ≤ 25 25– < 27 27– < 30 ≥ 30	62 total	 1.0 1.8 (0.4–7.2) 11.0 (2.9–41.9) 13.3 (1.4–123)	Age, country, history of gallstones

Table 2.2.5b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Máchová et al. (2007) Czech Republic 1987–2002	93 37 772 Population		BMI Men: 18.5–24.9 25–30 ≥ 30 Women: 18.5–24.9 25–30 ≥ 30	 14 total 79 total 	 1.00 1.01 (0.24–4.32) 0.76 (0.08–7.41) 1.00 1.07 (0.58–1.95) 0.73 (0.36–1.50)	Age, smoking, height, hypertension
Hsing et al. (2008) China 1997–2001	627 959 Population	Gall bladder, excluding extrahepatic bile ducts and ampulla of Vater	Usual adult BMI < 18.5 18.5–22.9 23.0–24.9 ≥ 25 [P_{trend}] Maximum adult BMI < 18.5 18.5–22.9 23.0–24.9 ≥ 25 [P_{trend}] BMI change in adulthood ≤ 0.74 0.75–2.77 2.78–5.21 > 5.21 [P_{trend}]	 17 30 73 145 6 74 83 185 74 62 86 93 	 0.62 (0.35–1.09) 1.0 1.20 (0.85–1.68) 1.56 (1.17–2.10) [< 0.001] 1.24 (0.47–3.29) 1.00 1.35 (0.94–1.95) 1.48 (1.08–2.03) [0.02] 1.00 0.93 (0.62–1.39) 1.45 (0.98–2.14) 1.47 (1.00–2.16) [0.01]	Age (continuous), sex (male, female), and education level (none/ primary, junior middle, senior, some college)
Grainge et al. (2009) United Kingdom 1987–2002	184 3007 Population	Gall bladder, excluding cholangiocarcinomas and unspecified biliary tract cancers	BMI < 25 25–29.9 ≥ 30	 36 31 19	 1.00 1.03 (0.62–1.72) 1.51 (0.83–2.75)	Smoking, alcohol consumption, NSAID use

Table 2.2.5b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Nakadaira et al. (2009) Hungary 2003–2006	41 30 Hospital		BMI ≤ 24.9 25–29.9 ≥ 30	 13 9 19	 1.0 1.5 (0.4–5.0) 0.8 (0.3–1.8)	Age
Alvi et al. (2011) Pakistan 1988–2007	60 120 (70% of cases were women) Hospital		BMI < 23 > 23	 14 46	 1.00 1.98 (0.62–6.28)	Sex, hypertension, diabetes, smoking
Shebl et al. (2011) China 1997–2001	627 959 Population	Gall bladder, excluding extrahepatic bile ducts and ampulla of Vater	WC (cm) Low High (men: ≥ 90; women: ≥ 80)	 83 111	 1.00 0.98 (0.65–1.47)	Age, sex, BMI
Cha (2015) Republic of Korea 2008–2013	78 78 Population		BMI < 23 ≥ 23	 18 23	 1.00 0.74 (0.28–1.97)	Age, sex, hypertension, diabetes mellitus, vascular occlusive disease, alcohol consumption, smoking, polypoid lesions of gall bladder, gallstone disease

BMI, body mass index (in kg/m^2); CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; WC, waist circumference

Table 2.2.5c Meta-analyses of measures of body fatness and cancer of the gall bladder

Reference Period	Number and type of studies	Population Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates, comments
Larsson & Wolk (2007) 1966–2007	8 cohort studies	Men and women Incidence and mortality	Obese vs normal (definition varies by study)		1.69 (1.48–1.92)	See also Table 2.2.5b
	8 cohort studies, 4 case–control studies	Men and women Incidence and mortality	Obese vs normal (definition varies by study)	-	1.66 (1.47–1.88)	
Renehan et al. (2008) 1966–2007	2 cohort studies	Women Incidence	BMI, per 5 kg/m²	1111 total	1.59 (1.02–2.47)	Also split up by geographical region
	4 cohort studies	Men Incidence	BMI, per 5 kg/m²	928 total	1.09 (0.99–1.21)	
Tan et al. (2015) Cohort studies: 1964–2006	12 cohort studies	Men and women Incidence and mortality	Overweight Obese	5101 total	1.15 (1.02–1.29) 1.62 (1.45–1.81)	Normal BMI used as reference
Case–control studies: 1984–2007	8 case–control studies		Overweight Obese		1.16 (0.96–1.41) 1.37 (1.10–1.71)	
	12 cohort studies, 8 case–control studies		BMI Overall: 25–30 > 30 Men: 25–30 > 30 Women: 25–30 > 30		 1.14 (1.04–1.25) 1.56 (1.41–1.73) 1.06 (0.94–1.20) 1.42 (1.21–1.66) 1.26 (1.13–1.40) 1.67 (1.38–2.02)	
WCRF/AICR (2015) NR	8 cohort studies	Men and women Incidence and mortality	BMI, per 5 kg/m²	6004 total	1.25 (1.15–1.37)	

BMI, body mass index (in kg/m²); CI, confidence interval; ICD, International Classification of Diseases; NR, not reported; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research

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2.2.6 Cancers of the biliary tract

Intrahepatic bile duct cancers occur in the smaller bile duct branches within the liver and comprise about 10% of bile duct cancers. Extrahepatic bile duct cancers occur outside of the liver. Perihilar (also called hilar) extrahepatic bile duct cancers occur where the left and right hepatic ducts join and are the most common type of bile duct cancer, accounting for about two thirds of all bile duct cancers. Nearly all bile duct cancers are cholangiocarcinomas, of which most are adenocarcinomas. This section reviews studies of all subtypes of cancer of the biliary tract.

(a) Cohort studies

See Table 2.2.6a (web only; available at: http://publications.iarc.fr/570).

Only one prospective study (i.e. the EPIC cohort) assessed the association between body weight and intrahepatic bile duct cancer specifically; relative risk estimates for all measurements (BMI, weight, waist or hip circumference, waist-to-hip ratio, or weight change) as continuous measures were greater than 1, but none of the associations were statistically significant (Schlesinger et al., 2013).

The association between BMI and extrahepatic bile duct cancer specifically (excluding the gall bladder) was examined in the Japan Public Health Center Study. In that study, BMI was positively associated with risk in men and women combined, with a relative risk of 1.78 for BMI ≥ 27 kg/m^2 compared with < 23 kg/m^2 (P_{trend} = 0.03) (Ishiguro et al., 2008).

The association between BMI and intra- or extrahepatic bile duct cancer was examined in the Korea National Health Insurance Corporation Study, which included only men and found a statistically significant positive dose–response relationship (P_{trend} = 0.005) (Oh et al., 2005).

The association between BMI and cancer of the bile ducts and gall bladder combined was examined in two prospective studies. In the Japan Public Health Center Study, the relative risk estimates for the highest versus lowest categories of BMI in men and in women were greater than 1 but were not statistically significant (Ishiguro et al., 2008). In the EPIC study, in which cancers of the extrahepatic bile ducts included cancers of the gall bladder, associations of BMI and weight in men and women combined were not statistically significant. [The median BMI in the highest tertile was 29.9 kg/m^2 for men and 29.6 kg/m^2 for women, which includes people with a BMI in the overweight and obese category.] Similarly, no association was found with average annual weight change from age 20 years, or with waist circumference (Schlesinger et al., 2013).

In a meta-analysis of gall bladder or biliary tract cancer incidence or mortality that included seven studies, BMI was statistically significantly positively associated with risk in men and women combined (RR for highest vs lowest category of BMI, 1.40; 95% CI, 1.15–1.65) (Park et al., 2014).

(b) Case–control studies

See Table 2.2.6b (web only; available at: http://publications.iarc.fr/570).

The associations of BMI with cancers of the biliary tract system (including gall bladder or not) were examined in six population- or hospital-based case–control studies.

For extrahepatic bile duct cancer, two population-based case–control studies, one in Europe (Ahrens et al., 2007) and one in China (Hsing et al., 2008), showed a statistically significant higher risk for BMI > 25 kg/m^2 versus 18.5–25 kg/m^2, whereas a lower risk with high BMI was observed in one study in China (Kato et al., 1989). No association was observed in a study of cholangiocarcinoma (Grainge et al., 2009). No association was observed with waist circumference in the only study that examined such association (Shebl et al., 2011).

For overall biliary tract cancer, a 2.5-fold increase in risk was observed with BMI ≥ 30 kg/m^2 at age 35 years, but not with BMI 1–5 years before study entry (Ahrens et al., 2007).

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2.2.7 Cancer of the pancreas

Cancer of the pancreas is the seventh leading cause of cancer death worldwide (Ferlay et al., 2015). Even in developed countries, few individuals diagnosed with pancreatic cancer survive more than 5 years (Sirri et al., 2016). Pancreatic cancer incidence and mortality rates have been increasing both in the USA (Kohler et al., 2015) and in western Europe (Bosetti et al., 2013), despite declines in cigarette smoking, an established risk factor for pancreatic cancer. It has been suggested that these increases may be at least partly attributable to increases in the prevalence of obesity (Ma & Jemal, 2013). Notably, type 2 diabetes mellitus, which is caused by obesity, is also an established risk factor for pancreatic cancer, and the incidence of diabetes is also increasing.

The great majority (> 85%) of pancreatic tumours are ductal adenocarcinomas and derive from the exocrine component of the pancreas. Other pancreatic tumours are a more heterogeneous collection of different tumour types and include, among others, acinar cell carcinoma of the pancreas (about 5% of exocrine pancreatic cancers), cystadenocarcinomas, adenosquamous carcinomas, pancreatic mucinous cystic neoplasms, and pancreatic neuroendocrine (islet cell) tumours (1–2% of all pancreatic cancers).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and pancreatic cancer was *inadequate*. Because of the high case fatality of pancreatic cancer, results from studies of pancreatic cancer incidence and mortality can be considered comparable. Results from individual cohort studies with more than 100 cases of pancreatic cancer (Table 2.2.7a), from case–control studies (Table 2.2.7b), and from meta-analyses or pooled analyses (Table 2.2.7c) are summarized in this section.

(a) Cohort studies

Since 2000, more than 30 individual cohort studies including pooled analyses have reported on the associations of excess body fatness with pancreatic cancer incidence or mortality (Table 2.2.7a). In addition, seven meta-analyses of cohort studies have been published since then (Table 2.2.7c).

BMI, usually ascertained at study enrolment at or after middle age, was by far the most common measure of excess body weight examined in these cohort studies. In a comprehensive meta-analysis by the WCRF Continuous Update Project that included 23 cohort studies of pancreatic cancer incidence and more than 9500 incident cases of pancreatic cancer, the summary relative risk for a continuous 5 kg/m^2 increase in BMI was 1.10 (95% CI, 1.07–1.14), with similar results in men and in women (WCRF/AICR, 2012). Other meta-analyses or pooled cohort studies, all with considerable overlap in study populations, have reported similar results per 5 kg/m^2 increase in BMI (Larsson et al., 2007; Renehan et al., 2008; Genkinger et al., 2011, 2015).

The largest study that presented categorical BMI results was an analysis that included nearly 6000 pancreatic cancer deaths in White men and women in the Cancer Prevention Study II (Arnold et al., 2009). In that analysis, obesity (i.e. BMI ≥ 30 kg/m^2) was associated on average with a 40% higher risk of pancreatic cancer mortality compared with normal BMI (18.5– < 25 kg/m^2), and results were similar in men and in women separately. [No associations were found in Black men and women, but the sample size was very small compared with the group of White men and women.]

Relatively few large studies of BMI and pancreatic cancer have been conducted in populations that were not predominantly of European descent. Relative risks from the largest study in

African Americans, a pooled analysis of seven cohorts (Bethea et al., 2014), and from a study in the Republic of Korea with 1860 cases (Jee et al., 2008), the largest in an Asian population, appear consistent with those observed in meta-analyses of populations of Caucasians. However, BMI was not associated with risk of pancreatic cancer in a pooled analysis of the Asia Cohort Consortium (Lin et al., 2013b).

Some evidence suggests that the association between BMI and pancreatic cancer may differ by smoking status. In the large NIH-AARP cohort, there was a statistically significant interaction between BMI and smoking status, with a positive association between BMI and risk of pancreatic cancer in never-smokers and in former smokers but not in current smokers (Stolzenberg-Solomon et al., 2013). Similarly, increased BMI was associated with higher risk of pancreatic cancer in never-smokers and in former smokers in other studies, although these interactions were not statistically significant (Genkinger et al., 2011; Aune et al., 2012).

A limited number of individual cohort studies have examined the association between BMI in early adulthood, usually defined as age 18–21 years, and pancreatic cancer incidence or mortality (Patel et al., 2005; Lin, et al., 2007; Verhage et al., 2007; Stolzenberg-Solomon et al., 2013), with mixed results. [These studies calculated BMI in early adulthood based on weight in young adulthood recalled by participants who were middle-aged or older.]

The largest analysis of BMI in early adulthood, as well as BMI change after early adulthood in relation to pancreatic cancer mortality, is a pooled analysis including more than 3000 pancreatic cancer deaths from 14 cohorts (Genkinger et al., 2015). In that pooled analysis, an increase of 5 kg/m^2 in BMI in early adulthood was associated with a relative risk of 1.18 (95% CI, 1.11–1.25), and BMI change after early adulthood was also significantly associated with increased risk (RR per 5 kg/m^2 increase, 1.05, 95% CI, 1.01–1.10).

Several other individual cohort studies examined associations of change in weight (Samanic et al., 2006, Lin et al., 2007, Luo et al., 2008, Johansen et al., 2009) or change in BMI (Verhage et al., 2007) with risk of pancreatic cancer. None of these studies reported statistically significant associations, except for a study in Sweden that found higher risk in a small group of men with a weight increase of 15% or more in 6 years (Samanic et al., 2006) and another study that reported significant positive associations in a small group of men with a BMI increase of 8 kg/m^2 or more since age 20 years (Verhage et al., 2007).

Several individual cohort studies have examined associations of waist circumference with risk of pancreatic cancer (Larsson et al., 2005; Berrington de González et al., 2006; Luo et al., 2008; Stolzenberg-Solomon et al., 2008). In the WCRF meta-analysis, the relative risk per 10 cm increase in waist circumference was 1.11 (95% CI, 1.05–1.18) (WCRF/AICR, 2012). In addition, waist circumference was examined in a large pooled analysis of pancreatic cancer mortality including data from 11 cohort studies (Genkinger et al., 2015); a higher waist circumference was associated with increased risk of pancreatic cancer mortality (RR per 10 cm increase, 1.07; 95% CI, 1.00–1.14), and no differences in risk were observed between men and women.

(b) Case–control studies

A total of 15 independent case–control studies, conducted in Canada, China, Europe, Japan, North Africa (Egypt), and the USA, reported on the association of BMI with cancer of the pancreas (Table 2.2.7b). In all studies, the assessment of BMI was based on self-reported height and usual body weight or body weight during a relatively recent time frame before cancer diagnosis. In a few studies, additional self-reports were also obtained for body weight

up to 20 years before cancer diagnosis, or body weight at various pre-specified ages in the more distant past. In all but two studies (Pezzilli et al., 2005; Lo et al., 2007), the estimated association of BMI with risk of pancreatic cancer was adjusted for smoking, as well as for various other potential confounding factors.

For usual BMI before disease onset, 7 of the 14 studies reported statistically significant increases in risk, either overall or in sex-stratified analyses (Silverman et al., 1998; Hanley et al., 2001; Eberle et al., 2005; Anderson et al., 2009; Li et al., 2009; Halfdanarson et al., 2014; Zheng et al., 2016).

Of the remaining studies, the majority showed odds ratios above 1.0. In studies presenting sex-stratified analyses, positive associations with BMI appeared to be somewhat stronger and more often significant for men than for women (Hanley et al., 2001; Silverman, 2001; Eberle et al., 2005; Fryzek et al. 2005; Li et al., 2009).

The study by Fryzek et al. (2005) in the USA showed inverse associations of current BMI (at diagnosis) and cancer of the pancreas and no association with BMI 5 years before interview. However, analyses based on recalled BMI 20 years before interview showed a statistically significant direct association with risk of pancreatic cancer, although in men only. In a similar type of analysis, a case–control study in the Czech Republic and Slovakia (Urayama et al., 2011) also showed a statistically significant association of pancreatic cancer with recalled BMI at age 20 years and at age 40 years, but not with BMI 2 years before interview (OR, 0.98; 95% CI, 0.85–1.13).

In two studies, associations of BMI with risk of pancreatic cancer were estimated separately for never-smokers and ever-smokers.

In the USA, Fryzek et al. (2005) reported a statistically significant and up to 3.3-fold increase in risk of pancreatic cancer (95% CI, 1.2–9.2) only in never-smokers in the highest category of BMI compared with those with low BMI, and no relationship was found in smokers. A second study, also in the USA (Li et al., 2009), reported a positive association of BMI with risk of pancreatic cancer both in ever-smokers (OR per 5 kg/m^2 increase, 1.75; 95% CI, 1.37–2.22) and in never-smokers (OR, 1.46; 95% CI, 1.16–1.84).

One case–control study in the USA (with 309 cases and 602 controls) specifically addressed the association of BMI with pancreatic neuroendocrine tumours, a rare pancreatic cancer tumour, and observed an increased risk in individuals who were obese (BMI ≥ 30 kg/m^2) compared with those with a lower BMI (OR, 1.65; 95% CI, 1.11–2.45) (Halfdanarson et al., 2014).

Table 2.2.7a Cohort studies of measures of body fatness and cancer of the pancreas

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Friedman & van den Eeden (1993) Nested case–control study within Kaiser Permanente USA 1964–1988	450 cases, 2687 controls Men and women Incidence	Pancreas	BMI, per 1 kg/m² increase Weight, per 5 kg	450	1.02 (1.00–1.04) 1.06 (1.01–1.11)	Age, cigarette smoking, race	
Gapstur et al. (2000) Chicago Heart Association Detection Project in Industry Cohort USA 1967–1995	20 475 Men Mortality 15 183 Women Mortality	Pancreas ICD-8: 157	BMI < 24.129 24.129–26.292 26.293–28.630 ≥ 28.631 BMI < 20.978 20.978–23.240 23.241–26.156 ≥ 26.157	 10 21 23 42 9 6 16 12	 1.00 1.76 (0.83–3.74) 1.68 (0.80–3.53) 3.04 (1.52–6.08) 1.00 0.48 (0.17–1.26) 1.09 (0.47–2.51) 0.73 (0.30–1.80)	Age Age	
Isaksson et al. (2002) Swedish Twin Registry Sweden 1969–1997	21 884 Men and women Incidence	Pancreas	BMI < 18.5 18.5–24.99 25–30 > 30	 5 84 70 4	 2.30 (0.93–5.71) 1.00 1.36 (0.99–1.88) 0.56 (0.20–1.52)	Age, sex, smoking	No associations were observed for adult weight gain (in kg)
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Pancreas ICD-9: 157	Obesity Non-obese Obese Non-obese Obese	 White men: 5483 391 Black men: 1638 83	 1.00 1.20 (1.07–1.33) 1.00 1.07 (0.86–1.34)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Batty et al. (2005) Whitehall Study United Kingdom 1967–2002	18 403 Men Mortality	Pancreas ICD-8/9: 157 ICD-10: C25	BMI 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 75 69 3	 1.00 1.18 (0.83–1.68) 0.58 (0.18–1.91) [0.80]	Age, employment grade, physical activity, smoking, marital status, prevalent disease, weight loss in past year, BP medication, height, skinfold thickness, systolic BP, plasma cholesterol, glucose intolerance, diabetes	
Larsson et al. (2005) Swedish Mammography Cohort (SMC) Sweden 1987–2004 Cohort of Swedish Men (COSM) Sweden 1997–2004	83 053 Men and women Incidence	Pancreas ICD-9: 157, excluding 157.4	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}] WC (cm), quartiles (sex-specific) Men: Women: < 90 < 76 90–94 76–81 95–101 82–89 ≥ 102 ≥ 90 [P_{trend}]	 5 50 54 19 16 20 34 36	 0.96 (0.38–2.46) 1.00 1.25 (0.84–1.86) 1.81 (1.04–3.15) [0.04] 1.00 1.15 (0.59–2.25) 1.59 (0.87–2.93) 1.72 (0.93–3.20) [0.05]	Age, education level, physical activity, smoking, alcohol consumption, sex	In stratified analyses, stronger associations with BMI in men than in women

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Patel et al. (2005) Cancer Prevention Study II (CPS II) Nutrition Cohort 1992–1999	145 627 Men and women Incidence and mortality	Pancreas ICD-9: 157.0–157.9 ICD-10: C25.0–25.9	BMI at baseline			Age, smoking, years since quitting smoking, education level, family history of pancreatic cancer, gall bladder disease, diabetes, height, energy intake, physical activity	In stratified analyses, association with BMI at baseline was stronger in men than in women
			< 25	50	1.00		
			25–29.9	33	1.03 (0.76–1.38)		
			≥ 30	22	2.08 (1.48–2.93)		
			[P_{trend}]		[0.0001]		
			BMI at age 18 yr				
			< 21	59	1.00		
			21–22.9	25	1.07 (0.77–1.49)		
			≥ 23	17	1.33 (0.95–1.85)		
			[P_{trend}]		[0.11]		
			Adult weight change (kg)				
			< –2.27	4	1.74 (0.94–3.22)		
			–2.27 to 4.54	20	1.00		
			4.55–9.07	18	1.12 (0.70–1.79)		
			9.08–13.61	21	0.97 (0.60–1.58)		
			≥ 13.62	38	0.96 (0.61–1.52)		
			[P_{trend}]		[0.16]		
Sinner et al. (2005) Iowa Women's Health Study USA 1986–2001	28 002 Women Incidence	Pancreas ICD-10: C25	BMI			Age, smoking status, multivitamin use	
			< 25	84	1.00		
			25–29.9	72	0.94 (0.69–1.29)		
			≥ 30	53	1.14 (0.81–1.62)		
Berrington de González et al. (2006) EPIC cohort 10 European countries 1991–2004	438 405 Men and women Incidence	Pancreas	BMI			Sex, smoking, diabetes Weight and WC estimates also adjusted for height	
			< 20	9	0.67 (0.33–1.37)		
			20–22.9	48	1.00		
			23–24.9	85	0.99 (0.69–1.41)		
			25–26.9	71	0.82 (0.56–1.19)		
			27–29.9	43	0.76 (0.50–1.16)		
			30–34.9	50	1.16 (0.77–1.76)		
			≥ 35	13	1.19 (0.64–2.23)		
			per 5 kg/m^2		1.09 (0.95–1.24)		
			[P_{trend}]		[0.24]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Berrington de González et al. (2006) (cont.)			Weight (kg), quartiles (sex-specific) Men: Women: < 73 < 58 73–79 58–63 80–87 64–71 ≥ 88 ≥ 72 per 5 kg [P_{trend}]	 66 65 85 103 	 1.00 0.90 (0.63–1.28) 1.02(0.73–1.44) 1.14 (0.82–1.61) 1.05 (0.99–1.10) [0.06]		
			WC (cm), quartiles (sex-specific) Men: Women: < 88 < 73 88–93 73–78 94–100 79–87 ≥ 101 ≥ 88 per 10 cm [P_{trend}]	 51 59 79 91 	 1.00 0.96 (0.65–1.41) 1.05(0.72–1.53) 1.33 (0.93–1.92) 1.24 (1.04–1.48) [0.03]		
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 (107 815 in weight change analysis) Men Incidence	Pancreas ICD-7: 157	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}] 6-yr weight change –4% to +4.9% 5–9.9% 10–14.9% ≥ 15% [P_{trend}]	 352 289 57 86 41 13 7 	 1.00 0.95 (0.82–1.12) 1.16 (0.87–1.53) [> 0.5] 1.00 1.45 (1.00–2.11) 1.53 (0.85–2.77) 2.67 (1.22–5.84) [> 0.5]	Attained age, calendar year, smoking	

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lin et al. (2007) JACC cohort Japan 1988–2003	43 579 Men Mortality	Pancreas ICD-10: C25	BMI at baseline			Age, smoking, diabetes, gall bladder disease	
			< 20	46	1.12 (0.76–1.63)		
			20–22.4	71	1.00		
			22.5–24.9	57	0.94 (0.66–1.34)		
			25–27.4	26	1.02 (0.65–1.62)		
			27.5–29.9	6	0.62 (0.23–1.70)		
			≥ 30	1	0.58 (0.08–4.16)		
			[P_{trend}]		[0.47]		
			BMI at age 20 yr				
			< 20	27	1.39 (0.86–2.24)		
			20–22.4	45	1.00		
			22.5–24.9	45	1.13 (0.75–1.71)		
			25–27.4	21	1.54 (0.92–2.58)		
			27.5–29.9	6	1.65 (0.70–3.86)		
			≥ 30	4	3.51 (1.26–9.78)		
			[P_{trend}]		[0.01]		
			Weight change (kg)				
			< –5	45	1.63 (1.05–2.53)		
			–5 to < 0	22	1.39 (0.82–2.33)		
			0	47	1.00		
			> 0–4.9	12	1.11 (0.58–2.12)		
			≥ 5	21	0.85 (0.49–1.47)		
	59 107 Women Mortality	Pancreas ICD-10: C25	BMI at baseline			Age, smoking, diabetes, gall bladder disease	
			< 20	33	1.15 (0.74–1.80)		
			20–22.4	50	1.00		
			22.5–24.9	62	1.33 (0.91–1.95)		
			25–27.4	30	1.21 (0.77–1.92)		
			27.5–29.9	16	1.57 (0.86–2.86)		
			≥ 30	4	1.04 (0.37–2.89)		
			[P_{trend}]		[0.28]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lin et al. (2007) (cont.)			BMI at age 20 yr				
			< 20	25	0.81 (0.50–1.31)		
			20–22.4	51	1.00		
			22.5–24.9	48	1.08 (0.73–1.61)		
			25–27.4	15	0.69 (0.39–1.23)		
			27.5–29.9	3	0.46 (0.14–1.48)		
			≥ 30	1	0.43 (0.06–3.15)		
			[P_{trend}]		[0.09]		
			Weight change (kg)				
			< –5	14	0.41 (0.22–0.74)		
			–5 to < 0	14	0.61 (0.34–1.11)		
			0	59	1.00		
			> 0–4.9	13	0.70 (0.38–1.28)		
			≥ 5	43	0.93 (0.60–1.45)		
Luo et al. (2007) Japan Public Health Center Prospective Study Japan 1990–2003	47 499 Men Incidence	Pancreas ICD-10: C25	BMI			Smoking, diabetes, physical activity, study area, age, alcohol use, history of cholelithiasis	
			14–20.9	37	1.4 (0.8–2.5)		
			21–24.9	69	1.0		
			25–40	22	0.7 (0.4–1.1)		
			[P_{trend}]		[0.01]		
	52 161 Women Incidence		BMI				
			14–20.9	14	0.7 (0.4–1.3)		
			21–24.9	49	1.0		
			25–40	33	1.1 (0.7–1.6)		
			[P_{trend}]		[0.3]		
Máchová et al. (2007) National Cancer Registry, nested case–control study Czech Republic 1987–2002	17 110 Men Incidence	Pancreas ICD-10: C25	BMI	114 total		Age, smoking, hypertension, height	Nested case–control study, reporting odds ratios
			18.5–24.9		1.00		
			25–29.9		1.24 (0.74–2.07)		
			≥ 30		1.81 (0.98–3.31)		
	20 856 Women Incidence		BMI	80 total			
			18.5–24.9		1.00		
			25–29.9		0.68 (0.37–1.26)		
			≥ 30		0.95 (0.50–1.79)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Nöthlings et al. (2007) Multiethnic Cohort Study USA 1993–2002	77 255 Men Incidence	Pancreas ICD-10: C25.0–25.3, C25.7–25.9	BMI			Ethnicity, smoking, family history of pancreatic cancer, diabetes, age, energy intake, intake of red meat, intake of processed meat, physical activity	
			< 25	110	1.00		
			25–29.9	89	0.99 (0.74–1.33)		
			≥ 30	38	1.51 (1.02–2.26)		
			[P_{trend}]		[0.085]		
	90 175 Women Incidence		BMI				
			< 25	52	1		
			25–29.9	62	0.80 (0.59–1.09)		
			≥ 30	62	0.65 (0.43–0.99)		
			[P_{trend}]	61	[0.031]		
Verhage et al. (2007) Netherlands Cohort Study on Diet and Cancer The Netherlands 1986–1999	2366 Men Incidence	Pancreas ICD-10: C25	BMI at baseline			Age, smoking, diabetes, hypertension	When restricting to microscopically confirmed exocrine pancreatic cancer, significant positive associations were found with increased BMI and weight at baseline, and with BMI change since age 20 yr
			< 23	44	1.10 (0.72–1.69)		
			23–24.9	67	1.00		
			25–26.9	50	0.93 (0.61–1.39)		
			27–29.9	39	1.17 (0.75–1.81)		
			≥ 30	20	2.69 (1.47–4.92)		
			[P_{trend}]		[0.141]		
			per 1 kg/m²		1.05 (0.99–1.12)		
			BMI at age 20 yr				
			< 20	35	1.00		
			20–20.9	26	0.80 (0.46–1.40)		
			21–22.9	60	0.99 (0.62–1.59)		
			≥ 23	52	1.07 (0.67–1.73)		
			[P_{trend}]		[0.56]		
			per 1 kg/m²		1.03 (0.96–1.10)		
			BMI change since age 20 yr				
			< 0	14	0.99 (0.53–1.85)		
			0–3.9	84	1.00		
			4–7.9	60	1.34 (0.90–1.99)		
			≥ 8	15	2.21 (1.09–4.49)		
			[P_{trend}]		[0.052]		
			per 1 kg/m²		1.07 (0.99–1.15)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Verhage et al. (2007) (cont.)			Weight at baseline (kg)				
			< 65	74	1.00		
			65–69	47	1.16 (0.76–1.76)		
			70–74	46	1.13 (0.75–1.70)		
			75–79	21	0.92 (0.53–1.59)		
			≥ 80	36	1.55 (0.99–2.45)		
			[P_{trend}]		[0.18]		
			continuous per kg		1.01 (0.99–1.03)		
	2438 Women Incidence	Pancreas ICD-10: C25	BMI at baseline			Age, smoking, diabetes, hypertension	When restricting to microscopically confirmed exocrine pancreatic cancer, significant positive associations were found with increased weight at baseline and with BMI change since age 20 yr. A significant P_{trend} was also observed with increased BMI at baseline
			< 23	46	1.02 (0.66–1.58)		
			23–24.9	45	1.00		
			25–26.9	55	1.69 (1.11–2.58)		
			27–29.9	38	1.41 (0.89–2.25)		
			≥ 30	19	1.31 (0.74–2.31)		
			[P_{trend}]		[0.052]		
			per 1 kg/m²		1.04 (1.00–1.08)		
			BMI at age 20 yr				
			< 20	65	1.00		
			20–20.9	27	0.93 (0.58–1.51)		
			21–22.9	42	0.69 (0.46–1.04)		
			≥ 23	52	0.97 (0.66–1.44)		
			[P_{trend}]		[0.535]		
			per 1 kg/m²		1.02 (0.95–1.09)		
			BMI change since age 20 yr				
			< 0	15	0.67 (0.37–1.21)		
			0–3.9	76	1.00		
			4–7.9	63	1.08 (0.75–1.55)		
			≥ 8	31	1.72 (1.11–2.67)		
			[P_{trend}]	185	[0.004]		
			per 1 kg/m²		1.05 (1.01–1.10)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Verhage et al. (2007) (cont.)			Weight at baseline (kg) < 65 65–69 70–74 75–79 ≥ 80 [P_{trend}] continuous per kg	 59 42 39 31 39	 1.00 1.23 (0.81–1.88) 1.30 (0.84–1.99) 1.58 (0.99–2.52) 1.64 (1.07–2.52) [0.010] 1.02 (1.01–1.03)		
Jee et al. (2008) National Health Insurance Corporation Republic of Korea 1992–2006	770 556 Men Incidence	Pancreas	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 199 678 524 442 17	 0.87 (0.71–1.08) 1.01 (0.87–1.16) 1.00 1.06 (0.90–1.24) 1.34 (0.75–2.38) [0.1139]	Age, smoking	
	423 273 Women Incidence		BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 80 246 178 253 34	 0.88 (0.62–1.24) 1.09 (0.84–1.40) 1.00 1.35 (1.05–1.74) 1.80 (1.14–2.86) [0.0014]	Age, smoking	
Luo et al. (2008) Women's Health Initiative USA 1993–2005	138 503 Women Incidence	Pancreas	BMI < 22.0 22.0–24.9 25.0–29.9 30.0–34.9 ≥ 35.0 [P_{trend}]	 25 62 84 56 24	 0.8 (0.5–1.2) 1.0 0.9 (0.6–1.2) 1.1 (0.7–1.5) 0.8 (0.5–1.3) [0.9]	Age, treatment assignments, cigarette smoking, diabetes	Study of postmenopausal women

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Luo et al. (2008) (cont.)			WC (cm), quintiles (range, median)				
			35.0–74.5, 70.5	41	1.0		
			74.6–81.0, 78.0	50	1.1 (0.7–1.7)		
			81.1–88.0, 85.0	46	1.0 (0.7–1.6)		
			88.1–97.4, 92.4	63	1.4 (0.9–2.0)		
			97.5–194.2, 105.0	51	1.1 (0.7–1.6)		
			[P_{trend}]		[0.6]		
			per 10 cm		1.05 (0.95–1.15)		
			Type of weight change:				
			Stable weight	85	1.0		
			Steady gain in weight	77	0.9 (0.6–1.2)		
			Lost weight and kept it off	5	0.6 (0.3–1.5)		
			Weight up and down (> 10 lb)	83	0.9 (0.7–1.2)		
Stolzenberg-Solomon et al. (2008) NIH-AARP cohort USA 1995–2000	293 562 Men Incidence	Pancreatic adenocarcinoma ICD-10: C25.0–25.9 Excludes endocrine tumours	BMI			Age, smoking, race, energy intake, energy-adjusted total fat intake, diabetes; for WC, also adjusted for BMI	
			18.5– < 25.0	110	1.00		
			25.0–29.9	227	1.22 (0.97–1.54)		
			30.0–34.9	66	1.09 (0.80–1.48)		
			≥ 35.0	26	1.61 (1.05–2.49)		
			[P_{trend}]		[0.07]		
			WC (cm)				
			< 88.9	40	1.00		
			88.9–93.3	35	1.00 (0.62–1.61)		
			93.3–98.4	39	0.81 (0.49–1.32)		
			98.4–106	46	0.96 (0.58–1.58)		
			≥ 106	52	0.95 (0.54–1.67)		
			[P_{trend}]		[0.91]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stolzenberg-Solomon et al. (2008) (cont.)	201 473 Women Incidence		BMI 18.5– < 25.0 25.0–29.9 30.0–34.9 35.0 [P_{trend}] WC (cm) < 74.9 74.9–83.2 83.2–92.1 ≥ 92.1 [P_{trend}]	 84 84 38 19 14 24 28 34 	 1.00 1.33 (0.98–1.81) 1.40 (0.95–2.07) 1.29 (0.78–2.16) [0.09] 1.00 1.74 (0.89–3.41) 1.88 (0.92–3.85) 2.53 (1.13–5.65) [0.04]	Age, smoking, race, energy intake, energy-adjusted total fat intake, diabetes; for WC, also adjusted for BMI	
Arnold et al. (2009) Cancer Prevention Study II (CPS II) USA 1984–2004	48 525 Black men and women Mortality	Pancreas ICD-9: 157	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 2 122 136 80	 0.44 (0.11–1.77) 1.00 0.89 (0.70–1.40) 1.06 (0.80–1.42)	Age, diabetes, family history of pancreatic cancer, cholecystectomy, smoking status; analysis for men and women also adjusted for sex	
	17 602 Black men Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 0 45 65 33	 – 1.00 1.02 (0.69–1.49) 1.66 (1.05–2.63)		
	30 923 Black women Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 2 77 71 47	 0.60 (0.15, 2.44) 1.00 0.82 (0.59–1.14) 0.82 (0.56–1.18)		
	1 011 864 White men and women Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 86 2644 2351 690	 0.93 (0.75–1.16) 1.00 1.15 (1.08–1.22) 1.40 (1.28–1.52)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Arnold et al. (2009) (cont.)	444 351 White men Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 19 1080 1479 336	 0.83 (0.53–1.31) 1.00 1.11 (1.02–1.20) 1.42 (1.25–1.60)		
	567 513 White women Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 67 1564 872 354	 0.97 (0.76–1.24) 1.00 1.20 (1.10–1.30) 1.37 (1.22–1.54)		
Johansen et al. (2009) Malmö Preventive Project Sweden 1974–2004	33 325 Men and women Incidence	Pancreas ICD-7: 157 ICD-10: C25	BMI < 20 20–24.9 25–29.9 ≥ 30 continuous Weight gain > 10 kg No Yes Missing	 10 101 54 18 118 52 13	 0.84 (0.44–1.61) 1.00 0.83 (0.60–1.16) 1.38 (0.83–2.28) 1.04 (0.995–1.08) 1.00 1.07 (0.77–1.48) 0.65 (0.34–1.27)	Age, sex, smoking, alcohol consumption	
Meinhold et al. (2009) ATBC subcohort of non-diabetics Finland 1985–2004	27 035 Men Incidence	Pancreas ICD-9: 157, excluding 157.4	BMI, quartiles Q1 Q2 Q3 Q4 continuous [P_{trend}]	 117 139 41 8	 1.00 0.97 (0.76–1.24) 1.03 (0.72–1.47) 1.42 (0.69–2.93) 1.01 (0.94–1.08) [0.80]	Age, smoking, energy intake, diabetes mellitus (self-reported)	
Stevens et al. (2009) Million Women Study USA 1996–2006	1.29 million Women Incidence	Pancreas ICD-10: C25	BMI < 22.5 22–24.9 25–27.4 27.5–29.9 30–32.4 ≥ 32.5	 246 311 260 188 119 152	RR (floating SE) 1.02 (0.07) 1.00 (0.06) 0.99 (0.06) 1.17 (0.09) 1.27 (0.12) 1.42 (0.12)	Age, region, SES, smoking, height	

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stevens et al. (2009) (cont.)	1.29 million Women Mortality		BMI < 22.5 22–24.9 25–27.4 27.5–29.9 30–32.4 ≥ 32.5	 334 400 347 227 139 188	RR (floating SE) 1.08 (0.06) 1.00 (0.05) 1.03 (0.05) 1.09 (0.07) 1.14 (0.10) 1.36 (0.10)	Age, region, SES, smoking, height	
Whitlock et al. (2009) Pooled analysis of 57 cohort studies Europe, Japan, and USA Follow-up varied by cohort	894 576 Men and women Mortality	Pancreas ICD-9: 157	BMI, per 5 kg/m² For BMI 15–25 For BMI 25–50 For BMI 15–50	 470 520	 0.87 (0.65–1.17) 1.04 (0.86–1.25) 1.07 (0.97–1.19)	Study, sex, age, baseline smoking	
Arslan et al. (2010) Pancreatic Cancer Cohort Consortium (PanScan) pooled analysis, nested case–control Follow-up varies by cohort	2170 (men: 1059; women: 1111) Incidence	Pancreas	BMI < 18.5 ≥ 18.5– < 25.0 ≥ 25– < 30 ≥ 30– < 35 ≥ 35 [P_{trend}]	 19 759 868 325 124	 0.84 (0.44–1.59) 1.00 1.15 (1.00–1.33) 1.13 (0.93–1.37) 1.26 (0.93–1.71) [0.047]	Cohort, age, sex, anthropometry source, smoking, diabetes history	Non-significant positive associations were observed with WC (P_{trend} = 0.09)
Jiao et al. (2010) Pooled analysis of 7 cohort studies Follow-up varies by cohort	943 759 Men and women Incidence	Pancreatic adenocarcinoma ICD-10: C25 excluding C25.4 ICD-8/9: 157 excluding 157.4	BMI 16.5–18.4 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] per 5 kg/m²	 17 855 1109 381 92	 0.89 (0.55–1.44) 1.00 1.13 (1.03–1.23) 1.19 (1.05–1.35) 1.19 (0.96–1.48) [0.001] 1.08 (1.03–1.14)	Age, sex, cohort, smoking	

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Jiao et al. (2010) (cont.)	458 070 Men Incidence		BMI 16.5–18.4 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] per 5 kg/m²	 7 465 793 240 43	 0.88 (0.42–1.86) 1.00 1.11 (0.99–1.25) 1.11 (0.95–1.30) 1.34 (0.98–1.84) [0.03] 1.05 (0.98–1.12)		
	485 689 Women Incidence		BMI 16.5–18.4 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] per 5 kg/m²	 10 390 316 141 49	 0.91 (0.48–1.70) 1.00 1.15 (0.99–1.34) 1.34 (1.11–1.64) 1.09 (0.81–1.47) [0.01] 1.12 (1.05–1.19)		
Parr et al. (2010) Pooled analysis of 39 cohort studies Asia, Australia, and New Zealand 1961–1999, median follow-up 4 yr	326 387 Men and women Mortality	Pancreas ICD-9: 157 ICD-10: C25	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 5 kg/m² [P_{trend}]	 11 114 65 90 21	 0.71 (0.38–1.31) 1.00 (0.86–1.16) 0.93 (0.75–1.15) 0.75 (0.48–1.18) 0.93 (0.78–1.11) [0.24]	Age, sex, smoking	
Genkinger et al. (2011) Pooling project of prospective studies of diet and cancer (14 cohort studies)	Women: 531 755 Men: 314 585 Incidence and mortality	Pancreas	BMI at baseline < 21 21–22.9 23–24.9 25–29.9 ≥ 30 [P_{trend}] per 5 kg/m²	All: 196 290 457 847 345	 1.16 (0.96–1.40) 1.00 1.07 (0.92–1.25) 1.18 (1.03–1.36) 1.47 (1.23–1.75) [< 0.001] 1.14 (1.07–1.21)	Smoking, diabetes, alcohol consumption, energy intake, age, baseline year	No statistically significant interaction by sex was found for BMI at baseline, BMI in early adulthood, or BMI change

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Genkinger et al. (2011) (cont.)	Women: 531 755 Men: 314 585 Incidence and mortality	Pancreas	BMI at baseline	Women:			
			< 21	148	1.15 (0.92–1.44)		
			21–22.9	177	1.00		
			23–24.9	221	1.08 (0.88–1.32)		
			25–29.9	378	1.29 (1.04–1.61)		
			≥ 30	192	1.46 (1.17–1.80)		
			[P_{trend}]		[0.002]		
			per 5 kg/m²		1.13 (1.06–1.21)		
			BMI at baseline	Men:			
			< 21	48	1.19 (0.85–1.68)		
			21–22.9	113	1.00		
			23–24.9	236	1.07 (0.85–1.34)		
			25–29.9	469	1.09 (0.88–1.34)		
			≥ 30	153	1.50 (1.07–2.11)		
			[P_{trend}]		[0.06]		
			per 5 kg/m²		1.14 (1.01–1.29)		
			BMI in early adulthood	All:			
			< 18.5	163	0.95 (0.79–1.15)		
			18.5–20.9	519	0.99 (0.87–1.13)		
			21–22.9	426	1.00		
			23–24.9	276	1.09 (0.92–1.29)		
			≥ 25	214	1.21 (1.01–1.45)		
			[P_{trend}]		[0.03]		
			per 5 kg/m²		1.20 (1.10–1.30)		
			BMI in early adulthood	Women:			
			< 18.5	121	0.92 (0.70–1.21)		
			18.5–20.9	351	0.96 (0.81–1.14)		
			21–22.9	239	1.00		
			23–24.9	113	0.98 (0.78–1.24)		
			≥ 25	94	1.16 (0.90–1.50)		
			[P_{trend}]		[0.18]		
			per 5 kg/m²		1.14 (1.02–1.28)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Genkinger et al. (2011) (cont.)	Women: 531 755 Men: 314 585 Incidence and mortality	Pancreas	BMI in early adulthood < 18.5 18.5–20.9 21–22.9 23–24.9 ≥ 25 [P_{trend}] per 5 kg/m^2 BMI change < –2 –2 to +2 2–5 5–10 > 10 [P_{trend}]	Men: 42 168 187 163 120 All: 79 391 493 491 144	 1.02 (0.72–1.45) 1.03 (0.78–1.35) 1.00 1.19 (0.87–1.62) 1.21 (0.88–1.68) [0.06] 1.27 (1.12–1.44) 1.44 (1.13–1.85) 1 0.98 (0.85–1.12) 1.13 (0.98–1.30) 1.40 (1.13–1.72) [0.04]		
Klein et al. (2013) Pancreatic Cancer Cohort Consortium (PanScan)	3349 Men and women Incidence	Pancreas	BMI < 18.5 18.5–24.9 25–30 > 30	NR	 0.91 (0.54–1.53) 1.00 1.08 (0.96–1.22) 1.26 (1.09–1.45)	Sex, age, study	
Lin et al. (2013b) Pooled analysis of 16 cohort studies from Asia Cohort Consortium Follow-up varies by cohort	799 542 Men and women Mortality	Pancreas	BMI < 18.5 18.5–19.9 20–22.4 22.5–24.9 25–27.4 27.5–29.9 ≥ 30	All: 116 130 432 454 232 89 36	 1.04 (0.84–1.30) 0.82 (0.67–1.00) 0.91 (0.80–1.05) 1.00 0.95 (0.80–1.11) 1.01 (0.80–1.29) 0.96 (0.67–1.37)	Age, sex, cohort, smoking, type 2 diabetes	No associations were observed when results were stratified by Asian region (i.e. East Asia vs South Asia)

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lin et al. (2013b) (cont.)			BMI	Women:			
			< 18.5	53	0.89 (0.64–1.24)		
			18.5–19.9	59	0.85 (0.63–1.15)		
			20–22.4	174	0.78 (0.63–0.96)		
			22.5–24.9	213	1.00		
			25–27.4	129	1.01 (0.81–1.27)		
			27.5–29.9	52	1.02 (0.74–1.39)		
			≥ 30	28	1.09 (0.72–1.65		
			BMI	Men:			
			< 18.5	63	1.20 (0.90–1.61)		
			18.5–19.9	71	0.80 (0.61–1.05)		
			20–22.4	258	1.03 (0.86–1.24)		
			22.5–24.9	241	1.00		
			25–27.4	103	0.87 (0.69–1.10)		
			27.5–29.9	37	0.99 (0.69–1.42)		
			≥ 30	8	0.64 (0.30–1.35)		
Stolzenberg-Solomon et al. (2013) NIH-AARP cohort USA 1995–2006	501 698 Men and women Incidence	Pancreatic adenocarcinoma ICD-10: C25.0–25.9	BMI at age 18 yr			Smoking, total fat consumption, energy intake, sex	
			< 18.5	188	1.08 (0.92–1.27)		
			18.5–22.4	652	1.00		
			22.5–24.9	216	1.07 (0.92–1.25)		
			25–27.4	91	1.11 (0.89–1.39)		
			≥ 27.5	59	1.56 (1.19–2.03)		
			[P_{trend}]		[0.005]		
			BMI at age 35 yr				
			< 18.5	34	1.04 (0.73–1.48)		
			18.5–22.4	405	1.00		
			22.5–24.9	350	1.08 (0.94–1.25)		
			25–29.9	346	1.22 (1.05–1.41)		
			≥ 30	71	1.37 (1.06–1.79)		
			[P_{trend}]		[0.001]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stolzenberg-Solomon et al. (2013) (cont.)			BMI at age 50 yr				
			< 18.5	27	1.26 (0.85–1.85)		
			18.5–24.9	532	1.00		
			25–29.9	499	1.13 (1.00–1.29)		
			≥ 30	148	1.22 (1.02–1.47)		
			[P_{trend}]		[0.01]		
			BMI at age > 50 yr				
			< 18.5	25	1.18 (0.79–1.75)		
			18.5–24.9	689	1.00		
			25–29.9	934	1.09 (0.98–1.20)		
			30–34.9	340	1.14 (1.00–1.30)		
			≥ 35	134	1.29 (1.07–1.55)		
			[P_{trend}]		[0.01]		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Pancreas ICD-10: C25	BMI, per 5 kg/m²	3851 total	1.05 (1.00–1.10)	Age, diabetes, smoking, alcohol consumption, SES, calendar year, sex	A 11% significant risk was observed when restricting to non-smokers only
Bethea et al. (2014) Pooled study of African Americans (7 cohorts) USA Follow-up times differ across cohorts (at least 5 yr)	239 597 Men and women Mortality	Pancreas ICD-10: C25 ICD-9: 157	BMI			Age, smoking, education level, marital status, alcohol consumption, physical activity; analysis for men and women also adjusted for sex	
			18.5–24.9	187	1.00		
			25–29.9	270	1.08 (0.90–1.31)		
			30–34.9	128	1.25 (0.99–1.57)		
			≥ 35	60	1.31 (0.97–1.77)		
			[P_{trend}]		[0.03]		
	NR Men Mortality		BMI				
			18.5–24.9	68	1.00		
			25–29.9	123	1.15 (0.85–1.55)		
			30–34.9	45	1.36 (0.93–2.00)		
			≥ 35	10	1.14 (0.58–2.24)		
			[P_{trend}]		[0.20]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bethea et al. (2014) (cont.)	NR Women Mortality		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 119 147 83 50	 1.00 1.03 (0.80–1.31) 1.16 (0.87–1.55) 1.34 (0.95–1.89) [0.08]		
Untawale et al. (2014) Singapore Chinese Health Study China 1993–2011	51 251 Men and women Incidence	Pancreas	BMI < 18.5 18.5–21.4 21.5–24.4 24.5–27.4 ≥ 27.5 [P_{trend}]	 23 55 53 47 16	 1.89 (1.15–3.09) 1.34 (0.92–1.96) 1.00 1.46 (0.99–2.17) 1.02 (0.58–1.79) [0.08]	Age, sex, enrolment year, dialect, education level, diabetes, smoking history, alcohol consumption, diet, physical activity, sleep duration, energy intake	
Genkinger et al. (2015) National Cancer Institute BMI and Mortality Cohort Consortium (pooled analysis of 20 cohort studies) Follow-up varies by cohort	1 564 218 for BMI at baseline 1 096 492 for BMI in early adulthood 647 478 for WC Men and women Mortality	Pancreas ICD-9: 157 ICD-10: C25	BMI at baseline 15–18.4 18.5–21 21–22.9 23–24.9 25–27.4 27.5–29.9 30–34.9 35– < 60 continuous	 51 296 574 908 1134 653 617 212	 1.10 (0.83–1.47) 1.01 (0.87–1.16) 1.00 1.12 (1.01–1.24) 1.14 (1.03–1.26) 1.14 (1.01–1.27) 1.27 (1.13–1.43) 1.34 (1.14–1.57) 1.09 (1.05–1.12)	Age, race, education level, marital status, alcohol consumption, physical activity, smoking status	The positive association of WC with increased risk of pancreatic cancer mortality remained significant when additionally adjusting for BMI No differences between men and women in associations with BMI at baseline and in early adulthood, or with WC Stronger positive associations of pancreatic cancer risk with BMI change in women than in men

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Genkinger et al. (2015) (cont.)			BMI in early adulthood				
			15–18.4	376	1.01 (0.89–1.14)		
			18.5–21	1036	0.98 (0.89–1.08)		
			21–22.9	814	1.00		
			23–24.9	510	1.13 (1.01–1.26)		
			25–27.4	331	1.36 (1.20–1.55)		
			27.5–29.9	93	1.48 (1.20–1.84)		
			30–39.9	61	1.43 (1.11–1.85)		
			per 5 kg/m^2		1.18 (1.11–1.25)		
			BMI change				
			< –2.5	117	1.24 (1.01–1.53)		
			–2.5 to 0	269	1.12 (0.97–1.29)		
			0–2.4	658	1.00		
			2.5–4.9	828	1.07 (0.97–1.19)		
			5–7.4	640	1.11 (0.99–1.24)		
			7.5–9.9	357	1.11 (0.98–1.27)		
			≥ 10	354	1.28 (1.12–1.47)		
			per 5 kg/m^2		1.05 (1.01–1.10)		
			WC (cm), quartiles (sex-specific)				
			Men: Women:				
			< 90 < 70	385	1.00		
			90–99 70–79	660	1.11 (0.98–1.27)		
			110–109 80–89	531	1.26 (1.10–1.45)		
			≥ 110 ≥ 90	371	1.31 (1.12–1.54)		
			per 10 cm		1.09 (1.04–1.13)		
			[P_{trend}]		[< 0.0001]		
Meyer et al. (2015) Swiss cohort study Switzerland 1977–2008	35 703 Men and women Mortality	Pancreas ICD-8: 157 ICD-10: C25	BMI < 25 25–29.9 ≥ 30	127 total	 1.00 1.20 (0.81–1.78) 1.60 (0.93–2.75)	Sex, age, survey, alcohol consumption, physical activity, civil status, years of education, nationality, diet	

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index (in kg/m^2); BP, blood pressure; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; SE, standard error; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.7b Case–control studies of measures of body fatness and cancer of the pancreas

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Bueno de Mesquita et al. (1990) The Netherlands 1984–1988	Men: 89 Women: 79 Population	BMI 2 yr before diagnosis < 23 > 27.9 [P_{trend}] BMI 2 yr before diagnosis < 21.6 > 28.7 [P_{trend}]	Men: 20 20 Women: 15 12 	 1.00 0.88 (0.40–1.90) [> 0.50] 1.00 1.10 (0.46–2.80) [> 0.90]	10-yr age group, response status, total smoking	
Ghadirian et al. (1991) Canada 1984–1988	179 Population	BMI < 21.1 > 26.5	 42 40	 1.00 0.88 (0.42–1.80)	Age, sex, response status, cigarette smoking	
Ji et al. (1996) China 1990–1993	Men: 255 Women: 183 Population	BMI < 19.4 > 22.5 [P_{trend}] BMI < 19.4 > 23.2 [P_{trend}]	Men: 72 59 Women: 43 54 	 1.0 1.40 (0.91–2.10) [0.14] 1.00 1.50 (0.85–2.50) [0.57]	Age, income, smoking, physical activity, response status, diabetes, vitamin C, total energy In women only: green tea drinking	
Hanley et al. (2001) Canada (7 Canadian provinces) 1994–1997	312 Population	BMI 2 yr before interview < 23.7 23.7– < 25.8 25.8– < 28.3 ≥ 28.3 [P_{trend}]	Men: 31 44 40 57 	 1.0 1.79 (1.01–3.19) 1.36 (0.74–2.49) 1.90 (1.08–3.35) [0.03]	Age, province, percentage weight change, energy intake, composite index of physical activity	Men who reported a 2.9% or greater decrease in weight from their maximum lifetime weight were at significantly reduced risk of pancreatic cancer
		BMI 2 yr before interview < 22.1 22.1– < 24.5 24.5– < 27.4 ≥ 27.4 [P_{trend}]	Women: 32 22 34 51 	 1.0 0.64 (0.35–1.18) 0.78 (0.44–1.40) 1.21 (0.70–2.06) [0.39]	Age, province, energy intake, age at first menstruation, cigarette smoking	Women who reported a 12.5% or greater decrease in weight from their maximum lifetime weight were at significantly reduced risk of pancreatic cancer

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Silverman (2001) USA (Atlanta, Detroit, New Jersey) 1986–1989	Men: 218 Women: 213 Population	BMI	Men:		Age at diagnosis/interview, race, area, diabetes mellitus, gall bladder disease, cigarette smoking, alcohol consumption, income (men), marital status (women), energy intake from food	An interaction was observed between BMI and total energy intake in relation to pancreatic cancer risk; those with high BMI and high energy intake were at 60% increased risk.
		17.35–23.13	51	1.0		
		23.17–25.07	39	0.8 (0.5–1.3)		
		25.09–27.18	55	1.1 (0.7–1.7)		
		≥ 27.2	73	1.5 (1.0–2.3)		
		[P_{trend}]		[0.019]		
		BMI	Women:			
		20.49–27.54	40	1.0		
		27.56–30.25	54	1.4 (0.9–2.3)		
		30.30–34.21	57	1.5 (0.9–2.4)		
		≥ 34.43	62	1.5 (0.9–2.5)		
		[P_{trend}]		[0.129]		
Eberle et al. (2005) USA 1995–1999	Men: 291 Women: 241 Population	Adult BMI	Men:		Age, cigarette smoking only for usual BMI in men	
		< 23.1	48	1.0		
		23.1– < 25.1	70	1.6 (1.04–2.5)		
		25.1– < 27.1	75	1.6 (1.1–2.5)		
		≥ 27.1	95	2.1 (1.4–3.2)		
		[P_{trend}]		[0.0007]		
		Adult BMI	Women:			
		< 21.5	67	1.0		
		21.5– < 23.4	51	0.72 (0.47–1.1)		
		23.4– < 25.8	62	0.86 (0.58–1.3)		
		≥ 25.8	61	0.91 (0.61–1.4)		
		[P_{trend}]		[NS]		
		BMI at age 25 yr	Men:			
		< 20.9	44	1.0		
		20.9– < 22.8	76	1.7 (1.1–2.6)		
		22.8– < 24.7	79	1.8 (1.2–2.8)		
		≥ 24.7	91	2.0 (1.4–3.1)		
		[P_{trend}]		[0.001]		
		BMI at age 25 yr	Women:			
		< 19.7	54	1.0		
		19.7– < 21.0	50	0.88 (0.57–1.4)		
		21.0– < 22.5	64	1.2 (0.77–1.7)		
		≥ 22.5	72	1.3 (0.84–1.9)		
		[P_{trend}]		[0.13]		

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Fryzek et al. (2005) USA (South-eastern Michigan) 1996–1999	Men: 119 Women: 112 Population	Current BMI, quartiles			Age, sex, race, county group, smoking, relative with pancreatic cancer, income, medical history of diabetes	
		Q1: ≤ 24.4	33	1.0		
		Q2: 24.5–27.3	59	0.4 (0.3–0.7)		
		Q3: 27.4–31.5	22	0.2 (0.1–0.3)		
		Q4: 31.5–67.8	17	0.1 (0.0–0.2)		
		[P_{trend}]		[< 0.0001]		
		BMI 5 yr before interview, quartiles				
		Q1: ≤ 24.1	46	1.0		
		Q2: 24.2–26.5	56	1.1 (0.6–1.8)		
		Q3: 26.6–30.3	68	1.3 (0.8–2.2)		
		Q4: 30.4–68.5	61	1.0 (0.6–1.8)		
		[P_{trend}]		[0.77]		
		BMI 20 yr before interview, quartiles				
			All:			
		Q1: 0.0–22.2	43	1.0		
		Q2: 22.3–24.4	48	1.1 (0.6–1.9)		
		Q3: 24.5–27.4	71	1.6 (0.9–2.6)		
		Q4: 27.5–43.0	69	1.4 (0.8–2.5)		
		[P_{trend}]		[0.15]		
			Men:			
		Q1: 0.0–22.2	8	1.0		
		Q2: 22.3–24.4	25	1.6 (0.6–4.1)		
		Q3: 24.5–27.4	43	2.6 (1.0–6.4)		
		Q4: 27.5–43.0	43	2.4 (1.0–6.2)		
		[P_{trend}]		[0.048]		
			Women:			
		Q1: 0.0–22.2	35	1.0		
		Q2: 22.3–24.4	23	1.2 (0.6–2.5)		
		Q3: 24.5–27.4	28	1.5 (0.7–3.0)		
		Q4: 27.5–43.0	26	1.4 (0.7–3.0)		
		[P_{trend}]		[0.37]		

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Fryzek et al. (2005) (cont.)		BMI, ever-smokers				
		≤ 22.2	34	1.0		
		22.3–24.4	32	1.0 (0.5–1.8)		
		24.5–27.4	52	1.7 (0.9–3.1)		
		27.5–43.0	36	0.9 (0.5–1.8)		
		[P_{trend}]		[0.94]		
		BMI, never-smokers				
		≤ 22.2	9	1.0		
		22.3–24.4	16	1.6 (0.6–0.46)		
		24.5–27.4	19	1.5 (0.5–4.0)		
		27.5–43.0	33	3.3 (1.2–9.2)		
		[P_{trend}]		[0.014]		
Pezzilli et al. (2005) Italy	400 Hospital	BMI before diagnosis			Matched for sex, age (± 5 yr), social class, geographical region	
		< 23	110	1.01 (0.72–1.41)		
		23–29.9	246	1.00		
		≥ 30	44	0.96 (0.60–1.53)		
Lo et al. (2007) Egypt 2001–2004	194 Hospital	BMI 1 yr before			Age, sex, residence	
		< 27	99	1.0		
		27–31	59	1.4 (0.9–2.2)		
		≥ 32	28	1.5 (0.8–2.9)		
Anderson et al. (2009) Canada (Ontario) 2003–2007	422 Population	BMI 1 yr before			Age, education level, smoking status, family history of pancreatic cancer, weekly fruit servings, alcohol consumption, caffeinated beverages, allergies	
		< 25	148	1.00		
		25–29.9	183	1.77 (1.19–2.62)		
		≥ 30	83	3.51 (1.92–6.39)		

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Li et al. (2009) USA (Texas) 2004–2008	841 (men: 496; women: 282) Population (proxy controls)	Mean lifetime BMI, per 5 kg/m² increase	All: 841 Men: 496 Women: 345	 1.55 (1.32–1.84) 1.80 (1.45–2.23) 1.32 (1.02–1.70)	Age, race, sex, smoking, alcohol consumption, history of diabetes, family history of cancer	Associations were somewhat stronger in ever-smokers than in never-smokers (1.75 vs 1.46) When stratifying BMI by age ranges, the greatest risk of pancreatic cancer was found at the ages of onset of overweight and/or obesity between 14–19 yr and 20–29 yr
Urayama et al. (2011) Czech Republic and Slovakia 2004–2009	574 Population	BMI at age 20 yr 18.5–21.1 21.2–22.8 22.9–24.5 > 24.5 per 5 kg/m² BMI at age 40 yr 18.5–23.0 23.1–24.8 24.9–27.3 > 27.3 per 5 kg/m² BMI 2 yr before interview 18.5–24.3 24.4–27.1 27.2–30.4 > 30.4 per 5 kg/m²	 101 113 161 164 106 114 154 173 131 151 153 130 	 1.00 1.15 (0.79–1.69) 1.81 (1.24–2.63) 1.79 (1.23–2.61) 1.45 (1.15–1.84) 1.00 1.04 (0.72–1.52) 1.40 (0.97–2.03) 1.57 (1.09–2.27) 1.24 (1.04–1.47) 1.00 1.07 (0.75–1.52) 1.04 (0.73–1.47) 0.91 (0.63–1.30) 0.98 (0.85–1.13)	Centre, age at interview, sex, diabetes mellitus, chronic pancreatitis, smoking, alcohol consumption	
Lin et al. (2013a) Japan 2010–2012	360 (men: 145; women: 215) Hospital	BMI in the yr before study entry < 25 25.0–29.9 ≥ 30	 278 64 16	 1.00 0.96 (0.65–1.43) 1.21 (0.53–2.77)	Age, sex, history of diabetes, cigarette smoking	

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Zheng et al. (2016) China 2011–2013	323 Population (family members of other inpatients)	Current BMI < 24.0 ≥ 24.0	 197 126	 1.00 1.77 (1.22–2.57)	Age, sex, race, residential areas, smoking, tea drinking, mental pressure, family history of pancreatic cancer, diabetes, gallstone, intake of pickles and vegetables	
Pancreatic neuroendocrine tumours						
Halfdanarson et al. (2014) USA (Mayo Clinic Rochester 2004–2011	309 Hospital	Current BMI < 30 ≥ 30	 141 61	 1.00 1.65 (1.11–2.45)		

BMI, body mass index (in kg/m^2); CI, confidence interval; NS, not significant; yr, year or years

Table 2.2.7c Meta-analyses of measures of body fatness and cancer of the pancreas

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Michaud et al. (2001)	2 cohort studies 350	BMI < 23 23–24.9 25.0–26.9 27.0–39.9 ≥ 30 [P_{trend}]	 1.00 1.09 (0.79–1.49) 1.29 (0.92–1.80) 1.30 (0.91–1.87) 1.72 (1.19–2.48) [0.003]	Height, BMI at baseline, age, smoking, history of diabetes mellitus, cholecystectomy	
Berrington de Gonzalez et al. (2003)	6 case–control studies 8 cohort studies 6391	BMI, per 1 kg/m² increase	1.02 (1.01–1.03)	Age (all), smoking and diabetes (not all studies)	No differences were observed between men and women or when stratifying by study design (cohort vs case–control)
Larsson et al. (2007)	21 prospective studies (13 in men and 10 in women) 8062	BMI, per 5 kg/m² increase	All: 1.12 (1.06–1.17) Men: 1.16 (1.05–1.28) Women: 1.10 (1.02–1.19)	All studies adjusted for age, cigarette smoking; 13 studies also adjusted for diabetes	
Renehan et al. (2008)	12 prospective studies All studies: Men: 2390 Women: 2053 Studies with both sexes: Men: 839 Women: 778	BMI, per 5 kg/m² increase	Men: 1.07 (0.93–1.23) Women: 1.12 (1.03–1.23) Men: 1.07 (0.83–1.39) Women: 1.12 (0.95–1.33)	Method of BMI determination, extent of cancer site-specific risk factor adjustment, geographical region	When stratifying by region, the highest risk ratios were reported in North America (n = 2 studies)
Guh et al. (2009)	10 prospective studies (4 in men and 6 in women) NR	BMI Normal Overweight Obesity BMI Normal Overweight Obesity	Men: 1.00 1.28 (0.94–1.75) 2.29 (1.65–3.19) Women: 1.00 1.24 (0.98–1.56) 1.60 (1.17–2.20)		

Table 2.2.7c (continued)

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Aune et al. (2012)	23 prospective studies 9504	BMI, per 5 kg/m^2 increase	All (23 studies): 1.10 (1.07–1.14) Men (14 studies): 1.13 (1.04–1.22) Women (15 studies): 1.10 (1.04–1.16) Never-smoker (5 studies): 1.11 (1.04–1.17) Ever-smoker (4 studies): 1.03 (0.95–1.10)		Non-linear association between BMI and pancreatic cancer risk, with the most pronounced increase in risk in those with BMI > 35
WCRF/AICR (2012)	23 cohort studies 9504	BMI, per 5 kg/m^2 increase	Incidence: 1.10 (1.07–1.14)	NR	No differences were observed between men and women. Some evidence for a non-linear dose–response with an increase in risk from BMI ≥ 25
		BMI, per 5 kg/m^2 increase	Mortality: 1.10 (1.02–1.19)		
	5 cohort studies 949	WC, per 10 cm increase	1.11 (1.05–1.18)	NR	
	4 cohort studies 900	BMI at age 20 yr, per 5 kg/m^2 increase	1.12 (0.97–1.29)	NR	

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported; WC, waist circumference; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; yr, year or years

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2.2.8 Cancer of the lung

The lung is the leading cancer site for deaths, accounting for about 19% of all deaths from cancer. Most (80–90%) cases of lung cancer can be attributed to long-term smoking. Because of the large influence of tobacco smoking, any errors in estimating tobacco exposure could lead to errors in attribution of risk to any other factor known to be associated with tobacco use, including adiposity, resulting in residual confounding, even after statistical adjustment for tobacco exposure, as measured.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and lung cancer was *inadequate*. The 2007 WCRF review concluded that there was "limited evidence suggesting that low body fatness (underweight) is a cause of lung cancer" (WCRF/AICR, 2007).

(a) Cohort studies

The evidence from cohort studies published since 2000 includes 18 reports (excluding analyses that were later updated and analyses based on fewer than 100 incident cases) and is summarized in Table 2.2.8a (web only; available at: http://publications.iarc.fr/570).

In general, studies consistently showed an inverse association between BMI and risk of lung cancer. The inverse association is linear across categories of BMI, with about 20–30% lower risk for those with BMI ≥ 30 kg/m^2. The association is generally stronger for current smokers than for never-smokers (Samanic et al., 2006; Kabat et al., 2008; Koh et al., 2010; Smith et al., 2012; Bhaskaran et al., 2014). A meta-analysis of 29 cohort studies found consistency of the association by sex and region of the world, with a relative risk estimate for obesity (compared with normal weight) of 0.78 (95% CI, 0.74–0.83) (Duan et al., 2015).

Few investigators have explored weight across the life-course as related to lung cancer risk. In general, BMI at cohort baseline (recruitment into the cohort) seems to be more strongly (inversely) associated with lung cancer risk than is BMI earlier in life (Olson et al., 2002; Fujino et al., 2007; Kabat et al., 2008; Lam et al., 2013).

Several cohorts have included measurements of waist and hip circumferences (Olson et al., 2002; Kabat et al., 2008; Bethea et al., 2013). In general, waist circumference and waist-to-hip ratio were less associated with lung cancer risk than was BMI.

(b) Case–control studies

There were a total of 11 independent reports from case–control studies on the association of BMI with lung cancer, conducted in Europe, Japan, and the USA (Table 2.2.8b, web only; available at: http://publications.iarc.fr/570). The studies were highly variable in size, some including fewer than 200 lung cancer cases, whereas others included about 1000 (El-Zein et al., 2013), more than 2000 (Brennan et al., 2009; ICARE study, France, Tarnaud et al., 2012), and more than 3000 (NECSS study, Canada, Pan et al., 2004; Kabat & Wynder, 1992). In all studies except those of Kubík et al. (2004) and Kanashiki et al. (2005), BMI was assessed on the basis of self-reported height and body weight referring to a recent period (mostly 1 year or 2 years) before disease diagnosis. Several studies collected recalled body weight in the more distant past, for example at age 20–30 years (Goodman & Wilkens, 1993; Tarleton et al., 2012; Tarnaud et al., 2012; El-Zein et al., 2013). In addition to various other adjustments for potential confounding factors, all studies except one (Heck et al., 2009) adjusted for smoking, although the degree of the adjustment varied from smoking status only (current, former, never) to lifetime cumulative exposure to tobacco smoke. The large studies by Kabat & Wynder (1992) in the USA, Pan et al. (2004) in Canada, Kanashiki et al. (2005) in Japan, and

Tarnaud et al. (2012) in France also provided estimates within separate strata of current smokers, former smokers, and never-smokers. Furthermore, one study in the USA, by Rauscher et al. (2000), provided odds ratio estimates only for former smokers and never-smokers (244 and 188 case–control pairs, respectively).

Among the studies for which the reference time frames for BMI assessment were within 5 years before lung cancer diagnosis, all studies except that of Rauscher et al. (2000), which included only former smokers and never-smokers, showed inverse associations of BMI with lung cancer risk. Several studies showed an increased risk of lung cancer particularly in individuals with low BMI, compared with individuals with BMI in the normal mid-range or higher (Tarnaud et al., 2012: OR, 2.7; 95% CI, 1.2–6.2 for BMI < 18.5 vs 18.5– < 25 kg/m^2 as reference category; El-Zein et al., 2013: OR, 2.30; 95% CI, 1.30–4.10 for BMI < 18.5 vs 18.5– < 25 kg/m^2 as reference category; and Kanashiki et al., 2005: OR, 2.0; 95% CI, 1.2–3.4 for BMI categories < 22.9 vs 22.9– < 25 kg/m^2 as reference category). However, other studies showed a more linear inverse relationship between BMI and relative risk over a wider range of BMI values, from < 18.5 kg/m^2 to > 30 kg/m^2.

In several larger studies that stratified the analysis by current smokers, former smokers, and never–smokers, an increased risk in underweight individuals, and more generally an inverse relationship between BMI and lung cancer risk, was observed only in current smokers and former smokers (Kabat & Wynder, 1992; Pan et al., 2004; Kanashiki et al., 2005; Tarleton et al., 2012; Tarnaud et al., 2012; El-Zein et al., 2013), whereas in never-smokers there was no significant association. The study of Rauscher et al. (2000), which included only former smokers and never-smokers, showed an increase in lung cancer risk with increasing BMI.

In studies that collected information about weight at ages 20–30 years, BMI in early adulthood showed no significant association (Goodman & Wilkens, 1993; Tarleton et al., 2012; El-Zein et al., 2013) with lung cancer risk or a weaker (inverse) association than that reported for BMI shortly before diagnosis (Tarnaud et al., 2012). In all four studies, cases tended to gain less weight during adult life than did controls. In one study that analysed lung cancer risk according to weight gained since early adulthood (Tarleton et al., 2012), weight gain was significantly inversely related to lung cancer risk, and more so in current smokers than in never-smokers or former smokers.

(c) Mendelian randomization studies

Two studies have applied Mendelian randomization in the context of lung cancer (Table 2.2.8c, web only; available at: http://publications.iarc.fr/570). Brennan et al. (2009) used the *FTO* rs9939609 SNP, which is robustly associated with BMI (Frayling et al., 2007; Scuteri et al., 2007; Peeters et al., 2008), as an instrument for BMI. Mendelian randomization analyses showed that each 1 kg/m^2 increase in BMI was associated with a reduced risk of lung cancer (OR, 0.85; 95% CI, 0.72–0.99; P = 0.04), including adenocarcinoma (OR, 0.51; 95% CI, 0.33–0.82; P = 0.004) and squamous cell carcinoma (OR, 0.72; 95% CI, 0.57–0.90; P = 0.01). An inverse association was observed in never-smokers (OR, 0.57; 95% CI, 0.35–0.94; P = 0.03) but not in former smokers or current smokers.

Gao et al. (2016) used genetic risk scores comprising 15 SNPs for childhood BMI and 77 SNPs for adult BMI in Mendelian randomization analyses to assess association between these measures of adiposity and all lung cancer and lung cancer subtypes. Each 1 kg/m^2 increase in adult BMI was associated with a 5% increased risk of all lung cancer (95% CI, 1.02–1.09; $P = 2.9 \times 10^{-3}$) and a 10% increased risk of squamous cell carcinoma (95% CI, 1.04–1.16; $P = 6.6 \times 10^{-4}$) (assuming that a standard deviation was equivalent to 4.5 kg/m^2). There was no association with

childhood BMI. There was minimal evidence for a positive directional pleiotropy from Mendelian randomization Egger regression, and results were null, suggesting that the positive association between adult BMI and both all lung cancer and squamous cell lung cancer may be overestimated. [The Working Group noted that interpretation of this finding is limited because individual-level data were not available on smoking status, which may be an important effect modifier. In addition, there is a potential violation of the Mendelian randomization assumptions in this analysis.]

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2.2.9 Cancer of the breast in women

In women, cancer of the breast constitutes about 25% of all incident cancers and about 15% of all cancer deaths worldwide. There are several established risk factors for breast cancer, including age at menarche, age at menopause, age at first birth, parity, breastfeeding, alcohol consumption, physical activity, and use of exogenous estrogens. Breast cancer diagnosed before menopause differs from breast cancer diagnosed after menopause in both risk factors and clinical characteristics. There are several molecular subtypes of breast cancer; the most important aspect is the presence or absence of estrogen receptors in the tumour, because this substantially affects treatment options and prognosis.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for postmenopausal breast cancer.

(a) Cohort studies

The evidence published since 2000 includes about 30 publications from cohort studies (excluding analyses that were later updated and analyses based on fewer than 100 incident cases). These findings are displayed for BMI at baseline in Table 2.2.9a for postmenopausal women and Table 2.2.9b (web only; available at: http://publications.iarc.fr/570) for premenopausal women, with comments on findings according to other measures of body fatness, such as weight changes over the life-course.

(i) BMI

In general, the findings are quite consistent across the studies, showing an inverse association between baseline BMI and premenopausal breast cancer risk and a positive association between baseline BMI and postmenopausal breast cancer risk.

For premenopausal breast cancer, the risk diminishes with increasing BMI on an approximately linear scale, and for postmenopausal breast cancer the risk increases on an approximately linear scale. Two large meta-analyses estimated a 7–8% decrease in premenopausal breast cancer risk and a 12–13% increase in postmenopausal breast cancer risk per 5 kg/m^2 (Renehan et al., 2008; WCRF/AICR, 2010).

Among those studies that have assessed the association between BMI and breast cancer risk by estrogen receptor (ER) status (for postmenopausal and premenopausal breast cancer combined), the association was most robust for women with ER-positive tumours (MacInnis et al., 2004; Suzuki et al., 2006; Vrieling et al., 2010; Canchola et al., 2012; Bandera et al., 2015; Neuhouser et al., 2015).

Among postmenopausal women, the majority of studies that have assessed the interaction between obesity and use of HRT have found the association between BMI and breast cancer risk to be apparent only among non-users of HRT (Feigelson et al., 2004; Lahmann et al., 2004; Eliassen et al., 2006; Mellemkjaer et al., 2006; Ahn et al., 2007; White et al., 2012). Similar conclusions were reported by several meta-analyses and systematic literature reviews (WCRF/AICR, 2010).

(ii) BMI or weight at earlier time points and weight change

Several investigators have assessed the association of BMI or weight at earlier time points and weight change with subsequent breast cancer risk.

For postmenopausal breast cancer, BMI in middle adulthood (ages 35–50 years) is associated with a risk similar to that with baseline BMI (Ahn et al., 2007), but BMI in early adulthood (generally reported at age 18 years) is either not associated or modestly inversely associated with postmenopausal breast cancer risk (Sweeney

et al., 2004; Ahn et al., 2007; Canchola et al., 2012; Bandera et al., 2015).

Weight gain since age 18 years has been shown to be associated with postmenopausal breast cancer risk (Sweeney et al., 2004; Eliassen et al., 2006). Also, weight gain after age 50 years is positively associated with postmenopausal breast cancer risk (Eng et al., 2005).

Weight loss in adulthood has been examined in six studies (Eliassen et al., 2006; Ahn et al., 2007; Teras et al., 2011; Emaus et al., 2014; Neuhouser et al., 2015; Rosner et al., 2015). Across these studies, there is not consistent evidence that weight loss from about age 50 years to the baseline of entry into the cohort affects postmenopausal breast cancer risk.

(iii) Waist circumference

Seven cohort studies have included measurements of waist circumference (Lahmann et al., 2004; Sweeney et al., 2004; Krebs et al., 2006; Ahn et al., 2007; Canchola et al., 2012; Fourkala et al., 2014; Kabat et al., 2015). Waist circumference (either as measured or as indicated by skirt size) or waist-to-hip ratio was generally positively associated with postmenopausal breast cancer risk, and the strengths of those associations are approximately equivalent to those reported for BMI.

(b) Case–control studies

For the current evaluation, data from more than 400 case–control studies published after 2000 were reviewed. Only studies with more than 100 cases are summarized.

(i) BMI

In postmenopausal women, case–control studies yielded consistent results, with increased risk of breast cancer with higher BMI (Table 2.2.9c).

In premenopausal women, the results are less consistent despite the substantial number of studies; they mostly indicate an inverse association (Table 2.2.9d; web only; available at: http://publications.iarc.fr/570).

Studies that assessed weight gave similar results to those with BMI for both postmenopausal women (Table 2.2.9e; web only; available at: http://publications.iarc.fr/570) and premenopausal women (Table 2.2.9f; web only; available at: http://publications.iarc.fr/570).

Comparable associations were observed for tumours that are both ER-positive and progesterone receptor (PR)-positive, especially for postmenopausal women; see Table 2.2.9g for postmenopausal women and Table 2.2.9h (web only; available at: http://publications.iarc.fr/570) for premenopausal women.

A meta-analysis based on 35 case–control studies involving 71 216 subjects showed an increased risk of postmenopausal breast cancer (OR, 1.15; 95% CI, 1.07–1.24) but not of premenopausal breast cancer, for which the estimates were suggestive of an inverse association with higher BMI (overweight and obese subjects) (OR, 0.93; 95% CI, 0.86–1.02) (Cheraghi et al., 2012).

(ii) BMI and ethnicity

More than 20 studies were carried out in Caucasian women in North America and western Europe (Wenten et al., 2002; Magnusson et al., 2005; Tsakountakis et al., 2005; Verla-Tebit & Chang-Claude, 2005; Dinger et al., 2006; Rosenberg et al., 2006; Kruk, 2007; Slattery et al., 2007; Justenhoven et al., 2008; Berstad et al., 2010; Healy et al., 2010; Barnes et al., 2011; Cerne et al., 2011; John et al., 2011; Rosato et al., 2011; Attner et al., 2012; Bandera et al., 2013a; Robinson et al., 2014; John et al., 2015a, b; Sanderson et al., 2015), 16 studies in women in East Asia (Hirose et al., 2001, 2003; Shu et al., 2001; Yoo et al., 2001; Adegoke et al., 2004; Chow et al., 2005; Nichols et al., 2005; Tian et al., 2007; Wu et al., 2006; Gao et al., 2009; Shin et al., 2009; Shi et al., 2010; Bao et al., 2011; Kawai et al., 2013; Noh et al., 2013; Sangrajrang et al., 2013; Minatoya et al., 2014), 12 studies in Hispanic or Latina women

(de Vasconcelos et al., 2001; Wenten et al., 2002; Ibarluzea et al., 2004; Ziv et al., 2006; Garmendia et al., 2007; Slattery et al., 2007; Justenhoven et al., 2008; John et al., 2011, 2015a, b; Ronco et al., 2012; Amadou et al., 2014), 8 studies in women in South Asia (Gilani & Kamal, 2004; Mathew et al., 2008; Montazeri et al., 2008; Dey et al., 2009; Dogan et al., 2011; Lodha et al., 2011; Ghiasvand et al., 2012; Singh & Jangra, 2013), and 4 studies in Arab women (Alothaimeen et al., 2004; Dogan et al., 2011; Msolly et al., 2011; Elkum et al., 2014).

Except for Asian populations, there are not clear differences in risk estimates between ethnic groups for either postmenopausal women (Table 2.2.9i; web only; available at: http://publications.iarc.fr/570) or premenopausal women (Table 2.2.9j; web only; available at: http://publications.iarc.fr/570).

The incidence of breast cancer in Hispanic Whites is lower than that in non-Hispanic Whites. In the case–control studies that have evaluated the associations of BMI (or other anthropometric measures) or weight change with breast cancer risk and compared Hispanic Whites with non-Hispanic Whites (Wenten et al., 2002; Slattery et al., 2007; John et al., 2015b), the positive association observed in postmenopausal women was generally stronger in non-Hispanic Whites than in Hispanic Whites.

Most studies in Asian women observed an increased risk of breast cancer with higher BMI, especially for postmenopausal women (Table 2.2.9i; web only; available at: http://publications.iarc.fr/570) and/or tumours that were hormone receptor-positive (ER-positive and/or PR-positive). However, the associations between BMI and breast cancer risk in postmenopausal women are observed at lower BMI levels in Asian populations than in Caucasian populations. Some studies in East Asian women (Bao et al., 2011; Kawai et al., 2013) used BMI < 21 kg/m^2 or BMI < 18.5 kg/m^2 as a reference and categories of lower BMI for overweight and obesity, and observed a positive association in both categories. Such lower BMI categories were not specifically examined in most studies in South Asian women.

(iii) Waist circumference

As for BMI, results from case–control studies using waist circumference as an indicator of body fatness yielded consistent results in postmenopausal women, with mostly positive associations (Table 2.2.9k).

In premenopausal women, the results of the 11 available studies were not consistent (Table 2.2.9l; web only; available at: http://publications.iarc.fr/570); two studies (Bandera et al., 2013b; Robinson et al., 2014) showed significant positive associations, whereas two studies showed an inverse association (John et al., 2011 in ER-positive, PR-positive tumours only; Amadou et al., 2014). Interestingly, the significant positive associations were observed in women of African ancestry.

Evidence is scarce about waist circumference and risk of breast cancer by hormone receptor status. The three studies in postmenopausal women (John et al., 2011, 2013; Bandera et al., 2013b; Table 2.2.9k) provided conflicting results.

(iv) Change in BMI or weight

Changes in BMI or weight were mostly studied as an increase from the value at age 18, 21, 25, or 30 years to the value at the reference date or 1 year before the reference date.

In postmenopausal women (Table 2.2.9m), 12 of the 20 studies found a positive association between weight gain and risk of breast cancer (Li et al., 2000; Trentham-Dietz et al., 2000; Shu et al., 2001; Friedenreich et al., 2002; Carpenter et al., 2003, Eng et al., 2005; Han et al., 2006; Wu et al., 2006; Shin et al., 2009), in three studies in non-Hispanic White women only (Wenten et al., 2002; Slattery et al., 2007; John et al., 2013). One of the two studies of BMI gain also found a positive association (Hirose et al., 2001). The remaining studies found no significant association.

In the two studies that assessed weight gain specifically after menopause (weight gain after age 50 years or in the past 10 years) (Shu et al., 2001; Eng et al., 2005), the association was still significant but was slightly weaker than that with weight change since early adulthood.

When premenopausal women were considered (Table 2.2.9n; web only; available at: http://publications.iarc.fr/570), BMI change was consistently not associated with risk of breast cancer in all four available studies (Hirose et al., 2001; Verla-Tebit & Chang-Claude, 2005; Kawai et al., 2014; Robinson et al., 2014). Of 16 studies, 10 confirmed no association between body weight gain and breast cancer risk (Shu et al., 2001; Friedenreich et al., 2002; Wenten et al., 2002; Slattery et al., 2007; Wu et al., 2006; Berstad et al., 2010; Bandera et al., 2013a; Troisi et al., 2013; Robinson et al., 2014; Sanderson et al., 2015). The remaining studies were inconsistent; two found an increased risk with increasing body weight gain (Shin et al., 2009; Cribb et al., 2011), and three found a protective effect of body weight gain in at least one measure of exposure (Verla-Tebit & Chang-Claude, 2005; John et al., 2011; Sangaramoorthy et al., 2011).

(v) Weight loss

When assessing weight change during adulthood, several studies also assessed the impact of weight loss on breast cancer risk (Trentham-Dietz et al., 2000; de Vasconcelos et al., 2001; Eliassen et al., 2006). The results were inconsistent, probably because of heterogeneity of ethnicity and current BMI between studies.

(c) Mendelian randomization studies

One Mendelian randomization study has been conducted to assess the association of childhood and adult BMI with all and ER-negative breast cancer risk (Gao et al., 2016; Table 2.2.9o). In this study, each unit increase in adult BMI was associated with a 9% decrease in risk (95% CI, 6–12%; $P = 2.5 \times 10^{-7}$) in all breast cancers, and an 11% decrease in risk (95% CI, 6–16%; $P = 2.0 \times 10^{-5}$) in ER-negative tumours (assuming that a standard deviation [SD] was equivalent to 4.5 kg/m^2; Locke et al., 2015). Childhood BMI was inversely associated with all (OR per SD increase, 0.71; 95% CI, 0.60–0.80; $P = 6.5 \times 10^{-5}$) and ER-negative breast cancer risk (OR per SD increase, 0.69; 95% CI, 0.53–0.98; $P = 5.8 \times 10^{-3}$), where each SD increase was equivalent to 0.073 kg/m^2 (Felix et al., 2016). [There was minimal evidence for positive directional pleiotropy in the associations with childhood BMI, suggesting that estimates may be underestimated.]

[Although the inverse association observed between adult BMI and breast cancer risk in this study is inconsistent with the positive associations observed for postmenopausal women in observational studies, Mendelian randomization analyses represent a lifelong predisposition to increased BMI (especially because there is a high correlation between the otherwise independent childhood and adult BMI genetic risk scores). The results may suggest that the positive association between adult BMI and breast cancer risk may be driven by adult weight gain, as a result of environmental factors not captured by genetic risk scores.]

Table 2.2.9a Cohort studies of body mass index and cancer of the breast in postmenopausal women

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Feigelson et al. (2004) CPS2 cohort USA 1992–2001	62 756 Incidence	BMI		Non-HRT users	Age, race, age at menarche, age at menopause, parity, OC use, family history of BC in first-degree relative, benign breast disease, mammography, height, education level, physical activity, alcohol consumption	Positive association also with adult weight gain
		< 22	187	1.00		
		22–24.9	304	1.06 (0.88–1.27)		
		25–26.9	182	1.11 (0.91–1.36)		
		27–29.9	233	1.41 (1.16–1.71)		
		30–34.9	204	1.74 (1.42–2.13)		
		≥ 35	72	1.61 (1.22–2.12)		
		[P_{trend}]		[< 0.0001]		
		BMI		Current HRT users		No association with adult weight gain
		< 22	223	1.0		
		22–24.9	253	0.89 (0.74–1.06)		
		25–26.9	102	0.74 (0.59–0.94)		
		27–29.9	101	0.86 (0.68–1.09)		
		30–34.9	51	0.72 (0.53–0.98)		
		≥ 35	22	1.09 (0.70–1.69)		
		[P_{trend}]		[0.12]		
Lahmann et al. (2004) EPIC cohort Europe 1992–2002	103 334 Incidence	BMI, quintiles		Non-HRT users	Age, centre, education level, smoking, alcohol consumption, parity, age at first pregnancy, age at menarche	WC and WHR both showed no association
		Q1	98	1.00		
		Q2	127	1.02 (0.78–1.33)		
		Q3	206	1.35 (1.06–1.73)		
		Q4	241	1.38 (1.08–1.76)		
		Q5	239	1.36 (1.06–1.75)		
		[P_{trend}]		[0.002]		
		BMI, quintiles		HRT users		
		Q1	122	1.0		
		Q2	116	0.90 (0.69–1.17)		
		Q3	113	0.91 (0.70–1.19)		
		Q4	92	0.85 (0.64–1.13)		
		Q5	51	0.71 (0.50–1.10)		
		[P_{trend}]		[0.07]		
MacInnis et al. (2004) Population-based cohort Australia 1990–2003	13 598 Incidence	BMI, quartiles	357 total		Age, education level, country of birth, HRT use	Association limited to ER+ cases
		Q1		1.0		
		Q2		1.2 (0.9–1.5)		
		Q3		1.4 (1.0–1.9)		
		Q4		–		
		[P_{trend}]		[0.02]		

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Sweeney et al. (2004) Iowa women's cohort USA 1986–2001	36 658 Incidence	BMI		55–64 yr	Age, education level, age at first birth, age at menarche, family history of BC, height	Associations with WHR and weight change since age 18 yr similar to those for BMI
		< 23.5	101	1.00		
		23.5–26	78	0.86 (0.64–1.16)		
		26–29.5	119	1.26 (0.96–1.64)		
		≥ 29.5	130	1.34 (1.03–1.75)		
		[P_{trend}]		[0.004]		
		BMI		65–74 yr		
		< 23.5	274	1.00		
		23.5–26	306	1.21 (1.03–1.42)		
		26–29.5	335	1.26 (1.08–1.49)		
		≥ 29.5	382	1.48 (1.26–1.73)		
		[P_{trend}]		[< 0.0001]		
		BMI		75–84 yr		
		< 23.5	112	1.00		
		23.5–26	129	1.19 (0.92–1.53)		
		26–29.5	167	1.45 (1.14–1.85)		
		≥ 29.5	153	1.44 (1.12–1.84)		
		[P_{trend}]		[0.001]		
Kuriyama et al. (2005) Population-based cohort Japan 1984–1992	15 054 Incidence	BMI			Age, smoking, alcohol consumption, diet, age at menopause, age at menarche, age at first pregnancy	
		< 18.5–24.9	73	1.00		
		25–27.4	23	1.20 (0.75–1.93)		
		27.5–29.9	12	1.55 (0.84–2.87)		
		≥ 30	7	1.90 (0.87–4.15)		
		[P_{trend}]		[0.04]		
Rapp et al. (2005) Population-based cohort Austria 1985–2002	78 484 Incidence	BMI	NR		Age, smoking, occupation	
		18.5–24.9		1.00		
		30–34.9		1.48 (1.12–1.95)		
		≥ 35		1.29 (0.79–2.11)		
		[P_{trend}]		[0.02]		
Chang et al. (2006) USA PLCO cohort 1993–2003	38 660 Incidence	BMI			Age, study centre, race, family history of BC in first-degree relative, age at menarche, age at menopause, HRT use, education level	
		< 22.4	139	1.00		
		22.5–24.9	177	1.20 (0.96–1.51)		
		25–27.4	168	1.24 (0.99–1.56)		
		27.5–29.9	114	1.42 (1.11–1.83)		
		≥ 30	166	1.35 (1.06–1.70)		
		[P_{trend}]		[0.014]		

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Eliassen et al. (2006) NHS1 and NHS2 USA	87 143 Incidence	Weight change (kg), age 18 yr to baseline			Age, age at menarche, parity, age at first birth, height, weight at age 18 yr, first-degree family history of BC, benign breast disease, alcohol consumption, use of HRT, age at menopause	Weight change since menopause associated more weakly. Association was much weaker among users of HRT
		loss ≥ 10	22	1.05 (0.64–1.70)		
		loss 5–9.9	35	1.14 (0.76–1.70)		
		loss 2–4.9	33	0.77 (0.51–1.15)		
		stable	85	1.00		
		gain 2–4.9	108	1.02 (0.77–1.36)		
		gain 5–9.9	204	1.08 (0.83–1.39)		
		gain 10–19.9	435	1.34 (1.06–1.69)		
		gain 20–24.9	159	1.55 (1.18–2.02)		
		gain ≥ 25	313	1.98 (1.55–2.53)		
		[P_{trend}]		[< 0.001]		
Krebs et al. (2006) Cohort of older women for osteoporosis USA 1986 Average follow-up, 11.3 yr	7523 Incidence	BMI, quartiles	350 total		Age, HRT use, bone density, family history of BC, exercise, education level, parity, age at menarche, age at menopause, smoking	WC and WHR both showed no association
		Q1		1.00		
		Q2		0.82 (0.58–1.15)		
		Q3		1.01 (0.72–1.41)		
		Q4		1.29 (0.92–1.81)		
		[P_{trend}]		[0.06]		
Lukanova et al. (2006) Population-based cohort Sweden 1994–2004	35 362 Incidence	BMI			Age, tobacco use	
		18.5–24.9	213	1.00		
		25–29.9	140	0.92 (0.74–1.14)		
		≥ 30	69	1.09 (0.83–1.43)		
		[P_{trend}]		[0.70]		
Mellemkjaer et al. (2006) Population-based cohort Denmark 1993–2002	11 992 Incidence	BMI			Parity, age at first birth, education level, benign breast disease, alcohol consumption	WC and WHR both showed no association
		< 18.5	7	1.23 (0.58–2.63)		
		18.5–24.9	237	1.00		
		25–29.9	130	0.88 (0.71–1.09)		
		≥ 30	42	0.94 (0.67–1.31)		
		[P_{trend}]		[0.74]		
	11 796 Incidence	BMI			Parity, age at first birth, education level, benign breast disease, alcohol consumption	WC and WHR both showed no association
		< 18.5	1	–		
		18.5–24.9	96	1.00		
		25–29.9	85	1.34 (1.00–1.80)		
		≥ 30	35	1.17 (0.79–1.73)		
		[P_{trend}]		[0.28]		

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Silvera et al. (2006) Canadian mammography screening cohort Canada 1980–2000	40 318 Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	662 total	 1.00 1.12 (0.91–1.38) 1.26 (0.95–1.67) [0.08]	Age, alcohol consumption, smoking, HRT use, age at menarche, age at first birth, family history of BC	
Suzuki et al. (2006) Swedish mammography cohort Sweden 1987–2003	51 823 Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}] BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 11 345 249 111 2 83 52 6 	ER+PR+: 1.03 (0.55–1.95) 1.00 1.23 (1.05–1.46) 1.67 (1.34–2.07) [< 0.0001] ER–PR–: 0.80 (0.20–3.27) 1.00 0.96 (0.67–1.38) 0.52 (0.26–1.04) [0.017]	Age, family history of BC, age at menarche, parity, age at first birth, education level, OC use, HRT use, diet, alcohol consumption	
Ahn et al. (2007) NIH-AARP USA 1995–2000	99 039 Incidence	BMI 15–18.4 18.5–22.4 22.5–24.9 25.0–27.4 27.5–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 6 134 179 197 136 175 77 44 	Non-HRT users: 0.64 (0.28–1.45) 1.00 1.19 (0.95–1.49) 1.35 (1.08–1.68) 1.52 (1.29–1.94) 1.55 (1.22–1.96) 1.89 (1.40–2.55) 2.08 (1.44–2.99) [< 0.001]	Age, age at first pregnancy, age at menopause, age at first birth, parity, smoking, education level, race, family history of BC, alcohol consumption, diet, physical activity, oophorectomy	Associations with BMI at age 50 yr similar to BMI at baseline. Association null at age 35 yr, inverse at age 18 yr. Both WC and WHR positively associated with risk

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Ahn et al. (2007) (cont.)	99 039 Incidence	BMI 15–18.4 18.5–22.4 22.5–24.9 25.0–27.4 27.5–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 11 280 313 257 117 129 40 15	HRT users: 0.79 (0.43–1.44) 1.00 1.13 (0.96–1.33) 1.19 (1.00–1.42) 1.04 (0.83–1.30) 1.14 (0.91–1.42) 1.13 (0.80–1.61) 1.10 (0.64–1.88) [0.22]	Age, age at first pregnancy, age at menopause, age at first birth, parity, smoking, education level, race, family history of BC, alcohol consumption, diet, physical activity, oophorectomy	
Ericson et al. (2007) Malmö cohort Sweden 1991–2003	11 699 Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 183 147 62	 1.00 1.20 (0.96–1.49) 1.19 (0.89–1.59) [0.41]	Age	
Lundqvist et al. (2007) Twin cohort studies Sweden and Finland 1961–2004	14 058 older twins (mean age at baseline, 56 yr) Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 12 411 274 59	 0.9 (0.5–1.5) 1.0 1.2 (1.0–1.4) 1.3 (1.0–1.7) [< 0.007]	Smoking, physical activity, education level, diabetes	
Reeves et al. (2007) Population-based cohort United Kingdom 1996–2001	1.2 million Incidence	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 879 1336 1262 878 1274	 0.85 (0.80–0.91) 1.00 1.10 (1.04–1.16) 1.21 (1.13–1.29) 1.29 (1.22–1.36) 1.40 (1.21–1.49)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	
Reinier et al. (2007) Mammography screening cohort in Vermont USA 1996–2002	32 607 Incidence	BMI < 22.0 22–24.9 25.0–27.4 27.5–29.9 ≥ 30	572 total	 1.0 1.2 (0.9–1.6) 1.4 (1.0–1.8) 1.6 (1.1–2.1) 1.9 (1.4–2.5)	Age, family history of BC, age at first birth, breast density	

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Song et al. (2008) Korean medial insurance cohort Republic of Korea 1994–2003	107 481 Incidence	BMI < 18.5 18.5–20.9 21.0–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 per 1 kg/m^2	 11 59 132 186 159 130 36	 0.54 (0.17–1.73) 0.87 (0.54–1.41) 1.00 1.27 (0.90–1.80) 1.52 (1.07–2.15) 1.97 (1.37–2.83) 1.64 (0.91–2.97) 1.08 (1.04–1.12)	Age, smoking, alcohol consumption, exercise	
Andreotti et al. (2010) Agricultural workers USA 1993–2005	28 319 Incidence	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 5 186 156 93 24 	 – 1.00 1.22 (0.93–1.60) 1.62 (1.17–2.24) 1.07 (0.61–1.87) [0.02]	Age, race, smoking, vegetable intake, exercise, family history of cancer	
Parr et al. (2010) 39 cohorts Asia, Australia, and New Zealand 1961–NR	130 946 Mortality	BMI < 12–18.4 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	324 total	 0.71 (0.22–2.24) 1.00 1.13 (0.85–1.50) 1.63 (1.13–2.35) [0.03]	Age, sex, tobacco use	
Canchola et al. (2012) California Teachers Study USA 1995–2008	52 642 Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 740 413 218 	ER+PR+: 1.00 1.13 (1.00–1.28) 1.20 (1.03–1.40) [0.01]	Age, race, parity, age at menarche, age at first birth, family history of BC, alcohol consumption, HRT use	No association with BMI at age 18 yr. WC positively associated with risk
		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 156 91 33 	ER–PR–: 1.00 1.13 (0.87–1.47) 0.77 (0.53–1.12) [0.36]		No association with BMI at age 18 yr. WC not associated with risk

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
White et al. (2012) Population-based Multiethnic Cohort USA 1993–2004	35 495 Incidence	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 63 316 396 329	Never HRT users: 0.90 (0.69–1.18) 1.00 1.35 (1.17–1.57) 1.60 (1.36–1.87) [< 0.0001]	Age, family history of BC, age at first birth, age at menarche, parity, smoking, physical activity, alcohol consumption, height	Analyses available by race/ ethnicity: non-Hispanic White, Latina, Japanese, Native Hawaiian, African American
	28 200 Incidence	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 132 610 376 190	Current HRT users: 1.02 (0.84–1.23) 1.00 1.04 (0.91–1.18) 1.14 (0.97–1.35) [0.18]	Age, family history of BC, age at first birth, age at menarche, parity, smoking, physical activity, alcohol consumption, height	
Fourkala et al. (2014) Ovarian cancer screening cohort United Kingdom 2001–2012	1.2 million Incidence	BMI per 1 kg/m²	1090	1.06 (1.01–1.12)	Age, age at menarche, age at menopause	
	1.2 million Incidence	Skirt size per 1 unit	1090	1.05 (1.01–1.08)		Skirt size remained significant after adjustment for BMI
Gaudet et al. (2014) CPS2 cohort USA 1997–2006	28 965 Incidence	BMI < 25 25–29.9 ≥ 30 per 1 kg/m²	 441 401 246	 1.00 1.34 (1.17–1.54) 1.60 (1.36–1.89) 1.04 (1.02–1.06)	Age, family history of BC, education level, height, age at menopause, tobacco use, diabetes, race, age at first birth, physical activity, alcohol consumption, OC use, HRT use	Similar association with WC , but in multivariate adjustment, the BMI association persisted but the WC association did not. Cases overlap with Feigelson et al. (2004)
Bandera et al. (2015) Pooled data on African American women in 4 cohorts USA 1995–2013	15 234 Incidence	BMI < 25 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 254 469 361 329	ER+: 1.00 1.10 (0.93–1.30) 1.21 (1.01–1.45) 1.32 (1.09–1.60) [0.002]	Age, education level, study, family history of BC, age at menarche, parity, breastfeeding, age at first birth, HRT use, OC use	Inverse association with BMI in young adulthood and risk. WHR positively associated with risk

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bandera et al. (2015) (cont.)		BMI < 25 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 130 200 156 126	ER–: 1.00 0.87 (0.69–1.11) 0.90 (0.70–1.17) 0.82 (0.63–1.08) [0.23]	Age, education level, study, family history of BC, age at menarche, parity, breastfeeding, age at first birth, HRT use, OC use	Inverse association with BMI in young adulthood and risk. WHR positively associated with risk
Kabat et al. (2015) Women's Health Initiative cohort USA 1992–2013	143 901 Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	7039 total	 1.00 1.09 (1.01–1.18) 1.12 (1.04–1.21) 1.23 (1.14–1.33) 1.41 (1.31–1.53) [< 0.0001]	Age, alcohol consumption, smoking, physical activity, age at menarche, age at first birth, parity, HRT use, family history of BC, ethnicity, education level	WC, WHR not associated any more strongly than BMI
Dartois et al. (2016) E3N cohort France 1990–2008	67 634 Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 84 2310 610 134	 – 1.00 1.19 (1.10–1.30) 1.25 (1.07–1.46)	Age, family history of BC, education level, height, age at menarche, age at menopause, tobacco use, parity, physical activity, alcohol consumption, OC use, HRT use	Earlier study by Tehard & Clavel-Chapelon (2006) showed similar association between WC and risk, but no associations with WHR

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; CPS, Cancer Prevention Study; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; OC, oral contraceptive; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SES, socioeconomic status; WC, waist circumference; WHR, waist-to-hip ratio; yr, year or years

Table 2.2.9c Case–control studies of body mass index and cancer of the breast in postmenopausal women

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Li et al. (2000) USA 1988–1990	479 435 Population; Caucasian women	BMI at age 50–64 yr ≤ 21.5 21.6–24.1 24.2–27.5 ≥ 27.6	 111 126 120 122	 1.00 1.2 (0.9–1.8) 1.1 (0.8–1.6) 1.5 (1.1–2.3)	Age, family history of BC, parity
Trentham-Dietz et al. (2000) USA January 1992–December 1994	Postmenopausal women aged 50–79 yr 5031 5255 Population; matched by age	BMI 11.62–21.94 21.95–24.02 24.03–26.44 26.45–29.44 29.45–54.87 [P_{trend}]	 841 920 971 1013 1286	 1.0 1.0 (0.9–1.2) 1.1 (1.0–1.3) 1.2 (1.1–1.4) 1.6 (1.4–1.9) [< 0.001]	Logistic conditional models on age and state. Parity, age at FFTP, family history of BC, recent alcohol consumption, education level, age at menopause
de Vasconcelos et al. (2001) Brazil May 1995–February 1996	177 377 Hospital/population; visitors at hospital; 27 relatives of BC patients	Current BMI < 24.55 24.55–27.64 27.65–30.79 ≥ 30.80 [P_{trend}]	 38 29 35 29	 1.00 0.61 (0.33–1.14) 0.84 (0.46–1.53) 0.61 (0.33–1.14) [0.24]	Age, parity, family history of BC, education level
Shu et al. (2001) China August 1996–March 1998	1459 aged 25–64 yr enrolled from Shanghai Cancer Registry 1556 Population; randomly selected from female residents of Shanghai (Shanghai Resident Registry), matched to cases by age, 5-yr interval	BMI at diagnosis < 20.70 20.70–22.79 22.80–25.09 25.10–27.90 ≥ 28.0 [P_{trend}]	 63 95 134 125 83	 1.0 1.4 (0.9–2.1) 1.5 (1.0–2.3) 1.7 (1.1–2.6) 2.0 (1.2–3.2) [0.003]	Age, education level, family history of BC, ever had fibroadenoma, age at menarche, age at first live birth, exercise, age at menopause
Yoo et al. (2001) Japan 1988–1992	1154 aged ≥ 25 yr, with no previous history of cancer 21 714 Hospital	BMI per 1 kg/m^2		1.07 (1.04–1.10)	Age at interview, occupation, family history of BC, age at menarche, age at menopause, age at FFTP, number of FTPs, months of breastfeeding, alcohol consumption, cigarette smoking, weight, height

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Friedenreich et al. (2002) Canada, Alberta 1995–1997	1233 1241 Population; frequency-matched to cases by age, 5-yr interval, and place of residence (urban/rural)	BMI < 24.1 ≥ 24.1– < 27.3 ≥ 27.3– < 31.3 ≥ 31.3 [P_{trend}]	 206 179 187 199	 1.00 0.93 (0.69–1.24) 0.94 (0.70–1.26) 0.99 (0.74–1.32) [0.55]	Current age, total energy intake, total lifetime physical activity, education level, ever use of HRT, ever diagnosed with benign breast disease, first-degree family history of BC, ever alcohol consumption, current smoking
Adebamowo et al. (2003) Nigeria, urban 1998–2000	234 273 Population	BMI ≥ 30 vs < 30	 31	 1.82 (0.78–4.31)	Age, age at menarche, regularity of periods; only natural menopause
Carpenter et al. (2003) Canada, USA, and western Europe Group I: March 1987–December 1989 Group II: January 1992–December 1992 Group III: September 1995–April 1996	1883 Caucasian (including Hispanic), born in Canada, USA, or western Europe, diagnosed at age ≥ 55 yr 1628 Population; matched to cases by neighbourhood	BMI, 1 yr before diagnosis < 21.7 21.7–23.6 23.7–27.0 ≥ 27.1 [P_{trend}]	 366 379 497 641	 1.00 1.10 (0.88–1.37) 1.18 (0.95–1.46) 1.34 (1.09–1.66) [0.005]	Age at FFTP, age at menarche, age at menopause, family history of BC, interviewer, average MET hours per week of lifetime exercise activity
Li et al. (2003) USA 1997–1999	975 1007 Population	BMI at age 65–79 yr < 23.32 23.33–26.20 26.21–30.11 ≥ 30.12	 209 240 245 245	 1.00 1.3 (1.0–1.7) 1.4 (1.1–1.9) 1.4 (1.0–1.8)	Age, income
Pan et al. (2004) Canada 1994–1997	1449 postmenopausal 2492 Population	BMI < 25 25–30 ≥ 30 [P_{trend}]	1449	 1.00 1.17 (1.00–1.39) 1.66 (1.33–2.06) [< 0.0001]	
Chow et al. (2005) Hong Kong Special Administrative Region 1995–2000	Chinese women aged 24–85 yr 198 353 Hospital; followed up for benign breast disease; no BC	BMI at diagnosis < 19 19–23 23–27 27–31 > 31 [P_{trend}]	 10 38 42 20 10	 1.00 1.78 (0.79–4.04) 1.73 (1.04–2.86) 2.06 (1.08–3.93) 3.82 (1.03–14.27) [< 0.001]	

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Zhu et al. (2005) USA 1995–1998	African American, aged 20–64 yr 304, without previous cancer history, interviewed 1–3 yr after diagnosis 305 Population; no history of BC, matched to cases by age (5-yr intervals) and county; women were offered money to participate	BMI at diagnosis < 25 25– < 30 ≥ 30 [P_{trend}]	 45 55 61	 1.00 1.50 (0.70–3.21) 2.32 (1.04–5.19) [0.039]	Family history of BC, history of benign breast disease, alcohol consumption, smoking, menstrual status, age at menarche, menstrual cycle length, parity, age at first birth, miscarriages, history of radiotherapy, use of estrogen other than for birth control, history of losing weight, history of taking iron pills, age at first sexual intercourse, daily energy intake, physical activity, use of electric bedding devices, history of infertility, demographic variables
Okobia et al. (2006) Nigeria September 2002–April 2004	250 250 Hospital; patients recruited from the same hospitals as cases, treated for non-malignant and non-hormonal surgical disorders	BMI, mean (± SD) Cases, 24.74 (± 6.89) Controls, 25.03 (± 5.33)	108	0.76 (0.44–1.32)	Age
Wu et al. (2006) USA 1995–2001	Asian American (Chinese, Japanese and Filipino) women aged 25–74 yr 1277 1160 Population; neighbourhood controls, frequency-matched by ethnicity and 5-yr age groups	BMI, recent ≤ 20.43 > 20.43–22.32 > 22.32–24.60 > 24.60 [P_{trend}]	 139 138 187 241	 1.00 0.94 (0.65–1.36) 1.13 (0.79–1.62) 1.35 (0.95–1.93) [0.045]	Age, ethnicity, duration of residence in the USA, education level, age at menarche, number of live births, age at menopause, intake of tea and soy during adolescence and adult life, years of physical activity, height
Garmendia et al. (2007) Chile, Santiago 2005	170 diagnosed within 2 mo before recruitment, aged 33–86 yr 170 Population; mammography service of the same hospitals	BMI ≥ 30	 122	 0.66 (0.39–1.14)	Crude OR; controls matched to cases by 5-yr age interval and place of residence
Kruk (2007) Poland 2003–2007	858 1085 Hospital; controls frequency-matched by 5-yr age group and place of residence (urban/rural)	Current BMI < 22.5 22.6– < 25.0 25.0– < 30.0 ≥ 30.0 [P_{trend}]	 78 127 221 122	 1.00 1.85 (0.98–2.84) 2.13 (1.45–3.13) 2.62 (1.66–4.11) [< 0.0001]	Age, recreational activity, breastfeeding, stress, passive smoking $P_{interaction}$ = 0.002

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Tian et al. (2007) Taiwan, China January 2004–December 2005	244 aged 22–87 yr 244 Hospital; recruited from health examination clinics at the same hospital and time, no history of cancer, matched by menopausal status, date of enrolment, and duration of fasting	BMI ≤ 24.45 > 24.45	 54 49	 1.00 2.94 (1.53–5.68)	Age at enrolment, fasting status, levels of adiponectin
Mathew et al. (2008) India 2002–2005	1866 1873 Accompanying persons to cancer cases; matched by age ± 5 yr and residence type (urban/rural)	BMI < 25 25–29.9 ≥ 30	 559 297 76	 1.00 1.29 (1.00–1.66) 1.00 (0.64–1.54)	Age, centre, religion, marital status, education level, SES, residence status, parity, age at first birth, duration of breastfeeding, physical activity
Montazeri et al. (2008) Islamic Republic of Iran 1996–2000	116 in situ and invasive cancers 116 Hospital; women presenting for clinical breast examination	BMI 18.5–24.9 25–29.9 ≥ 30	 23 51 42	 1.00 2.53 (1.20–5.35) 3.21 (1.15–8.47)	Age, age at menopause, family history of BC, parity
Nemesure et al. (2009) Barbados July 2002–March 2006	Women of African descent aged ≥ 21 yr 222 454 Population; Barbados Statistical Services; frequency-matched by 5-yr age group	BMI at age ≥ 50 yr < 25 25–30 ≥ 30	 51 42 49	 1.00 0.67 (0.36–1.24) 0.70 (0.38–1.28)	Age, HRT use, parity, family history of BC, history of benign breast disease, age at first pregnancy, age at menarche, physical activity, other body size variable
Shin et al. (2009) China 1996–1998 (phase 1), 2002–2005 (phase 2)	3452 aged 20–64 yr (phase 1), 20–70 yr (phase 2) 3474 Population; controls frequency-matched to cases by age	Current BMI ≤ 20.9 21–22.9 23–24.9 ≥ 25 [P_{trend}]	 192 285 348 543	 1.0 1.3 (1.0–1.7) 1.5 (1.2–1.9) 1.8 (1.4–2.2) [< 0.001]	

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Berstad et al. (2010) USA 1994–1998	4575 4682 Caucasian: 2953 3021 African American: 1622 1661 Population	BMI, 5 yr before reference date < 25 25–29 30–34 ≥ 35 [P_{trend}]	 918 579 254 149	 1.00 0.98 (0.84–1.14) 1.02 (0.82–1.26) 1.09 (0.83–1.43) [0.67]	Age, race, education level, study site, first-degree family history of BC, parity, age at menopause, HRT use, BMI at age 18 yr
Healy et al. (2010) Ireland NR	200 519 (age-matched) healthy women	BMI, quartiles Q4 vs Q1 > 30 vs 20–25		 2.2 (1.3–3.7) 2.04 (1.3–3.3)	 $P = 0.002$ $P = 0.004$
Ogundiran et al. (2010) Nigeria 1998–2009	1233 1101 Population; community register of Ibadan	BMI < 21 21–23.9 24–27.9 ≥ 28 [P_{trend}]	 100 115 139 151	 1.00 1.04 (0.63–1.71) 0.88 (0.55–1.41) 0.76 (0.48–1.21) [0.15]	Age at diagnosis or interview, ethnicity, education level, age at menarche, number of live births, age at first live birth, duration of breastfeeding, age at menopause, family history of BC, benign breast disease, OC use, alcohol consumption, height $P_{interaction} = 0.85$
Barnes et al. (2011) Germany 2001 (Hamburg); 2002 (Rhein-Neckar-Karlsruhe) to 2005	3074 6386 Population; frequency-matched by year of birth and study region	BMI at age 50–74 yr ≤ 22.4 22.5–24.9 25–29.9 ≥ 30	 1354 993 622 105	 1.00 1.06 (0.95–1.17) 1.04 (0.92–1.18) 0.93 (0.73–1.19)	Family history of BC, benign breast disease, age at menarche, OC use, breastfeeding, parity, cause of menopause, age at menopause, alcohol consumption, HRT use, recent physical activity, occupational status, year of birth, study region, lifetime number of mammograms
Cerne et al. (2011) Slovenia January 2006–December 2008	Caucasian women 784, aged 50–69 yr at diagnosis 709 Hospital; no history of BC	BMI < 25 25–30 ≥ 30	 267 327 190	 1.00 1.34 (1.04–1.73) 1.89 (1.36–2.63)	

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Cribb et al. (2011) Canada, Prince Edward Island 1999–2002	207 621 Population; women presenting for routine mammography screening; matched by age, menopausal status, and family history of BC	BMI > 25 vs ≤ 25	61%	1.71 (1.08–2.70)	
Rosato et al. (2011) Pooled analysis of 2 studies in Italy and Switzerland 1983–1994 (1st study), 1991–2007 (2nd study)	3869, postmenopausal 4082 Hospital; admitted for acute, non-neoplastic diseases, not related to gynaecological or hormonal conditions, matched by age and study centre	BMI < 30 ≥ 30	3292 578	1.00 1.26 (1.11–1.44)	Age, study centre, study period, education level, alcohol consumption, age at menarche, age at first birth, age at menopause, HRT use, family history of BC
Attner et al. (2012) Sweden, County of Scania 2005–2007	2613 19 898 Registry: Population Registry of Scania	Obesity	2.1%	0.79 (0.52–1.19)	90–1461 days (4 yr) before diagnosis Obesity defined as comorbidity diagnosis of obesity (ICD-10: E66)
Ghiasvand et al. (2012) Islamic Republic of Iran September 2005–December 2008 (cases), May–August 2009 (controls)	493 women aged ≥ 50 yr enrolled within 6 mo after diagnosis 493 Hospital; frequency-matched to cases by 5-yr age groups and province of residence; no history of BC	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 129 208 141	 0.60 (0.17–2.11) 1.00 1.39 (1.02–1.94) 1.61 (1.18–2.30) [0.01]	Age, parity, age at menarche, education level, occupation, height, family history of BC
Ronco et al. (2012) Uruguay 2004–2009	367 545 Hospital; non-hospitalized women aged 23–69 yr; age-matched, with normal mammography	BMI < 25 25–30 ≥ 30	165	 3.60 (0.33–39.8) 5.40 (1.77–16.6) 0.84 (0.33–2.12)	Age, residence, first-degree family history of BC, age at menarche, number of live births, age at first delivery, months of breastfeeding
Bandera et al. (2013a) USA, New York City and New Jersey NR	978 postmenopausal women of African ancestry 958 Population; random-digit dialling	Current BMI < 25 25–29.99 ≥ 30 [P_{trend}]	 74 131 304	 1.00 0.93 (0.60–1.44) 0.98 (0.66–1.45) [0.94]	Age, ethnicity, country of origin, education level, family history of BC, history of benign breast disease, age at menarche, age at menopause, parity, breastfeeding, age at first birth, HRT use, OC use

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
John et al. (2013) USA Hispanic cases: 1995–2002 African American cases: 1995–1999 Non-Hispanic White cases: 1995–1999	1389 of 2571 1644 of 2706 Hispanic: 1119 1462 African American: 543 598 Non-Hispanic White: 596 646 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	Current BMI < 25.0 25.0–29.9 ≥ 30 [P_{trend}]	 208 278 312	 1.00 0.95 (0.74–1.21) 0.94 (0.74–1.20) [0.64]	All non-users of HRT
Noh et al. (2013) Republic of Korea 1995–2011	270 540 Population; women attending routine health examination, with no evidence of malignant disease; matched by age, menopausal status, and time of visit to Health Promotion Center	BMI < 25 ≥ 25	106 69 37	 1.00 2.24 (1.22–4.10)	Number of live births, family history of BC, age at menarche, smoking, alcohol consumption, physical activity, use of HRT
Sangrajrang et al. (2013) Thailand May 2002–March 2004; August 2005–August 2006	1126 1135 Hospital/population; visitors of hospital patients admitted for conditions other than BC or ovarian cancer	Current BMI < 18.5 18.5–24.9 ≥ 25.0	 27 248 203	 1.94 (0.98–3.85) 1.00 1.67 (1.24–2.25)	
Singh & Jangra (2013) India August 2009–July 2010	128 aged 20–80 yr 128 Hospital; enrolled from the general surgical ward, without history of any type of cancer, matched to cases within 2-yr age interval	BMI < 18.5 18.5–23.0 23.0–25.0 25.0–30.0 > 30.0 [P_{trend}]	 4 34 14 21 6	 0.217 1.00 1.647 1.647 2.118 [0.016]	[No CIs provided]

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Troisi et al. (2013) USA 1974–2009	Women aged < 85 yr 22 646 with primary in situ or invasive cancer 224 721 Population; frequency-matched to cases by parity, age, calendar year of delivery, and race/ethnicity	Pre-pregnancy BMI (after 1992)			Age at delivery, race/ethnicity, parity at index birth, year of index birth
		Aged ≥ 50 yr at diagnosis:	144		
		< 18.5	3	0.62 (0.19–2.06)	
		18.5– < 25	105	1.00	
		25– < 30	19	0.60 (0.36–1.01)	
		≥ 30	17	0.84 (0.48–1.46)	
		[P_{trend}]		[0.33]	
Amadou et al. (2014) Mexico (Mexico City, Monterrey, Veracruz) 2004–2007	1000 1074 Population	BMI			Age, health-care system, region, SES, breastfeeding, family history of BC, alcohol consumption, physical activity, total energy intake, height, current BMI
		< 25	89	1.00	
		25–29.0	239	0.96 (0.64–1.44)	
		≥ 30	257	0.75 (0.51–1.12)	
		[P_{trend}]		[0.068]	
Elkum et al. (2014) Saudi Arabia 2007–2012	Arab women 534 638 Population; unmatched, randomly selected from primary health care visitors; free of BC	BMI			None
		18.5–24.9	60	1.00	
		25–29.9	70	1.25 (0.73–2.15)	
		≥ 30	137	1.66 (1.02–2.70)	
		BMI			Age, BMI, marital status, HRT use, age at menarche, breastfeeding, education level
		18.5–24.9		1.00	
		≥ 25		2.22 (1.32–3.72)	
Minatoya et al. (2014) Japan September 2012–July 2013	66 66 Hospital; hospitalized for CVD, hypertension, arrhythmia, nephritis, nephrosis; no BC or diabetes; matched by age ± 3 yr and menopausal status	BMI			Age at menarche, smoking, alcohol consumption, parity, OC/HRT use P_{trend} based on χ^2 test of log-transformed continuous variables
		< 19.1	4	0.28 (0.07–1.11)	
		≥ 19.1– < 22.3	15	1.00	
		≥ 22.5	25	1.39 (0.50–3.86)	
		[P_{trend}]		[0.043]	
Trentham-Dietz et al. (2014) USA Pooled analysis of 5 case–control studies 1988–2008	Women aged < 75 yr 23 959 28 304 Population	BMI	16 517		Age, state of residence, study period, family history of BC, alcohol consumption, age at menarche, parity, age at first pregnancy, OC use, smoking status
		< 18.5		0.75 (0.64–0.88)	
		18.5–24.9		1.00	
		25–29.9		1.11 (1.06–1.17)	
		≥ 30		1.32 (1.24–1.40)	

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; CVD, cardiovascular diseases; FFTP, first full-term pregnancy; FTP, full-term pregnancy; HRT, hormone replacement therapy; MET, metabolic equivalent; mo, month or months; NR, not reported; OC, oral contraceptive; OR, odds ratio; SES, socioeconomic status; yr, year or years

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9g Case–control studies of body mass index and cancer of the breast in postmenopausal women, by hormone receptor status

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Enger et al. (2000) USA 1997–1989	760 1091 Population; matched by age, race (Hispanic/non-Hispanic), parity, and residential neighbourhood	BMI ER+PR+: < 21.7 21.7–23.6 23.7–27.0 ≥ 27.1 [P_{trend}] ER+PR–: < 21.7 21.7–23.6 23.7–27.0 ≥ 27.1 [P_{trend}] ER–PR–: < 21.7 21.7–23.6 23.7–27.0 ≥ 27.1 [P_{trend}]	 71 101 127 151 34 38 46 41 31 36 25 35	 1.00 1.36 (0.96–1.94) 1.78 (1.26–2.51) 2.45 (1.73–3.47) [0.0001] 1.00 1.12 (0.68–1.85) 1.35 (0.83–2.20) 1.29 (0.78–2.15) [0.24] 1.00 1.19 (0.71–1.99) 0.80 (0.45–1.40) 1.20 (0.70–2.05) [0.85]	Age at reference year, SES, number of FTPs, months of breastfeeding, age at menopause, HRT use, family history of BC, alcohol consumption, physical activity Results available for BMI at age 18 yr
Huang et al. (2000) USA 1993–1996	862 790 Population	BMI ER+PR+: < 23 23–31 > 31 ER–PR–: < 23 23–31 > 31	213 111 	 1.0 1.1 (0.7–1.8) 1.6 (0.9–3.0) 1.0 1.0 (0.6–1.9) 0.8 (0.4–1.7)	Age at selection, race, age at menarche, nulliparity/age at FFTP, breastfeeding, abortion or miscarriage, WHR, OC use, HRT use, first-degree family history of BC, medical radiation to the chest, cigarette smoking, alcohol consumption, education level, and the offset term
Yoo et al. (2001) Japan 1988–1992	Women aged ≥ 25 yr 1154, no previous history of cancer 21 714 Hospital	BMI per 1 kg/m^2 ER+ ER– PR+ PR–		 1.09 (1.05–1.13) 1.05 (0.99–1.12) 1.09 (1.04–1.14) 1.07 (1.02–1.11)	

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Cotterchio et al. (2003) Canada ECSS study: April 1995–March 1996 WHS study: July 1996–September 1998	1867 2452 Population; frequency-matched to cases within 5-yr age groups	BMI			$P_{heterogeneity}$ = 0.29
		ER+PR+:			
		< 20	45	0.72 (0.43–1.21)	
		20–25	489	1.00	
		25.1–27	208	1.10 (0.84–1.43)	
		> 27	631	1.61 (1.32–1.98)	
		ER–PR–:			
		< 20	25	1.34 (0.72–2.49)	
		20–25	172	1.00	
		25.1–27	72	1.09 (0.74–1.61)	
		> 27	190	1.48 (1.09–1.99)	
Rusiecki et al. (2005) USA January 1994–December 1997	Women aged 40–80 yr 420, no prior BC or benign breast disease 406 Hospital; no BC or benign breast disease or incident fibroadenoma, or atypical hyperplasia, no previous cancer disease except for non-melanoma of the skin, frequency-matched by age within 5-yr intervals	BMI			
		ER+PR+:	104		Age, age at menarche, parity (nulliparous treated separately), age at FFTP, lifetime lactation, ever use of estrogen, alcohol consumption, smoking, family history of BC, race
		< 25.0		1.0	
		25.0–29.99		0.7 (0.4–1.2)	
		≥ 30.0		1.0 (0.6–1.9)	
		ER+PR–:	65		
		< 25.0		1.0	
		25.0–29.99		0.7 (0.4–1.4)	
		≥ 30.0		0.8 (0.4–1.8)	
		ER–PR+:	41		
		< 25.0		1.0	
		25.0–29.99		1.3 (0.6–2.8)	
		≥ 30.0		0.9 (0.3–2.3)	
		ER–PR–:	107		
		< 25.0		1.0	
		25.0–29.99		1.3 (0.7–2.1)	
		≥ 30.0		1.3 (0.7–2.3)	
		ER+PR+ vs ER–PR–:	104		*P* for four categories (ER+PR+, ER+PR–, ER–PR+, ER–PR–), 0.54
		< 25.0		1.0	
		25.0–29.99		0.7 (0.3–1.4)	
		≥ 30.0		0.7 (0.3–1.4)	

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Tsakountakis et al. (2005) Greece 1996–2002	384 women with primary invasive BC 566 Hospital; women referred for breast screening and who did not develop cancer	BMI > 29 vs ≤ 29: HER2/neu+ HER2/neu– Ratio HER2/neu+ to HER2/neu– ER+ cases: HER2/neu+ HER2/neu– Ratio HER2/neu+ to HER2/neu– ER– cases: HER2/neu+ HER2/neu– Ratio HER2/neu+ to HER2/neu–	 180 total 197 total 	 4.83 (2.75–8.49) 2.67 (1.56–4.55) 2.23 (1.20–4.15) 5.59 (2.58–12.13) 2.48 (1.52–5.32) NS 5.33 (2.59–10.94) 2.41 (1.15–5.04) 2.46 (0.97–6.21)	Age, residence, menopausal age, OC use, HRT use, first-degree family history of BC, age at FFTP, parity, abortion, lactation, medication to suppress lactation, radiation to the chest, BMI, benign breast disease
Li et al. (2006) USA 1997–1999	975 1007 Population	BMI, 65–79 yr ER+PR+: ≤ 24.9 25.0–29.9 ≥ 30.0 ER+PR–: ≤ 24.9 25.0–29.9 ≥ 30.0 ER–PR–: ≤ 24.9 25.0–29.9 ≥ 30.0	 615 218 223 174 139 55 48 36 95 38 35 22	 1.0 1.3 (1.0–1.6) 1.3 (1.0–1.7) 1.0 1.1 (0.7–1.7) 1.1 (0.7–1.7) 1.0 1.1 (0.7–1.8) 0.9 (0.5–1.6)	Age at diagnosis, reference year, type of menopause
Rosenberg et al. (2006) Sweden October 1993–March 1995	Women aged 50–74 yr 2643 3065 Population: frequency-matched to cases, with no history of invasive cancer other than non-melanoma of the skin	Recent BMI ER+PR+: < 22.2 22.2–24.0 24.1–25.8 25.9–28.2 ≥ 28.3	 105 128 135 176 228	 1.0 1.3 (1.0–1.7) 1.3 (1.0–1.8) 1.7 (1.3–2.3) 2.2 (1.7–2.8)	*P* for ER+PR+ vs ER–PR–, 0.48 Exclusion: women who are ever-users of HRT Adjusted for age, age at first birth

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Rosenberg et al. (2006) (cont.)		ER+PR–:			
		< 22.2	45	1.0	
		22.2–24.0	35	0.8 (0.5–1.3)	
		24.1–25.8	40	0.9 (0.6–1.5)	
		25.9–28.2	37	0.9 (0.5–1.3)	
		≥ 28.3	45	1.0 (0.7–1.6)	
		ER–PR+:			
		< 22.2	7	1.0	
		22.2–24.0	2	0.3 (0.1–1.5)	
		24.1–25.8	11	1.7 (0.7–4.5)	
		25.9–28.2	7	1.1 (0.4–3.1)	
		≥ 28.3	14	2.2 (0.9–5.6)	
		ER–PR–:			
		< 22.2	35	1.0	
		22.2–24.0	41	1.3 (0.8–2.0)	
		24.1–25.8	45	1.4 (0.9–2.2)	
		25.9–28.2	50	1.5 (0.9–2.3)	
		≥ 28.3	55	1.6 (1.0–2.5)	
Phipps et al. (2008) USA Study 1: April 1997–May 1999 Study 2: January 2000–March 2004	1233 (ductal only), aged 65–79 yr at diagnosis (study 1), and 55–74 yr at diagnosis (study 2) (study 1: 975; study 2: 1044) 1447 (study 1: 1007; study 2: 469) Population; from Health Care Financing Administration records, frequency-matched to cases by age	BMI			Age, reference year
		HER2-overexpressing cases:			
		< 25.0	15	1.0	
		25.0–29.0	11	0.8 (0.4–1.8)	
		≥ 30.0	13	1.1 (0.5–2.4)	
		[P_{trend}]		[0.78]	
		Triple-negative cases:			
		< 25.0	24	1.0	
		25.0–29.0	26	1.2 (0.7–2.1)	
		≥ 30.0	27	1.4 (0.8–2.5)	
		[P_{trend}]		[0.26]	
		BMI at age 30 yr			
		HER2-overexpressing cases:			
		< 20.8	11	1.0	
		20.8–22.3	9	0.8 (0.3–2.0)	
		22.4–24.3	6	0.6 (0.2–1.6)	
		> 24.3	13	1.2 (0.5–2.8)	
		[P_{trend}]		[0.74]	

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Phipps et al. (2008) (cont.)		Triple-negative cases:			
		< 20.8	21	1.0	
		20.8–22.3	18	0.9 (0.5–1.7)	
		22.4–24.3	11	0.6 (0.3–1.2)	
		> 24.3	27	1.4 (0.8–2.5)	
		[P_{trend}]		[0.41]	
Dey et al. (2009) South India 2002–2005	431 387 Population; visitors of non-BC patients, matched to cases by age (5-yr groups) and residence type (urban/rural)	BMI			Age, religion, education level, SES, age at menarche, parity, age at marriage, total duration of breastfeeding, physical activity per day
		ER+:	170		
		≤ 21.4		1.00	
		21.4–25.1		1.72 (1.04–2.84)	
		> 25.1		1.34 (0.81–2.23)	
		[P_{trend}]		[0.32]	
		ER–:	261		
		≤ 21.4		1.00	
		21.4–25.1		1.35 (0.88–2.07)	
		> 25.1		1.51 (0.98–2.30)	
		[P_{trend}]		[0.07]	
Bao et al. (2011) China Phase I: 1996–1998, Phase II: 2002–2005	1045 1508 Population; randomly selected, Shanghai Resident Registry; frequency-matched by 5-yr age groups ER+PR+: 522 ER–PR–: 299	BMI			Age, education, history of breast fibroadenoma, first-degree family history of BC, regular exercise, years of menstruation, history of live birth, parity, study phase (I or II)
		ER+PR+:			
		< 21.00	54	1.00	
		21.00–23.02	100	1.59 (1.09–2.33)	
		23.03–25.15	152	1.93 (1.34–2.79)	
		≥ 25.16	215	2.40 (1.65–3.47)	
		[P_{trend}]		[< 0.01]	
		ER–PR–:			
		< 21.00	46	1.00	
		21.00–23.02	67	1.10 (0.72–1.68)	
		23.03–25.15	87	1.06 (0.70–1.60)	
		≥ 25.16	99	1.00 (0.66–1.53)	
		[P_{trend}]		[0.88]	

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Barnes et al. (2011) Germany 2001–2005	3074 6386 Population; frequency-matched by year of birth and study region	BMI ER+PR+: ≤ 22.4 22.5–24.9 25–29.9 ≥ 30 ER+PR–: ≤ 22.4 22.5–24.9 25–29.9 ≥ 30 ER–PR–: ≤ 22.4 22.5–24.9 25–29.9 ≥ 30	 831 653 402 70 226 152 90 12 252 156 110 22	 1.00 1.15 (1.02–1.30) 1.13 (0.97–1.31) 1.06 (0.80–1.42) 1.00 0.96 (0.78–1.20) 0.90 (0.69–1.18) 0.63 (0.34–1.16) 1.00 0.87 (0.70–1.07) 0.92 (0.72–1.18) 0.94 (0.59–1.50)	Family history of BC, benign breast disease, age at menarche, duration of OC use, duration of breastfeeding, parity, cause of menopause, age at menopause, alcohol consumption, HRT use, recent physical activity, occupational status, year of birth, study region, lifetime number of mammograms
Dogan et al. (2011) Turkey NR	250 250 Hospital	BMI, mean ER+ PR+ Luminal		 1.144 (1.063–1.746) 1.053 (1.095–1.756) 1.245 (1.023–1.456)	Mostly postmenopausal women, but not clearly stated
Gaudet et al. (2011) USA December 1980–December 1982	890 3432 Population; frequency-matched, aged ≤ 56 yr	BMI treated as ordinal variable Underweight, < 18.5 Normal weight, 18.5– < 25.0 Overweight, 25.0– < 30.0 Obese, ≥ 30.0 Luminal A (n = 455) Luminal B (n = 72) HER2/neu+ (n = 117) Triple-negative (n = 246)	 151 18 57 86	 1.16 (0.87–1.54) 0.83 (0.36–1.93) 0.93 (0.57–1.52) 1.02 (0.70–1.48)	Age at diagnosis, age at menarche, nulliparity, age at first birth per 5-yr interval, duration of breastfeeding, ever use of OC, benign breast disease, family history of BC *P* for subtype vs luminal A: 0.58 0.53 0.72
Bandera et al. (2013b) USA NR	Postmenopausal women of African ancestry 978 958 Population; random-digit dialling	Current BMI ER+PR+: < 25 25–29.99 ≥ 30 [P_{trend}]	 26 49 131 	 1.00 1.05 (0.55–1.98) 1.04 (0.50–2.18) [0.95]	Age, ethnicity, country of origin, education level, family history of BC, history of benign breast disease, age at menarche, parity, breastfeeding, age at first birth, HRT use, OC use

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Bandera et al. (2013b) (cont.)		ER–PR–: < 25 25–29.99 ≥ 30 [P_{trend}]	 20 34 47	 1.00 0.77 (0.38–1.59) 0.37 (0.15–0.96) [0.03]	
John et al. (2013) USA Hispanic cases: 1995–2002 African American cases: 1995–1999 Non-Hispanic White cases: 1995–1999	1389 of 2571 1644 of 2706 Hispanic: 1119 1462 African American: 543 598 Non-Hispanic White: 596 646 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	Current BMI ER+PR+: < 25.0 25.0–29.9 ≥ 30 [P_{trend}] ER–PR–: < 25.0 25.0–29.9 ≥ 30 [P_{trend}]	 98 141 175 34 46 54 	 1.00 1.09 (0.80–1.49) 1.30 (0.95–1.78) [0.09] 1.00 0.75 (0.46–1.22) 0.72 (0.45–1.16) [0.21]	All non-users of HRT Results available for Hispanic, African American, and non-Hispanic White women separately
		BMI in young adulthood ER+PR+: T1: ≤ 21.2 T2: 21.3–23.7 T3: > 23.7 [P_{trend}] ER–PR–: T1: ≤ 21.2 T2: 21.3–23.7 T3: > 23.7 [P_{trend}]	 147 133 116 46 43 37 	 1.00 0.87 (0.65–1.15) 0.73 (0.54–0.98) [0.04] 1.00 0.82 (0.52–1.29) 0.61 (0.38–0.97) [0.04]	All non-users of HRT Results available for Hispanic, African American, and non-Hispanic White women separately
Kawai et al. (2013) Japan 1997–2009	1017 2902 Hospital; female non-cancer patients = benign tumours, cardiovascular diseases, digestive tract diseases, respiratory tract disease, urological–gynaecological disease	BMI ER+PR+: < 18.5 18.5–22.1 22.1–25.0 25.0–30.0 ≥ 30.0 [P_{trend}]	 277 10 54 84 95 34 	 1.00 0.88 (0.41–1.87) 1.29 (0.61–2.72) 1.72 (0.82–3.60) 6.24 (2.68–14.53) [< 0.0001]	Age, smoking, alcohol consumption, family history of BC, occupation, age at menarche, age at first birth, parity, use of exogenous female hormones or OC, year of recruitment, area, referral base (screening, other), height, time spent exercising

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Kawai et al. (2013) (cont.)		ER–PR–:	142		$P_{heterogeneity}$ = 0.0002
		< 18.5	5	1.00	
		18.5–22.1	45	1.49 (0.56–3.96)	
		22.1–25.0	47	1.43 (0.53–3.80)	
		25.0–30.0	36	1.19 (0.44–3.21)	
		≥ 30.0	9	2.43 (0.74–7.95)	
		[P_{trend}]		[0.86]	

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; ER, estrogen receptor; FFTP, first full-term pregnancy; HER2, human epidermal growth factor receptor 2; HRT, hormone replacement therapy; NR, not reported; NS, not significant; OC, oral contraceptive; PR, progesterone receptor; SES, socioeconomic status; WHR, waist-to-hip ratio; yr, year or years

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9i Case–control studies of body mass index and cancer of the breast in postmenopausal women, by ethnicity

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Wenten et al. (2002) USA January 1992–December 1994	Women aged 30–70 yr 712 diagnosed with invasive or in situ breast cancer 1039 Hispanic: 332 511 Non-Hispanic White: 380 528 Population	Usual BMI Hispanic: < 22 22– < 25 25– < 30 ≥ 30 [P_{trend}] Non-Hispanic White: < 22 22– < 25 25– < 30 ≥ 30 [P_{trend}]	NR	 1.00 1.53 (0.67–3.50) 1.60 (0.67–3.82) 1.32 (0.47–3.72) [0.58] 1.00 0.90 (0.51–1.61) 1.15 (0.53–2.47) 2.77 (0.86–8.89) [0.16]	Age, first-degree family history of BC, total METs, parity, OC use, months of breastfeeding, age at first full-term birth, HRT use, weight at age 18 yr Results also reported for BMI at age 18 yr
Ziv et al. (2006) USA 1995–2002	Hispanic/Latina women 357 diagnosed 1997–1999 479 Completed interview: 324 421 Provided blood sample: 241 333 Population; matched to cases by ethnicity and 5-yr age groups	BMI All Latinas: < 25 25–29.9 ≥ 30 Latinas born in USA: < 25 25–29.9 ≥ 30 Foreign-born Latinas: < 25 25–29.9 ≥ 30	 48 71 115 106 total 128 total 	 1.00 1.93 (1.38–2.69) 1.51 (1.12–2.04) 1.00 1.25 (0.79–1.96) 1.26 (0.83–1.92) 1.00 3.44 (1.97–5.99) 1.95 (1.24–3.06)	Age, case–control status, grandparents' place of birth, age at migration, education level, place of birth (born in USA vs foreign-born) Age, case–control status, grandparents' place of birth, education level Age, case–control status, grandparents' place of birth, age at migration, education level

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Slattery et al. (2007) USA 1999–2004	Hispanic women living in non-reservations and non-Hispanic White women 2325 2525 Non-Hispanic White: 1527 1601 Hispanic: 798 924 Population; matched by ethnicity, age in 5-yr classes, random selection	BMI in reference year, no recent hormone exposure			Age, height, physical activity, energy intake, parity, alcohol consumption, age at first pregnancy, age at menopause, centre Analyses of BMI at age 18 yr also reported
		Non-Hispanic White:			
		< 25	146	1.00	
		25–29.9	122	1.60 (1.06–2.40)	
		≥ 30	112	1.61 (1.05–2.45)	
		[P_{trend}]		[0.03]	
		Hispanic:			
		< 25	43	1.00	
		25–29.9	91	0.68 (0.38–1.24)	
		≥ 30	104	0.80 (0.44–1.45)	
		[P_{trend}]		[0.61]	
		BMI in reference year, recent hormone exposure			
		Non-Hispanic White:			
		< 25	306	1.00	
		25–29.9	194	1.02 (0.79–1.32)	
		≥ 30	202	0.72 (0.54–0.96)	
		[P_{trend}]		[0.04]	
		Hispanic:			
		< 25	92	1.00	
		25–29.9	120	0.91 (0.60–1.38)	
		≥ 30	114	0.74 (0.47–1.15)	
		[P_{trend}]		[0.17]	
Berstad et al. (2010) USA: Atlanta (Georgia), Seattle (Washington), Detroit (Michigan), Philadelphia (Pennsylvania), Los Angeles (California); July 1994–April 1998	4575 4682 Caucasian: 2953 3021 African American: 1622 1661 Population	BMI at age 18 yr			Age, race, education level, study site, first-degree family history of BC, parity, age at menopause, HRT use, BMI at the other time point Results available by hormonal status for BMI by age 18 yr and 5 yr before reference date, for each ethnic group
		Caucasian:	1261		
		< 20	682	1.00	
		20–24	517	0.89 (0.75–1.05)	
		≥ 25	62	0.70 (0.49–1.00)	
		[P_{trend}]		[0.03]	
		African American:	639		
		< 20	297	1.00	
		20–24	286	0.91 (0.72–1.14)	
		≥ 25	56	0.80 (0.54–1.19)	
		[P_{trend}]		[0.22]	

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Berstad et al. (2010) (cont.)		BMI 5 yr before reference date			
		Caucasian:			
		< 25	733	1.00	
		25–29	333	0.93 (0.77–1.12)	
		30–34	127	0.94 (0.72–1.24)	
		≥ 35	68	0.75 (0.53–1.06)	
		[P_{trend}]		[0.13]	
		African American:			
		< 25	185	1.00	
		25–29	246	1.05 (0.80–1.37)	
		30–34	127	0.98 (0.71–1.35)	
		≥ 35	81	1.26 (0.85–1.85)	
		[P_{trend}]		[0.44]	
Bandera et al. (2013a) USA New York City: 2002–2008 New Jersey: 2006–2012	Postmenopausal women of African and Caucasian ancestry 1751 1673 African American: 979 958 European American: 772 715 Population	BMI at age 20 yr			Age, ethnicity (Hispanic/non-Hispanic), country of origin, family history of BC, history of benign breast disease, age at menarche, parity, breastfeeding status, age at first birth, HRT use, OC use, height and weight at menarche
		African American:			
		< 25	392	1.00	
		25–29.9	52	1.01 (0.65–1.58)	
		≥ 30	17	0.88 (0.43–1.81)	
		[P_{trend}]		[0.82]	
		European American:			
		< 25	342	1.00	
		25–29.9	17	0.82 (0.38–1.77)	
		≥ 30	4	0.15 (0.04–0.60)	
		[P_{trend}]		[0.01]	

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
John et al. (2013) USA Hispanic cases: 1995–2002 African American cases: 1995–1999 Non-Hispanic White cases: 1995–1999	1389 of 2571 1644 of 2706 Hispanic: 1119 1462 African American: 543 598 Non-Hispanic White: 596 646 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	Current BMI			Non-users of HRT Results available for ER+PR+ tumours (for both current BMI and BMI in young adulthood, separated by race)
		Hispanic:			
		< 25.0	81	1.00	
		25.0–29.9	133	0.78 (0.54–1.14)	
		≥ 30	161	0.77 (0.53–1.12)	
		[P_{trend}]		[0.24]	
		African American:			
		< 25.0	51	1.00	
		25.0–29.9	90	1.19 (0.74–1.94)	
		≥ 30	101	1.07 (0.66–1.73)	
		[P_{trend}]		[0.88]	
		Non-Hispanic White:			
		< 25.0	76	1.00	
		25.0–29.9	55	0.90 (0.56–1.43)	
		≥ 30	50	1.19 (0.72–1.99)	
		[P_{trend}]		[0.58]	
		BMI in young adulthood			
		Hispanic:			
		T1: ≤ 21.2	109	1.00	
		T2: 21.3–23.7	122	0.85 (0.60–1.20)	
		T3: > 23.7	115	0.63 (0.45–0.90)	
		[P_{trend}]		[0.01]	
		African American:			
		T1: ≤ 21.2	93	1.00	
		T2: 21.3–23.7	77	1.17 (0.76–1.79)	
		T3: > 23.7	67	0.93 (0.59–1.45)	
		[P_{trend}]		[0.80]	
		Non-Hispanic White:			
		T1: ≤ 21.2	84	1.00	
		T2: 21.3–23.7	60	0.65 (0.41–1.02)	
		T3: > 23.7	34	0.52 (0.30–0.90)	
		[P_{trend}]		[0.01]	

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Robinson et al. (2014) USA 1993–2001	Women aged 20–74 yr 1783 1536 Black: 788 718 White: 995 818 Population; frequency-matched to cases by 5-yr age group	Measured BMI Black: < 25 25–30 30–35 ≥ 35 [P_{trend}] White: < 25 25–30 30–35 ≥ 35 [P_{trend}]	 74 121 118 113 212 165 69 30 	 1.00 0.61 (0.38–0.98) 0.77 (0.47–1.28) 0.58 (0.35–0.94) [0.11] 1.00 0.91 (0.67–1.25) 0.83 (0.55–1.25) 0.61 (0.35–1.06) [0.08]	Age, age squared, family history of BC, alcohol consumption, menarche, parity, age at FFTP composite, lactation, education level, smoking Data also reported for BMI at age 18 yr, 35 yr, and one yr before interview, by ethnicity; all of these associations were null
John et al. (2015b) USA 2 population-based case–control studies San Francisco Bay Area Study 4-Corners Breast Cancer Study Hispanic: 1995–2002 Non-Hispanic White: 1995–2004	4271 4713 Population	ER+PR+: Current BMI Hispanic: per 5 kg/m^2 Non-Hispanic White: per 5 kg/m^2 ER–PR–: Current BMI Hispanic: per 5 kg/m^2 Non-Hispanic White: per 5 kg/m^2	 294 292 153 	 0.81 (0.65–1.01) 0.94 (0.74–1.19) 0.76 (0.57–1.01) 0.63 (0.43–0.92)	Age, study, ethnicity/English language acculturation, education level, first-degree family history of BC, age at menarche, number of FTPs, age at FFTP, lifetime months of breastfeeding, average alcohol consumption Age, study, ethnicity, education level, first-degree family history of BC, age at menarche, number of FTPs, age at FFTP, lifetime months of breastfeeding, average alcohol consumption Age, study, ethnicity/English language acculturation, first-degree family history of BC, age at menarche, HRT use Age, study, ethnicity, first-degree family history of BC, age at menarche, HRT use

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Sanderson et al. (2015) USA 2001–2011	Women aged 25–75 yr 2614 with primary ductal carcinoma in situ or invasive breast cancer 2306 Population; matched by 5-yr age groups, race, and county of residence	BMI Black: < 25.0 25.0–29.9 30.0–34.9 ≥ 35 [P_{trend}] White: < 25.0 25.0–29.9 30.0–34.9 ≥ 35 [P_{trend}]	 75 129 123 113 493 433 223 121 	 1.0 1.0 (0.6–1.7) 1.2 (0.7–2.0) 1.0 (0.6–1.7) [0.90] 1.0 1.1 (0.9–1.3) 1.1 (0.9–1.4) 0.8 (0.6–1.1) [0.67]	Age, education level, first-degree family history of BC, OC use, age at menarche $P_{interaction}$ = 0.43

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; ER, estrogen receptor; HRT, hormone replacement therapy; MET, metabolic equivalent; NR, not reported; OC, oral contraceptive; PR, progesterone receptor; yr, year or years

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9k Case–control studies of waist circumference and cancer of the breast in postmenopausal women

Reference, study location and period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories (cm, unless otherwise stated)	Exposed cases	Relative risk (95% CI)	Covariates
Friedenreich et al. (2002) Canada 1995–1997	771 762 Population-based using Waksberg method; frequency-matched to cases by age, 5-yr intervals, and place of residence (urban/rural)	< 75.6 ≥ 75.6– < 82.8 ≥ 82.8– < 91.5 ≥ 91.5 [P_{trend}]	1533 175 159 187 242	1.00 0.89 (0.66–1.20) 1.06 (0.79–1.42) 1.30 (0.97–1.73) [0.07]	Current age, total energy intake, total lifetime physical activity, education level, ever use of HRT, ever diagnosed with benign breast disease, first-degree family history of BC, ever alcohol consumption, current smoking
Slattery et al. (2007) USA 1999–2004	Hispanic women living in non-reservations and non-Hispanic White women Non-Hispanic White: 858 1008 Hispanic: 399 522 Population; matched by ethnicity, age in 5-yr classes, random selection	WC (in), no recent hormone exposure Non-Hispanic White: < 35 35–40 > 40 [P_{trend}] Hispanic: < 35 35–40 > 40 [P_{trend}] WC (in), recent hormone exposure Non-Hispanic White: < 35 35–40 > 40 [P_{trend}] Hispanic: < 35 35–40 > 40 [P_{trend}]	 197 95 83 80 83 71 393 180 115 148 108 65 	 1.00 1.73 (1.16–2.58) 1.29 (0.83–1.99) [0.11] 1.00 0.98 (0.59–1.63) 0.81 (1.47–1.39) [0.45] 1.00 0.99 (0.76–1.28) 0.88 (0.64–1.21) [0.48] 1.00 1.18 (0.80–1.75) 0.86 (0.53–1.38) [0.74]	Age, height, physical activity, energy intake, parity, alcohol consumption, age at first pregnancy, age at menopause, centre

Table 2.2.9k (continued)

Reference, study location and period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories (cm, unless otherwise stated)	Exposed cases	Relative risk (95% CI)	Covariates
Tian et al. (2007) Taiwan 2004–2005	102 aged 22–87 yr 103 Hospital; recruited from health examination clinics at the same hospital and time, free for cancer history, matched by menopausal status, date of enrolment, duration of fasting	≤ 81.00 > 81.00	54 48	1.00 2.02 (1.05–3.91)	Age at enrolment, fasting status, levels of adiponectin
Mathew et al. (2008) India 2002–2005	968 691 Accompanying persons to cancer cases; matched by age ± 5 yr and residence type (urban/rural)	≤ 85 > 85 Unknown	57 380 31	1.00 1.61 (1.22–2.12) 2.88 (0.76–10.90)	Age, centre, religion, marital status, education level, SES, residence status, parity, age at first birth, duration of breastfeeding, physical activity
Nemesure et al. (2009) Barbados 2002–2006	Women of African descent aged ≥ 21 yr 222 454 Population; Barbados Statistical Services; frequency-matched by 5-yr age group	Aged ≥ 50 yr: < 80 80–101 ≥ 101	 18 88 38	 1.00 1.35 (0.57–3.18) 2.98 (0.91–9.71)	Current age, HRT use, parity, family history of BC, history of benign breast disease, age at first pregnancy, age at menarche, physical activity, other body size variable
Rosato et al. (2011) Italy, Switzerland 1983–1994 (Italy), 1991–2007 (Switzerland)	Postmenopausal women 1747 1935 Hospital; admitted for acute, non-neoplastic diseases, not related to gynaecological or hormonal conditions, matched by age and study centre	< 88 ≥ 88	869 878	1.00 1.17 (1.02–1.35)	Age, study centre, study period, education level, alcohol consumption, age at menarche, age at first birth, age at menopause, HRT use, family history of BC

Table 2.2.9k (continued)

Reference, study location and period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories (cm, unless otherwise stated)	Exposed cases	Relative risk (95% CI)	Covariates
Bandera et al. (2013b) USA NR	Postmenopausal women of African ancestry 978 958 Population; random-digit dialling	≤ 87.88	87	1.00	BMI, age, ethnicity, country of origin, education level, family history of BC, history of benign breast disease, age at menarche, age at menopause, parity, breastfeeding, age at first birth, HRT use, OC use
		87.89–97.75	119	1.13 (0.73–1.76)	
		97.76–110.25	154	1.51 (0.92–2.48)	
		> 110.25	140	1.23 (0.64–2.34)	
		[P_{trend}]		[0.48]	
		ER+PR+:			
		≤ 87.88	36	1.00	
		87.89–97.75	39	0.88 (0.48–1.60)	
		97.76–110.25	56	1.30 (0.68–2.48)	
		> 110.25	74	1.55 (0.68–3.55)	
		[P_{trend}]		[0.20]	
		ER–PR–:			
		≤ 87.88	23	1.00	
		87.89–97.75	25	0.93 (0.45–1.92)	
		97.76–110.25	25	1.11 (0.48–2.57)	
		> 110.25	27	1.08 (0.35–3.31)	
		[P_{trend}]		[0.83]	
John et al. (2013) USA 1995–2002	1389 postmenopausal women 1644 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	All:			All non-users of HRT
		≤ 85.0	198	1.00	
		85.1–96.4	214	0.99 (0.77–1.27)	
		> 96.4	293	1.32 (1.03–1.69)	
		[P_{trend}]		[0.02]	
		ER+PR+:			
		≤ 85.0	95	1.00	
		85.1–96.4	106	1.11 (0.80–1.54)	
		> 96.4	162	1.76 (1.28–2.41)	
		[P_{trend}]		[< 0.01]	
		ER–PR–:			
		≤ 85.0	28	1.00	
		85.1–96.4	40	1.13 (0.67–1.89)	
		> 96.4	48	1.24 (0.75–2.06)	
		[P_{trend}]		[0.41]	

Table 2.2.9k (continued)

Reference, study location and period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories (cm, unless otherwise stated)	Exposed cases	Relative risk (95% CI)	Covariates
Sangrajrang et al. (2013) Thailand May 2002–March 2004; August 2005–August 2006	470 385 Hospital/population; female visitors of hospital patients admitted for conditions other than BC or ovarian cancer	< 80 ≥ 80	199 271	1.00 1.18 (0.89–1.57)	
Amadou et al. (2014) Mexico 2004–2007	585 598 Population	< 93 93–103 ≥ 103 [P_{trend}]	187 218 180	1.00 0.96 (0.70–1.32) 0.62 (0.44–0.85) [0.003]	Age, health care system, region, SES, breastfeeding, family history of BC, alcohol consumption, physical activity, total energy intake, height, current BMI
Robinson et al. (2014) USA 1993–2001	Women aged 20–74 yr 911 825 Black: 434 380 White: 477 445 Population; frequency-matched to cases by 5-yr age group	Black: ≤ 88 > 88 [P_{trend}] White: ≤ 88 > 88 [P_{trend}]	 113 321 314 163	 1.00 1.39 (0.92–2.10) [0.11] 1.00 1.31 (0.88–1.95) [0.18]	Age, age squared, family history of BC, alcohol consumption, menarche, parity, age at FFTP composite, lactation, education level, smoking, reference BMI

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; ER, estrogen receptor; FFTP, first full-term pregnancy; HRT, hormone replacement therapy; NR, not reported; OC, oral contraceptive; PR, progesterone receptor; SES, socioeconomic status; WC, waist circumference (in cm); yr, year or years

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9m Case–control studies of change in body mass index or weight and cancer of the breast in postmenopausal women

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
BMI change					
Hirose et al. (2001) Japan 1988–1997	1584 15 331 First visit outpatients (screening) without any previous diagnosis of cancer	BMI change from age 20 yr, without family history of BC			Age, age at menarche, menstrual regularity in the 20s, age at first birth, parity
		< 0	127	0.69 (0.52–0.92)	
		0–1.24	89	1.00	
		1.25–2.99	137	1.02 (0.77–1.40)	
		≥ 3	238	1.34 (1.00–1.70)	
		[P_{trend}]		[< 0.001]	
		BMI change from age 20 yr, with family history of BC			
		< 0	9	1.56 (0.44–5.60)	
		0–1.24	4	1.00	
		1.25–2.99	13	2.74 (0.82–9.10)	
		≥ 3	17	2.19 (0.68–7.00)	
		[P_{trend}]		[0.26]	
Robinson et al. (2014) USA 1993–2001	1783 women aged 20–74 yr 1536 Black: 788 718 White: 995 818 Population; frequency-matched to cases by 5-yr age group	BMI change, ages 18–35 yr			Age, age squared, family history of BC, alcohol consumption, menarche, parity, age at FFTP composite, lactation, education level, smoking, reference BMI
		Black:			
		< 1.77	103	1.0	
		1.77–4.44	151	1.47 (0.98–2.18)	
		≥ 4.44	161	1.14 (0.76–1.70)	
		[P_{trend}]		[0.63]	
		White:			
		< 1.77	194	1.0	
		1.77–4.44	172	1.17 (0.85–1.60)	
		≥ 4.44	98	1.33 (0.88–2.02)	
		[P_{trend}]		[0.16]	
Weight change					
Li et al. (2000) USA January 1988–June 1990	479 435 Population; Caucasian women	Weight change (lb), age 18 yr to reference date, 50–64 yr			Age, height, weight at age 18 yr, family history of BC, parity, HRT use, OC use
		< –10	14	0.9 (0.4–1.9)	
		–10 to 10	113	1.0	
		11–30	153	1.1 (0.7–1.5)	
		31–50	100	1.2 (0.8–1.7)	
		51–70	43	1.3 (0.7–2.1)	
		> 70	55	2.7 (1.5–4.9)	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Trentham-Dietz et al. (2000) USA January 1992–December 1994	Postmenopausal women aged 50–79 yr 5031 5255 Population; matched by age and state	Weight loss (kg), overall			Parity, age at FFTP, family history of BC, recent alcohol consumption, education level, age at menopause, height, highest weight and age at highest weight Analyses of weight loss since age 11–45 yr and since age > 45 yr gave similar results to weight loss overall
		0.0	1690	1.0	
		0.1–4.9	1637	1.1 (1.0–1.2)	
		5.0–9.9	809	1.0 (0.9–1.2)	
		≥ 10.0	668	1.0 (0.9–1.2)	
		[P_{trend}]		[0.1]	
		Weight gain (kg), overall			Parity, age at FFTP, family history of BC, recent alcohol consumption, education level, age at menopause, height, lowest weight and time since lowest weight Analyses of weight gain since age 20, since age 21–30 yr and since age > 30 yr gave similar results to weight gain overall
		0–5.0	730	1.0	
		5.1–10.0	853	1.1 (0.9–1.3)	
		10.1–15.0	872	1.1 (1.0–1.3)	
		15.1–25.0	1409	1.4 (1.2–1.6)	
		> 25.0	1008	1.7 (1.5–2.0)	
		[P_{trend}]		[< 0.001]	
de Vasconcelos et al. (2001) Brazil May 1995–February 1996	177 377 Hospital/population; visitors at hospital; 27 relatives of breast cancer patients	Weight change (kg) since age 18 yr			Age, parity, age at menarche, family history of BC, weight and height at 18 yr Analyses of weight change from age 18 yr to age 30 yr and weight change since age 30 yr gave similar results
		> 22.3	31	1.00	
		13.11–22.3	38	1.39 (0.75–2.59)	
		0–13.10	28	1.24 (0.62–2.50)	
		Weight loss	12	2.05 (0.75–5.59)	
		[P_{trend}]		[0.24]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Shu et al. (2001) China August 1996–March 1998	Women aged 25–64 yr 1459 of 1602 1556 of 1724 Population; randomly selected from female residents of Shanghai (Shanghai Resident Registry), matched to cases by age, 5-yr interval	Weight gain (kg) since age 20 yr			Age, education level, family history of BC, ever had fibroadenoma, age at menarche, age at first live birth, exercise, age at menopause
		< 1.15	20.4%	1.0	
		1.15–3.41	31.7%	1.4 (1.0–2.1)	
		3.42–5.64	26.6%	1.3 (0.9–1.9)	
		≥ 5.65	21.3%	2.7 (1.7–4.2)	
		[P_{trend}]		[< 0.001]	
		Weight gain (kg) during past 10 yr			
		< 1.15	37.1%	1.0	
		1.15–3.41	19.8%	1.6 (1.1–2.2)	
		3.42–5.64	14.3%	1.2 (0.8–1.8)	
		≥ 5.65	28.8%	1.5 (1.1–2.1)	
		[P_{trend}]		[0.03]	
Friedenreich et al. (2002) Canada 1995–1997	1233 1241 Population-based using Waksberg method; frequency-matched to cases by age, 5-yr interval, and place of residence (urban/rural)	Weight gain (kg) since age 20 yr			Current age, total energy intake, total lifetime physical activity, education level, ever use of HRT, ever diagnosed with benign breast disease, first-degree family history of BC, ever alcohol consumption, current smoking
		< 7.80	181	1.00	
		≥ 7.80– < 15.7	173	1.02 (0.75–1.37)	
		≥ 15.7– < 25.0	182	1.08 (0.80–1.45)	
		≥ 25.0	231	1.35 (1.01–1.81)	
		[P_{trend}]		[0.05]	
		Difference, maximum − minimum weight (kg) over adult lifetime			
		< 9.07	161	1.00	
		≥ 9.07– < 15.4	161	0.94 (0.69–1.28)	
		≥ 15.4– < 22.7	184	1.21 (0.89–1.64)	
		≥ 22.7	265	1.56 (1.16–2.08)	
		[P_{trend}]		[0.0007]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Wenten et al. (2002) USA January 1992–December 1994	712 women aged 30–70 yr diagnosed with invasive or in situ breast cancer 1039 Hispanic: 332 511 Non-Hispanic White: 380 528 Population	Weight change (kg), age 18 yr to usual adult weight			Age, first-degree family history of BC, total METs, parity, OC use, months of breastfeeding, age at first full-term birth, HRT use, weight at age 18 yr
		Hispanic:			
		< 4		1.00	
		4–7		2.48 (0.89–6.93)	
		8–14		2.04 (0.73–5.68)	
		> 14		2.46 (0.98–6.17)	
		[P_{trend}]		[0.14]	
		Non-Hispanic White:			
		< 4		1.00	
		4–7		1.34 (0.66–2.74)	
		8–14		1.33 (0.63–2.77)	
		> 14		2.27 (1.09–4.73)	
		[P_{trend}]		[0.04]	
Carpenter et al. (2003) Canada, USA, western Europe Group I: March 1987–December 1989 Group II: January 1992–December 1992 Group III: September 1995–April 1996	Caucasian (including Hispanic), born in Canada, USA, or western Europe 1883 diagnosed at age 55–64 yr (Group I), age 55–69 yr (Group II), or age 55–72 yr (Group III) 1628 Population; matched to cases by neighbourhood	Weight change (%), age 18 yr to reference date (1 yr before diagnosis)			Age at FFTP, ages at menarche and menopause, family history of BC, interviewer, average MET hours per week of lifetime exercise activity
		Negative change to no change	229	1.00	
		> 0–16.9%	573	1.16 (0.92–1.47)	
		17.0–29.1%	404	1.13 (0.88–1.45)	
		≥ 29.2%	677	1.36 (1.08–1.73)	
		[P_{trend}]		[0.01]	
Eng et al. (2005) USA August 1996–July 1997	1006 990 Population; frequency-matched by 5-yr age group	Weight change (kg), age 20 yr to 1 yr before reference date			Age at reference date, number of pregnancies, months of HRT use, history of BC in a first-degree relative, history of benign breast disease, BMI at age 20 yr
		–44.91 to –3.01	36	0.55 (0.32–0.96)	
		–3.00 to 3.00	103	1.00	
		3.01–7.71	141	1.03 (0.70–1.50)	
		7.71–8.15	241	1.18 (0.84–1.74)	
		8.16–14.96	209	1.21 (0.84–1.74)	
		14.97–87.09	256	1.58 (1.11–2.26)	
		[P_{trend}]		[0.0001]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Eng et al. (2005) (cont.)		Weight change (kg), age 50 yr to 1 yr before reference date			Age at reference date, number of pregnancies, months of HRT use, history of BC in a first-degree relative, history of benign breast disease, BMI at age 50 yr
		−68.04 to −0.01	157	1.19 (0.85–1.67)	
		0.00	167	1.00	
		0.01–2.71	133	1.19 (0.84–1.69)	
		2.72–4.98	124	0.96 (0.68–1.37)	
		4.99–11.33	195	1.58 (1.14–2.23)	
		11.34–62.14	171	1.62 (1.14–2.30)	
		[P_{trend}]		[0.003]	
Han et al. (2006) USA 1996–2001	1166 2105 Population; frequency-matched by age, race, and county of residence	Weight change (kg), age 20 yr to 1 yr before study enrolment			Age, education level, previous benign disease, age at menarche, age at first birth, family history of BC, age at menopause, HRT use, BMI residuals Weight change (kg) from age at first pregnancy to age at menopause also showed a positive association with breast cancer risk (P_{trend} = 0.01)
		≤ 0	841	0.90 (0.56–1.45)	
		0–9.1	47	1.00	
		9.1–17.7	137	1.45 (1.06–1.96)	
		17.7–27.3	208	1.53 (1.12–2.08)	
		> 27.3	227	1.71 (1.23–2.37)	
		[P_{trend}]	222	[0.05]	
Wu et al. (2006) USA 1995–2001	Asian American women 1277 aged 25–74 yr at diagnosis 1160 Chinese: 450 486 Japanese: 352 311 Filipino: 475 363 Population; neighbourhood controls; frequency-matched by ethnicity and 5-yr age group	Weight gain (kg) since age 18 yr (recent weight − weight at age 18 yr)			Age, ethnicity, duration of residence in the USA, education level, age at menarche, number of live births, age at menopause, intake of tea and soy during adolescence and adult life, years of physical activity, height
		≤ 10	319	1.00	
		> 10– ≤ 15	138	1.24 (0.90–1.72)	
		> 15– ≤ 20	95	1.10 (0.75–1.62)	
		> 20	95	1.66 (1.09–2.53)	
		[P_{trend}]		[0.036]	
		Weight gain (kg) since age 30 yr (recent weight − weight at age 30 yr)			
		≤ 10	518	1.00	
		> 10– ≤ 15	91	1.51 (1.02–2.22)	
		> 15– ≤ 20	44	1.17 (0.70–1.96)	
		> 20	27	2.23 (1.00–4.94)	
		[P_{trend}]		[0.023]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Slattery et al. (2007) USA 1999–2004	Hispanic women living in non-reservations and non-Hispanic White women 2325 2525 Non-Hispanic White: 1527 1601 Hispanic: 798 924 Population; matched by ethnicity, age in 5-yr classes, random selection	Total weight gain (kg) between age 15 yr and reference year			Age, height, physical activity, energy intake, parity, alcohol consumption, age at first pregnancy, age at menopause, centre
		No recent hormone exposure			
		Non-Hispanic White:			
		≤ 5.0	57	1.00	
		5.1–15.0	99	1.19 (0.67–2.09)	
		15.1–25.0	94	1.40 (0.79–2.48)	
		> 25.0	104	1.75 (1.00–3.05)	
		[P_{trend}]		[0.03]	
		Hispanic:			
		≤ 5.0	22	1.00	
		5.1–15.0	37	1.14 (0.49–2.67)	
		15.1–25.0	79	0.70 (0.32–1.52)	
		> 25.0	78	0.76 (0.35–1.65)	
		[P_{trend}]		[0.25]	
		Recent hormone exposure			
		Non-Hispanic White:			
		≤ 5.0	115	1.00	
		5.1–15.0	176	1.14 (0.80–1.61)	
		15.1–25.0	182	1.08 (0.77–1.53)	
		> 25.0	200	0.95 (0.66–1.35)	
		[P_{trend}]		[0.57]	
		Hispanic:			
		≤ 5.0	25	1.00	
		5.1–15.0	77	0.73 (0.37–1.43)	
		15.1–25.0	98	0.79 (0.41–1.51)	
		> 25.0	108	0.64 (0.34–1.23)	
		[P_{trend}]		[0.26]	
Shin et al. (2009) China 1996–1998 (phase 1), April 2002–February 2005 (phase 2)	3452 aged 20–64 yr (phase 1), 20–70 yr (phase 2) 3474 Population; controls frequency-matched to cases by age	Weight change (kg) since age 20 yr			
		≤ 0	141	1.0	
		0.1–9.4	383	1.3 (1.0–1.6)	
		9.5–14.9	307	1.5 (1.1–2.0)	
		≥ 15	471	1.8 (1.4–2.4)	
		[P_{trend}]		[< 0.001]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Berstad et al. (2010) USA July 1994–April 1998	4575 4682 Caucasian: 2953 3021 African American: 1622 1661 Population	Weight change (kg) since age 18 yr ≤ 5 5.1–15.0 15.1–25.0 ≥ 25.1 [P_{trend}]	1900 363 641 507 389	 1.00 1.10 (0.91–1.32) 1.01 (0.83–1.23) 1.03 (0.84–1.27) [0.92]	Also adjusted for BMI at age 18 yr
Cribb et al. (2011) Canada 1999–2002	207 621 Population; women presenting for routine mammography screening; matched by age, menopausal status, and family history of BC	Weight gain (kg) since age 25 yr > 10	 61%	 1.34 (0.85–2.12)	Parity, OC use, BMI, smoking
Sangaramoorthy et al. (2011) USA 1998–2002	Women aged 35–79 yr 931 of 1031 1050 of 1198 Hispanic: 650 766 African American: 134 137 Non-Hispanic White: 147 147 Population; frequency-matched by race and age in 5-yr groups, without history of BC	Relative weight vs peers at age 10 yr Women not currently using HRT Lighter Same Heavier [P_{trend}]	 205 114 61 23	 1.00 0.84 (0.55–1.29) 0.68 (0.37–1.25) [0.19]	Analysis of Hispanic women only Age, country of birth, education level, first-degree family history of BC, prior biopsy history of benign breast disease, number of FTPs, age at FFTP, lifetime breastfeeding, OC use, adult height, alcohol consumption, average energy intake, BMI Measures of relative weight vs peers at 15 yr and 20 yr gave similar results

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Bandera et al. (2013b) USA New York City: 2002–2008 New Jersey: 2006–2012	Postmenopausal women of African and European ancestry 1751 1673 African American: 979 958 European American: 772 715 Population	Weight gain (kg) since age 20 yr, quartiles			Age, ethnicity (Hispanic/non-Hispanic), country of origin, family history of BC, history of benign breast disease, age at menarche, age at menopause, parity, breastfeeding status, age at first birth, HRT use, OC use, current BMI
		African American:			
		Q1: ≤ 13.82	75	1.00	
		Q2: 13.83–23.72	115	1.35 (0.87–2.10)	
		Q3: 23.73–34.56	110	1.29 (0.80–2.09)	
		Q4: > 34.56	139	1.42 (0.80–2.53)	
		[P_{trend}]		[0.34]	
		European American:			
		Q1: ≤ 7.57	75	1.00	
		Q2: 7.58–14.57	77	0.97 (0.56–1.66)	
		Q3: 14.58–24.52	91	0.90 (0.52–1.57)	
		Q4: > 24.52	90	0.95 (0.46–1.95)	
		[P_{trend}]		[0.88]	
John et al. (2013) USA Hispanic cases: 1995–2002 African American cases: 1995–1999 Non-Hispanic White cases: 1995–1999	1389 of 2571 1644 of 2706 Hispanic: 1119 1462 African American: 543 598 Non-Hispanic White: 596 646 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	Weight gain (kg) from 20s, all non-users of HRT			Subanalysis by race/ethnicity showed a positive association in White non-Hispanic women only
		Stable	78	1.00	
		3.0–9.9	180	1.15 (0.82–1.63)	
		10.0–19.9	217	1.06 (0.76–1.48)	
		20.0–29.9	142	1.03 (0.72–1.48)	
		≥ 30.0	111	1.19 (0.81–1.75)	
		[P_{trend}]		[0.75]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Troisi et al. (2013) USA 1974–2009	22 646 women aged < 85 yr, with primary in situ or invasive cancer 224 721 Population; frequency-matched to cases by parity, age, calendar year of delivery, and race/ethnicity	Weight gain (lb), since 1989			Age at delivery, race/ethnicity, parity at index birth, year of index birth
		Aged ≥ 50 yr at diagnosis:	299		
		< 25	62	1.00	
		25– < 31	99	1.33 (0.95–1.86)	
		31– < 40	72	1.23 (0.86–1.76)	
		≥ 40	66	1.06 (0.74–1.54)	
Robinson et al. (2014) USA 1993–2001	Women aged 20–74 yr 1783 1536 Black: 788 718 White: 995 818 Population; frequency-matched to cases by 5-yr age group	Adult weight gain (lb) since age 18 yr			Age, age squared, family history of BC, alcohol consumption, age at menarche, parity, age at FFTP composite, lactation, education level, smoking, reference BMI
		Black:			
		≤ 25	81	1.00	
		26–54	126	0.70 (0.44–1.12)	
		≥ 55	222	0.84 (0.50–1.40)	
		[P_{trend}]		[0.64]	
		White:			
		≤ 25	185	1.00	
		26–54	184	1.17 (0.82–1.65)	
		≥ 55	101	1.25 (0.70–2.23)	
		[P_{trend}]		[0.38]	
Sanderson et al. (2015) USA 2001–2011	2614 aged 25–75 yr, primary ductal carcinoma in situ or invasive breast cancer 2306 Population; matched by 5-yr age groups, race, and county of residence	Weight change (lb) since age 18 yr			Age, education level, first-degree family history of BC, OC use, age at menarche, weight at 18 yr
		Black:			
		≤ 0	23	1.0	
		1–31	79	0.8 (0.3–2.1)	
		32–60	138	0.9 (0.4–2.3)	
		> 61	200	0.9 (0.4–2.2)	
		[P_{trend}]		[0.90]	
		White:			
		≤ 0	71	1.0	$P_{interaction}$ = 0.62
		1–31	406	1.2 (0.8–1.6)	
		32–60	460	1.3 (0.9–1.9)	
		> 61	329	1.1 (0.8–1.6)	
		[P_{trend}]		[0.76]	

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; FFTP, first full-term pregnancy; FTP, full-term pregnancy; HRT, hormone replacement therapy; MET, metabolic equivalent of task; OC, oral contraceptive; yr, year(s)

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9o Mendelian randomization studies of body mass index and cancer of the breast

Reference Study	Study population	Sample size	Exposure assessment	Outcome	Relative risk (95% CI)
Gao et al. (2016) Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium	Women from 11 studies of individuals of European ancestry	33 832 (15 748 cases and 18 084 controls)	Adult BMI: Increase of 1 SD (equivalent to 4.5 kg/m^2) in genetically predicted adult BMI	Adult BMI: All breast cancer ER– breast cancer	0.91 (0.88–0.94) 0.89 (0.84–0.94)
			Increase of 1 SD (~0.073 kg/m^2) in genetically predicted childhood BMI	Childhood BMI: All breast cancer ER– breast cancer	0.71 (0.60–0.80) 0.69 (0.53–0.98)

BMI, body mass index (in kg/m^2); CI, confidence interval; ER, estrogen receptor; SD, standard deviation

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2.2.10 Cancer of the breast in men

Breast cancer in men is uncommon, with an incidence that is often cited as being less than 1% of that for breast cancer in women. Risk factors for breast cancer in men include Klinefelter syndrome, a rare hereditary condition characterized by a chromosomal abnormality of 46 XXY karyotype with associated hormonal alterations, and gynaecomastia, a condition linked with excess estrogen. Like for breast cancer in women, risk is likely to be mediated through hormonal mechanisms.

The single largest study of the association of BMI with breast cancer in men is the Male Breast Cancer Pooling Project, a consortium of 11 case–control studies and 10 cohort studies involving 2405 cases (1190 from case–control studies and 1215 from cohort studies) and 52 013 controls (Brinton et al., 2014).

(a) Adult body mass index

BMI at baseline was associated with a small but significant positive association between increased BMI and risk of male breast cancer. However, this association was observed only with case–control studies (OR per 5 kg/m^2, 1.24; 95% CI, 1.12–1.38), whereas the risk estimates based on cohort studies were not significant (OR per 5 kg/m^2, 1.11; 95% CI, 0.97–1.28).

(b) Body mass index at earlier ages

Recalled BMI at age 18–21 years (based on six cohort studies) showed no association with risk of male breast cancer (OR per 5 kg/m^2, 1.05; 95% CI, 0.80–1.38).

Reference

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2.2.11 Cancer of the endometrium

Cancer of the endometrium is the sixth most common cancer diagnosis in women (WCRF/AICR, 2013). Known risk factors for endometrial cancer include exogenous estrogens, as delivered in menopausal estrogen replacement therapies unopposed with progesterone, and diabetes. Tobacco smoking is associated with reduced risk, by mechanisms that are not well understood. There are two subtypes of endometrial cancer: type 1, which is most common (accounting for about 80–90% of endometrial cancer), and type 2, which is more lethal but much less common (about 10–20%).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for cancer of the endometrium. The 2007 WCRF review concluded that there was convincing evidence of a positive association between body fatness and risk of endometrial cancer (WCRF/AICR, 2007), and this was later reaffirmed (WCRF/AICR, 2013).

(a) Cohort studies

The scientific evidence since 2000 includes 20 publications from cohort studies (excluding analyses that were later updated and analyses based on fewer than 100 incident cases). Table 2.2.11a presents those findings by BMI at baseline, with comments on findings according to smoking status, use of HRT, weight change over the life-course, and waist circumference.

In general, findings are very consistent across studies, showing a strongly positive association between BMI and endometrial cancer risk. All of the 20 cohort studies showed a statistically significant positive association. There is an approximately linear pattern of increasing risk with increasing BMI. The relative risk per 5 kg/m^2 has been estimated to be 1.6–1.9 (Renehan et al., 2008; Yang et al., 2012; Bhaskaran et al., 2014).

Among those studies that distinguished endometrial cancers by type (Bjørge et al., 2007; McCullough et al., 2008; Yang et al., 2013), all studies showed positive associations with BMI for both type 1 and type 2, with a stronger association for type 1 cancers.

The association between BMI and endometrial cancer risk was much stronger in never-users of HRT than in ever-users (McCullough et al., 2008; Canchola et al., 2010); in a meta-analysis of 24 studies (Crosbie et al., 2010), the relative risk per 5 kg/m^2 was 1.18 in ever-users compared with 1.90 in never-users.

In the two studies that reported differences by smoking status, there was no difference in the association of BMI with endometrial cancer risk between smokers and never-smokers (Reeves et al., 2007; Bhaskaran et al., 2014).

In those studies that included measurements of waist circumference and hip circumference (Conroy et al., 2009; Canchola et al., 2010; Reeves et al., 2011; Kabat et al., 2015), waist circumference and waist-to-hip ratio were less strongly associated with risk than was BMI.

In those studies that examined the association between BMI at different ages and subsequent risk of endometrial cancer (Jonsson et al., 2003; Chang et al., 2007; McCullough et al., 2008; Canchola et al., 2010; Park et al., 2010; Yang et al., 2012), BMI at earlier times in life was generally more weakly related or was not related to risk of endometrial cancer, compared with BMI at baseline.

(b) Case–control studies

A total of 30 case–control studies have been published since 2000 on the association between BMI at diagnosis and endometrial cancer risk, including 21 population-based studies and 9 hospital-based studies (Table 2.2.11b). Studies were conducted in the USA (n = 10), Australia,

Canada, China, the Czech Republic, Israel, Italy, Japan, Mexico, Puerto Rico, the Republic of Korea, Switzerland, and the United Kingdom. In most of the studies, a statistically significant increased risk of endometrial cancer was observed in overweight and obese women compared with normal-weight women.

Among the case–control studies that evaluated BMI measured or recalled at different ages (Xu et al., 2006; Lucenteforte et al., 2007; Thomas et al., 2009; Dal Maso et al., 2011; Hosono et al., 2011; Lu et al., 2011; Nagle et al., 2013), an increased risk of endometrial cancer was also observed; the BMI measured or recalled closer to the date of diagnosis was usually related to the highest risk.

Six studies reported associations between waist circumference and endometrial cancer risk, showing a 2–5-fold increase in risk for women in the highest category of waist circumference versus the lowest.

(c) Pooled analyses and meta-analyses

Several recent pooled analyses and meta-analyses have been published on the association between BMI and endometrial cancer risk (Dobbins et al., 2013; Felix et al., 2013; Setiawan et al., 2013; Cote et al., 2015; Jenabi & Poorolajal, 2015; Table 2.2.11c).

A large meta-analysis of 20 case–control studies reported a relative risk of 1.43 (95% CI, 1.30–1.56) for overweight and of 3.33 (95% CI, 2.87–3.79) for obese women compared with normal-weight women (Jenabi & Poorolajal, 2015). In a pooled analysis of 7 cohort studies and 14 case–control studies, the risk of endometrial cancer was similar for obese Black and White women compared with their normal-weight counterparts (Cote et al., 2015).

A recent pooled analysis of 10 cohort studies and 14 case–control studies explored the heterogeneity of the association between BMI and endometrial cancer risk according to tumour types (Setiawan et al., 2013). They reported stronger associations among type 1 (RR per 2 kg/m^2, 1.20; 95% CI, 1.19–1.21) compared with type 2 tumours (RR, 1.12; 95% CI, 1.09–1.14) and among endometrioid grade 1 and 2 compared with endometrioid grade 3. The heterogeneity was present when cohort studies and case–control studies were considered separately, or when registry-based studies were compared with those where cases were further ascertained through pathology reports.

(d) Mendelian randomization studies

Nead et al. (2015) applied Mendelian randomization to assess the association of markers of metabolic disease, including BMI, with risk of endometrial cancer using 32 genetic variants as instrumental variables for BMI (Speliotes et al., 2010). Mendelian randomization analyses showed that each increase of 1 standard deviation in BMI was associated with a significant increase in risk of endometrial cancer (OR, 3.86; 95% CI, 2.24–6.64) (Table 2.2.11d).

Table 2.2.11a Cohort studies of measures of body fatness and cancer of the endometrium

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Population-based cohort USA 1982–1998	495 477 Mortality		BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 333 225 105 25 16	 1.00 1.50 (1.26–1.78) 2.53 (2.02–3.18) 2.77 (1.83–4.18) 6.25 (3.75–10.42) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin use, fat intake, vegetable intake, HRT use	
Jonsson et al. (2003) Swedish Twin Registry Sweden 1969–1997	14 131 Incidence		BMI < 18.49 18.5–24.99 25–29.99 ≥ 30	 1 69 46 21	 0.4 (0.1–3.1) 1.0 1.3 (0.9–1.9) 3.2 (2.0–5.2)	Age	Recalled BMI at ages 25 yr and 40 yr gave RR for BMI ≥ 25.0 vs < 25.0 of 1.9 (1.2–3.0) and 2.0 (0.9–4.4), respectively
Rapp et al. (2005) Population-based cohort Austria 1985–2002	78 484 Incidence		BMI 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 [P_{trend}]	 63 59 33 20	 1.0 1.29 (0.90–1.86) 2.13 (1.38–3.27) 3.93 (2.35–6.56) [< 0.001]	Age, smoking, occupation	
Lukanova et al. (2006) Population-based cohort Sweden 1994–2004	35 362 Incidence		BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 42 41 35	 1.0 1.45 (0.93–2.24) 2.93 (1.85–4.61) [0.0001]	Age, tobacco use	
Bjørge et al. (2007) Norwegian health surveys Norway 1963–2003	1 million Incidence	Type 1	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 82 2960 2361 1761	 0.90 (0.72–1.12) 1.00 1.39 (1.32–1.47) 2.72 (2.56–2.90) [< 0.001]	Age, birth cohort	Similar association for BMI at ages 20–49 yr and 50–74 yr
		Type 2	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 366 369 253	 0.42 (0.16–1.13) 1.00 1.26 (1.09–1.46) 1.94 (1.64–2.30) [< 0.001]	Age, birth cohort	Similar association for BMI at ages 20–49 yr and 50–74 yr

Table 2.2.11a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Chang et al. (2007) NIH-AARP cohort USA 1995–2000	103 882 Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 200 181 296	 1.0 1.31 (1.07–1.61) 3.03 (2.50–3.68) [< 0.0001]	Age, physical activity, diabetes, HRT use, age at menarche, parity, age at menopause, OC use, smoking, race	BMI at ages 18 yr, 35 yr, and 50 yr not associated with risk
Friberg et al. (2007) Swedish mammography cohort Sweden 1987–2003	36 773 Incidence		BMI < 30 ≥ 30	 154 43	 1.0 2.49 (1.77–3.51)	Age, physical activity	Women without diabetes
Lundqvist et al. (2007) Twin cohort studies Sweden and Finland 1961–2004	14 017 older twins (mean baseline age, 56 yr) Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 1 kg/m^2 [P_{trend}]	 1 92 57 30	 0.3 (0.1–2.5) 1.0 1.2 (0.8–1.6) 3.2 (2.1–4.8) 1.11 (1.06–1.15) [< 0.0001]	Smoking, physical activity, education level, diabetes	
Reeves et al. (2007) Population-based cohort United Kingdom 1996–2001	1.2 million Incidence		BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 340 524 516 366 911	 0.84 (0.75–0.93) 1.00 1.21 (1.11–1.32) 1.43 (1.29–1.58) 2.73 (2.55–2.92) 2.89 (2.62–3.18)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	Association similar in never-smokers
Lindemann et al. (2008) HUNT cohort Norway 1984–2002	36 761 Incidence		BMI < 20 20–24 25–29 30–34 35–39 ≥ 40 [P_{trend}]	 4 64 90 32 23 9	 0.53 (0.19–1.47) 1.00 1.74 (1.25–2.43) 1.66 (1.06–2.59) 4.28 (2.58–7.09) 6.36 (3.08–13.16) [< 0.0001]	Age, physical activity, hypertension, alcohol consumption	Similar associations for women aged < 55 yr and aged ≥ 55 yr

Table 2.2.11a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
McCullough et al. (2008) Cancer Prevention Study II (CPS II) USA 1992–2003	33 436 Incidence		BMI < 22.5 22.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 54 53 91 76 44	 0.92 (0.63–1.34) 1.00 1.40 (0.99–1.96) 3.27 (2.29–4.67) 4.70 (3.12–7.07) [< 0.0001]	Age, age at menarche, age at menopause, parity, HRT use, smoking, exercise, OC use	Stronger association for never- vs ever-users of HRT. Stronger association for type 1 vs type 2 cancer; null association with BMI at age 18 yr
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1994–2003	107 481 Incidence		BMI < 18.5 18.5–20.9 21–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 per 1 kg/m²	 2 6 16 22 28 31 7	 1.26 (0.29–5.51) 0.74 (0.29–1.90) 1.00 1.20 (0.62–2.32) 1.61 (0.84–3.09) 2.70 (1.42–5.13) 2.95 (1.20–7.24) 1.13 (1.07–1.20)	Age, smoking, alcohol consumption, exercise	
Conroy et al. (2009) Women's Health Study USA 1992–2007	19 917 Incidence		BMI < 22.5 22.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 57 50 68 89	 1.00 0.97 (0.65–1.44) 1.09 (0.75–1.58) 2.49 (1.73–3.59) [< 0.0001]	Age, physical activity, smoking, alcohol consumption, diet, parity, HRT use	Weaker association with WC
Epstein et al. (2009) Lund cohort Sweden 1990–2007	17 822 Incidence		BMI < 25 25–29.9 ≥ 30	 45 41 36	 1.0 1.4 (0.9–2.2) 3.5 (2.2–5.4)	Age	
Canchola et al. (2010) California Teachers Study Cohort USA 1995–2006	28 418 never-users of HRT Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}] per 1 kg/m²	 34 26 48	 1.0 1.2 (0.74–2.1) 3.5 (2.2–5.5) [< 0.001] 1.07 (1.04–1.09)	Age, parity, age at first pregnancy, physical activity, OC use	Much weaker association among HRT users. Similar risk for recalled BMI at age 18 yr; association also observed with WC

Table 2.2.11a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Dossus et al. (2010) EPIC cohort Europe 1992–2003	370 000 Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 81 82 61	 1.0 1.23 (0.82–1.84) 2.02 (1.26–3.23) [0.005]	Age, centre	
Park et al. (2010) Multiethnic Cohort USA (California, Hawaii) 1993–2004	50 376 women aged 45–75 yr, from 5 racial/ ethnic populations		BMI at baseline < 25 25– < 30 ≥ 30 [P_{trend}]	 175 119 169	 1.00 1.36 (1.06–1.75) 3.54 (2.70–4.63) [< 0.001]	Age, ethnicity, education level, age at menarche, menopausal status, age at menopause, HRT use, OC use, parity, smoking history, diabetes, hypertension	Results available for BMI at age 21 yr, BMI change since age 21 yr, weight at baseline, and weight at age 21 yr
Reeves et al. (2011) Women's Health Initiative USA 1993–NR	86 937 Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 264 207 334	 1.0 0.84 (0.67–1.05) 1.68 (1.33–2.13) [0.0001]	Age, race, education level, smoking, physical activity, intake of fruits and vegetables, diabetes, dietary fat, fibre intake	WHR more weakly associated, and association disappears with BMI adjustment
Ollberding et al. (2012) Multiethnic Cohort USA 1993–2007	46 027 Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	489 total	 1.00 1.38 (1.09–1.74) 2.68 (2.10–3.42) [< 0.01]	Age, race, ethnicity, hypertension, diabetes, smoking, HRT use, OC use, parity	
Yang et al. (2012) Million Women Study United Kingdom 1996–2009	249 791 Incidence		BMI < 22.5 22.5–27.4 27.5–32.4 32.5–34.9 ≥ 35 per 5 kg/m^2	 139 465 390 158 258	 1.00 1.40 (1.27–1.53) 2.63 (2.39–2.91) 5.07 (4.33–5.93) 7.72 (6.79–8.77) 1.87 (1.77–1.96)	Age, region, height, age at menarche, age at menopause, parity, HRT use, alcohol consumption, smoking, exercise	(Update of study by Reeves et al., 2007) Body size and BMI at ages 10 yr and 20 yr less associated than BMI at baseline
Yang et al. (2013) NIH-AARP cohort USA 1995–2006	114 409 Incidence	Type 1	BMI < 30 ≥ 30	 708 570	 1.00 2.93 (2.62–3.28)	Age, OC use, HRT use, parity, age at menarche, menopausal status, race, smoking	Most women postmenopausal at time of study entry

Table 2.2.11a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Yang et al. (2013) (cont.)		Type 2	BMI < 30 ≥ 30	 86 47	 1.00 1.83 (1.27–2.63)	Age, OC use, HRT use, parity, menarche, menopause, race, smoking	
Bhaskaran et al. (2014) Health system clinical database United Kingdom 1987–2012	5.24 million Incidence		BMI per 5 kg/m²	2758	1.62 (1.56–1.69)	Age, sex, year, diabetes, alcohol consumption, smoking, SES	Similar association in never-smokers
Kabat et al. (2015) Women's Health Initiative cohort USA 1992–2013	143 901 Incidence		BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	1157 total	 1.0 0.93 (0.76–1.14) 1.08 (0.89–1.32) 1.29 (1.06–1.58) 2.32 (1.93–2.80) [< 0.0001]	Age, alcohol consumption, smoking, parity, HRT use, OC use, ethnicity, education	Similar association with WC

BMI, body mass index (in kg/m²); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; OC, oral contraceptive; RR, relative risk; SES, socioeconomic status; WC, waist circumference; WHR, waist-to-hip ratio; yr, year or years

Table 2.2.11b Case–control studies of measures of body fatness and cancer of the endometrium

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
McCann et al. (2000) USA 1986–1991	232 639 Population	BMI < 27.5 ≥ 27.5	 112 120	 1.0 2.6 (1.9–3.6)	Age
Salazar-Martínez et al. (2000) Mexico 1995–1997	85 668 Population	BMI < 25 25–30 > 30	 21 28 35	 1.0 1.1 (0.61–2.1) 2.2 (1.2–4.2)	Age, an ovulatory index, smoking, physical activity, menopausal status, hypertension, diabetes
Benshushan et al. (2001, 2002) Israel 1989–1992	128 255 Population	BMI < 27 ≥ 27	 49 79	 1.00 2.47 [1.51–4.06]	
Newcomer et al. (2001) USA 1991–1994	740 2372 Population	BMI < 22.55 22.55–25.34 25.35–29.14 ≥ 29.15	 97 120 150 293	 1.0 1.2 (0.9–1.7) 1.6 (1.2–2.1) 3.0 (2.3–3.9)	Age
McElroy et al. (2002) USA 1991–1994	148 659 Population	BMI < 22.7 22.7–25.5 25.6–29.0 ≥ 29.1	 13 18 20 45	 1.00 1.52 (0.80–2.88) 1.60 (0.84–3.03) 3.72 (2.10–6.57)	Age
Augustin et al. (2003) Italy and Switzerland 1988 –1998	410 753 Hospital	BMI < 20 20–25 25– < 30 ≥ 30	 33 162 131 84	 1.0 1.2 (0.8–2.0) 1.3 (0.8–2.2) 2.2 (1.2–3.8)	Age, study centre, education level, history of diabetes and hypertension, HRT use, total energy intake
Dal Maso et al. (2004) Italy 1999–2002	87 132 Hospital	BMI < 25 25–29 ≥ 30	 20 34 33	 1.00 1.80 (0.90–3.59) 5.87 (2.58–13.38)	Age, education level

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Xu et al. (2005, 2006) China 1997–2001	832 846 Population	BMI, quartiles Recent BMI > 25.69 vs < 21.03 BMI at age 20 yr > 21.09 vs < 17.63 BMI at age 30 yr > 22.43 vs < 18.81 BMI at age 40 yr > 24.00 vs < 19.83 BMI at age 50 yr > 25.30 vs < 20.83 BMI at age 60 yr > 25.97 vs < 21.48	 302 205 226 269 217 122	 3.3 (2.4–4.5) 1.3 (1.0–1.8) 1.5 (1.1–2.0) 2.0 (1.5–2.8) 2.5 (1.7–3.6) 2.9 (1.7–4.9)	Age, education level, years of menstruation, OC use, number of pregnancies, menopausal status, family history of cancer; for recent BMI, additionally adjusted for BMI at age 20 yr
Xu et al. (2005) China 1997–2001	832 846 Population	WC (cm) ≤ 73 74–79 80–86 > 86	 102 157 215 357	 1.0 1.9 (1.4–2.7) 2.6 (1.9–3.6) 4.7 (3.4–6.4)	Age, education level, years of menstruation, number of pregnancies, BMI
Okamura et al. (2006) Japan 1998–2000	155 96 Hospital	BMI < 20.04 20.04–21.63 21.64–23.92 ≥ 23.93	 36 27 45 47	 1.00 0.47 (0.22–0.99) 1.24 (0.58–2.67) 1.92 (0.86–4.30)	Age
Trentham-Dietz et al. (2006) USA 1991–1994	740 2342 Population	BMI 14.5–22.6 22.6–25.4 25.5–29.2 29.1–82.4	 100 123 153 313	 1.00 1.19 (0.88–1.61) 1.62 (1.21–2.18) 3.20 (2.42–4.24)	Age, age at menarche, parity, menopausal status, age at menopause, smoking, HRT use, recent physical activity, diabetes
Weiss et al. (2006) USA 1985–1991, 1994–1995, 1997–1999	1304 1779 Population	BMI < 30.0 30.0–34.9 ≥ 35.0	Low tumour aggressiveness: 374 57 65	 1.0 1.6 (1.2–2.3) 5.1 (3.5–7.4)	HRT use, age, county of residence, reference year Tumours with moderate or high aggressiveness gave very similar results

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Lucenteforte et al. (2007) Italy and Switzerland 1988–2006	777 1550 Hospital	BMI at diagnosis < 30 ≥ 30 BMI at age 30–39 yr < 25 ≥ 25	 555 218 532 215	 1.0 2.4 (1.9–3.1) 1.0 1.6 (1.3–2.0)	Age, history of diabetes, physical activity, history of hypertension, year of interview, study centre, education level, parity, menopausal status, OC use, HRT use
Máchová et al. (2007) Czech Republic 1987–2002	87 20 776 Population	BMI < 25 ≥ 25– < 30 ≥ 30	NR	 1.00 1.84 (0.95–3.57) 3.25 (1.65–6.37)	Age, smoking, hypertension, height
Niwa et al. (2007) Japan 2001–2004	110 220 Hospital	BMI < 25.0 ≥ 25.0	 75 35	 1.00 2.35 (1.32–4.17)	
Wen et al. (2008) China 1997–2003	1046 1035 Population	BMI < 20.92 20.93–22.68 22.69–24.32 24.33–26.47 > 26.47 WC (cm) < 71 72–76 77–80 81–87 > 87	 104 128 190 214 408 71 141 168 282 382	 1.1 (0.9–1.5) 1.0 (0.9–1.1) 1.0 1.0 (0.9–1.2) 1.1 (0.8–1.5) 0.5 (0.3–0.6) 0.7 (0.6–0.8) 1.0 1.5 (1.3–1.7) 2.3 (1.7–3.1)	Age at menarche, menopausal status, total years of menstruation, OC use, cancer history in first-degree relatives, and BMI (for WC) or WC (for BMI)
Fortuny et al. (2009) USA 2001–2005	469 467 Population	BMI < 25 25– < 30 30– < 35 ≥ 35	 118 127 80 142	 1.0 1.6 (1.1–2.2) 2.0 (1.4–3.0) 7.6 (4.8–11.8)	Age
Thomas et al. (2009) USA 1980–1982	421 3159 Population	Adult BMI < 25.0 25.0–29.9 30.0–34.9 ≥ 35.0	LMP < 45 yr: 59 26 23 30	 1.0 2.9 (1.7–4.8) 6.0 (3.3–10.7) 21.7 (11.3–41.7)	Age, race, education level, OC use, parity, use of estrogen therapy, menopausal status, history of high blood pressure

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Thomas et al. (2009) (cont.)		Adult BMI	LMP ≥ 45 yr:		Weaker associations with BMI at age 18 yr vs adult BMI for both LMP < 45 yr and LMP ≥ 45 yr
		< 25.0	168	1.0	
		25.0–29.9	60	1.5 (1.0–2.1)	
		30.0–34.9	31	2.3 (1.4–3.6)	
		≥ 35.0	24	3.7 (2.0–6.6)	
Tong et al. (2009) Republic of Korea 1998–2006	125 302 Hospital	BMI			Age
		< 23	30	1.0	
		23–25	34	1.19 (0.62–2.29)	
		≥ 25	61	2.65 (1.44–4.89)	
Chandran et al. (2010) USA 2001–2005	424 398 Population	BMI			Age
		< 25	105	1.00	
		25–29.9	121	1.93 (1.36–2.75)	
		30–34.9	68	2.02 (1.32–3.08)	
		≥ 35	123	8.47 (5.16–13.89)	
Charneco et al. (2010) Puerto Rico 2004–2007	74 88 Hospital	BMI			Crude Age, education level, employment status, poultry consumption, OC use, diabetes, hypertension
		≤ 24.9	6	1.00	
		25.0–29.9	25	4.44 (1.60–12.26)	
		≥ 30	43	9.85 (3.61–26.87)	
		BMI			
		< 30	31	1.00	
		≥ 30	43	4.11 (1.76–9.93)	
John et al. (2010) USA 1996–1999	472 443 Population	BMI			Age, race/ethnicity
		< 25	176	1.00	
		25–29.9	135	0.92 (0.67–1.26)	
		≥ 30	184	1.93 (1.39–2.68)	
Zhang et al. (2010) China 2004–2008	942 1721 Population	BMI			
		18.5–24.9	571	1.00	
		25.0–29.9	284	1.51 (1.26–1.81)	
		≥ 30.0	80	6.15 (3.98–9.51)	
Dal Maso et al. (2011) Italy 1992–2006	454 908 Hospital	BMI ≥ 30:			Age, study centre, calendar period of interview, years of education, smoking habits, age at menarche, age at menopause, parity, OC use, HRT use
		BMI at baseline	168	4.08 (2.90–5.74)	
		BMI at age 30 yr	29	1.78 (1.01–3.14)	
		BMI at age 50 yr	96	3.37 (2.26–5.04)	
		BMI, 5 kg/m² increase		1.89 (1.65–2.17)	
		WC (cm)			
		≥ 96 vs < 84	127	2.68 (1.78–4.03)	

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Delahanty et al. (2011) China 1996–2005	832 2049 Population	BMI < 21.7 21.7–24.5 > 24.5	 14.0% 28.3% 57.7%	 1.00 1.68 (1.30–2.18) 3.13 (2.44–4.01)	Age, income, education level
Friedenreich et al. (2011) Canada 2002–2006	515 962 Population	WC (cm) ≥ 88	 343	 2.32 (1.82–2.96)	Reference WC not reported Age
Hosono et al. (2011) Japan 2001–2005	222 2162 Hospital	BMI at baseline < 25 ≥ 25 BMI at age 20 yr < 25 ≥ 25 BMI change from age 20 yr to enrolment ≤ 0 0–3 > 3	 152 65 196 17 57 73 82	 1.00 2.22 (1.59–3.09) 1.00 2.30 (1.29–4.11) 1.00 1.26 (0.86–1.84) 1.48 (0.95–2.29)	Age, smoking, alcohol consumption, regular exercise, age at menarche, duration of menstruation, parity, diabetes history, history of OC use, history of HRT use
Lu et al. (2011) USA 2004–2009	668 674 Population	BMI > 30 vs < 25: current 5 yr in the past at age 20s at age 30s at age 40s at age 50s at age 60s	 354 321 60 106 150 156 67	 4.76 (3.50–6.49) 4.22 (3.05–5.84) 1.96 (1.16–3.29) 2.19 (1.46–3.28) 3.84 (2.62–5.61) 5.44 (3.62–8.17) 4.09 (2.32–7.21)	Age, ethnic group, education level, pregnancy, family history of cancer, estrogen use, OC use, smoking, alcohol consumption
Rosato et al. (2011) Italy 1992–2006	454 798 Hospital	BMI ≤ 30 > 30 WC (cm) < 80 vs ≥ 80 ≤ 88 vs > 88	 312 142 266 195	 1.00 3.83 (2.74–5.36) 1.62 (1.00–2.62) 1.90 (1.34–2.71)	Age, study centre, year of interview, education level, age at menarche, parity, menopausal status, OC use, HRT use
Friedenreich et al. (2012) Canada 2002–2006	541 961 Population	BMI per 1 kg/m^2 increase	 	 1.10 (1.08–1.12)	Same study/data set as Friedenreich et al. (2011) Adjusted for age

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Amankwah et al. (2013) Canada 2002–2006	524 1032 Population	BMI < 25 25– < 30 ≥ 30 [P_{trend}] WC (cm) > 96.0 vs ≤ 76.5	 87 124 256 220	 1.00 1.26 (0.91–1.73) 2.81 (2.06–3.84) [< 0.001] 4.21 (2.90–6.10)	Age, residence type (rural or urban), age at menarche, menopausal status/ hormone use, parity/age at first pregnancy, hypertension
Becker et al. (2013) United Kingdom 1995–2012	2554 15 324 Population	BMI < 25 25–29.9 30–59.9	 560 560 877	 1.00 1.49 (1.32–1.68) 3.18 (2.82–3.57)	Crude estimates
King et al. (2013) USA 2001–2005	424 398 Population	BMI < 25 25–29.9 30–34.9 ≥ 35	 105 121 68 123	 1.00 1.93 (1.36–2.75) 2.02 (1.32–3.08) 8.47 (5.16–13.89)	Age
Nagle et al. (2013) Australia 2005–2007	1398 1538 Population	Recent BMI ≥ 40 vs < 25 Maximum BMI ≥ 40 vs < 25 BMI at age 20 yr ≥ 30 vs < 25 BMI change from age 20 yr Always overweight vs always normal Change from maximum to recent BMI Always ≥ 30 vs always < 25	 192 257 72 203 637	 7.98 (5.41–11.77) 6.62 (4.72–9.29) 0.75 (0.43–1.33) 3.60 (2.62–4.95) 3.71 (2.96–4.67)	Age, age at menarche, parity, duration of OC use, HRT use ≥ 3 months, smoking status, diabetes

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; LMP, last menstrual period; NR, not reported; OC, oral contraceptive; WC, waist circumference; yr, year or years

Table 2.2.11c Pooled analyses and meta-analyses of measures of body fatness and cancer of the endometrium

Reference	Number and type of studies	Population size and type	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustments Comments
Crosbie et al. (2010)	Meta-analysis of 24 studies published 1966–2009	17 710 cases	BMI 27 32 37 42 per 5 kg/m^2		 1.22 (1.19–1.24) 2.09 (1.94–2.26) 4.36 (3.75–5.10) 9.11 (7.26–11.51) 1.60 (1.52–1.68)	$P_{heterogeneity}$ = 0.215
Dobbins et al. (2013)	Meta-analysis of 16 cohort and case–control studies		Obese vs normal-weight		1.85 (1.30–2.65)	$P_{heterogeneity}$ = 0.00001
Felix et al. (2013)	Pooled analysis of 13 studies (E2C2)	8096 cases (primarily endometrioid endometrial carcinomas) and 28 829 controls	BMI < 25 25–30 ≥ 30 [P_{trend}]	 2675 2246 2479	 1.00 1.37 (1.28–1.46) 3.03 (2.82–3.26) [0.0001]	Age, race, age at menarche, parity, menopausal status, menopausal estrogen plus progestin, menopausal estrogen use, OC use, smoking status, history of diabetes, site
Setiawan et al. (2013)	Pooled analysis of 10 cohort studies and 14 case–control studies in China, Europe, and North America (E2C2)	14 069 cases and 35 312 controls	BMI 18– < 25 25– < 30 30– < 35 35– < 40 ≥ 40 [P_{trend}]	Type 1: 4602 3718 2294 1247 992	 1.00 1.45 (1.37–1.53) 2.52 (2.35–2.69) 4.45 (4.05–4.89) 7.14 (6.33–8.06) [< 0.0001]	Age, study, race/ethnicity, age at menarche, parity, OC use, menopausal status, menopausal HRT use, smoking status
			BMI 18– < 25 25– < 30 30– < 35 35– < 40 ≥ 40 [P_{trend}]	Type 2: 330 253 159 65 47	 1.00 1.16 (0.98–1.38) 1.73 (1.40–2.12) 2.15 (1.60–2.88) 3.11 (2.19–4.44) [< 0.0001]	
Cote et al. (2015)	Pooled analysis of 7 cohort studies and 4 case–control studies	2011 Black women (516 cases and 1495 controls)	BMI 18.5–24.9 25–29.9 ≥ 30	Black women: 76 129 300	 1.00 1.37 (0.97–1.94) 2.93 (2.11–4.07)	Age, smoking, OC use, diabetes, study site, age at menarche, parity as a continuous variable
		19 297 White women (5693 cases and 13 604 controls)	BMI 18.5–24.9 25–29.9 ≥ 30	White women: 1950 1541 2107	 1.00 1.43 (1.32–1.56) 2.99 (2.74–3.26)	

Table 2.2.11c (continued)

Reference	Number and type of studies	Population size and type	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustments Comments
Jenabi & Poorolajal (2015)	Meta-analysis of 20 cohort studies	32 281 242 participants total	BMI			
			Normal		1.00	$P_{heterogeneity}$:
			Overweight		1.34 (1.20–1.48)	Overweight: $P = 0.001$
			Obese		2.54 (2.27–2.81)	Obesity: $P = 0.001$
	Meta-analysis of 20 case–control studies		BMI			
			Normal		1.00	$P_{heterogeneity}$:
			Overweight		1.43 (1.30–1.56)	Overweight: $P = 0.017$
			Obese		3.33 (2.87–3.79)	Obesity: $P = 0.001$

BMI, body mass index (in kg/m^2); CI, confidence interval; E2C2, Epidemiology of Endometrial Cancer Consortium; OC, oral contraceptive; yr, year or years

Table 2.2.11d Mendelian randomization studies of measures of body fatness and cancer of the endometrium

Reference	Characteristics of study population	Sample size	Exposure	Outcome	Odds ratio (95% CI) with each SD increase in exposure
Nead et al. (2015)	Cases were from the Australian National Endometrial Cancer Study (ANECS) or the Studies of Epidemiology and Risk Factors in Cancer Heredity study (SEARCH), United Kingdom Control participants were from the Wellcome Trust Case Control Consortium (WTCCC), and Australian control participants were from parents of twins in the Brisbane Adolescent Twin Study and from the Hunter Community Study	9560 (1287 cases and 8273 controls)	BMI	Endometrial cancer	3.86 (2.24–6.64)

BMI, body mass index (in kg/m^2); CI, confidence interval; SD, standard deviation; yr, year or years

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2.2.12 Cancer of the cervix

Cancer of the cervix is the fourth most common cancer in women. Human papillomavirus (HPV) infection, which is present in almost all cases of cervical cancer, is not related to adiposity (Wee et al., 2008). In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and cervical cancer was *inadequate*.

(a) Cohort studies

Since 2001, at least eight cohort studies of cervical cancer and body weight (Wolk et al., 2001; Calle et al., 2003; Rapp et al., 2005; Reeves et al., 2007; Song et al., 2008; Ulmer et al., 2012; Lee et al., 2013; Bhaskaran et al., 2014) and one pooled analysis of 39 cohort studies (Parr et al., 2010) have been published (Table 2.2.12a; web only; available at: http://publications.iarc.fr/570). Although some studies reported statistically significant increases, the data overall remained inconsistent.

(b) Case–control studies

The five case–control studies assessing the association between body fatness and cervical cancer (Cusimano et al., 1989; Brinton et al., 1993; Ursin et al., 1996; Lacey et al., 2003; Máchová et al., 2007) had relatively small sample sizes (< 150 cases), and the results are inconsistent (Table 2.2.12b; web only; available at: http://publications.iarc.fr/570).

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2.2.13 Cancer of the ovary

Cancer of the ovary accounts for about 4% of all cancer diagnoses in women. Risk of ovarian cancer is known to be reduced with use of oral contraceptives, and increased with *BRCA* gene mutations and use of estrogen (unopposed) HRT. There are histologically distinct subtypes of ovarian cancer, including serous, mucinous, clear cell, endometrioid, and other/mixed types (Jayson et al., 2014).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and ovarian cancer was *inadequate*. The 2007 WCRF review did not draw any conclusions regarding body fatness and ovarian cancer risk (WCRF/AICR, 2007). On the basis of many more studies, including pooled analyses, the WCRF Continuous Update Project in 2014 concluded that there was a small but convincing positive association between BMI and ovarian cancer risk, but limited and inconsistent evidence regarding waist circumference (WCRF/AICR, 2014).

Table 2.2.13a, Table 2.2.13b, and Table 2.2.13c present the findings from cohort studies, case–control studies, and meta-analyses, respectively, published since 2000. Findings are presented by BMI at baseline, with comments on findings according to weight change over the life-course and waist circumference.

(a) Cohort studies

The evidence published since 2000 includes 15 cohort studies (excluding analyses that were later updated and analyses based on fewer than 100 incident cases) (Table 2.2.13a) and several meta-analyses of cohort studies (Table 2.2.13c). In general, findings were consistent across studies, suggesting a modest positive association between baseline BMI and ovarian cancer risk. A meta-analysis including 13 cohort studies found significant increases in risk of 7% in overweight women and of 23% in obese women compared with women of normal BMI (Liu et al., 2015). Aune et al. (2015), in a meta-analysis including 25 prospective studies, found a summary relative risk per 5 kg/m^2 increase in BMI of 1.07 (95% CI, 1.03–1.11) [moderate heterogeneity (54%) across studies was reported] (Aune et al., 2015).

The association is stronger in never-users of HRT (Leitzmann et al., 2009). The Collaborative Group on Epidemiological Studies of Ovarian Cancer found the relative risk per 5 kg/m^2 increase in BMI to be 1.10 (95% CI, 1.07–1.13; P_{trend} = 0.02) in never-users of HRT, but 0.95 (95% CI, 0.92–0.99; P_{trend} = 0.02) in ever-users of HRT (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012).

The Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012) also examined the relationship between BMI and ovarian cancer risk separately by histological type. The association was broadly similar across the common histological subtypes of ovarian cancer, except for serous tumours of borderline malignancy, for which the association was considerably greater than for the other tumour subtypes.

There was no consistency in the evidence for whether BMI earlier in life is more or less predictive of ovarian cancer than is BMI at a later age. The systematic review by Aune et al. (2015) and a twin cohort study by Lundqvist and collaborators (Lundqvist et al., 2007) found marginally stronger associations with BMI in early adulthood than with BMI later in life. However, a pooled analysis including 13 548 cases found the opposite (Olsen et al., 2013). Two cohort studies examining weight gain from age 18–20 years reported positive associations (Ma et al., 2013 based on 152 cases; P_{trend} = 0.05; Canchola et al., 2010), whereas the meta-analyses by Aune et al. (2015) based on 6 cohort studies and 1338 cases did not find evidence of this association [significant heterogeneity was reported in this study; $P_{heterogeneity}$ = 0.01].

In three of the four cohorts that included measurements of waist circumference, this was found to be less associated with ovarian cancer risk than was BMI (Chionh et al., 2010; Lahmann et al., 2010; Ma et al., 2013); one study showed significant positive associations stronger than those reported with BMI (Canchola et al., 2010).

(b) *Case–control studies*

A total of 35 case–control studies (including 7 hospital-based studies) from Asia, Australia, Canada, Europe, and the USA and several meta-analyses including case–control studies have been published since 2000 on the association between BMI at diagnosis and ovarian cancer risk (Table 2.2.13b and Table 2.2.13c). An increase in risk was generally observed, although estimates were not statistically significant in most individual studies. However, a meta-analysis including 13 case–control studies and presenting low heterogeneity (I^2 = 11.3%) found significant increased risk of ovarian cancer in overweight women (RR, 1.09; 95% CI, 1.00–1.19) and in obese women (RR, 1.31; 95% CI, 1.12–1.54) compared with women of normal BMI (Liu et al., 2015). Another meta-analysis of 47 epidemiological studies, which included 30 case–control studies, showed a significant 5% increase in risk in those studies with population-based controls (n = 17) and a significant 8% decrease in risk in those studies with hospital-based controls (n = 13) [the decreased risk in hospital-based studies is probably due to selection bias related to BMI] (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012).

When stratifying by menopausal status or HRT use, the Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012) reported a significant interaction with HRT use, with evidence of a 10% increased risk only among never-users of HRT (n = 11 456 cases). A pooled analysis from 15 case–control studies (Olsen et al., 2013) also reported that the associations were stronger among premenopausal women who had never used HRT.

In the few studies that examined the relationship between BMI and ovarian cancer risk separately by histological type, the associations seemed to be confined to non-serous and low-grade serous tumours (Olsen et al., 2013). An earlier pooled analysis of 10 case–control studies found no association for serous cancers, but there was an association for all other ovarian cancer types (Kurian et al., 2005). The risk was significantly increased in both invasive and borderline ovarian cancer subtypes, with a somewhat stronger association with borderline tumours (Olsen et al., 2013).

Among the 10 studies that reported on the association between BMI in young adulthood and ovarian cancer risk, 7 observed a non-significant increase in risk, two observed a significant increase in risk (Lubin et al., 2003; Olsen et al., 2013), and one observed a significant decrease in risk (Kuper et al., 2002). Four studies evaluated BMI change between early adulthood and diagnosis and showed no significant association with ovarian cancer risk (Lubin et al., 2003; Zhang et al., 2005; Greer et al., 2006; Peterson et al., 2006).

(c) *Mendelian randomization studies*

One large-scale Mendelian randomization study has been conducted to assess the association of childhood and adult BMI with ovarian cancer risk, separated into histological subtypes including clear cell, endometrioid, and serous cancer (Gao et al., 2016; Table 2.2.13d). With each 1 kg/m^2 increase in adult BMI (assuming that a standard deviation was equivalent to 4.5 kg/m^2), there was evidence for an increased risk of all ovarian cancer (OR, 1.07; 95% CI, 1.01–1.13; P = 0.02) and weak, not statistically significant, evidence for an increased risk of clear cell ovarian cancer (OR, 1.12; 95% CI, 0.96–1.31; P = 0.14) and serous ovarian cancer (OR, 1.06; 95% CI, 0.99–1.13; P = 0.09). There was no evidence for

statistically significant associations between childhood BMI and risk of any ovarian cancer types.

In sensitivity analyses exploring the validity of the genetic variants used, there was evidence for negative pleiotropy in the association between adult BMI and endometrioid ovarian cancer [thus suggesting that the positive association may have been underestimated in the main analyses].

Table 2.2.13a Cohort studies of measures of body fatness and cancer of the ovary

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Population-based cohort USA 1982–1998	495 477 Mortality	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 873 437 126 49	 1.00 1.15 (1.02–1.29) 1.16 (0.96–1.40) 1.51 (1.12–2.02) [0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin use, fat intake, vegetable intake, HRT use	Women who had either a hysterectomy or ovarian surgery were excluded
Rapp et al. (2005) Population-based cohort Austria 1985–2002	78 484 Incidence	BMI 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 61 39 21	 1.0 1.03 (0.68–1.56) 1.25 (0.75–2.08) [0.44]	Age, smoking, occupation	
Lacey et al. (2006) Breast Cancer Detection Demonstration Project Follow-Up Study USA 1973–1997	46 026 Incidence	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 per 1 kg/m^2	 7 219 83 20 11	 0.95 (0.45–2.01) 1.00 1.00 (0.78–1.29) 0.94 (0.59–1.48) 1.55 (0.84–2.84) 1.01 (0.98–1.03)	Age, race, menopausal status, parity, OC use, HRT use	
Lundqvist et al. (2007) Twin cohort studies Sweden and Finland 1961–2004	14 058 twins (mean age, 56 yr) Incidence	BMI at baseline < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 1 86 57 7	 0.4 (0.1–2.6) 1.0 1.2 (0.8–1.6) 0.7 (0.3–1.5) [0.95]	Age, country, smoking, physical activity, education level, diabetes, parity	
	22 432 twins (mean age, 30 yr) Incidence	BMI at baseline < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 8 120 31 3	 0.7 (0.3–1.4) 1.0 1.5 (1.0–2.3) 0.8 (0.2–2.6) [0.01]	Age, smoking, physical activity, education level, diabetes, parity	

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) Million Women Study United Kingdom 1996–2001	1.2 million Incidence	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	 478 631 510 349 438	 0.98 (0.89–1.07) 1.00 0.99 (0.91–1.08) 1.13 (1.02–1.25) 1.12 (1.02–1.23) 1.14 (1.03–1.27)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	
Schouten et al. (2008) Pooling Project of Prospective Studies of Diet and Cancer (12 cohorts pooled) North America and western Europe Follow-up varied by cohort	531 583 Incidence	BMI < 23 23–24.9 25.0–26.9 27–29.9 ≥ 30 [P_{trend}] BMI < 23 23–24.9 25.0–26.9 27–29.9 ≥ 30 [P_{trend}]	Postmenopausal: 426 291 222 206 191 Premenopausal: 64 34 14 14 22	 1.0 0.91 (0.78–1.06) 0.95 (0.80–1.13) 0.96 (0.80–1.14) 1.07 (0.87–1.33) [0.53] 1.0 1.29 (0.83–2.00) 0.95 (0.50–1.81) 1.28 (0.59–2.79) 1.72 (1.02–2.29) [0.13]		
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1994–2003	107 481, postmenopausal Incidence	BMI < 18.5 18.5–20.9 21–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 per 1 kg/m²	 3 13 30 53 42 30 5	 0.98 (0.29–3.24) 0.85 (0.43–1.68) 1.00 1.63 (1.01–2.63) 1.62 (0.98–2.67) 1.57 (0.91–2.73) 0.93 (0.32–2.67) 1.04 (0.99–1.09)	Age, smoking, alcohol consumption, physical exercise, income level at study entry	Ovary and other unspecified female genital organs
Leitzmann et al. (2009) NIH-AARP cohort USA 1996–2003	94 525 Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	Never-users of HRT: 39 43 43	 1.00 1.39 (0.89–2.14) 1.83 (1.18–2.84) [0.007]	Age, race/ethnicity, family history, OC use, physical activity	

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Leitzmann et al. (2009) (cont.)		BMI	Ever-users of HRT:			
		< 25	102	1.00		
		25–29.9	43	0.68 (0.48–0.98)		
		≥ 30	33	0.96 (0.65–1.43)		
		[P_{trend}]		[0.53]		
Canchola et al. (2010) California Teachers Study Cohort USA 1995–2007	56 091 Never-users of HRT Incidence	BMI			Race, OC use, parity, wine intake, physical activity, smoking, tubal ligation	Weight gain from age 18 yr to baseline positively associated
		< 25	57	1.0		
		25–29.9	29	1.1 (0.71–1.8)		
		≥ 30	21	1.2 (0.72–2.0)		
		WC (in)				
		< 35	32	1.0		
		≥ 35	29	1.8 (1.1–3.0)		
Chionh et al. (2010) Melbourne Collaborative Cohort Study Australia 1990–2008	18 700 Incidence	BMI			Country of birth, education level, age at menarche, parity, OC use, hysterectomy, tobacco use, physical activity, energy intake from diet	
		< 25	39	1.00		
		25–29.9	40	1.05 (0.66–1.65)		
		≥ 30	34	1.58 (0.96–2.62)		
		per 5 kg/m^2		1.22 (1.00–1.48)		
		[P_{trend}]		[0.06]		
		WC, quartiles				
		Q1	24	1.00		
		Q2	27	0.97 (0.56–1.69)		
		Q3	30	1.03 (0.59–1.78)		
		Q4	32	0.96 (0.54–1.69)		
		[P_{trend}]		[0.71]		
Kotsopoulos et al. (2010) Nurses' Health Study 1 and 2 USA 1976–2006	182 700 Incidence	BMI			Age, age at menarche, parity, OC use, tubal ligation, height, family history of breast or ovarian cancer, caffeine intake, hysterectomy; for WC, additionally adjusted for BMI	
		< 21	125	1.00		
		21–22.9	155	0.97 (0.77–1.23)		
		23–24.9	168	1.02 (0.81–1.29)		
		25.0–29.9	242	0.96 (0.77–1.19)		
		≥ 30	177	1.12 (0.89–1.42)		
		[P_{trend}]		[0.29]		

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kotsopoulos et al. (2010) (cont.)		WC (in)				
		< 28	67	1.0		
		28–29.9	65	0.91 (0.64–1.29)		
		30–31.9	56	0.89 (0.61–1.30)		
		32–34.9	68	0.90 (0.61–1.33)		
		≥ 35	79	1.00 (0.62–1.88)		
		[P_{trend}]		[0.65]		
Lahmann et al. (2010) EPIC cohort Europe 1992–2007	226 798 Incidence	BMI			Age, parity, age at menarche, smoking, OC use	Stronger association in postmenopausal women than in premenopausal women
		< 25	287	1.00		
		25–29.9	211	1.14 (0.94–1.37)		
		≥ 30	113	1.33 (1.05–1.68)		
		[P_{trend}]		[0.02]		
		WC, quartiles				Similar association in premenopausal and postmenopausal women
		Q1	122	1.00		
		Q2	155	1.03 (0.81–1.31)		
		Q3	175	1.10 (0.87–1.41)		
		Q4	159	1.12 (0.86–1.45)		
		[P_{trend}]		[0.32]		
Yang et al. (2012) NIH-AARP cohort USA 1995–2006	169 391 Incidence	BMI			Age, OC use, HRT use, parity	Stronger association with endometrioid histological subtype
		< 30	617	1.00		
		≥ 30	197	1.15 (0.98–1.35)		
Ma et al. (2013) Shanghai Women's Health Study (SWHS) (population-based cohort) Shanghai, China 1996–2009	70 258 Incidence	BMI			Age, education level	Weight gain from age 20 yr also positively associated with risk
		< 18.5	7	1.73 (0.80–3.75)		
		18.5–24.9	75	1.00		
		25.0–29.9	55	1.49 (1.05–2.13)		
		≥ 30	15	2.42 (1.37–4.28)		
		[P_{trend}]		[0.008]		
		WC, quartiles			Age, education level	
		Q1	27	1.00		
		Q2	34	1.36 (0.82–2.26)		
		Q3	41	1.50 (0.92–2.46)		
		Q4	50	1.61 (0.98–2.64)		
		[P_{trend}]		[0.06]		

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bhaskaran et al. (2014) Health system clinical database United Kingdom 1987–2012	2 864 658 Incidence	BMI per 5 kg/m^2	3684	1.09 (1.04–1.14)	Age, sex, year, diabetes, alcohol consumption, smoking, SES	Similar association in never-smokers
Gay et al. (2015) Singapore Breast Cancer Screening Project (SBCSP) Singapore 1994–2012	28 234 Incidence	BMI < 18.5 18.5–22.9 23–27.4 ≥ 27.5 [P_{trend}]	 6 28 56 17	 1.96 (0.64–5.97) 1.00 1.34 (0.69–2.58) 0.55 (0.19–1.55) [0.22]	Age, housing, family history of breast cancer	

BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; OC, oral contraceptive; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.13b Case–control studies of measures of body fatness and cancer of the ovary

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Greggi et al. (2000) Italy 1998	440 Hospital	BMI < 22.5 22.5–26 > 26	 118 129 140	 1.0 (0.8–1.5) (0.8–1.6)	Age, education level, parity, OC use, family history of ovarian cancer	
Purdie et al. (2001) Australia 1990–1993	775 Population	BMI, percentiles < 15th 15th–35th 35th–65th 65th–85th ≥ 85th [P_{trend}]	518 total	 1.0 (0.7–1.6) 1.5 (1.0–2.2) 1.0 1.3 (0.9–1.9) 1.7 (1.1–2.6) [0.12]	Age, age squared, geographical location, education level, parity, duration of OC use, smoking history, ever-use of talc in the perineal region, tubal sterilization, hysterectomy, history of breast or ovarian cancer in a first-degree relative	Stronger risks were observed in premenopausal women above the 65th percentile
Dal Maso et al. (2002) Italy 1992–1999	1031 Hospital	BMI < 21 21– < 25 25– < 30 ≥ 30 [P_{trend}]	 143 406 299 173	 1.00 0.99 (0.77–1.27) 0.76 (0.58–0.99) 1.07 (0.79–1.44) [0.53]	Age, education level, parity, OC use	A significant association was observed with waist-to-hip ratio. No association was observed with increased body weight
Kuper et al. (2002) USA 1992–1997	563 Population	BMI < 20 ≥ 20– < 25 ≥ 25– < 30 ≥ 30	 67 255 138 104	 1.00 0.97 (0.64–1.45) 1.02 (0.65–1.60) 1.24 (0.77–2.01)	Age, site, parity, OC use, family history of breast, ovarian, or prostate cancer in a first-degree relative, tubal ligation, education level, marital status	In stratified analyses, a higher risk with BMI and weight was observed in premenopausal women
Lubin et al. (2003) Israel 1994–1999	1269 Population	BMI at age 18 yr < 19.1 19.1–20.9 21.0–22.8 22.9–35.2 [P_{trend}]		 1.00 1.16 (0.89–1.51) 1.13 (0.87–1.48) 1.42 (1.08–1.85) [0.009]		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Lubin et al. (2003) (cont.)		BMI change from age 18 yr				
		< 0.73		1.00		
		0.73–2.70		0.82 (0.63–1.06)		
		2.71–5.71		0.79 (0.60–1.03)		
		≥ 5.72		0.91 (0.69–1.20)		
		[P_{trend}]		[0.50]		
Yen et al. (2003) Taiwan, China 1993–1998	86 Hospital	BMI			Age, income during marriage, education level	
		< 25	63	1.00		
		≥ 25	23	0.77 (0.45–1.33)		
Pan et al. (2004) Canada 1994–1997	442 Population	BMI	442 total		5-year age group, province of residence, education level, pack-years of smoking, alcohol consumption, total energy intake, vegetable intake, dietary fibre intake, recreational physical activity, menopausal status, number of live births, age at menarche, age at end of first pregnancy	
		< 25		1.00		
		25– < 30		1.16 (0.90–1.50)		
		≥ 30		1.95 (1.44–2.64)		
Pike et al. (2004) USA 1992–1998	477 Population	BMI			Ethnicity, age, education level, SES, family history of ovarian cancer, tubal legation, use of talc in the genital area, nulliparity, age at last birth, number of births, number of incomplete pregnancies, OC use, menopausal status, age at natural menopause, age at surgical menopause, HRT use	
		< 25	261	1.00		
		25–29	120	0.97 (0.71–1.33)		
		30–34	56	1.29 (0.83–1.99)		
		≥ 35	40	1.46 (0.87–2.44)		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Riman et al. (2004) Sweden 1993–1995	655 Population	BMI 1 yr ago < 22 22– < 25 25– < 27 27– < 30 ≥ 30	 122 197 127 115 93	 1.00 0.99 (0.77–1.28) 1.06 (0.80–1.40) 1.10 (0.83–1.46) 1.37 (1.01–1.85)	Age, parity, and age at menopause as categorized variables, duration of OC use, ever-use of HRT	Stronger associations were observed for the mucinous histological subgroup, and no associations for the serous and endometrioid types
Hoyo et al. (2005) USA 1999–2003	593 Population	BMI < 25 25–29.99 ≥ 30	 230 158 192	 1.0 1.0 (0.7–1.3) 1.4 (1.0–1.8)	Race, age, parity, history of ovarian cancer, history of breast cancer, hysterectomy, OC use, menstrual status	Positive non-significant associations with weight gain from age 18 yr (3rd tertile, 204 cases) and with WC (3rd tertile, 213 cases). In stratified analyses, associations with recent BMI were only significant among Whites (vs African Americans)
Kurian et al. (2005) Pooled analysis of 10 case–control studies of ovarian cancer in the USA	1834 cases with invasive epithelial ovarian cancer Serous: 1067 Mucinous: 254 Endometrioid: 373 Clear cell: 140 Controls: 7 population, 3 hospital	BMI < 24 ≥ 24 BMI < 24 ≥ 24 BMI < 24 ≥ 24 BMI < 24 ≥ 24	Serous: 241 Mucinous: 57 Endometrioid: 82 Clear cell: 28 	 1.00 0.72 (0.59–0.88) 1.0 1.3 (0.88–2.0) 1.0 1.3 (0.95–1.9) 1.0 0.9 (0.55–1.6)	Parity, OC use	
Zhang et al. (2005) China 1999–2000	254 Hospital	BMI at diagnosis < 18.5 18.5–21.9 22.0–24.9 ≥ 25.0 [P_{trend}]	 93 28 86 47	 1.60 (0.91–2.83) 1.00 0.98 (0.69–1.41) 0.88 (0.57–1.34) [0.19]	Age at diagnosis, locality, tobacco smoking, alcohol consumption, parity, menopausal status, HRT, OC use, ovarian cancer in first-degree relatives, total energy intake	No significant associations were observed with body weight at diagnosis or with BMI/weight change. Statistically significant associations with BMI and weight were observed 5 yr before diagnosis

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Zhang et al. (2005) (cont.)		BMI at age 21 yr				
		< 18.5	134	0.94 (0.62–1.45)		
		18.5–21.9	41	1.00		
		22.0–24.9	66	1.04 (0.73–1.50)		
		≥ 25.0	11	1.20 (0.56–2.56)		
		[P_{trend}]		[0.37]		
Beehler et al. (2006) USA 1982–1998	427 Hospital	BMI			Age, geographical area, year of study participation	
		≤ 24.9	229	1.00		
		25.0–29.9	116	1.02 (0.77–1.36)		
		≥ 30.0	82	1.17 (0.84–1.65)		
Greer et al. (2006) USA 1994–1998	762 Population	BMI, quartiles			Age, race, number of live births, family history of ovarian cancer, tubal ligation, OC use	Highest BMI (4th quartile, 69 cases) and adult weight gain were associated with increased ovarian cancer risk among nulliparous women only
		Q1	173	1.00		
		Q2	196	1.10 (0.85–1.44)		
		Q3	192	1.14 (0.87–1.49)		
		Q4	201	1.24 (0.95–1.63)		
		[P_{trend}]		[0.12]		
Huusom et al. (2006) Denmark 1995–1999	202 Population	BMI			Age, childbirth, number of additional births, age at first birth, breastfeeding, duration of OC use, smoking, intake of milk	Significant associations with BMI among the serous histological subgroup only
		< 22	67	1.00		
		22–24	52	0.76 (0.51–1.14)		
		25–26	29	1.06 (0.64–1.74)		
		27–29	29	1.33 (0.80–2.19)		
		≥ 30	24	1.09 (0.64–1.84)		
Peterson et al. (2006) USA 1993–2001	700 Population	Recent BMI			Age, state, enrolment period, education level, family history of breast or ovarian cancer, OC use, parity, history of bilateral tubal ligation	Positive, non-significant association with recent weight was reported
		< 18.5	13	1.12 (0.62–2.03)		
		18.5–24.9	304	1.00		
		25.0–29.9	232	1.23 (0.67–2.23)		
		30.0	151	1.29 (0.70–2.37)		
		[P_{trend}]		[0.15]		
		Weight change (kg)				
		Loss	45	1.00 (0.68–1.48)		
		0–9.06 gain	93	1.00		
		9.07–15.87 gain	121	0.89 (0.66–1.20)		
		15.88–23.58 gain	90	0.90 (0.65–1.24)		
		23.59 gain	85	0.77 (0.56–1.06)		
		[P_{trend}]		[0.14]		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Rossing et al. (2006) USA 1994–1998	355 Population	BMI 5 yr before diagnosis or reference date < 25 25– < 30 ≥ 30	 130 96 127	 1.0 1.2 (0.9–1.7) 1.5 (0.9–2.4)	Age, race, study site, number of full-term births, duration of OC use, weight/BMI	Similar associations were observed for BMI and for weight at ages 18 yr and 30 yr
Máchová et al. (2007) Czech Republic 1987–2002	174 Population	BMI 18.5– < 25 ≥ 25– < 30 ≥ 30	174 total	 1.00 1.05 (0.68–1.61) 1.38 (0.87–2.20)	Age, smoking, hypertension, height	
Olsen et al. (2007) Meta-analysis (Australia, North America, western Europe)	Meta-analysis Population	BMI at age 17–20 yr ≥ 25 vs < 25 ≥ 25 vs < 25		Overall: 1.22 (1.02–1.45) Case–control: 1.21 (0.97–1.52)		
Soegaard et al. (2007) Denmark 1995–1999	554 Population	BMI at age 30–39 yr, quartiles Q1 Q2 Q3 Q4	 124 153 114 138	 1.00 1.31 (0.98–1.73) 1.00 (0.74–1.36) 1.23 (0.92–1.65)	Age, pregnancy, additional pregnancies, duration of OC use	Associations seemed somewhat stronger in mucinous and endometrioid tumours; no association with BMI ≥ 25 in adulthood
Lurie et al. (2008) USA 1993–2006	274 Population	BMI ≤ 18.5 18.5– < 25 25– < 30 ≥ 30	 6 141 64 64	 1.00 1.72 (0.64–4.75) 1.44 (0.50–4.09) 1.63 (0.57–4.71)		
Nagle et al. (2008) Australia NR	Endometrioid: 142 Clear cell: 90 Controls: 1508 Population	BMI 1 yr before diagnosis < 18 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	Endometrioid: 2 52 46 30	 0.9 (0.2–4.0) 1.0 1.3 (0.8–2.0) 1.2 (0.7–1.9) [0.41]	Age, education level, parity, OC use	

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Nagle et al. (2008) (cont.)			Clear cell:			
		< 18	3	2.9 (0.8–11.1)		
		18.5–24.9	23	1.0		
		25–29.9	27	1.7 (0.9–3.0)		
		≥ 30	25	2.2 (1.2–4.1)		
		[P_{trend}]		[0.01]		
Boyce et al. (2009) USA 1988–2008	72 Population	BMI			Age, race	This study investigated granulosa cell tumours
		20–24.9	14	1.00		
		25–29.9	15	1.72 (0.82–3.59)		
		30–39.9	22	5.02 (2.52–10.0)		
		> 40	5	6.60 (2.19–19.8)		
Delort et al. (2009) Auvergne, France 1996–1999, 2005–2006	55 (with no *BRCA* mutation) Mammographic screening centre	BMI			Age	BMI at age 20 yr not significantly associated with increased risk. WC significantly associated with increased risk
		< 20	10	1.00		
		20–25	29	0.88 (0.62–1.26)		
		25.1–30	9	0.78 (0.38–1.60)		
		> 30	6	0.69 (0.24–2.02)		
Moorman et al. (2009) USA 1999–2008	African American: 143/189 White: 943/868 Population	BMI	White:		Age	
		< 25	312	1.00		
		25– < 30	212	0.96 (0.76–1.22)		
		30– < 35	114	1.08 (0.80–1.45)		
		≥ 35	83	1.04 (0.75–1.45)		
		BMI	African American:			
		< 25	17	1.00		
		25– < 30	26	0.84 (0.39–1.78)		
		30– < 35	22	0.94 (0.43–2.07)		
		≥ 35	42	1.62 (0.79–3.35)		
Reis & Kizilkayabeji (2010) Turkey 2002–2003	217 Hospital	BMI			Not specified	
		18.5–24.99	86	1.00		
		≥ 25	131	1.96 (1.41–2.72)		
		[P_{trend}]		[< 0.001]		
Bandera et al. (2011) USA 2004–2008	205 Population	BMI			Age	
		18.5–25	90	1.00		
		25–29.9	54	1.07 (0.69–1.65)		
		30–34.9	36	1.39 (0.83–2.32)		
		≥ 35	24	1.54 (0.81–2.89)		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Bodmer et al. (2011) United Kingdom 1995–2009	1611 Hospital	BMI < 25 25–29.9 ≥ 30	 562 453 293	 1.00 1.08 (0.94–1.23) 1.11 (0.95–1.29)		
Su et al. (2012) China 2006–2008	500 Hospital	BMI 5 yr ago ≤ 18.49 18.5–22.9 ≥ 23 BMI 5 yr ago ≤ 18.49 18.5–22.9 ≥ 23 BMI 5 yr ago ≤ 18.49 18.5–22.9 ≥ 23	All: 36 348 116 Serous: 15 175 60 Mucinous: 8 58 14	 1.00 1.15 (0.72–1.85) 1.77 (1.04–3.02) 1.00 1.43 (0.77–2.69) 2.26 (1.13–4.52) 1.00 0.87 (0.38–1.98) 1.00 (0.38–2.61)	Age, OC use, parity, menopausal status, ovarian and/or breast cancer in a first-degree relative, age at menarche, smoking status, alcohol consumption; for weight, additional adjustment for height	Asian population cut-offs used for BMI Significant associations were observed for weight (kg), especially in the serous ovarian cancer subtype
Su et al. (2012) China 2006–2008	500 Hospital	BMI 5 yr ago, tertiles vs T1: ≤ 20.00 T2: 20.01–21.88 T3: ≥ 21.89 T2: 20.01–21.88 T3: ≥ 21.89 T2: 20.01–21.88 T3: ≥ 21.89 Weight (kg), tertiles vs T1: ≤ 50 T3: ≥ 55.1 T3: ≥ 55.1 T3: ≥ 55.1	All: 158 221 Serous: 83 112 Mucinous: 26 35 All: 187 Serous: 100 Mucinous: 27	 1.24 (0.89–1.72) 1.75 (1.28–2.40) 1.47 (0.97–2.22) 1.98 (1.33–2.95) 1.31 (0.69–2.49) 1.84 (1.00–3.38) 1.84 (1.34–2.54) 2.23 (1.50–3.33) 1.67 (0.91–3.06)	Age, OC use, parity, menopausal status, ovarian or breast cancer in a first-degree relative, age at menarche, smoking status, alcohol consumption	

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
King et al. (2013) USA 2001–2008	205 Population	BMI < 25 25–29.9 30–34.9 ≥ 35	 91 54 36 24	 1.00 1.07 (0.69–1.65) 1.39 (0.83–2.32) 1.54 (0.82–2.89)	Age	
Olsen et al. (2013) Pooled analyses of 15 case–control studies	13 548 cases Invasive: 8763 Borderline: 2465 1 study hospital -based, 14 studies population-based	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.5 35–39.9 ≥ 40 per 5 kg/m² BMI < 18.5 18.5–24.9 25.0–29.9 30–34.5 35–39.9 ≥ 40 per 5 kg/m²	Invasive: 183 4020 2500 1166 511 383 Borderline: 57 1080 662 379 150 137	 1.08 (0.84–1.39) 1.00 1.00 (0.92–1.09) 1.06 (0.97–1.16) 1.21 (1.07–1.38) 1.22 (1.05–1.41) 1.04 (1.00–1.08) 1.13 (0.82–1.55) 1.00 1.23 (1.09–1.39) 1.61 (1.40–1.85) 1.68 (1.37–2.06) 1.96 (1.57–2.46) 1.18 (1.14–1.23)	Age, parity, OC use, family history of breast or ovarian cancer in a first-degree relative, race/ethnicity where appropriate	BMI in early adulthood was significantly associated with 8% and 15% increased risk of invasive and borderline ovarian cancer subtypes, respectively
Le et al. (2014) Canada 2001–2007	608 Population	BMI < 25 25–30 30–35 ≥ 35	 330 180 57 41	 1.00 0.80 (0.59–1.09) 0.87 (0.54–1.41) 0.91 (0.53–1.58)	Age	
Schildkraut et al. (2014) USA 2010–2014	403 Population	BMI < 24.9 25–29.9 30–34.9 ≥ 35	 54 95 107 113	 1.00 1.31 (0.86–1.99) 1.50 (0.99–2.27) 1.27 (0.85–1.91)	Age, months of OC use, parity	Study in African American women

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Burghaus et al. (2015) Germany 2002–2013	289 Hospital	BMI, tertiles (median) Low (21.7) Medium (25.0) High (30.1)	NR	Low vs medium: 0.99 (0.83–1.17) High vs medium: 1.26 (1.09–1.46) High vs low: 1.28 (0.95–1.72)	Age, OC use, pregnancies, self-reported endometriosis	

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; NR, not reported; OC, oral contraceptive; WC, waist circumference; yr, year or years

Table 2.2.13c Meta-analyses of measures of body fatness and cancer of the ovary

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Olsen et al. (2007)	16 studies for adult BMI (8 case–control and 8 cohort) and 9 for BMI in early adulthood (5 case–control and 4 cohort) NR	Adult BMI 18.5–24.9 25.0–29.9 ≥ 30 BMI at age 17–20 yr 18.5–24.9 ≥ 25	 1.00 1.16 (1.01–1.32) 1.30 (1.12–1.50) 1.00 1.22 (1.02–1.45)		In adult BMI, no difference was observed when stratifying by study design type
Guh et al. (2009)	9 cohort studies NR	BMI 18.5–24.9 25.0–29.9 ≥ 30	 1.00 1.18 (1.12–1.23) 1.28 (1.20–1.36)	Unadjusted RRs	
Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012)	47 studies (17 prospective and 30 case–control) 25 157 cases	BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 1.00 (0.95–1.05) 1.05 (1.00–1.11) 1.08 (1.02–1.13) 1.07 (0.99–1.17) 1.13 (1.06–1.20) [0.01]	Study, age at diagnosis, parity, menopausal status/hysterectomy, OC use, HRT use, height	In stratified analyses, associations were only significant among never-users of HRT (RR, ~1.1 for overweight; ~1.2 for obesity)
Poorolajal et al. (2014)	10 cohort studies and 9 case–control studies NR	BMI 18.5–24.9 25.0–29.9 ≥ 30 BMI 18.5–24.9 25.0–29.9 ≥ 30	Case–control: 1.00 1.08 (0.90–1.31) 1.27 (1.19–1.35) Cohort: 1.00 1.26 (0.97–1.63) 1.26 (1.06–1.50)	NR	In stratified analysis by menopausal status, stronger associations were found in all cases in the premenopausal period
Aune et al. (2015)	25 studies 19 825 cases	BMI per 5 kg/m^2 increase	1.07 (1.03–1.11)	Maximally adjusted HR, RR, or OR were used (covariates NR)	Non-linearity, with risk increasing significantly from BMI above 28 kg/m^2; relatively stronger risk with BMI increase in early adulthood, based on 6 studies (RR, 1.12); no association with weight gain

Table 2.2.13c (continued)

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Liu et al. (2015)	26 studies (13 case–control and 13 cohort) 12 963 cases	BMI 18.5–24.9 25.0–29.9 ≥ 30	Case–control: 1.00 1.09 (1.00–1.18) 1.31 (1.21–1.54)		No associations with BMI were found in postmenopausal women
		BMI 18.5–24.9 25.0–29.9 ≥ 30	Cohort: 1.00 1.07 (1.01–1.13) 1.23 (1.10–1.39)		
		BMI 18.5–24.9 25.0–29.9 ≥ 30	Overall: 1.00 1.07 (1.02–1.12) 1.28 (1.16–1.41)		

BMI, body mass index (in kg/m^2); CI, confidence interval; HR, hazard ratio; HRT, hormone replacement therapy; NR, not reported; OC, oral contraceptive; OR, odds ratio; RR, relative risk; yr, year or years

Table 2.2.13d Mendelian randomization studies of measures of body fatness and cancer of the ovary

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI) P_{trend}	Comments
Gao et al. (2016) Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium	Women from 3 studies of individuals of European ancestry	13 492 (4369 cases and 9123 controls)	Increase of 1 SD in genetically predicted childhood BMI or adult BMI	Childhood BMI: 1.07 (0.82–1.39) P_{trend} = 0.62 Adult BMI: 1.07 (1.01–1.13) P_{trend} = 0.02	Similar associations were found for adult BMI with serous ovarian cancer, and moderate but not statistically significant with clear cell and endometrioid histological subtypes. No associations were observed between childhood BMI and subtypes of ovarian cancer

BMI, body mass index (in kg/m^2); CI, confidence interval; SD, standard deviation

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2.2.14 Cancer of the prostate

Cancer of the prostate is the fourth most commonly diagnosed cancer worldwide, and one of the most frequent causes of cancer-related mortality in developed countries.

The relationship between body weight and prostate cancer risk is complex, for several reasons. First, prostate cancer-specific mortality (death attributed to the underlying cancer) is a proxy for incidence in some studies, whereas it is a primary end-point in other studies, along with different types of prostate cancer incidence defined by tumour characteristics. However, prostate cancer-specific mortality may be over-represented in patients who die *with* but not *of* the disease. This is a particular concern if, for example, obese patients with prostate cancer have other comorbid disease and more regular contact with the health-care system; the cancer may be more prominent in their management and may be recorded on the death certificate, even if heart disease is the underlying cause of death. Second, detection bias could also be a concern in studies of prostate cancer incidence; because obese men have lower levels of prostate-specific antigen (PSA), their tumours are more difficult to detect, and they are less likely to undergo a biopsy (Allot et al., 2013). However, potential biological mechanisms have also been proposed to explain a lower risk of early-stage prostate cancer in men who are overweight or obese (see Section 4.3.1d).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and prostate cancer was *inadequate*. Since then, numerous prospective studies with at least 100 cases (Table 2.2.14a) and case–control studies (Table 2.2.14b) have been published, as well as several meta-analyses of observational studies addressing different measures of body fatness (Table 2.2.14c).

(a) Cohort studies

The *IARC Handbook* on weight control and physical activity (IARC, 2002), in the evaluation of prostate cancer risk and measures of body fatness, included 13 prospective cohort studies with at least 100 cases (not shown in Table 2.2.14a). Of those, four found a positive association and nine found no association. Notably, across all prospective studies, the highest category of BMI was overweight (25–29.9 kg/m^2) but not obese (≥ 30 kg/m^2).

Since 2000, associations of body fatness assessed at baseline with total prostate cancer incidence have been examined in numerous individual prospective studies with at least 100 cases and in at least two meta-analyses. In most studies, neither BMI nor weight was associated with risk (Habel et al., 2000; Schuurman et al., 2000; Lee et al., 2001; Jonsson et al., 2003; Rapp et al., 2005; Gong et al., 2006; Lukanova et al., 2006; Tande et al., 2006; Fujino et al., 2007; Giovannucci et al., 2007; Littman et al., 2007; Máchová et al., 2007; Rodriguez et al., 2007; Pischon et al., 2008; Wallström et al., 2009; Andreotti et al., 2010; Stocks et al., 2010; Bassett et al., 2012). However, in some studies statistically significant positive associations (or trends) between BMI at baseline and prostate cancer incidence were found (Engeland et al., 2003; Samanic et al., 2004, 2006; Jee et al., 2008; Barrington et al., 2015), and four prospective studies found lower risk of prostate cancer with increasing BMI (Wright et al., 2007; Bhaskaran et al., 2014; Møller et al., 2015). In a meta-analysis of 27 prospective studies, there was a statistically significant positive association with prostate cancer incidence (RR per 5 kg/m^2 increase in BMI, 1.03; 95% CI, 1.00–1.07) (Renehan et al., 2008).

Associations of body fatness at baseline with stage of the disease were examined in several studies. Regarding the incidence of localized, low-grade, or non-aggressive disease, although five studies found no association (Schuurman et

al., 2000; Giovannucci et al., 2007; Pischon et al., 2008; Wallström et al., 2009; Bassett et al., 2012), at least seven other studies found an inverse association of BMI and/or weight with the incidence of non-aggressive (Littman et al., 2007; Stocks et al., 2010), non-metastatic low- to moderate-grade (Gong et al., 2006; Rodriguez et al., 2007; Møller et al., 2016 for BMI at age 21 years), or localized (Wright et al., 2007; Discacciati et al., 2011; Hernandez et al., 2009 for BMI at age 21 years) prostate cancer. In the Selenium and Vitamin E Cancer Prevention Trial (SELECT), there was evidence of a significant inverse trend between BMI and the incidence of low-grade prostate cancer in non-Hispanic White men, and a statistically significant positive association in African American men (Barrington et al., 2015).

Nine prospective studies found no associations of BMI and/or weight with the incidence of regional or distant prostate cancer (Habel et al., 2000), advanced, high-grade, or moderately to poorly differentiated prostate cancer (Schuurman et al., 2000; Pischon et al., 2008; Discacciati et al., 2011; Møller et al., 2015), aggressive prostate cancer (Littman et al., 2007; Wallström et al., 2009; Stocks et al., 2010), or extraprostatic prostate cancer (Wright et al., 2007). However, five other studies found positive associations or trends of BMI and/or weight with the incidence of high-grade or advanced prostate cancer (Gong et al., 2006; Giovannucci et al., 2007; Rodriguez et al., 2007; Hernandez et al., 2009 for BMI at age 21 years; Bassett et al., 2012; Barrington et al., 2015). A meta-analysis combining data from 24 prospective studies found a statistically significant positive association between BMI and risk of advanced, high-grade, or fatal prostate cancer (RR per 5 kg/m^2 increase in BMI, 1.08; 95% CI, 1.04–1.12) (WCRF/AICR, 2014).

There is considerable evidence of a positive association of BMI with prostate cancer mortality, based on findings from both individual prospective studies (Rodriguez et al., 2001; Calle et al., 2003; Giovannucci et al., 2007; Wright et al., 2007; Stocks et al., 2010 Bassett et al., 2012) and a large pooled analysis of 57 prospective studies from Europe, Japan, and the USA, reporting a relative risk of mortality per 5 kg/m^2 increase in BMI of 1.13 (95% CI, 1.02–1.24) across the BMI range of 15–50 kg/m^2 (Whitlock et al., 2009). However, at least six other individual prospective studies found no association between BMI at baseline and death from prostate cancer (Batty et al., 2005; Fujino et al., 2007; Burton et al., 2010 for BMI at age < 30 years; Discacciati et al., 2011; Meyer et al., 2015; Møller et al., 2015). Similarly, BMI was not associated with prostate cancer mortality in a pooled analysis from the Asia Cohort Consortium (Fowke et al., 2015). [The Working Group noted that in this analysis, the reference group was men with a BMI of 22.5–24.9 kg/m^2, compared with men with a BMI of 25–50 kg/m^2. A possible effect of obesity (BMI > 30 kg/m^2) on prostate cancer mortality might have been missed in this study.]

At least six prospective studies found no associations between BMI or weight at younger ages of adulthood and risk of prostate cancer (total, localized, advanced, or fatal) (Giovannucci et al., 1997; Jonsson et al., 2003; Fujino et al., 2007; Hernandez et al., 2009; Burton et al., 2010; Discacciati et al., 2011; Bassett et al., 2012), whereas in two other studies higher BMI (Schuurman et al., 2000) or weight (Littman et al., 2007) in young adulthood was significantly associated with increased total prostate cancer incidence. In the NIH-AARP cohort, both BMI and weight at age 18 years were not associated with the incidence of total prostate cancer or extraprostatic prostate cancer, whereas inverse associations with localized prostate cancer were reported (P_{trend} = 0.04) (Wright et al., 2007). Similarly, in the Multiethnic Cohort Study and the Health Professionals Follow-up Study, BMI at age 21 years was inversely associated with the incidence of total, localized, and low- and moderate-grade prostate cancer and was not associated with the incidence of high-grade or fatal prostate cancer (Hernandez et al.,

2009; Møller et al., 2016). Similarly, in the study by Littman et al. (2007), the positive association with weight in young adulthood (ages 18, 30, or 45 years) was restricted to the aggressive type. In a meta-analysis of nine prospective studies, Robinson et al. (2008) found a positive association between BMI in early life (i.e. < 29 years) and prostate cancer incidence or mortality (RR per 5 kg/m^2 increase in BMI, 1.08).

In at least four individual prospective studies, change in neither BMI nor weight during adulthood was associated with prostate cancer incidence (Jonsson et al., 2003; Samanic et al., 2006; Rodriguez et al., 2007; Rapp et al., 2008). Similarly, a meta-analysis of four prospective studies also found no associations of adult weight gain [after adjustment for age and baseline BMI or weight in all studies] with total, localized, or advanced prostate cancer incidence (Keum et al., 2015). However, in the Netherlands Cohort Study, there was suggestive evidence of an inverse trend between increase in BMI from age 20 years to baseline (≥ 6 kg/m^2) and total prostate cancer incidence (P_{trend} = 0.07), and this association was statistically significant for poorly differentiated or undifferentiated prostate tumours (Schuurman et al., 2000). In the Vitamins and Lifestyle (VITAL) cohort, both weight loss and weight gain were associated with a lower risk of non-aggressive prostate cancer, but there was no association with aggressive prostate cancer (Littman et al., 2007). In the NIH-AARP cohort, weight gain from age 18 years to baseline was not associated with prostate cancer incidence (total, localized, or extraprostatic), but was associated with prostate cancer mortality (P_{trend} = 0.009) (Wright et al., 2007).

The association between waist circumference and total prostate cancer incidence was examined in at least eight individual prospective studies, and no study found evidence of statistically significant associations with total prostate cancer incidence (Giovannucci et al., 1997; Lee et al., 2001; MacInnis et al., 2003; Gong et al., 2006; Tande et al., 2006; Pischon et al., 2008; Wallström et al., 2009; Møller et al., 2015). On the basis of four prospective studies, the WCRF Continuous Update Project summary (WCRF/AICR, 2014) found no dose–response association between waist circumference and risk of total or non-advanced prostate cancer, but a statistically significant positive association with risk of advanced or fatal prostate cancer (RR per 10 cm increase, 1.12; 95% CI, 1.04–1.21).

(b) Case–control studies

Case–control studies of BMI and other adiposity indices in relation to prostate cancer risk are presented in Table 2.2.14b. In the *IARC Handbook* on weight control and physical activity (IARC, 2002), 15 case–control studies of BMI and prostate cancer were reviewed (not shown here). Since then, at least 35 case–control studies and 5 meta-analyses including case–control study designs, focused on the association between weight, BMI, or waist circumference and prostate cancer, have been conducted in Asia (China, India, Japan, and Pakistan), the Caribbean (Barbados and Jamaica), Europe, the Islamic Republic of Iran, Nigeria, North America, and Oceania (Australia and New Zealand). In all of these studies, BMI was assessed on the basis of self-reported height and body weight, or body weight and height verified at the time of a hospital consultation.

Positive associations between high BMI and total prostate cancer incidence were reported in six of the case–control studies. Bashir et al. (2014), in a hospital-based case–control study in Pakistan with 140 cases and 280 controls, found a significant increase in the risk of prostate cancer for men with BMI > 25 kg/m^2 (OR, 5.78; 95% CI, 2.67–12.6). In a multicentre hospital-based case–control study in Italy, Dal Maso et al. (2004) identified a dose–response relationship between BMI at age 30 years and prostate cancer risk, based on 1257 cases (P_{trend} = 0.004). Ganesh et al. (2011) reported a 2-fold greater risk of prostate cancer

in Indian men with BMI ≥ 25 kg/m² (OR, 2.1; 95% CI, 1.1–4.4). A hospital-based case–control study in France found a positive association between BMI > 29 kg/m² and risk of prostate cancer (OR, 2.47; 95% CI, 1.41–4.34) (Irani et al., 2003). Similarly, a study in Canada reported a significant 27% increase in risk of prostate cancer in men with BMI ≥ 30 kg/m² compared with those with BMI < 25 kg/m² (Pan et al., 2004).

An inverse association between BMI and prostate cancer has also been reported in several studies. Beebe-Dimmer et al. (2009), in a hospital-based case–control study in the USA, found an inverse relationship between high BMI (≥ 30 kg/m²) and prostate cancer risk in Caucasian men, based on 494 cases (OR, 0.51; 95% CI, 0.33–0.80), but not in African American men. Similarly, a study in Canada found a statistically significant inverse relationship between BMI ≥ 30 kg/m² and prostate cancer risk (OR, 0.72; 95% CI, 0.60–0.87), but no associations with waist circumference or waist-to-hip ratio were found (Boehm et al., 2015). A population-based case–control study in the Islamic Republic of Iran (Hosseini et al., 2010), with 137 cases and 137 controls, also found a significant inverse relationship between high BMI (≥ 25 kg/m²) and prostate cancer risk (OR, 0.4; 95% CI, 0.2–0.8). Finally, Agalliu et al. (2015) conducted a small hospital-based case–control study in Nigeria, with 50 cases and 50 controls. Inverse associations were reported for weight (OR per kg increase, 0.97; 95% CI, 0.94–1.00) and waist circumference (OR per cm increase, 0.91; 95% CI, 0.87–0.96).

One additional case–control study found an increased risk of total prostate cancer in men with an increased waist circumference (Beebe-Dimmer et al., 2007).

Three meta-analyses that included case–control studies suggested a small increase in risk of prostate cancer associated with higher BMI (Bergström et al., 2001; MacInnis & English, 2006; Robinson et al., 2008). In one additional meta-analysis, a significant positive association with adult weight was observed for high-risk (RR, 1.13; 95% CI, 1.00–1.28) and fatal (RR, 1.58; 95% CI, 1.01–2.47) prostate cancer subtypes (Chen et al., 2016).

Six case–control studies differentiated prostate cancer by grade, stage, or aggressiveness, and generally reported positive associations of BMI, waist circumference, or waist-to-hip ratio with prostate cancers with higher Gleason scores. Fowke et al. (2012) analysed 809 hospital-based cases and 1057 controls in the USA by Gleason score. On the basis of 135 cases, BMI and waist circumference were marginally associated with increased risk of high-grade prostate cancer (OR per 1 kg/m² increase in BMI, 1.04; 95% CI, 1.00–1.08 and OR per 1 cm increase in waist circumference, 1.01; 95% CI, 0.99–1.03). Jackson et al. (2010) separated patients with high-grade prostate cancer in their hospital-based case–control study (243 cases and 275 controls) in Jamaica. Waist circumference and waist-to-hip ratio were positively associated with high-grade prostate cancer after adjustment for BMI. A dose–response relationship was also observed for waist circumference, and no association was found with BMI. A case–control study in Italy observed significant positive associations of BMI and prostate cancer of Gleason score 7–10 only (P_{trend} < 0.01) (Dal Maso et al., 2004). Liu et al. (2005) conducted a population-based sibling case–control study in the USA with 439 cases and 479 controls and found no association of aggressive prostate cancer (defined as Gleason score ≥ 7 or tumour stage T2C or greater) with increased BMI, whereas an inverse association was observed for lean body mass (P_{trend} = 0.02). Nemesure et al. (2012) conducted a population-based case–control study in Barbados with 963 cases and 941 controls and reported a positive association of waist circumference with all prostate cancers (OR for highest versus lowest quartiles, 1.84; 95% CI, 1.19–2.85), which did not hold when stratifying by disease grade. Robinson et al. (2005) in the USA reported an inverse association between

BMI > 30 kg/m^2 at age 20–29 years and advanced prostate cancer [based on 12 cases].

Several studies assessed BMI and body weight at different ages, and BMI/weight change. In a population-based case–control study in Sweden, Gerdtsson et al. (2015) investigated several anthropometric measures, including BMI and weight, at multiple time points in life. Weight increase in adolescence (age 16–22 years) was associated with increased risk of prostate cancer (OR per 5 kg increase in weight, 1.05; 95% CI, 1.01–1.09), and increase in BMI and weight in middle age (age 44–50 years) was associated with increased mortality from prostate cancer, and with increased metastasis. Weight gain of 10.0–14.9 kg in adulthood was significantly associated with a 3–4-fold greater risk of prostate cancer in a population-based case–control study in Japan (Mori et al., 2011). In the same study, BMI of 23.0–24.9 kg/m^2 at age 20 years was associated with a reduced risk of prostate cancer (OR, 0.47; 95% CI, 0.22–0.98) (Mori et al., 2011) [based on 11 cases only]. In contrast, a total of 16 case–control studies conducted in Australia, Canada, the Czech Republic, Italy, Japan, New Zealand, Spain, Sweden, Switzerland, the United Kingdom, and the USA reported no associations between risk of total prostate cancer and BMI or other adiposity indices at different ages (Putnam et al., 2000; Sharpe & Siemiatycki, 2001; Giles et al., 2003; Friedenreich et al., 2004; Porter & Stanford, 2005; Robinson et al., 2005; Wuermli et al., 2005; Cox et al., 2006; Gallus et al., 2007; Máchová et al., 2007; Nagata et al., 2007; Magura et al., 2008; Dimitropoulou et al., 2011; Pelucchi et al., 2011; Möller et al., 2013; Alvarez-Cubero et al., 2015; Zhang et al., 2015) or BMI change or weight gain from early adulthood (Putnam et al., 2000; Giles et al., 2003; Friedenreich et al., 2004).

(c) Mendelian randomization studies

Three Mendelian randomization studies have been conducted in this context (Table 2.2.14d).

Lewis et al. (2010) showed that each additional A allele of the *FTO* rs9939609 SNP was associated with an increase of 0.56 kg/m^2 (P = 0.007) in BMI across all groups (cases and controls). Estimates obtained from Mendelian randomization analyses provided odds ratios of 0.77 (95% CI, 0.52–1.15; P = 0.20) for prostate cancer and 1.35 (95% CI, 0.90–2.03; P = 0.14) for high-grade versus low-grade cancer with each 1 kg/m^2 increase in BMI.

Davies et al. (2015) extended this work by using a genetic risk score based on 32 SNPs associated with BMI (Speliotes et al., 2010) as an instrument for BMI within a much larger sample size. Each increase of 1 standard deviation in genetically predicted BMI was associated on average with a nonsignificant 2% reduction in risk (95% CI, 0.96–1.00; P = 0.07) in any prostate cancer diagnosis.

In Mendelian randomization analyses that used genetic risk scores based on 77 SNPs for adult BMI (Locke et al., 2015) and 15 SNPs for childhood BMI (Felix et al., 2016), Gao et al. (2016) found no strong evidence for associations of childhood or adult BMI with either total or aggressive prostate cancer risk.

[Although results from Lewis et al. (2010) and Davies et al. (2015) point towards an inverse association between BMI and prostate cancer risk, this association was not significant and was not consistently found in all three studies.]

Table 2.2.14a Cohort studies of measures of body fatness and cancer of the prostate

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Giovannucci et al. (1997) Health Professionals Follow-up Study USA 1986–1994	47 781 Incidence	Prostate, advanced	BMI at age 21 yr			Age, height	
			< 20	81	1.00		
			20–21.9	117	0.91 (0.69–1.22)		
			22–22.9	59	0.88 (0.62–1.24)		
			23–23.9	56	0.77 (0.54–1.10)		
			24–25.9	60	0.71 (0.50–1.02)		
			≥ 26	26	0.53 (0.33–0.86)		
			[P_{trend}]		[< 0.006]		
		Prostate, all	BMI at age 21 yr				WC also not associated with increased risk
			< 20	229	1.00		
			20–21.9	353	0.98 (0.83–1.16)		
			22–22.9	188	1.00 (0.82–1.22)		
			23–23.9	200	1.03 (0.84–1.26)		
			24–25.9	223	1.00 (0.82–1.22)		
			≥ 26	104	0.87 (0.67–1.12)		
			[P_{trend}]		[0.60]		
Habel et al. (2000) Kaiser Permanente USA 1964–1973 to 1996	70 712 Incidence	Prostate	BMI	2079 total		Age, race, year of birth	Weight also not associated with increased risk No associations were observed in results stratified by race
			< 22.7		1.00		
			22.7–24.3		1.09 (0.93–1.27)		
			24.4–25.9		1.04 (0.89–1.21)		
			26–27.9		1.04 (0.90–1.21)		
			> 27.9		0.99 (0.85–1.15)		
		Prostate, regional/distant	BMI	578 total			
			< 22.7		1.00		
			22.7–24.3		0.84 (0.62–1.13)		
			24.4–25.9		1.05 (0.80–1.39)		
			26–27.9		1.04 (0.79–1.37)		
			> 27.9		0.91 (0.69–1.20)		
Schuurman et al. (2000) Netherlands Cohort Study The Netherlands 1986–1982	58 279 Incidence	Prostate	BMI at baseline			Age, family history of prostate cancer, SES; BMI change results also adjusted for BMI at age 20 yr	
			< 22	63	1.00		
			22–23	164	1.20 (0.84–1.73)		
			24–25	236	1.35 (0.95–1.90)		
			26–27	150	1.26 (0.87–1.83)		
			≥ 28	62	0.89 (0.58–1.37)		
			[P_{trend}]		[0.73]		
			per 2 kg/m^2		1.00 (0.92–1.07)		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schuurman et al. (2000) (cont.)	58 279 Incidence		BMI at age 20 yr				
			< 19	57	1.00		
			19–20.9	122	1.06 (0.72–1.56)		
			21–22.9	176	1.09 (0.76–1.58)		
			23–24.9	119	1.39 (0.93–2.06)		
			≥ 25	44	1.33 (0.81–2.19)		
			[P_{trend}]		[0.02]		
			per 2 kg/m^2		1.08 (0.99–1.18)		
			BMI change				
			−9.2 to < 0	47	1.19 (0.74–1.90)		
			0–1.9	120	1.00		
			2–3.9	176	1.32 (0.98–1.79)		
			4–5.9	113	1.04 (0.74–1.47)		
			6–7.9	43	0.83 (0.52–1.31)		
			≥ 8	19	0.67 (0.36–1.23)		
			[P_{trend}]		[0.07]		
			per 2 kg/m^2		0.93 (0.84–1.03)		
		Prostate, localized TNM: T0–2, M0	BMI, per 2 kg/m^2	239 total			
			BMI at baseline		0.96 (0.86–1.06)		
			BMI at age 20 yr		1.18 (1.04–1.35)		
			BMI change		0.87 (0.74–1.02)		
		Prostate, advanced TNM: T3–4, M0; T0–4, M1	BMI, per 2 kg/m^2	226 total			
			BMI at baseline		1.01 (0.90–1.13)		
			BMI at age 20 yr		1.03 (0.91–1.18)		
			BMI change		0.93 (0.80–1.08)		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schuurman et al. (2000) (cont.)		Prostate, well-differentiated	BMI, per 2 kg/m^2	194 total			
			BMI at baseline		0.92 (0.82–1.04)		
			BMI at age 20 yr		1.09 (0.94–1.26)		
			BMI change		0.77 (0.65–0.92)		
		Prostate, moderately differentiated	BMI, per 2 kg/m^2	247 total			
			BMI at baseline		1.02 (0.93–1.13)		
			BMI at age 20 yr		1.15 (1.01–1.31)		
			BMI change		0.97 (0.83–1.13)		
		Prostate, poorly differentiated or undifferentiated	BMI, per 2 kg/m^2	174 total			
			BMI at baseline		1.01 (0.89–1.14)		
			BMI at age 20 yr		0.97 (0.83–1.13)		
			BMI change		0.68 (0.58–0.81)		
Lee et al. (2001) Harvard Alumni Health Study USA 1988–1993	8922 Incidence	Prostate	BMI at baseline			Age, smoking, alcohol consumption, paternal history of prostate cancer	WC also not associated with increased risk BMI at age 18 yr (available for 92% of the men) also not associated with increased risk
			< 22.5	87	1.00		
			22.5–24.9	172	1.27 (0.94–1.71)		
			25.0–27.4	134	1.26 (0.92–1.72)		
			27.5	46	1.02 (0.68–1.53)		
			[P_{trend}]		[0.71]		
Rodriguez et al. (2001) Cancer Prevention Study I (CPS I) USA 1959–1972	381 638 Mortality	Prostate ICD-7: 177	BMI			Age, race, height, education level, exercise, smoking status, family history of prostate cancer	
			< 25	782	1.00		
			25–29.99	698	1.02 (0.92–1.14)		
			≥ 30	110	1.27 (1.04–1.56)		
			[P_{trend}]		[0.06]		
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	404 576 Mortality	Prostate	BMI			Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat consumption, vegetable consumption	
			18.5–24.9	1681	1.00		
			25–29.9	1971	1.08 (1.01–1.15)		
			30–34.9	311	1.20 (1.06–1.36)		
			≥ 35	41	1.34 (0.98–1.83)		
			[P_{trend}]		[< 0.001]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Engeland et al. (2003) Norwegian clinical population Norway 1963–1999 to 2001	951 466 Incidence	Prostate ICD-7: 177	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 147 16 720 14 524 1923	 0.92 (0.78–1.08) 1.00 1.07 (1.05–1.09) 1.09 (1.04–1.15) [0.001]	Age at BMI measurement, birth cohort	In stratified analyses by age at BMI measurement, no differences in risk by age strata were observed
Jonsson et al. (2003) Swedish Twin Registry Sweden 1969–2003	8998 Incidence	Prostate ICD-7: 177	BMI at baseline < 18.5 18.5–24.9 25.0–29.9 ≥ 30 BMI at age 25 yr < 18.5 18.5–24.9 ≥ 25 BMI at age 40 yr < 18.5 18.5–24.9 25.0–29.9 ≥ 30 Adult weight change (kg) < 0 0–5 6–10 11–20 ≥ 21	 6 355 248 22 4 436 64 6 368 155 13 96 178 114 95 21	 1.4 (0.6–3.1) 1.0 1.0 (0.8–1.2) 1.0 (0.6–1.5) 0.5 (0.2–1.5) 1.0 1.0 (0.7–1.3) 2.5 (1.1–5.5) 1.0 0.9 (0.7–1.1) 0.9 (0.5–1.6) 0.9 (0.7–1.2) 1.0 1.0 (0.8–1.3) 0.9 (0.7–1.2) 1.1 (0.8–1.8)	Age; BMI at age 25 yr and 40 yr also controlled for BMI at baseline	No associations were observed in stratified analyses by age at diagnosis (≥ 70 yr vs < 70 yr)
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Incidence	Prostate ICD-9: 185	Obesity Non-obese Obese Non-obese Obese	 Black men: 15 272 815 White men: 45 901 3206	 1.00 1.12 (1.04–1.20) 1.00 1.19 (1.15–1.24)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Batty et al. (2005) Whitehall Study United Kingdom 1967–2002	18 403 Mortality	Prostate	BMI 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 243 175 13	 1.00 0.92 (0.75–1.13) 0.91 (0.51–1.63) [0.45]	Age, employment grade, physical activity, smoking, marital status, prevalent disease, past-year weight loss, BP medication, height, skinfold thickness, systolic BP, plasma cholesterol, glucose intolerance, diabetes	
Rapp et al. (2005) Vorarlberg VHM&PP Austria 1985–2001	67 447 Incidence	Prostate ICD-9: 185	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 446 583 99 10	 1.00 1.03 (0.91–1.17) 0.82 (0.66–1.03) 0.73 (0.39–1.37) [0.16]	Age, smoking status, occupation	
Gong et al. (2006) Prostate Cancer Prevention Trial (PCPT) USA N/A–2003	10 258 Incidence	Prostate	BMI < 25 25–26.9 27–29.9 ≥ 30 [P_{trend}]	1936 total	 1.00 0.91 (0.79–1.05) 0.96 (0.83–1.10) 0.96 (0.83–1.10) [0.67]	Age, race, treatment, diabetes, family history of prostate cancer	Analyses of the association of WC with total prostate, and low-grade and high-grade subtypes also reported
		Prostate, low-grade	BMI < 25 25–26.9 27–29.9 ≥ 30 [P_{trend}]	1300 total	 1.00 0.88 (0.74–1.04) 0.88 (0.75–1.04) 0.82 (0.69–0.98) [0.03]		
		Prostate, high-grade	BMI < 25 25–26.9 27–29.9 ≥ 30 [P_{trend}]	521 total	 1.00 0.97 (0.75–1.27) 1.09 (0.85–1.40) 1.29 (1.01–1.67) [0.04]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lukanova et al. (2006) Northern Sweden Health and Disease Cohort (NSHDC) 1985–2003	33 424 Incidence/ mortality	Prostate	BMI 18.5–23.4 23.5–25.3 25.4–27.6 ≥ 27.1 [P_{trend}]	 93 114 129 125	 1.00 1.00 (0.76–1.32) 0.96 (0.74–1.26) 0.89 (0.68–1.16) [0.31]	Age, calendar year, smoking	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Incidence 107 815 (in BMI change analysis) Incidence	Prostate ICD-7: 177	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}] 6-yr BMI change −4% to 4.9% 5–9.9% 10–14.9% ≥ 15% [P_{trend}]	 3003 3160 528 1281 417 97 22	 1.00 1.06 (1.01–1.12) 1.09 (0.99–1.19) [< 0.05] 1.00 1.09 (0.98–1.22) 0.93 (0.75–1.14) 0.75 (0.49–1.15) [> 0.5]	Attained age, calendar year, smoking	
Tande et al. (2006) Atherosclerosis Risk in Communities (ARIC) Study USA 1987–2000	6332 Incidence	Prostate	BMI < 24.7 24.7–26.9 27.0–29.7 ≥ 29.8	 94 99 91 101	 1.00 1.17 (0.88–1.55) 0.97 (0.72–1.29) 1.14 (0.86–1.50)	Age, race	WC also not associated with increased risk Men with metabolic syndrome were 27% less likely to develop prostate cancer
Fujino et al. (2007) Japan Collaborative Cohort Study for Evaluation of Cancer (JACC) Japan NR	NR Mortality	Prostate	BMI < 18.5 18.5–24 25–29 ≥ 30	 17 107 31 1	 1.39 (0.83–2.34) 1.00 1.56 (1.04–2.34) 0.87 (0.12–6.29)	Age, area of study	[No information reported on follow-up period or total number of participants included in the study] Weight at baseline and at age 20 yr also not associated with increased mortality

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Giovannucci et al. (2007) Health Professionals Follow-up Study USA 1986–2002 Updated follow-up from Giovannucci et al. (1997)	47 750 Incidence	Prostate	BMI < 21 21–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30 [P_{trend}]	3544 total	 1.00 1.21 1.36 1.24 1.24 1.13 (0.91–1.41) [0.84]	Age, time period, BMI at age 21 yr, height, pack-years of smoking, physical activity, family history of prostate cancer, diabetes, race, energy intake, intake of processed meat, fish, α-linolenic acid, tomato sauce, vitamin E supplements	[CI provided only for the last BMI category] No association was observed with BMI for low-grade or high-grade prostate cancer (based on Gleason score)
		Prostate, advanced TNM: T3b or T4 or N1 or M1	BMI < 21 ≥ 30 [P_{trend}]	523 total	 1.00 1.34 (0.79–2.26) [≤ 0.05]		
	47 750 Mortality	Prostate	BMI 21–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30	323 total	 1.00 1.44 1.30 1.43 1.80 (1.10–2.93)		
Littman et al. (2007) Vitamins and Lifestyle (VITAL) cohort USA 2000–2004	34 754 Incidence	Prostate	BMI at baseline < 25 25–29.9 ≥ 30 [P_{trend}]	 218 435 155	 1.0 1.1 (0.97–1.4) 0.87 (0.71–1.1) [0.13]	Age, family history of prostate cancer, race, baseline BMI, recent PSA screening	BMI at ages 18 yr, 30 yr, and 45 yr also not associated with increased risk
		Prostate, non-aggressive Gleason score < 7	BMI at baseline < 25 25–29.9 ≥ 30 [P_{trend}]	 129 222 73	 1.0 0.99 (0.79–1.2) 0.69 (0.52–0.93) [0.01]		BMI at ages 18 yr, 30 yr, and 45 yr also not associated with increased risk
		Prostate, aggressive Gleason score 7–10	BMI at baseline < 25 25–29.9 ≥ 30 [P_{trend}]	 85 209 179	 1.0 1.4 (1.1–1.8) 1.1 (0.83–1.6) [0.69]		BMI at ages 18 yr, 30 yr, and 45 yr also not associated with increased risk

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Littman et al. (2007) (cont.)	34 754 Incidence	Prostate	Weight (lb) at age 18 yr			Age, family history of prostate cancer, race, baseline BMI, recent PSA screening	For non-aggressive prostate cancer, weight at age 18 yr and 30 yr was not associated with an increased risk
			< 139	166	1.0		
			139–154	203	1.2 (0.96–1.5)		
			155–170	198	1.1 (0.93–1.4)		
			≥ 171	231	1.2 (1.0–1.5)		
			[P_{trend}]		[0.08]		
			Weight (lb) at age 30 yr				
			< 154	174	1.0		
			154–169	192	1.2 (0.95–1.4)		
			170–184	188	1.1 (0.93–1.4)		
			≥ 185	241	1.3 (1.0–1.6)		
			[P_{trend}]		[0.03]		
			Weight (lb) at age 45 yr				
			< 165	194	1.0		
			165–179	182	1.0 (0.82–1.2)		
			180–199	224	1.1 (0.91–1.3)		
			≥ 200	200	1.1 (0.87–1.3)		
			[P_{trend}]		[0.46]		
			Weight (lb) at baseline				
			< 173	211	1.0		
			174–189	181	1.0 (0.83–1.2)		
			190–214	233	0.99 (0.82–1.2)		
			≥ 215	192	0.92 (0.75–1.1)		
			[P_{trend}]		[0.35]		
		Prostate, non-aggressive Gleason score < 7	Weight (lb) at baseline				Weight gain of ≥ 30 lb since age 18 yr associated with 33% lower risk of incidence
			< 173	130	1.00		
			174–189	90	0.82 (0.62–1.1)		
			190–214	116	0.81 (0.63–1.1)		
			≥ 215	92	0.71 (0.54–0.93)		
			[P_{trend}]		[0.02]		
		Prostate, aggressive Gleason score 7–10	Weight (lb) at age 18 yr			Age, family history of prostate cancer, race, baseline BMI, recent PSA screening	
			< 139	71	1.00		
			139–154	94	1.3 (0.92–1.7)		
			155–170	89	1.2 (0.86–1.6)		
			≥ 171	117	1.4 (1.0–1.9)		
			[P_{trend}]		[0.04]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Littman et al. (2007) (cont.)	34 754 Incidence		Weight (lb) at age 30 yr				
			< 154	72	1.0		
			154–169	84	1.2 (0.90–1.7)		
			170–184	93	1.4 (0.99–1.9)		
			≥ 185	119	1.5 (1.1–2.0)		
			[P_{trend}]		[0.01]		
			Weight (lb) at age 45 yr				
			< 165	72	1.0		
			165–179	86	1.3 (0.93–1.8)		
			180–199	111	1.5 (1.1–2.0)		
			≥ 200	102	1.4 (1.1–2.0)		
			[P_{trend}]		[0.032]		
			Weight (lb) at baseline				Weight gain since age 18 yr not associated with risk of incidence
			< 173	78	1.0		
			174–189	87	1.3 (0.96–1.8)		
			190–214	115	1.3 (0.97–1.7)		
			≥ 215	98	1.3 (0.93–1.7)		
			[P_{trend}]		[0.23]		
Máchová et al. (2007) National Cancer Registry Nested case–control study in the population of the Šumperk District Czech Republic 1987–2002	17 334 Incidence	Prostate ICD-10: C61	BMI	338 total		Age, smoking, hypertension, height	
			18.5–24.9		1.00		
			25–29.9		1.05 (0.72–1.39)		
			≥ 30		0.97 (0.66–1.41)		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Rodriguez et al. (2007) Cancer Prevention Study II (CPS II) Nutrition Cohort USA 1992–2003	69 991 Incidence	Prostate	BMI			Age, race, education level, family history of prostate cancer, energy intake, smoking status, PSA testing, diabetes, physical activity; Weight change also adjusted for BMI in 1982 and height	When stratifying by subtype, weight change also not associated with increased risk for any subtype
			< 25	1935	1.00		
			25–27.4	1742	1.02 (0.96–1.09)		
			27.5–29.9	920	0.98 (0.90–1.06)		
			30–34.9	556	0.94 (0.85–1.04)		
			≥ 35	99	0.91 (0.75–1.12)		
			[P_{trend}]		[0.14]		
			Weight change (lb), 1982–1992				
			≥ 21 loss	113	0.84 (0.69–1.02)		
			11–20 loss	349	0.84 (0.75–0.95)		
			6–19 loss	541	0.98 (0.89–1.08)		
			5 loss to 5 gain	2450	1.00		
			6–10 gain	751	0.98 (0.90–1.06)		
			11–20 gain	687	0.97 (0.89–1.05)		
			≥ 21 gain	322	0.89 (0.79–1.00)		
		Prostate, non-metastatic, low-grade TNM: T1–3, N0, M0 Gleason score ≤ 8	BMI				
			< 25	1544	1.00		
			25–27.4	1409	1.03 (0.96–1.10)		
			27.5–29.9	700	0.92 (0.84–1.01)		
			30–34.9	412	0.86 (0.77–0.97)		
			≥ 35	73	0.84 (0.66–1.06)		
			[P_{trend}]		[0.002]		
		Prostate, non-metastatic high-grade TNM: T1–3, N0, M0 Gleason score > 8	BMI				
			< 25	239	1.00		
			25–27.4	180	0.87 (0.72–1.06)		
			27.5–29.9	140	1.23 (1.00–1.53)		
			≥ 30	103	1.22 (0.96–1.55)		
			[P_{trend}]		[0.03]		
	69 991 Incidence or mortality	Prostate, metastatic or fatal TNM: T4, Nx, Mx or Tx, N1–2, Mx or Tx, Nx, M1	BMI				
			< 25	92	1.00		
			25–27.4	104	1.41 (1.06–1.87)		
			27.5–29.9	46	1.14 (0.79–1.63)		
			≥ 30	46	1.54 (1.06–2.23)		
			[P_{trend}]		[0.05]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wright et al. (2007) NIH-AARP cohort USA 1995–2000	172 961 Incidence	Prostate ICD-9: 185 ICD-10: C61	BMI			Age, race, smoking status, education level, diabetes, family history of prostate cancer For BMI at age 18 yr, also BMI at baseline, height	
			< 25	3076	1.00		
			25–29.9	5054	1.00 (0.95–1.04)		
			30–34.9	1532	0.97 (0.91–1.03)		
			35–39.9	269	0.84 (0.74–0.95)		
			≥ 40	55	0.65 (0.50–0.85)		
			[P_{trend}]		[0.0008]		
			BMI at age 18 yr				
			< 18.5	723	0.95 (0.87–1.04)		
			18.5–20.9	1787	1.00		
			21–22.9	1510	1.01 (0.95–1.09)		
			23–24.9	775	0.90 (0.83–0.98)		
			≥ 25	641	0.93 (0.84–1.02)		
			[P_{trend}]		[0.17]		
			Weight (kg) at age 18 yr, quintiles			Age, race, smoking status, education level, diabetes, family history of prostate cancer, BMI, height	
			< 58.6	1004	1.0		
			58.7–64.5	1338	1.01 (0.93–1.10)		
			64.6–69.9	1043	0.99 (0.91–1.09)		
			70–76.7	1138	0.99 (0.91–1.09)		
			> 76.7	1071	0.92 (0.84–1.02)		
			[P_{trend}]		[0.08]		
			Weight (kg) at baseline, quintiles				Weight at baseline also not associated with increased risk for localized and with metastatic prostate cancer subtypes
			< 74.5	1126	1.0		
			74.6–81.3	1224	1.02 (0.93–1.11)		
			81.4–87.2	1204	1.01 (0.92–1.10)		
			87.3–97.2	1157	1.00 (0.91–1.09)		
			> 97.2	1014	0.91 (0.82–1.00)		
			[P_{trend}]		[0.99]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wright et al. (2007) (cont.)	172 961 Incidence		Weight change (kg), age 18 yr to baseline				Weight change also not associated with increased risk for localized and for extraprostatic prostate cancer subtypes
			< −4	161	1.00 (0.83–1.19)		
			−4 to 3.9	430	1.0		
			4–9.9	936	1.04 (0.93–1.17)		
			10–19.9	1896	1.12 (1.00–1.24)		
			20–29.9	1425	1.12 (1.00–1.26)		
			30–39.9	469	0.99 (0.87–1.14)		
			≥ 40	277	1.03 (0.88–1.20)		
			[P_{trend}]		[0.81]		
		Prostate, localized TNM: T1a to T2b, N0, M0	BMI			Age, race, smoking status, education level, diabetes, family history of prostate cancer For BMI at age 18 yr, also BMI at baseline, height	
			< 25	2652	1.00		
			25–29.9	4328	0.99 (0.94–1.04)		
			30–34.9	1277	0.94 (0.88–1.01)		
			35–39.9	236	0.86 (0.75–0.98)		
			≥ 40	48	0.67 (0.50–0.89)		
			[P_{trend}]		[0.0006]		
			BMI at age 18 yr				
			< 18.5	633	0.95 (0.86–1.04)		
			18.5–20.9	1570	1.0		
			21–22.9	1317	1.01 (0.94–1.09)		
			23–24.9	653	0.87 (0.80–0.96)		
			≥ 25	535	0.89 (0.80–0.99)		
			[P_{trend}]		[0.04]		
			Weight (kg) at age 18 yr, quintiles			Age, race, smoking status, education level, diabetes, family history of prostate cancer, BMI, height	
			< 58.6	881	0.95 (0.86–1.04)		
			58.7–64.5	1185	1.00		
			64.6–69.9	903	1.01 (0.94–1.09)		
			70–76.7	988	0.87 (0.80–0.96)		
			> 76.7	891	0.89 (0.80–0.99)		
			[P_{trend}]		[0.04]		
		Prostate, extraprostatic TNM: T3 or T4, N1, or M1	BMI			Age, race, smoking status, education level, diabetes, family history of prostate cancer For BMI at age 18 yr, also BMI, height	
			< 25	424	1.0		
			25–29.9	726	1.03 (0.91–1.16)		
			30–34.9	255	1.14 (0.97–1.33)		
			≥ 35	40	0.68 (0.49–0.94)		
			[P_{trend}]		[0.64]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wright et al. (2007) (cont.)	172 961 Incidence		BMI at age 18 yr				
			< 18.5	90	0.98 (0.77–1.26)		
			18.5–20.9	217	1.00		
			21–22.9	193	1.04 (0.86–1.27)		
			23–24.9	122	1.11 (0.88–1.39)		
			≥ 25	106	1.15 (0.90–1.47)		
			[P_{trend}]		[0.18]		
			Weight (kg) at age 18 yr, quintiles			Age, race, smoking status, education level, diabetes, family history of prostate cancer, BMI, height	
			< 58.6	123	1.0		
			58.7–64.5	153	0.95 (0.74–1.20)		
			64.6–69.9	140	1.08 (0.84–1.38)		
			70–76.7	150	1.03 (0.80–1.33)		
			> 76.7	180	1.18 (0.91–1.54)		
			[P_{trend}]		[0.13]		
Wright et al. (2007) NIH-AARP cohort USA 1995–2000	Mortality	Prostate ICD-9: 185 ICD-10: C61	BMI			Age, race, smoking status, education level, diabetes, family history of prostate cancer For BMI at age 18 yr, also BMI at baseline, height	Weight at baseline also associated with increased risk Weight (kg) at age 18 yr also not associated with increased mortality
			< 25	44	1.0		
			25–29.9	87	1.25 (0.87–1.80)		
			30–34.9	31	1.46 (0.92–2.33)		
			≥ 35	11	2.12 (1.08–4.15)		
			[P_{trend}]		[0.02]		
			BMI at age 18 yr				
			< 18.5	13	1.67 (0.82–3.42)		
			18.5–20.9	18	1.0		
			21–22.9	25	1.65 (0.90–3.02)		
			23–24.9	16	1.71 (0.86–3.39)		
			≥ 25	11	1.35 (0.62–2.95)		
			[P_{trend}]		[0.73]		
			Weight change (kg), age 18 yr to baseline			Age, race, smoking status, education level, diabetes, family history of prostate cancer, BMI, height	
			< –4	3	1.18 (0.29–4.74)		
			–4 to 3.9	6	1.0		
			4–9.9	12	1.06 (0.40–2.83)		
			10–19.9	23	1.17 (0.47–2.92)		
			20–29.9	24	1.74 (0.69–4.40)		
			30–39.9	10	2.05 (0.72–5.90)		
			40	8	2.98 (0.99–9.04)		
			[P_{trend}]		[0.009]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Jee et al. (2008) National Health Insurance Corporation (NHIC) medical evaluation Republic of Korea 1992–2006	770 556 Incidence	Prostate	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 265 896 747 638 23	 0.67 (0.56–0.80) 0.87 (0.77–0.98) 1.00 0.95 (0.83–1.08) 1.39 (0.90–2.17) [< 0.0001]	Age, smoking	
Pischon et al. (2008) EPIC cohort 8 European countries, 1992–2000 (8.5 yr follow-up on average)	129 502 Incidence	Prostate ICD-10: C61	BMI, quintiles < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] per 5 kg/m^2	2446 total	 1.00 1.06 (0.93–1.20) 1.08 (0.95–1.23) 0.95 (0.83–1.09) 0.99 (0.86–1.13) [0.37] 0.96 (0.90–1.02)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	Also examined hip circumference and waist-to-hip ratio WC also not associated with increased risk
		Prostate, localized TNM: T0–T2 and N0/Nx, M0	BMI, quintiles < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] continuous	991 total	 1.00 1.09 (0.89–1.34) 1.02 (0.83–1.25) 0.88 (0.71–1.10) 0.95 (0.77–1.18) [0.22] 0.92 (0.84–1.01)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	WC also not associated with increased risk
		Prostate, advanced TNM: T3–T4 and/or N1–N3 and/or M1	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] continuous	499 total	 1.00 1.05 (0.78–1.40) 1.25 (0.94–1.66) 1.08 (0.81–1.46) 1.17 (0.86–1.58) [0.34] 1.09 (0.96–1.24)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	WC also not associated with increased risk

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pischon et al. (2008) (cont.)	129 502 Incidence	Prostate, low-grade Gleason score < 7	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] continuous	841 total	 1.00 0.97 (0.78–1.21) 0.95 (0.77–1.19) 0.83 (0.66–1.04) 0.84 (0.66–1.06) [0.06] 0.88 (0.79–0.98)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	WC also not associated with increased risk
		Prostate, high-grade Gleason score ≥ 7	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] continuous	580 total	 1.00 1.26 (0.96–1.65) 1.34 (1.02–1.76) 1.16 (0.87–1.54) 1.23 (0.92–1.65) [0.37] 1.04 (0.92–1.18)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	WC also not associated with increased risk
Rapp et al. (2008) VHM&PP Austria 1985–2002	28 711 Incidence	Prostate ICD-10: C61	BMI change, annual < −0.1 −0.1– < 0.1 0.1– < 0.3 0.3– < 0.5 ≥ 0.5 [P_{trend}]	 164 317 231 72 12	 0.96 (0.79–1.16) 1.00 1.00 (0.85–1.19) 1.01 (0.78–1.31) 0.43 (0.24–0.76) [0.06]	Age, smoking status, blood glucose, occupational group, BMI at baseline	
Hernandez et al. (2009) Multiethnic Cohort USA 1993/1996–2002/2005	83 879 Incidence	Prostate, advanced	BMI at age 21 yr < 18.5 18.5–24.9 ≥ 25.0 [P_{trend}]	 41 475 86	 0.96 (0.69–1.35) 1.00 1.09 (0.85–1.40) [0.46]		No associations were observed with high grade either Inverse associations were observed with localized and with low-grade subtypes

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wallström et al. (2009) Malmö Diet and Cancer Study Sweden 1991–2005	11 063 Incidence	Prostate ICD-9: 185	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 8 287 417 105	 2.29 (1.13–4.63) 1.00 1.02 (0.88–1.19) 1.06 (0.84–1.33) [0.15]	Age, height, cohabitation status, SES, alcohol consumption, smoking, prevalent diabetes, physical activity, country of birth, total intake of eicosapentaenoic acid, docosahexaenoic acid, red meat, calcium	WC also not associated with increased risk
		Prostate, aggressive TNM: T3–T4, or N1 or M1, or Gleason score ≥ 8, or PSA > 50 ng/mL	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 102 140 35	 3.15 (1.15–8.62) 1.00 0.99 (0.76–1.29) 1.02 (0.69–1.52) [0.16]		WC also not associated with increased risk
		Prostate, non-aggressive Not stage T3–T4, or N1 or M1, or Gleason score ≥ 8, or PSA > 50 ng/mL	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 183 274 69	 0.84 (0.63–1.11) 1.00 1.16 (0.89–1.50) 1.11 (0.85–1.44) [0.65]		WC also not associated with increased risk
Whitlock et al. (2009) Prospective Studies Collaboration (pooled analysis of 57 cohorts from Europe, Japan, and the USA) Follow-up varied by cohort	894 576 Mortality	Prostate ICD-9: 185	BMI, per 5 kg/m^2 For BMI 15–25 For BMI 25–50 For BMI 15–50	 578 665	 1.00 (0.75–1.32) 1.09 (0.91–1.31) 1.13 (1.02–1.24)	Study, sex, age, smoking	

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Andreotti et al. (2010) Agricultural Health Study USA 1993–2005	39 628 Incidence	Prostate	BMI			Race, smoking status, exercise, family history of prostate cancer	
			< 18.5	0	–		
			18.5–24.9	308	1.00		
			25–29.9	696	1.06 (0.89–1.27)		
			30–34.9	226	0.89 (0.71–1.13)		
			≥ 35	44	0.94 (0.61–1.44)		
			[P_{trend}]		[0.56]		
Burton et al. (2010) Glasgow Alumni Cohort United Kingdom 1948–1968 to 2009	9549 Incidence	Prostate ICD-9: 185 ICD-10: C61	BMI, young adult (age < 30 yr)			Smoking, SES, height	
			< 19	25	1.30 (0.84–1.99)		
			19–22.9	125	1.00		
			23–24.9	33	1.14 (0.78–1.68)		
			≥ 25	14	1.18 (0.68–2.06)		
			per 1 kg/m^2		1.00 (0.93–1.06)		
			[P_{trend}]		[0.89]		
	9549 Mortality	Prostate ICD-9: 185 ICD-10: C61	BMI, young adult (age < 30 yr)				
			< 19	14	1.58 (0.88–2.83)		
			19–22.9	59	1.00		
			23–24.9	21	1.52 (0.92–2.50)		
			≥ 25	8	1.43 (0.68–3.00)		
			per 1 kg/m^2		1.02 (0.93–1.11)		
			[P_{trend}]		[0.74]		
Stocks et al. (2010) Swedish Construction Worker Cohort Sweden 1971–2004	336 159 Mortality	Prostate ICD-7: 177	BMI			Birth cohort, smoking	No association of BMI with incidence of prostate (total), or aggressive prostate cancer subtypes. Significant negative association observed between BMI and incidence for non-aggressive prostate cancer subtype
			< 21.9	230	1.00		
			21.9– < 23.5	383	1.17 (1.00–1.39)		
			23.5– < 25	476	1.09 (0.93–1.27)		
			25– < 27	702	1.26 (1.08–1.46)		
			≥ 27	810	1.28 (1.11–1.49)		
			[P_{trend}]		[0.0004]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Discacciati et al. (2011) Sweden 1998–2008	36 959 Incidence	Prostate, localized TNM: T1–2 and NX–0 and MX–0 or PSA < 20 ng/mL or Gleason score < 7	BMI at baseline			BMI at age 30 yr, age, energy intake, physical activity, education level, smoking, family history of prostate cancer, diabetes	
			< 21	62	0.78 (0.54–1.13)		
			21–22.9	245	1.00		
			23–24.9	401	1.00 (0.94–1.06)		
			25–27.4	467	0.95 (0.86–1.05)		
			27.5–29.9	204	0.88 (0.76–1.02)		
			≥ 30	124	0.71 (0.53–0.94)		
			BMI at age 30 yr				
			< 21	287	1.01 (0.91–1.12)		
			21–22.9	539	1.00		
			23–24.9	467	0.99 (0.94–1.05)		
			25–27.4	154	0.99 (0.89–1.10)		
			27.5–29.9	41	0.98 (0.82–1.16)		
			≥ 30	15	0.96 (0.69–1.34)		
			per 5 kg/m^2		0.98 (0.87–1.12)		
		Prostate, advanced TNM: T3–4 and NX–1 and MX–1 or PSA > 100 ng/mL or Gleason score > 7	BMI at baseline			BMI at age 30 yr, age, energy intake, physical activity, education level, smoking, family history of prostate cancer, diabetes	
			< 21	27	0.97 (0.85–1.10)		
			21–22.9	72	1.00		
			23–24.9	163	1.02 (0.95–1.08)		
			25–27.4	150	1.03 (0.90–1.18)		
			27.5–29.9	79	1.05 (0.85–1.31)		
			≥ 30	47	1.11 (0.73–1.68)		
			per 5 kg/m^2		1.04 (0.88–1.22)		
			BMI at age 30 yr				
			< 21	108	1.09 (0.92–1.29)		
			21–22.9	185	1.00		
			23–24.9	164	0.96 (0.88–1.04)		
			25–27.4	69	0.91 (0.77–1.09)		
			27.5–29.9	8	0.87 (0.65–1.15)		
			≥ 30	4	0.76 (0.44–1.30)		
			per 5 kg/m^2		0.90 (0.73–1.11)		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Discacciati et al. (2011) (cont.)	36 959 Mortality	Prostate	BMI at baseline < 21 21–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30 per 5 kg/m²	 11 35 62 59 29 23	 0.91 (0.75–1.11) 1.00 1.05 (0.95–1.16) 1.11 (0.89–1.36) 1.16 (0.83–1.63) 1.34 (0.70–2.55) 1.12 (0.87–1.43)	BMI at age 30 yr, age, energy intake, physical activity, education level, smoking, family history of prostate cancer, diabetes	BMI at age 30 yr also not associated with increased risk
Bassett et al. (2012) Melbourne Collaborative Cohort Study (MCCS) Australia 1990–2004 Same cohort as MacInnis et al. (2003)	16 525 Incidence	Prostate ICD-9: 185 ICD-10: C61	BMI at baseline < 18.5 18.5–22.9 23–24.9 ≥ 25 per 5 kg/m² [P_{trend}]	 111 259 757 247	 0.73 (0.59–0.91) 1.00 0.98 (0.85–1.12) 0.96 (0.80–1.15) 1.06 (0.97–1.17) [0.19]	Country of birth, education level	No associations were observed between weight at baseline, BMI or weight (kg) at age 18 yr, or WC, and prostate cancer risk (incidence)
		Prostate, non-aggressive Not Gleason score > 7, stage 4, or death from prostate cancer	BMI at baseline < 18.5 18.5–22.9 23–24.9 ≥ 25 per 5 kg/m² [P_{trend}]	 83 194 527 160	 0.73 (0.56–0.94) 1.00 0.91 (0.77–1.08) 0.83 (0.67–1.03) 0.99 (0.89–1.10) [0.83]	Country of birth, education level	No associations were observed between weight at baseline, BMI or weight (kg) at age 18 yr, or WC, and non-aggressive prostate cancer risk (incidence)
		Prostate, aggressive Gleason score > 7, stage 4, or death from prostate cancer	BMI at baseline < 18.5 18.5–22.9 23–24.9 ≥ 25 per 5 kg/m² [P_{trend}]	 28 65 230 87	 0.74 (0.47–1.15) 1.00 1.17 (0.89–1.54) 1.33 (0.96–1.84) 1.27 (1.08–1.49) [0.004]	Country of birth, education level	No associations were observed between weight at baseline, BMI or weight (kg) at age 18 yr, or WC, and aggressive prostate cancer risk (incidence)
	16 525 Mortality	Prostate ICD-9: 185 ICD-10: C61	BMI at baseline < 18.5 18.5–22.9 23–24.9 ≥ 25 per 5 kg/m² [P_{trend}]	 7 23 71 38	 0.53 (0.23–1.24) 1.00 0.95 (0.59–1.53) 1.52 (0.89–2.58) 1.49 (1.11–2.00) [0.01]	Country of birth, education level	Weight at baseline also associated with increased mortality No association was observed with BMI or weight at age 18 yr and mortality

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	2 379 320 Incidence	Prostate ICD-10: C61	BMI per 5 kg/m^2 [P_{trend}]	24 901 total	0.98 (0.95–1.00) [0.0042]	Age, diabetes, smoking, alcohol consumption, SES, calendar year, sex	No differences were found in non-smokers only
Barrington et al. (2015) Participants in the Selenium and Vitamin E cancer Prevention Trial (SELECT) USA 2001–2008	26 035 Incidence	Prostate	BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}] BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}]	Non-Hispanic White: 289 438 333 299 94 African American: 39 63 57 74 37 	 1.00 1.12 (0.97–1.30) 1.04 (0.89–1.22) 0.96 (0.82–1.13) 0.94 (0.74–1.19) [0.63] 1.28 (0.91–1.80) 1.67 (1.27–2.21) 1.64 (1.23–2.19) 1.68 (1.29–2.18) 1.90 (1.34–2.70) [0.03]	Age, education level, diabetes, smoking, family history of prostate cancer, study arm	For African Americans, BMI < 25.0 in Non-Hispanic Whites was taken as reference
	26 035 Incidence	Prostate, low-grade Gleason score 2–6	BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}] BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}]	Non-Hispanic White: 182 293 202 170 51 African American: 16 37 35 37 23 	 1.00 1.18 (0.98–1.42) 1.00 (0.82–1.22) 0.86 (0.70–1.06) 0.80 (0.58–1.09) [0.02] 0.80 (0.48–1.43) 1.47 (1.03–2.10) 1.52 (1.05–2.20) 1.27 (0.83–1.82) 1.77 (1.14–2.76) [0.05]	Age, education level, diabetes, smoking, family history of prostate cancer, study arm	

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Barrington et al. (2015) (cont.)	26 035 Incidence	Prostate, high-grade Gleason score 7–10	BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}] BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}]	Non-Hispanic White: 84 115 101 104 37 African American: 11 19 17 29 12	 1.00 1.03 (0.78–1.37) 1.11 (0.83–1.49) 1.18 (0.88–1.58) 1.33 (0.90–1.97) [0.01] 1.32 (0.70–2.51) 1.94 (1.17–3.22) 1.87 (1.10–3.16) 2.53 (1.64–3.90) 2.39 (1.29–4.43) [0.02]	Age, education level, diabetes, smoking, family history of prostate cancer, study arm	
Fowke et al. (2015) Pooled analysis in Asia Cohort Consortium (ACC) Different Asian countries (1963–2001) to 2006	522 736 Mortality	Prostate	BMI 12–19.9 20–22.4 22.5–24.9 25–50 [P_{trend}]	 142 188 184 120	 0.98 (0.78–1.23) 0.92 (0.75–1.13) 1.00 1.08 (0.85–1.36) [0.58]	Age, education level, population density, marital status, history of severe cancer, heart disease, or stroke at baseline	Similar results were observed in stratified analyses by region
Meyer et al. (2015) Population-based Swiss cohort study Switzerland 1977–2008	35 703 in cohort, number of men NR Mortality	Prostate ICD-8: 185 ICD-10: C61	BMI < 25 25–29.9 ≥ 30	170 total	 1.00 1.45 (1.03–2.04) 1.54 (0.93–2.55)	Age, survey, alcohol consumption, physical activity, civil status, years of education, nationality, diet	Those who were overweight and who also smoked (ever smoking) had a higher risk

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Møller et al. (2015) Diet, Cancer and Health Study Denmark 1993–2011	26 044 Incidence	Prostate	BMI 15.4–24.9 25–29.9 30–52.7 [P_{trend}]	 649 920 244	 1.00 0.94 (0.85–1.04) 0.86 (0.74–0.99) [0.03]	NR	WC showed no association with total prostate cancer incidence Inverse associations were observed with the upper quartile of body fat percentage (15% decreased risk)
		Prostate Stage 3–4	BMI 15.4–24.9 25–29.9 30–52.7 [P_{trend}]	 208 314 104	 1.00 1.00 (0.84–1.19) 1.14 (0.90–1.44) [0.37]	NR	WC also no associated with advanced prostate cancer incidence Positive associations were observed with the upper quartile of body fat percentage (31% increased risk)
	26 044 Mortality	Prostate	BMI 15.4–24.9 25–29.9 30–52.7 [P_{trend}]	 92 147 51	 1.00 1.10 (0.85–1.43) 1.27 (0.90–1.80) [0.19]	Stage at diagnosis	WC also not associated with increased mortality A positive association was observed with increasing body fat percentage
Møller et al. (2016) Health Professionals Follow-up Study USA 1986–2010	47 491 Incidence and mortality	Prostate	BMI at age 21 yr < 20 20–21.9 22–23.9 24–25.9 ≥ 26 [P_{trend}] per 5 kg/m^2	 825 1546 1852 1132 588	 0.99 (0.90–1.08) 1.00 0.98 (0.91–1.05) 0.92 (0.85–1.00) 0.89 (0.80–0.98) [0.01] 0.94 (0.89–0.98)	Age, calendar time, ethnicity, physical activity, energy intake, smoking, diabetes, family history of prostate cancer, PSA testing	When analysing cumulative BMI average, the significant decrease in risk persisted only in those younger than 65 yr

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Møller et al. (2016) (cont.)	47 491 Incidence and mortality	Prostate, fatal	BMI at age 21 yr				BMI at age 21 yr also not associated with lethal subtypes (incident cases and deaths due to prostate cancer or distant metastases at diagnosis or during follow-up)
			< 20	94	0.83 (0.64–1.07)		
			20–21.9	181	1.00		
			22–23.9	177	0.92 (0.74–1.14)		
			24–25.9	88	0.74 (0.57–0.97)		
			≥ 26	51	0.77 (0.56–1.07)		
			[P_{trend}]		[0.20]		
			per 5 kg/m²		0.88 (0.75–1.02)		
		Prostate, high-grade Gleason score 8–10	BMI at age 21 yr				
			< 20	85	0.82 (0.63–1.07)		
			20–21.9	181	1.00		
			22–23.9	204	0.93 (0.75–1.15)		
			24–25.9	130	0.91 (0.72–1.16)		
			≥ 26	79	1.10 (0.83–1.45)		
			[P_{trend}]		[0.27]		
			per 5 kg/m²		1.03 (0.90–1.19)		
		Prostate, moderate-grade Gleason score 7	BMI at age 21 yr			Age, calendar time, ethnicity, physical activity, energy intake, smoking, diabetes, family history of prostate cancer, PSA testing	
			< 20	233	0.98 (0.83–1.15)		
			20–21.9	446	1.00		
			22–23.9	548	0.98 (0.86–1.11)		
			24–25.9	333	0.90 (0.78–1.04)		
			≥ 26	159	0.77 (0.64–0.93)		
			[P_{trend}]		[0.01]		
			per 5 kg/m²		0.87 (0.80–0.95)		
		Prostate, low-grade Gleason score 2–6	BMI at age 21 yr				
			< 20	333	1.01 (0.88–1.16)		
			20–21.9	620	1.00		
			22–23.9	735	0.94 (0.84–1.05)		
			24–25.9	465	0.90 (0.79–1.02)		
			≥ 26	236	0.88 (0.75–1.03)		
			[P_{trend}]		[0.03]		
			per 5 kg/m²		0.93 (0.87–1.01)		

BMI, body mass index (in kg/m²); BP, blood pressure; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; N/A, not applicable; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; PSA, prostate-specific antigen; SD, standard deviation; SES, socioeconomic status; TNM, tumour–node–metastasis; VHM&PP, Vorarlberg Health Monitoring and Prevention Program; WC, waist circumference; yr, year or years

Table 2.2.14b Case–control studies of measures of body fatness and cancer of the prostate

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Putnam et al. (2000) USA 1986–1989	101 Population	BMI < 24.1 24.1–26.6 > 26.6 BMI change (%) from age 20 yr > 5% loss 5% loss to 5% gain 5.1–10.0% gain 10.1–15.0% gain > 15.0% gain Weight (kg) < 74.8 74.8–83.9 > 83.9	 27 31 38 1 12 15 14 51 22 41 33	 1.0 1.0 (0.6–1.7) 1.3 (0.8- 2.2) 0.2 (0.02–1.5) 1.0 1.3 (0.6–2.7) 1.0 (0.5–1.9) 1.3 (0.8–2.2) 1.0 1.4 (0.8–2.3) 1.2 (0.7–2.1)	Age	
Sharpe & Siemiatycki (2001) Canada 1979–1985	399 Population	BMI < 24.05 24.05–26.66 > 26.66	 127 128 141	 0.87 (0.6–1.22) 1.00 1.14 (0.81–1.61)	Age, ethnicity, respondent status, family income, alcohol consumption	
Giles et al. (2003) Australia 1994–1998	1476 Population	BMI at age 21 yr < 20.5 20.5–22.1 22.2–23.9 > 23.9	 353 372 337 332	 1.00 0.99 (0.79–1.23) 0.96 (0.76–1.20) 1.10 (0.88–1.39)	Age, country of birth, family history of prostate cancer, study centre, calendar year	No associations were observed for weight or WC at age 21 yr
Irani et al. (2003) France 1993–1999	194 Hospital	BMI < 29 > 29	NR	 1.00 2.47 (1.41–4.34)	Age	

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Dal Maso et al. (2004) Italy 1991–2002	1294 Hospital	BMI at baseline			Age, study centre, education level, physical activity, family history of prostate cancer	No associations were observed between weight (kg), waist-to-hip ratio, or lean body mass and prostate cancer. When stratified by grade, associations of BMI at diagnosis were only significant with prostate cancer of Gleason score 7–10 (384 cases, $P_{trend} < 0.01$)
		< 24.22	301	1.00		
		24.22–26.18	346	1.18 (0.95–1.47)		
		26.18–28.41	324	1.12 (0.89–1.40)		
		≥ 28.41	319	1.18 (0.94–1.47)		
		[P_{trend}]		[0.23]		
		BMI at age 30 yr				
		< 22.65	406	1.00		
		22.65–24.69	437	1.33 (1.09–1.62)		
		≥ 24.69	414	1.22 (1.01–1.48)		
		[P_{trend}]		[0.004]		
Friedenreich et al. (2004) Canada 1997–2000	988 Population	BMI, quartiles			Age, region, education level, average lifetime total alcohol intake, first-degree family history of prostate cancer, number of times had PSA test done, number of digital rectal exams, total lifetime physical activity	
		Q1	252	1.00		
		Q2	236	0.95 (0.74–1.23)		
		Q3	245	0.98 (0.76–1.26)		
		Q4	254	1.07 (0.83–1.38)		
		[P_{trend}]		[0.57]		
		Weight, quartiles				
		Q1	268	1.00		
		Q2	233	0.93 (0.72–1.21)		
		Q3	262	1.00 (0.78–1.28)		
		Q4	224	0.91 (0.70–1.18)		
		[P_{trend}]		[0.18]		
		Weight gain (kg) since age 20 yr				
		< 4.54	241	1.00		
		4.54–13.6	286	1.14 (0.89–1.47)		
		13.6–20.4	238	1.05 (0.82–1.36)		
		≥ 20.4	215	0.91 (0.70–1.19)		
		[P_{trend}]		[0.26]		

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Pan et al. (2004) Canada 1994–1997	1801 Population	BMI < 25 25–30 ≥ 30 [P_{trend}]		 1.00 1.16 (0.94–1.43) 1.27 (1.09–1.47) [0.026]	Age group, province of residence, education level, pack-years of smoking, alcohol consumption, total energy intake, vegetable intake, dietary fibre intake, recreational physical activity	
Liu et al. (2005) USA NR	439 Population (sibling-based)	BMI, quartiles Q1 Q2 Q3 Q4 [P_{trend}] LBM, quartiles Q1 Q2 Q3 Q4 [P_{trend}]	 106 112 110 106 LBM > 66.3: 113 104 114 103	 1.00 1.57 (0.85–2.89) 1.43 (0.78–2.61) 0.91 (0.49–1.70) [0.73] 1.00 0.58 (0.31–1.08) 0.43 (0.22–0.81) 0.41 (0.20–0.84) [0.02]	Age, education, calorie intake	Results are presented for high-aggressiveness prostate cancer (Gleason score ≥ 7, or tumour stage T2C or greater)
Porter & Stanford (2005) USA 1993–1996	753 Population	BMI 18–24.4 24.4–26.5 26.5–29.1 29.1–55 [P_{trend}] Weight (kg) < 77.2 77.2–85.8 85.9–95.3 > 95.3 [P_{trend}]	 195 202 178 178 175 222 193 163	 1.00 1.04 (0.78–1.39) 0.85 (0.64–1.14) 0.91 (0.66–1.21) [0.04] 1.00 0.96 (0.70–1.30) 0.77 (0.56–1.06) 0.74 (0.53–1.03) [0.03]	Age, race, education level, smoking, family history of prostate cancer, prostate cancer screening, dietary fat, energy intake	
Robinson et al. (2005) USA 1997–2000	568 Population	BMI at age 20–29 yr < 25.0 25.0–29.9 ≥ 30.0	 361 191 12	 1.00 1.13 (0.87–1.47) 0.40 (0.20–0.81)	Age, race, family history of prostate cancer, saturated fat intake	This study evaluated the association with advanced prostate cancer

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Wuermli et al. (2005) Switzerland 1997–2002	504 Hospital	BMI < 30 > 30	NR	 1.00 0.97 (0.93–1.01)	Age, BMI, diabetes, lipid-lowering drugs	
Cox et al. (2006) New Zealand 1996–1998	550 Population	BMI 5 yr before interview, quintiles Q1 Q2 Q3 Q4 Q5	 50 40 105 122 233	 1.0 0.9 (0.5–1.6) 0.8 (0.6–1.2) 0.9 (0.6–1.3) 0.9 (0.6–1.3)	Age	No associations were observed between BMI or weight at age 20 yr and prostate cancer
Beebe-Dimmer et al. (2007) USA 1996–2002	139 Population (community-based)	WC (cm) ≤ 102 > 102	59	 1.00 1.84 (1.17–2.91)	Age, smoking history	
Gallus et al. (2007) Italy 1991–2002	219 Hospital	BMI < 24.84 24.84–27.76 ≥ 27.77 [P_{trend}]	 69 80 70	 1.0 1.3 (0.8–2.0) 1.2 (0.8–1.9) [0.38]	Age, education level, study centre, occupational physical activity, family history of prostate cancer	
Máchová et al. (2007) Czech Republic 1987–2002	338 Population	BMI 18.5–< 25 25–30 ≥ 30	NR	 1.00 1.05 (0.72–1.39) 0.97 (0.66–1.41)	Age, smoking, hypertension, height	
Nagata et al. (2007) Japan 1996–2003	200 Hospital	BMI 1 yr before diagnosis < 23.0 23.0–24.9 > 25.0 [P_{trend}]	 81 60 59	 1.00 1.28 (0.87–1.87) 1.06 (0.72–1.55) [0.65]	Smoking	BMI at age 40–45 yr not associated with increased risk of prostate cancer
Magura et al. (2008) USA 2004–2006	312 Hospital	BMI < 25 ≥ 25	30 282	 1.00 1.04 (0.58–1.85)	Age, family history of prostate cancer, type 2 diabetes, smoking, use of multivitamins, use of statins	

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Beebe-Dimmer et al. (2009) USA 2001–2004	637 Hospital	BMI < 30 ≥ 30	 – 208	 1.00 0.51 (0.33–0.80)	Age, PSA screening history, hypertension, diabetes, low HDL, high triglycerides	Inverse association was observed only in Caucasians (n = 494). No association observed in African Americans (n = 381)
Hosseini et al. (2010) Islamic Republic of Iran 2005–2008	137 Population	BMI ≤ 25 > 25	 105 35	 1.0 0.4 (0.2–0.8)	Age, family history of prostate cancer, history of other cancers, history of prostatitis, alcohol consumption, smoking, physical activity	[Discrepancy in the number of reported cases]
Jackson et al. (2010) Jamaica 2005–2007	243 Hospital	BMI, quartiles Q4 vs Q1 (ref) [P_{trend}] WC, tertiles T3 vs T1 (ref) [P_{trend}] Waist-to-hip ratio < 0.95 ≥ 0.95	NR	 0.90 (0.42–1.91) [0.28] 5.57 (1.43–18.63) [0.008] 1.00 2.94 (1.34–6.38)	BMI: age, education level, medical history, first-degree family history of prostate cancer, smoking, physical activity WC and waist-to-hip ratio: age, height and BMI as continuous; education level, current smoker, physical activity	Results are presented for high-grade cancer (Gleason score ≥ 7) 12% of the cases were obese
Dimitropoulou et al. (2011) United Kingdom 2001–2008	960 Population	BMI < 25.0 25.0–29.9 > 30.0 [P_{trend}] WC, tertiles T1 T2 T3 [P_{trend}]	 264 481 174 385 286 289	 1.00 0.98 (0.82–1.16) 0.83 (0.67–1.03) [0.097] 1.00 1.01 (0.85–1.20) 0.94 (0.80–1.12) [0.517]	Age, family history of prostate cancer	
Ganesh et al. (2011) India 1999–2001	123 Hospital	BMI < 25 ≥ 25	 41 76	 1.0 2.1 (1.1–4.4)	Age, religion, education level, hypertension	

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Mori et al. (2011) Japan 2007–2008	117 Population	BMI < 21.0 21.0–22.9 23.0–24.9 ≥ 25.0 [P_{trend}] Weight (kg) < 55 55.0–64.9 65.0–74.9 ≥ 75.0 Weight gain (kg) in adult life < 5 5.0–9.9 10.0–14.9 ≥ 15	 14 29 41 33 7 52 45 13 18 24 43 32	 1.00 1.05 (0.50–2.21) 1.63 (0.77–3.45) 1.39 (0.66–2.96) [0.07] 1.00 1.49 (0.57–3.85) 1.74 (0.65–4.64) 1.64 (0.55–4.91) 1.00 1.22 (0.58–2.55) 3.55 (1.71–7.39) 1.73 (0.83–3.59)	Dietary intake, physical activity, smoking, alcohol consumption	BMI of 23–25 at age 20 yr associated with a 53% reduced risk (based on 11 cases) No associations between body weight at age 20 yr and prostate cancer risk
Pelucchi et al. (2011) Italy 1991–2002	1294 Hospital	BMI < 28 ≥ 28 WC (cm) < 94 ≥ 94 Abdominal obesity (combined WC, BMI) No Yes	 909 381 242 730 470 820	 1.00 0.98 (0.83–1.17) 1.00 1.13 (0.91–1.40) 1.00 1.02 (0.86–1.21)	Age, study centre, education level, smoking, alcohol consumption, physical activity, family history of prostate cancer, non-alcohol energy intake	
Fowke et al. (2012) USA NR	809 Hospital	BMI per 1 kg/m² increase WC per 1 cm increase	 135 135	 1.04 (1.00–1.08) 1.01 (0.99–1.03)	Age, PSA, prostate volume, race, family history of prostate cancer, current treatment for diabetes, benign prostatic hyperplasia, CVD, or hyperlipidaemia	Results are presented for high-grade (Gleason score 8–10) prostate cancer

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Nemesure et al. (2012) Barbados 2002–2011	963 Population	WC (cm), quartiles Q1: < 84 Q2: 84–92 Q3: 92–99 Q4: ≥ 99	NR	 1.00 1.36 (1.01–1.85) 1.67 (1.14–2.44) 1.84 (1.19–2.85)	Age, marital status, religion, occupation, smoking, family history of prostate cancer, BMI	Study in African Barbadian population. When stratifying by high-grade (n = 434) vs low-grade (n = 480) prostate cancer, the associations were not significant in either group
Möller et al. (2013) Sweden 2001–2002	1499 Population	BMI < 22.5 22.5– < 25 25– < 27.5 ≥ 27.5 per 5 kg/m^2 [P_{trend}]	 382 655 295 120	 1.00 0.94 (0.76–1.15) 0.90 (0.71–1.15) 0.96 (0.69–1.33) 0.98 (0.83–1.16) [0.54]	Age, region of residence, time span between first and last recalled weight	No associations with BMI when stratifying by low- and intermediate-grade vs high-grade prostate cancer No significant associations with BMI at age 20 yr
Bashir et al. (2014) Pakistan 2012–2013	140 Hospital	BMI ≤ 25 > 25	 66 74	 1.00 5.78 (2.67–12.6)	Age, lifestyle (physical activity), family history of prostate cancer, smoking, diet	
Agalliu et al. (2015) Nigeria 2011–2012	50 Hospital	BMI < 25 25–29.9 ≥ 30 Weight (kg) per kg increase WC (cm) per cm increase	 21 21 8	 1 1.39 (0.59–3.28) 1.35 (0.42–4.36) 0.97 (0.94–1.00) 0.91 (0.87–0.96)	Age	
Alvarez-Cubero et al. (2015) Spain 2011–2014	100 Hospital	BMI ≥ 30 vs < 30	31	1.65 (0.36–7.57)	Age, residential area, family history of prostate cancer	

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Boehm et al. (2015) Canada 2005–2012	1933 Population	BMI < 25 25–29.9 ≥ 30 WC (cm) < 102 ≥ 102	 649 922 351 1073 711	 1.00 0.87 (0.74–1.01) 0.72 (0.60–0.87) 1.00 1.03 (0.89–1.19)	Age, ancestry, first-degree family history of prostate cancer, annual physician visits, number of PSA tests within 5 yr before index date	No associations were observed with waist-to-hip ratio
Gerdtsson et al. (2015) Sweden 1974–1996	1355 Population	Weight at age 16–22 yr per 5 kg increase BMI at age 44–50 yr per 5 kg increase Weight at age 44–50 yr per 5 kg increase		Incidence: 1.05 (1.01–1.09) Mortality: 1.08 (1.03–1.13) Mortality: 1.11 (1.03–1.19)		No associations were observed with BMI or weight at age 44–50 yr and prostate cancer risk BMI and weight at age 44–50 yr also associated with metastasis
Zhang et al. (2015) China 2013–2014	101 Hospital	BMI < 24 ≥ 24	 35 66	 1.00 2.51 (0.18–9.52)	WC, BP, triglyceride levels, free blood glucose	

BMI, body mass index (in kg/m^2); BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; LBM, lean body mass; NR, not reported; PSA, prostate-specific antigen; SD, standard deviation; WC, waist circumference; yr, years or years

Table 2.2.14c Meta-analyses of measures of body fatness and cancer of the prostate

Reference	Total number of studies Total number of cases	Organ site or cancer subtype	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Bergström et al. (2001)	6 observational studies (4 cohort and 2 case–control) 4592	Prostate	BMI per 1 kg/m^2 increase	1.01 (1.00–1.02)	Different adjustment by study, some non-adjusted	
MacInnis & English (2006)	43 observational studies (22 cohort and 21 case–control) (9 studies for WC) 68 753	Prostate	BMI per 5 kg/m^2 increase	1.05 (1.01–1.08)	Different adjustment by study	No associations were found with WC
Renehan et al. (2008)	27 prospective studies 70 421	Prostate	BMI per 5 kg/m^2 increase	1.03 (1.00–1.07)		Between-study heterogeneity of I^2 = 73% No differences in the results were observed by region (Asia-Pacific, Australia, Europe, North America)
Robinson et al. (2008)	9 cohort studies and 7 case–control studies NR	Prostate	BMI before age 29 yr, per 5 kg/m^2 increase	Cohort: 1.08 (0.97–1.19) Case–control: 1.07 (0.98–1.17)	Age for all; other factors depending on the study	
Guh et al. (2009)	7 cohort studies NR	Prostate	BMI Normal Overweight Obesity	 1.00 1.14 (1.00–1.31) 1.05 (0.85–1.30)	NR	
Esposito et al. (2013)	13 observational studies (cohort and case–control) 4634	Prostate	BMI High vs low	 1.05 (0.97–1.15)	NR	[Cut-off values differ by study]
WCRF/AICR (2014) Continuous Update Project	24 prospective studies for BMI, 4 for WC 11 149	Prostate, advanced	BMI per 5 kg/m^2 increase WC per 10 cm increase	1.08 (1.04–1.12) 1.12 (1.04–1.21)	NR	Advanced prostate cancer includes advanced, high-grade, and fatal prostate cancers

Table 2.2.14c (continued)

Reference	Total number of studies Total number of cases	Organ site or cancer subtype	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Keum et al. (2015)	4 prospective studies 6882	Prostate	Weight gain per 5 kg increase	0.98 (0.94–1.02)	Age and baseline BMI or weight in all, and different additional covariates depending on the study	
		Prostate, localized	Weight gain per 5 kg increase	0.96 (0.92–1.00)		
		Prostate, advanced	Weight gain per 5 kg increase	1.04 (0.99–1.09)		
			WC per 10 cm increase	1.03 (0.99–1.07)		
Chen et al. (2016)	9 observational studies (5 cohort, 1 nested case–control, and 3 case–control) 22 338	All Low- and intermediate-grade High-grade Fatal	Adult weight per 5 kg increase	1.01 (0.94–1.08) 0.97 (0.87–1.07) 1.13 (1.00–1.28) 1.58 (1.01–2.47)	Age (in all studies except one) and different covariates depending on the study	

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported; WC, waist circumference; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; yr, years or years

Table 2.2.14d Mendelian randomization studies of measures of body fatness and cancer of the prostate

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI) and *P* value (with each unit increase in exposure) of the association between the exposure and outcome(s)	Adjustment for confounding
Lewis et al. (2010) Prostate Testing for Cancer and Treatment Study (ProtecT)	Men aged 50–69 yr from 300 general practices across 9 regions in the United Kingdom	4540 (1550 cases and 2990 controls)	BMI per 1 kg/m² increase per 1 kg/m² increase	All: 0.77 (0.52–1.15) *P* = 0.20 High-grade vs low-grade: 1.35 (0.90–2.03) *P* = 0.15	Age, centre
Davies et al. (2015) Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome (PRACTICAL) Consortium	19 independent studies of individuals of European descent	41 062 (20 848 cases and 20 214 controls)	Increase of 1 SD in genetically predicted BMI	0.98 (0.96–1.00) *P* = 0.07	8 principal components of population stratification
Gao et al. (2016) Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium	6 studies of individuals of European ancestry	26 884 (14 160 cases and 12 724 controls)	Increase of 1 SD in genetically predicted BMI (~0.073 kg/m²) Childhood BMI: Adult BMI:	 All: 1.01 (0.83–1.22) *P* = 0.91 Aggressive: 1.10 (0.83–1.45) *P* = 0.49 All: 1.00 (0.96–1.04) *P* = 0.97 Aggressive: 1.02 (0.96–1.08) *P* = 0.44	N/A

BMI, body mass index (in kg/m²); CI, confidence interval; N/A, not applicable; SD, standard deviation; vs, versus; yr, years or years

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2.2.15 Cancer of the testis

Cancer of the testis is a rare malignancy, accounting for 1% of incident cases of cancer in men, but the testis is the most common cancer site for men aged 15–44 years in developed countries. To date, the most important identified risk factor for testicular cancer is an undescended testicle. Increased risk has also been associated with family history of testicular cancer, various genetic factors, and several perinatal risk factors.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and testicular cancer was *inadequate*.

(a) Cohort studies

Since 2000, only one cohort study of excess body weight in relation to risk of testicular cancer has been published: a Norwegian cohort of approximately 600 000 men aged 14–44 years (Bjørge et al., 2006). For overweight and obesity compared with normal BMI, the relative risks were 0.89 (95% CI, 0.77–1.03) and 0.83 (95% CI, 0.58–1.17), respectively, and the relative risk per 1 kg/m^2 increase in BMI was 0.97 (95% CI, 0.95–1.00). There was no statistically significant heterogeneity of results between histological subtypes of testicular cancer.

(b) Case–control studies

A total of seven population- or hospital-based case–control studies published after 2000 focused on the association between BMI and weight and testicular cancer (Table 2.2.15; web only; available at: http://publications.iarc.fr/570). In four studies, there was no overall significant association with BMI for all testicular cancer cases (Dieckmann & Pichlmeier, 2002; Richiardi et al., 2003; Pan et al., 2004; McGlynn et al., 2007). Giannandrea et al. (2012) found an inverse association with all testicular cancer cases for men with BMI > 27.4 kg/m^2 (n = 26) compared with men with BMI ≤ 23.15 kg/m^2 (OR, 0.42; 95% CI, 0.24–0.75). One study showed that high BMI in men aged 18–29 years was significantly more frequent in testicular cancer cases than in controls (Dieckmann et al., 2009). In one study, analysis by subtype yielded an odds ratio of 3.66 (95% CI, 1.87–7.15) for obese men (BMI > 31 kg/m^2) with non-seminoma testicular cancer (n = 11) (Garner et al., 2003).

A meta-analysis of the earlier cohort study and 10 case–control studies showed an inverse association between overweight and testicular cancer (OR, 0.92; 95% CI, 0.86–0.98), which was not significant for obesity (OR, 0.93; 95% CI, 0.75–1.15) (Lerro et al., 2010).

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2.2.16 *Cancer of the kidney (renal cell carcinoma)*

Cancer of the kidney accounts for about 2% of all cancers diagnosed. Established epidemiological risk factors for kidney cancer include tobacco smoking, which can double the risk of the disease in smokers compared with non-smokers. Other established risk factors, which are closely associated with obesity, are high blood pressure and pre-existing diabetes mellitus.

The two most common types of kidney cancer are renal cell carcinoma (RCC) and transitional cell carcinoma (also known as urothelial cell carcinoma) of the renal pelvis. About 90% of kidney cancers are RCCs. Histological subtypes of RCC include clear cell tumours (about 70% of RCCs), papillary tumours (also called chromophilic RCC; about 10% of RCCs), and chromophobe RCC (about 5% of RCCs). Various rarer types of RCC exist, each representing less than 1% of RCCs.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for RCC. The 2007 WCRF review concluded that there was convincing evidence of a positive association between body fatness and kidney cancer risk (WCRF/AICR, 2007). In 2015, the WCRF Continuous Update Project reaffirmed the 2007 conclusions (WCRF/AICR, 2015).

(a) Cohort studies

Since 2000, 19 cohort studies of anthropomorphic measures and risk of kidney cancer have been published (excluding analyses that were later updated and analyses based on fewer than 100 incident cases). Table 2.2.16a shows those findings by BMI at baseline, with comments on findings according to other anthropometric measures of body fatness and weight changes over the life-course.

The findings are remarkably consistent across studies, showing increasing risk of kidney cancer with increasing BMI. The association is approximately linear with increasing BMI. A meta-analysis of 21 cohort studies concluded that there was consistency of the association across sexes and world regions, with a relative risk for obesity compared with normal weight of 1.63 (95% CI, 1.50–1.77) in men and 1.95 (95% CI, 1.81–2.10) in women (Wang & Xu, 2014).

Some investigators have assessed the association between BMI at different ages and subsequent risk of kidney cancer (Nicodemus et al., 2004; van Dijk et al., 2004; Adams et al., 2008). In general, the strong positive association between baseline BMI and kidney cancer risk was also seen for BMI in middle adulthood, but much less so for BMI in early adulthood (ages 18–20 years).

Five cohort studies reported on the association between measures of waist circumference and kidney cancer risk (Nicodemus et al., 2004; Pischon et al., 2006; Adams et al., 2008; Sanfilippo et al., 2014; Kabat et al., 2015). In all of the studies, measures of waist circumference were associated with kidney cancer risk similarly to BMI.

(b) Case–control studies

Since 2000, a total of nine case–control studies in China, Europe, and North America have reported on the association of BMI with risk of RCC (Table 2.2.16b). In all of the studies except one (Wang et al., 2012), BMI was assessed through self-reports by patients with RCC and control subjects, with reference to a variable time frame before cancer diagnosis and an equivalent time frame for the controls. Of the nine studies, seven adjusted for smoking and two did not. Other possible confounding factors considered and adjusted for in some studies included use of artificial sweeteners, pre-existing diabetes mellitus, use of anti-hypertensive drugs, and

exposures to pesticides, herbicides, or certain industrial exposures.

Most of the studies showed an increased risk of RCC with higher BMI, in men, women, or both sexes, although this positive association was not statistically significant in all studies. In all the larger studies, including the earlier studies, there was a statistically significant trend of increasing RCC risk with increasing BMI, up to an approximately 2–3-fold increased risk for the highest versus the lowest BMI categories, both in men and in women. In several studies, RCC risk was also found to be positively associated with BMI at younger ages (20–40 years) (Brock et al., 2007; Dal Maso et al., 2007; Beebe-Dimmer et al., 2012).

Purdue et al. (2013) combined the data from a large case–control study in the USA (Beebe-Dimmer et al., 2012) and a multicentre study in central and eastern Europe (Brennan et al., 2008) to examine the association of BMI with different histological subtypes of RCC and found a positive association of BMI with risk of clear cell RCC (n = 1524; OR per 5 kg/m^2, 1.2; 95% CI, 1.1–1.3) and chromophobe RCC (n = 80; OR per 5 kg/m^2, 1.2; 95% CI, 1.1–1.4), but not papillary RCC (n = 237; OR per 5 kg/m^2, 1.1; 95% CI, 1.0–1.2) or RCC not otherwise specified (n = 367; OR per 5 kg/m^2, 1.0; 95% CI, 0.7–1.4).

(c) Meta-analyses

Several meta-analyses of cohort and/or case–control studies assessed the association between BMI and kidney cancer risk (Table 2.2.16c). Bergström et al. (2001) combined data from 14 studies in men and 14 studies in women, and reported a summary relative risk of RCC of 1.07 per 1 kg/m^2 increase in BMI in both men and women. Two more recent meta-analyses reported summary relative risks for cohort studies and case–control studies separately, for women (Mathew et al., 2009) and for men (Ildaphonse et al., 2009) respectively, all in the range of 1.05 to 1.07.

(d) Mendelian randomization study

There has been one Mendelian randomization study, which used the *FTO* rs9939609 SNP, robustly associated with BMI (Frayling et al., 2007; Scuteri et al., 2007; Peeters et al., 2008), to estimate the causal association between BMI and kidney cancer, among other cancer types (Brennan et al., 2009; Table 2.2.16d). Those with the *FTO* AA genotype had a higher BMI than controls with the TT genotype (difference, 1.14 kg/m^2; 95% CI, 0.66–1.61; P < 0.00001). Mendelian randomization analyses showed that each 1 kg/m^2 increase in BMI was weakly associated with an increased risk of kidney cancer (OR, 1.11; 95% CI: 0.91–1.37; P = 0.31), which was more pronounced in those younger than 50 years (OR, 1.90; 95% CI, 1.16–2.27; P = 0.0002).

Table 2.2.16a Cohort studies of measures of body fatness and cancer of the kidney

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Population-based cohort USA 1982–1998	404 576 Men Mortality	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 305 437 81 14 	 1.00 1.18 (1.02–1.37) 1.36 (1.06–1.74) 1.70 (0.99–2.92) [0.002]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin, fat intake, vegetable intake	
	495 477 Women Mortality	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 243 153 55 12 10 	 1.00 1.33 (1.08–1.63) 1.66 (1.23–2.24) 1.70 (0.94–3.05) 4.75 (2.50–9.04) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin, fat intake, vegetable intake, HRT	
Bjørge et al. (2004) Population-based cohort Norway 1963–2001	1 037 788 Women Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 1061 977 568 	 1.00 1.32 (1.21–1.45) 1.85 (1.66–2.06) [< 0.001]	Age	Association weaker in current and former smokers than in never-smokers
	963 442 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 1908 1638 267 	 1.00 1.18 (1.11–1.26) 1.55 (1.36–1.76) [< 0.001]	Age	Association weaker in current and former smokers than in never-smokers
Nicodemus et al. (2004) Iowa Women's Health Study USA 1986–2000	34 637 Women Incidence	BMI < 22.9 22.9–25.0 25.0–27.4 27.4–30.6 > 30.6 [P_{trend}]	 16 13 24 31 40 	 1.00 0.80 (0.38–1.65) 1.46 (0.77–2.74) 1.87 (1.02–3.41) 2.49 (1.39–4.44) [< 0.0001]	Age	Postmenopausal women. Weight at ages 30 yr, 40 yr, and 50 yr (but not at 18 yr) associated similarly. WC also associated

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
van Dijk et al. (2004) Netherlands Cohort Study The Netherlands 1986–1995	120 852 Women and men Incidence	BMI 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}] per 1 kg/m²	 83 54 62 16 	 1.00 0.92 (0.61–1.38) 1.46 (0.97–2.21) 1.04 (0.54–1.99) [0.04] 1.07 (1.02–1.12)	Age, sex	No association with BMI at age 20 yr
Flaherty et al. (2005) Nurses' Health Study USA 1976–2000	118 191 Women Incidence	BMI < 22.0 22.0–24.9 25.0–27.9 28.0–29.9 ≥ 30 [P_{trend}]	 40 47 27 14 26 	 1.0 1.3 (0.9–2.0) 1.6 (0.9–2.5) 2.2 (1.2–4.1) 2.7 (1.6–4.4) [< 0.001]	Age, hypertension, smoking	RR for BMI ≥ 30 adjusted for age only
Flaherty et al. (2005) Health Professionals Follow-Up Study USA 1986–1998	48 953 Men Incidence	BMI < 22.0 22.0–24.9 25.0–27.9 28.0–29.9 ≥ 30 [P_{trend}]	 4 37 45 12 10 	 1.0 2.1 (0.7–5.9) 2.4 (0.9–6.8) 2.1 (0.7–6.6) 2.1 (0.7–6.8) [0.19]	Age, hypertension, smoking	
Rapp et al. (2005) Population-based cohort Austria 1985–2002	67 447 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 46 70 21 	 1.00 1.19 (0.82–1.74) 1.46 (0.87–2.46) [0.14]	Age, smoking, occupation	
	78 484 Women Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 32 44 12 	 1.00 1.81 (1.13–2.89) 1.14 (0.58–2.24) [0.3]	Age, smoking, occupation	

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pischon et al. (2006) EPIC cohort Europe 1992–2004	218 889 Women Incidence	BMI, quintiles < 21.8 21.8–23.7 23.8–25.9 26.0–28.9 > 29.0 [P_{trend}]	 12 22 24 37 37	 1.00 1.48 (0.73–3.01) 1.39 (0.69–2.80) 1.99 (1.03–3.88) 2.25 (1.14–4.44) [0.009]	Smoking, education level, alcohol consumption, physical activity	WC also associated
	129 660 Men Incidence	BMI, quintiles < 23.6 23.6–25.3 25.4–27.0 27.1–29.3 > 29.4 [P_{trend}]	 29 35 23 28 40	 1.00 1.07 (0.65–1.77) 0.67 (0.39–1.18) 0.84 (0.49–1.43) 1.22 (0.74–2.03) [0.51]		
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 444 448 94	 1.00 1.23 (1.08–1.42) 1.61 (1.27–2.04) [< 0.001]	Age, year, smoking, hypertension	
Reeves et al. (2007) Million Women Study United Kingdom 1995–2005	1.2 million Women Incidence	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 119 165 155 106 178	 0.95 (0.79–1.14) 1.00 (0.86–1.17) 1.10 (0.94–1.28) 1.19 (0.99–1.44) 1.52 (1.31–1.77) 1.53 (1.27–1.84)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	Association slightly weaker in never-smokers
Setiawan et al. (2007) Multiethnic Cohort USA 1993–2002	85 964 Women Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 38 52 37	 1.00 2.03 (1.31–3.15) 2.27 (1.37–3.74) [0.001]	Age, ethnicity, smoking, alcohol consumption, hypertension, physical activity	
	75 172 Men Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 77 93 50	 1.00 1.14 (0.84–1.55) 1.76 (1.20–2.58) [0.005]		

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Adams et al. (2008) NIH-AARP cohort USA 1995–2003	214 906 Women Incidence	BMI 18.5–22.5 22.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 17 33 46 27 64	 1.00 1.66 (0.92–2.98) 2.44 (1.39–4.26) 2.27 (1.23–4.20) 2.67 (1.53–4.66) [0.002]	Age, smoking, physical activity, protein intake, diabetes, hypertension	Similar association with BMI at age 50 yr; no association at age 18 yr or 35 yr. WC also associated
	312 500 Men Incidence	BMI 18.5–22.5 22.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 28 88 169 127 152	 1.00 1.12 (0.73–1.72) 1.51 (1.01–2.26) 1.74 (1.15–2.63) 1.87 (1.24–2.82) [< 0.0005]		Similar association with BMI at age 50 yr; no association at age 18 yr or 35 yr. WC also associated
Jee et al. (2008) Cohort from National Health Insurance Corporation Republic of Korea 1992–2007	443 273 Women Incidence	BMI < 20 20–22.9 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 22 95 100 100 14	 0.48 (0.28–0.82) 0.70 (0.49–0.99) 1.00 0.92 (0.64–1.31) 1.21 (0.58–2.53) [0.0042]	Age, smoking	
	770 556 Men Incidence	BMI < 20 20–22.9 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 97 430 425 392 16	 0.64 (0.49–0.84) 0.67 (0.56–0.79) 1.00 1.11 (0.93–1.31) 1.38 (0.76–2.52) [< 0.0001]	Age, smoking	Association weaker in ever-smokers than in non-smokers
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1993–2003	170 481 Women Incidence	BMI 21.0–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30.0 [P_{trend}]	 18 34 29 14 7	 1.00 1.74 (0.94–3.22) 1.74 (0.92–3.29) 1.37 (0.66–2.84) 2.61 (1.06–6.41) [< 0.05]	Age, height, smoking, alcohol consumption, physical activity, pay grade	

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wilson et al. (2009) ATBC cohort Finland 1985–2002	27 111 Men Incidence	BMI < 23.7 23.7–26.0 26.0–28.5 ≥ 28.5 [P_{trend}]	 41 70 65 69	 1.00 1.8 (1.3–2.7) 1.8 (1.2–2.7) 2.1 (1.4–3.1) [< 0.001]	Age, energy intake	
Sawada et al. (2010) Population sample of Japan Japan 1990–2006	46 837 Men Incidence	BMI < 21 21.0–22.9 23.0–24.9 25.0–26.9 ≥ 27.0	 22 20 21 18 20	 1.86 (1.01–3.45) 1.16 (0.62–2.16) 1.00 1.39 (0.73–2.63) 1.99 (1.04–3.81)	Age, area, tobacco use, alcohol consumption, physical activity, hypertension, diabetes	Analysis of data in women (n = 52 625) was based on very small number of cases; association unclear
Häggström et al. (2013) 3 cohorts Austria, Norway, Sweden 1994–2006	281 468 Women Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 24 28 61 66 84	 1.00 0.95 (0.52–1.74) 1.84 (1.08–3.13) 1.74 (1.02–2.94) 2.21 (1.32–3.70) [0.0002]	Age, time of measurement	
	278 920 Men Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 89 108 100 139 156	 1.00 1.11 (0.81–1.52) 0.94 (0.68–1.29) 1.28 (0.95–1.73) 1.51 (1.13–2.03) [0.001]		
Macleod et al. (2013) Population-based cohort USA 2000–2009	77 260 Women and men Incidence	BMI < 25 25–29.9 30–34.9 ≥ 35	 59 104 47 28	 1.00 1.23 (0.88–1.72) 1.20 (0.81–1.78) 1.71 (1.06–2.79)	Age, sex, race, smoking, alcohol consumption, hypertension, diabetes	
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5.24 million Women and men Incidence	BMI per 5 kg/m^2	1906 total	 1.25 (1.17–1.33)	Age, year, sex, diabetes, SES, alcohol consumption, tobacco use	Similar findings for never-smokers

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Sanfilippo et al. (2014) Women's Health Initiative cohort USA 1993–1998	156 774 Women Incidence	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40	 108 144 83 45 27	 1.00 1.32 (1.03–1.70) 1.47 (1.10–1.96) 1.91 (1.33–2.75) 2.48 (1.61–3.80)	Age, race/ethnicity, diastolic blood pressure	(See also Kabat et al., 2015) WC also associated with increased risk
Kabat et al. (2015) Women's Health Initiative cohort USA 1992–2013	143 901 Women Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	376 total	 1.00 0.89 (0.61–1.28) 1.21 (0.86–1.71) 1.36 (0.96–1.91) 1.73 (1.24–2.42) [< 0.0001]	Age, alcohol consumption, smoking, physical activity, age at menarche, age at first birth, parity, HRT use, family history of kidney cancer, ethnicity, education level	WC also associated with risk

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; RR, relative risk; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.16b Case–control studies of measures of body fatness and cancer of the kidney

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Shapiro et al. (1999) USA (western Washington state) 1980–1995	238 (155 men, 83 women) 616 (261 men, 355 women) Population	Median BMI	Women:		Age, diabetes mellitus, hypertension Median BMI calculated using median weight recorded in medical records during the 5-yr period immediately before the reference date (2 yr before date of diagnosis and corresponding index date for controls)
		< 22.20	5	1.0	
		22.20–24.85	16	3.3 (1.1–9.7)	
		24.86–28.25	20	3.6 (1.3–10.3)	
		> 28.25	29	4.1 (1.5–11.8)	
		Top 10% (> 32.99)		6.0 (1.9–18.8)	
		Median BMI	Men:		
		< 24.59	23	1.0	
		24.59–26.39	27	1.1 (0.5–2.1)	
		26.40–28.88	26	1.0 (0.5–2.0)	
		> 28.88	45	1.8 (0.9–3.5)	
		Top 10% (> 31.85)		2.2 (1.0–5.0)	
Hu et al. (2003) Canada (8 provinces) 1994–1997	1279 (691 men, 588 women) 5370 (2696 men, 2674 women) Population	BMI 2 yr before study entry	Women:		10-year age group, province, education level, pack-years of smoking, alcohol consumption, total intake of meat, vegetables, and fruit
		< 18.5–24.9	221	1.0	
		25.0–29.9	200	1.5 (1.20–1.90)	
		30.0–34.9	100	2.5 (1.90–3.40)	
		35.0–39.9	31	2.7 (1.70–4.40)	
		≥ 40.00	33	3.8 (2.30–6.40)	
		BMI 2 yr before study entry	Men:		
		< 18.5–24.9	147	1.0	
		25.0–29.9	369	2.20 (1.70–2.70)	
		30.0–34.9	144	2.80 (2.20–3.80)	
		35.0–39.9	21	1.90 (1.10–3.30)	
		≥ 40.00	8	3.70 (1.50–9.40)	

Table 2.2.16b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Chiu et al. (2006) USA 1986–1990	406 (261 men, 145 women) 2434 (1601 men, 833 women) Population	BMI in 60s	Men:		All respondents: age, total energy intake, intake of red meat, intake of vegetables, hypertension, education level, smoking, family history of kidney cancer, proxy status; women only: marital status Analyses for BMI at age 20 yr and age 40 yr gave very similar results to BMI at age 60 yr
		≤ 23.48	49	1.0	
		23.49–25.17	33	0.6 (0.3–1.1)	
		25.18–27.35	34	0.6 (0.3–1.1)	
		27.36–30.07	27	0.8 (0.4–1.7)	
		≥ 30.08	20	0.4 (0.2–1.0)	
		[P_{trend}]		[0.2]	
		BMI in 60s	Women:		
		≤ 22.20	23	1.0	
		22.21–24.32	18	0.5 (0.2–1.4)	
		24.33–27.31	20	1.0 (0.4–2.5)	
		27.33–30.13	13	0.7 (0.3–2.1)	
		≥ 30.14	21	2.3 (0.9–6.0)	
		[P_{trend}]		[0.1]	
Brock et al. (2007) USA (Iowa) 1985–1989	406 (261 men, 145 women) 2434 (1601 men, 833 women) Population	BMI at age 20 yr			Age, sex, proxy status, pack-years of smoking Analysis also reported for men and women separately
		< 25	271	1.00	
		25–30	62	1.54 (1.10–2.17)	
		≥ 30	21	2.75 (1.51–5.01)	
		BMI at age 40 yr			
		< 25	180	1.00	
		25–30	130	1.36 (1.04–1.79)	
		≥ 30	51	2.08 (1.39–3.12)	
		BMI at age 60 yr			
		< 25	111	1.00	
		25–30	93	1.12 (0.81–1.55)	
		≥ 30	39	1.46 (0.94–2.28)	
Dal Maso et al. (2007) Italy 1992–2004	767 (494 men, 273 women) 1534 (988 men, 546 women) Hospital	BMI at age 30 yr			Calendar period of interview, years of education, smoking habits, family history of kidney cancer
		< 25	492	1.00	
		25– < 30	194	1.17 (0.95–1.45)	
		≥ 30	38	1.46 (0.95–2.25)	
		[P_{trend}]		[0.04]	
		BMI at age 50 yr			
		< 25	256	1.00	
		25– < 30	265	1.17 (0.94–1.45)	
		≥ 30	89	1.48 (1.07–2.03)	
		[P_{trend}]		[0.02]	

Table 2.2.16b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Dal Maso et al. (2007) (cont.)		BMI 1 yr before diagnosis			
		< 25	281	1.00	
		25– < 30	347	0.95 (0.78–1.16)	
		≥ 30	136	1.29 (0.99–1.69)	
		[P_{trend}]		[0.16]	
		By smoking status			
		Never-smokers:			
		< 25	39	1.00	
		25– < 30	62	1.25 (0.74–2.09)	
		≥ 30	82	1.83 (1.10–3.04)	
		Ever-smokers:			
		< 25	87	1.00	
		25– < 30	93	0.96 (0.66–1.41)	
		≥ 30	112	1.37 (0.95–1.98)	
		By histological type			
		Clear cell subtype:			
		< 25	71	1.00	
		25– < 30	89	0.99 (0.68–1.44)	
		≥ 30	121	1.40 (0.98–1.99)	
		Other subtype:			
		< 25	23	1.00	
		25– < 30	38	1.30 (0.73–2.30)	
		≥ 30	41	1.62 (0.92–2.85)	
Brennan et al. (2008) Czech Republic, Poland, Romania, Russian Federation (7 centres) 1998–2003	1097 (648 men, 449 women) 1476 (952 men, 524 women) Hospital	BMI 2 yr before interview	Men:		Age, smoking, history of hypertension, country
		< 25	191	1.00	
		25–27.5	166	1.19 (0.91–1.56)	
		27.5–29.99	125	1.32 (0.98–1.79)	
		30–35	133	1.70 (1.25–2.31)	
		> 35	32	1.72 (1.01–2.94)	
		[P_{trend}]		[0.001]	
		BMI 2 yr before interview	Women:		
		< 25	136	1.00	
		25–27.5	87	0.86 (0.60–1.25)	
		27.5–29.99	98	1.16 (0.80–1.70)	
		30–35	98	0.95 (0.66–1.38)	
		> 35	30	0.85 (0.49–1.48)	
		[P_{trend}]		[0.68]	

Table 2.2.16b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Beebe-Dimmer et al. (2012) USA 2002–2007	1214 (720 men, 494 women) 1234 (689 men, 545 women) Population	BMI 5 yr before interview			Age, education level, hypertension, family history of renal cancer, smoking history, study centre Analysis of BMI at age 21 yr gave similar results
		< 25.0	240	1.0	
		25.0–29.9	436	1.2 (0.9–1.5)	
		30.0–34.9	298	1.5 (1.2–2.1)	
		≥ 35	230	1.6 (1.1–2.2)	
		per 1 kg/m²		1.02 (1.01–1.04)	
		[P_{trend}]		[0.0013]	
Wang et al. (2012) China 2007–2009	250 299 Hospital	Current BMI			Univariate analysis
		< 25	157	1.00	
		≥ 25	93	1.94 (1.34–2.81)	
Purdue et al. (2013) USA (Detroit and Chicago; USKC study) and Europe (Czech Republic, Poland, Romania, Russian Federation; CEERCC study) 2002–2007	2314 2711 Population (USKC), hospital (CEERCC)	BMI a few years before interview			Study centre, age, sex, race, education level, BMI, smoking status, history of diagnosed hypertension, family history of kidney cancer Time before interview: 5 yr (USKC), 2 yr (CEERCC)
		Clear cell:	1524		
		per 5 kg/m²		1.2 (1.1–1.3)	
		Papillary:	237		
		per 5 kg/m²		1.1 (1.0–1.2)	
		Chromophobe:	80		
		per 5 kg/m²		1.2 (1.1–1.4)	
		Other/NOS:	367		
		per 5 kg/m²		1.0 (0.7–1.4)	

BMI, body mass index (in kg/m²); CEERCC, Central and Eastern European Renal Cell Cancer Study; CI, confidence interval; NOS, not otherwise specified; USKC, United States Kidney Cancer; yr, year or years

Table 2.2.16c Meta-analyses of measures of body fatness and cancer of the kidney

Reference	Total number of studies Sex	Exposure categories	Relative risk (95% CI)	Heterogeneity values
Bergström et al. (2001)	28 studies (6 cohort studies, 22 case–control studies; 16 population-based, 6 hospital-based) Men: 14 studies Women: 14 studies	BMI, per 1 kg/m^2 All Men Women	 1.07 (1.05–1.09) 1.07 (1.04–1.09) 1.07 (1.05–1.09)	 $P_{heterogeneity}$ = 0.03 $P_{heterogeneity}$ = 0.08 $P_{heterogeneity}$ = 0.24
Mathew et al. (2009)	28 studies (15 cohort studies, 13 case–control studies) Women	BMI, per 1 kg/m^2 Cohort studies Case–control studies	 1.06 (1.05–1.07) 1.07 (1.06–1.08)	 $P_{heterogeneity}$ = 0.081 $P_{heterogeneity}$ = 0.0643
Ildaphonse et al. (2009)	27 studies (13 cohort studies, 14 case–control studies) Men	BMI, per 1 kg/m^2 Cohort studies Case–control studies	 1.05 (1.04–1.06) 1.08 (1.06–1.09)	 $P_{heterogeneity}$ = 0.78 $P_{heterogeneity}$ = 0.4238
Wang & Xu (2014)	21 cohort studies Men and women	BMI, vs normal weight All: Pre-obesity Obesity Men: Pre-obesity Obesity Women: Pre-obesity Obesity	 1.28 (1.24–1.33) 1.77 (1.68–1.87) 1.22 (1.17–1.28) 1.63 (1.50–1.77) 1.38 (1.29–1.47) 1.95 (1.81–2.10)	BMI in adults was classified as follows: normal weight, 18.50–24.99; pre-obesity, 25.00–29.99; obesity, ≥ 30.00

BMI, body mass index (in kg/m^2); CI, confidence interval

Table 2.2.16d Mendelian randomization studies of measures of body fatness and cancer of the kidney

Reference	Characteristics of study population	Sample size	Exposure (unit)	Outcome	Odds ratio (95% CI); *P* value (with each unit increase in exposure) of the association between the exposure and outcome
Brennan et al. (2009)	Men and women from 15 centres in 6 countries in central and eastern Europe (Czech Republic, Hungary, Poland, Romania, Russian Federation, and Slovakia)	7067 (4015 cases and 3052 controls)	BMI (kg/m^2)	Kidney cancer	All subjects: 1.11 (0.91–1.37); $P = 0.31$ Subjects aged < 50 yr: 1.90 (1.16–2.27); $P = 0.0002$

BMI, body mass index (in kg/m^2); CI, confidence interval; OR, odds ratio; yr, year or years

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2.2.17 Cancer of the urinary bladder

Cancer of the urinary bladder accounts for approximately 3% of all cancers and is the ninth most common cancer worldwide. The incidence of urinary bladder cancer in men is approximately 4 times that in women. The average age of diagnosis is after age 70 years. Globally, incidence rates are highest in Europe and North America and lowest in Asia and Latin America.

The strongest risk factor is smoking, as was established several decades ago (IARC, 1986). Compared with never-smokers, smokers have a 6-fold increase in the risk of developing urinary bladder cancer (WCRF/AICR, 2015). Other risk factors include occupational exposure to aromatic amines and polyaromatic hydrocarbons.

About 90% of urinary bladder cancers are transitional cell carcinoma; the remainder are squamous cell carcinoma, adenocarcinoma, and small cell carcinoma.

(a) Cohort studies

See Table 2.2.17a (web only; available at: http://publications.iarc.fr/570).

A total of 23 prospective cohorts were identified that evaluated associations between BMI and either urinary bladder cancer incidence (19 studies) (Tulinius et al., 1997; Nagano et al., 2000; Tripathi et al., 2002; Samanic et al., 2004, 2006; Oh et al., 2005; Rapp et al., 2005; Cantwell et al., 2006; Holick et al., 2007; Reeves et al., 2007; Jee et al., 2008; Koebnick et al., 2008; Larsson et al., 2008; Prentice et al., 2009; Andreotti et al., 2010; Häggström et al., 2011; Bhaskaran et al., 2014; Roswall et al., 2014; Song et al., 2014) or urinary bladder cancer-related mortality (5 studies) (Calle et al., 2003; Batty et al., 2005; Fujino et al., 2007; Reeves et al., 2007; Parr et al., 2010) as the end-point. The large majority of these studies reported no significant association with urinary bladder cancer incidence or mortality. Two studies did show a positive association between BMI and risk of urinary bladder cancer. The NIH-AARP cohort (Koebnick et al., 2008) reported significantly increased associations with overweight (RR, 1.16; 95% CI, 1.03–1.29), obesity I (RR, 1.23; 95% CI, 1.06–1.43), and obesity II (RR, 1.30; 95% CI, 1.04–1.63) in men and women combined, compared with normal weight; stratified analysis indicated that these positive associations were limited to men. The EPIC study (Roswall et al., 2014) found a small but significant association for BMI in men only (RR per 2 kg/m^2, 1.05; 95% CI, 1.02–1.08), with a strong dose–response relationship. Findings from the Iowa Women's Health Study (Tripathi et al., 2002) demonstrated a statistically marginal inverse association between BMI and urinary bladder cancer incidence also in men only (P_{trend} = 0.06 after adjustments).

Almost all studies adjusted for smoking. Stratified analyses suggested that the associations were stronger in former smokers than in never-smokers. Four studies (Calle et al., 2003; Reeves et al., 2007; Koebnick et al., 2008; Bhaskaran et al., 2014) specifically stratified by never versus ever smoking status and statistically tested for interactions. None of those interactions were significant.

Several studies reported on the associations between BMI and urinary bladder cancer in Asian populations (Nagano et al., 2000; Oh et al., 2005; Fujino et al., 2007; Jee et al., 2008; Parr et al., 2010). No pattern of difference compared with European or North American populations was noted.

From a large meta-analysis for the association between BMI and urinary bladder cancer risk, based on 22 prospective cohort studies, the summary risk estimate was 1.03 (95% CI, 0.97–1.09) (WCRF/AICR, 2015). Two additional meta-analyses, of 11 cohort studies (Qin et al., 2013) and 15 cohort studies (Sun et al., 2015), reported summary risk estimates of positive

associations between BMI and urinary bladder cancer. [These differences in part reflect variations in study inclusion. In the meta-analysis by Sun et al., (2015), the summary estimate may have been disproportionally influenced by an incorrect data extraction of risk estimates from the FINRISK study (Song et al., 2014).]

Three studies evaluated the relationship between waist circumference and urinary bladder cancer risk. Two studies (Tripathi et al., 2002; Larsson et al., 2008) found no significant association; the third study, based on the EPIC cohort (Roswall et al., 2014), found a small but significant association with waist circumference in men only (RR per 5 cm, 1.04; 95% CI, 1.01–1.08).

(b) Case–control studies

See Table 2.2.17b (web only; available at: http://publications.iarc.fr/570).

The four case–control studies that evaluated the relationship between BMI and urinary bladder cancer incidence (Pelucchi et al., 2002; Lin et al., 2010; MacKenzie et al., 2011; Attner et al., 2012) found no significant associations.

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2.2.18 *Primary tumours of the brain and central nervous system*

Primary tumours of the brain are a relatively uncommon group of heterogeneous neoplastic diseases with variable natural histories from benign to malignant. There are about 130 histological types arising from the many cell types that support and line the brain tissue and the central nervous system. Primary brain tumours occur across the age spectrum, from childhood through adulthood. The most common type, which arises from the glial cells, is called glioma and accounts for approximately 30% of all brain tumours in adults (Wiedmann et al., 2013). In turn, gliomas are of at least three types – astrocytoma, oligodendroglioma, and ependymoma – and are graded into four grades (1 and 2 are low-grade; 3 and 4, also known as glioblastoma multiforme, are high-grade) (Ricard et al., 2012).

The next most common group is meningioma, which accounts for approximately 20% of brain tumours. Many of these are benign and slow-growing, but – as occurs with other brain tumour types – benign tumours can undergo malignant transformation.

Established risk factors for brain tumours include hereditary conditions, such as neurofibromatosis, and ionizing radiation.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and brain cancers, including meningioma, was *inadequate*.

(a) *Cohort studies of tumours of the brain and central nervous system combined*

Essentially all of the evidence of associations between measures of body fatness and primary brain tumours applies to tumours in adulthood.

Five large prospective cohort studies reported associations between BMI and cancers of the brain and central nervous system in terms of incidence or mortality without specifying the histological type (Table 2.2.18a; Calle et al., 2003; Oh et al., 2005; Samanic et al., 2006; Reeves et al., 2007; Bhaskaran et al., 2014). There is consistently no evidence of associations between BMI and the development of all brain tumours. [This observation was robust when restricting the analyses to non-smokers only (Reeves et al., 2007; Bhaskaran et al., 2014).]

(b) *Cohort studies of glioma*

Five cohort studies (all in European and North American populations) (Benson et al., 2008; Moore et al., 2009; Michaud et al., 2011; Edlinger et al., 2012; Wiedmann et al., 2013) reported on associations between baseline BMI and the development of glioma (Table 2.2.18a). There is consistently no evidence of associations between BMI and the development of glioma. One study stratified by low- and high-grade glioma and reported no difference.

The NIH-AARP cohort study (Moore et al., 2009) reported on the associations between recalled BMI at age 18 years and the development of glioma later in life and noted a positive association (P = 0.003) [the numbers of cases in the upper BMI categories were small; n = 11 for BMI of 30–34.9 kg/m^2, and no cases in the highest category of BMI ≥ 35 kg/m^2].

(c) *Cohort studies of meningioma*

Five cohort studies (all in European and North American populations) (Jhawar et al., 2003; Benson et al., 2008; Johnson et al., 2011; Michaud et al., 2011; Wiedmann et al., 2013) reported on associations between baseline BMI and the development of meningioma (Table 2.2.18a). All reported statistically significant or borderline significant positive associations, with increased risks ranging from 1.4 to 2.13.

Two cohort studies (Johnson et al., 2011; Michaud et al., 2011) reported on associations between baseline waist circumference and meningioma incidence. In both, significant positive associations were noted.

(d) Case–control studies

See Table 2.2.18b.

Two case–control studies (Cabaniols et al., 2011; Little et al., 2013) examined relationships between BMI and risk of glioma, and no associations were found. Two further case–control studies, one in women only (Claus et al., 2013) and the other in men only (Schildkraut et al., 2014), examined relationships between BMI and meningioma and found positive associations in both studies, similar to those found in the cohort studies.

A meta-analysis (Niedermaier et al., 2015), including 2982 meningioma cases from 12 cohort and case–control studies reported positive associations with meningioma: with normal weight as the reference group, the relative risk was 1.21 (95% CI, 1.01–1.43) for overweight and 1.54 (95% CI, 1.32–1.79) for obesity.

Table 2.2.18a Cohort studies of measures of body fatness and cancers of the brain and central nervous system

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Brain and central nervous system combined							
Calle et al. (2003) Cancer Prevention Study II population-based cohort USA 1982–1998	404 576 Men Mortality	Brain	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 370 461 68 – 	 1.00 0.98 (0.85–1.13) 0.79 (0.61–1.03) – [0.14]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat intake, vegetable intake; in women, also adjusted for HRT use	
	495 477 Women Mortality	Brain	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 467 213 64 12 – 	 1.00 1.02 (0.87–1.21) 1.10 (0.84–1.44) 0.74 (0.42–1.32) – [0.96]		
Oh et al. (2005) Korean civil servants and teachers from the Korea National Health Insurance Corporation Republic of Korea 1992–2001	781 283 Men Incidence	Brain	BMI < 18.5 18.5–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30 [P_{trend}]	 4 105 69 32 21 3 	 1.07 (0.39–2.93) 1.00 1.09 (0.79–1.50) 0.84 (0.55–1.28) 1.47 (0.90–2.38) 1.79 (0.57–2.66) [0.241]	Age, smoking status, alcohol consumption, frequency of regular exercise, family history of cancer, area of residence	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	Brain ICD-7: 193.0	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 519 353 46 	 1.00 1.03 (0.89–1.18) 0.86 (0.63–1.16) [> 0.5]	Age, year, smoking	

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) Million Women Study United Kingdom 1995–2005	1.2 million Women Incidence	Brain ICD-10: C71	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 113 133 143 83 99	 1.14 (0.95–1.38) 1.00 (0.84–1.19) 1.27 (1.08–1.50) 1.19 (0.96–1.47) 1.08 (0.88–1.32) 1.01 (0.81–1.26)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity Where appropriate: time since menopause, HRT use	Similar results when restricting to never-smokers or excluding the first 2 yr of follow-up
	1.2 million Women Mortality		BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 123 143 158 90 131	 1.17 (0.98–1.40) 1.00 (0.85–1.18) 1.29 (1.10–1.51) 1.18 (0.96–1.45) 1.31 (1.10–1.56) 1.17 (0.95–1.43)		
Bhaskaran et al. (2014) United Kingdom Clinical Practice Research Database United Kingdom 1987–2012	5.24 million Men and women Incidence	Brain and central nervous system	BMI per 5 kg/m^2	2974	1.04 (0.99–1.10)	Age, diabetes status, smoking, alcohol consumption, calendar year, SES	Very similar risk estimates for never-smokers (n = 1359 incident cases)
Glioma							
Benson et al. (2008) Million Women Study United Kingdom 1996–2001	1 184 225 Women Incidence	Glioma ICD-O: 9380–9481	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 259 241 106	 1.00 1.20 (1.01–1.44) 1.07 (0.84–1.34) [0.10]	Height, SES, smoking, alcohol intake, parity, age (yr) at first birth, duration of OC use, physical activity, study region	
Moore et al. (2009) NIH-AARP cohort USA (8.2 years)	270 395 Men and women Incidence	Glioma ICD-O-3: 9380–9460	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 4 82 95 46 9	 1.66 (0.59–4.64) 1.00 0.90 (0.67–1.22) 1.29 (0.89–1.86) 0.74 (0.37–1.48) [0.95]	Age at baseline, age squared, sex, race, highest level of education, marital status	

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Moore et al. (2009) (cont.)			BMI at age 18 yr < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 26 175 24 11 – 	 0.69 (0.45–1.05) 1.00 1.04 (0.67–1.59) 3.74 (2.03–6.90) – [0.003]		No significant associations observed with BMI at age 35 yr or at age 50 yr
Michaud et al. (2011) EPIC cohort From 1999 (8.4 years)	380 775 Men and women Incidence	Glioma ICD-O-2: 9380–9460, 9505	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 13 125 147 55 	 1.08 (0.60–1.92) 1.00 1.04 (0.81–1.34) 1.06 (0.76–1.48) [0.80]	Age, country, sex, education level	
			WC, quartiles Q1 Q2 Q3 Q4 [P_{trend}]	 73 82 73 90 	 1.00 0.90 (0.65–1.24) 0.82 (0.59–1.16) 0.97 (0.69–1.35) [0.81]	Age, country, sex, education level, height	
Edlinger et al. (2012) Metabolic Syndrome and Cancer Project (Me-Can) Austria, Norway, Sweden 1972–2005	578 462 Men and women Incidence	Low-grade glioma ICD-7: 193	BMI, quintiles Q1 Q2 Q3 Q4 Q5	 21 16 21 24 16	 1.00 0.69 (0.33–1.42) 0.90 (0.46–1.77) 1.00 (0.51–1.95) 0.66 (0.31–1.38)	Year of birth (in decades), cohort, smoking status	
		High-grade glioma ICD-7: 193	BMI, quintiles Q1 Q2 Q3 Q4 Q5	 65 72 82 99 92	 1.00 0.98 (0.68–1.43) 1.06 (0.73–1.52) 1.23 (0.87–1.75) 1.14 (0.80–1.64)		

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wiedmann et al. (2013) Nord-Trøndelag Health Study (HUNT 1 Study) Norway From 1991 (23.5 yr)	74 242 Men and women Incidence	Glioma ICD-O-3: 9380–9480	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 6 79 49 14	 0.67 (0.29–1.56) 1.00 0.88 (0.61–1.27) 1.04 (0.58–1.85) [0.87]	Age, sex	
Meningioma							
Jhawar et al. (2003) Nurses' Health Study USA 1.2 million person-years	121 700 Women Incidence	Meningioma (self-reported)	BMI < 22 22–24.9 ≥ 25 [P_{trend}]	 22 31 58	 1.00 1.10 (0.61–1.97) 1.61 (0.96–2.70) [0.06]	Age, menopausal status, postmenopausal HRT use	
Benson et al. (2008) Million Women Study United Kingdom 1996–2001	1 184 225 Women Incidence	Meningioma	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 154 120 84	 1.00 1.01 (0.79–1.29) 1.40 (1.08–1.87) [0.03]	Height, SES, smoking, alcohol intake, parity, age (yr) at first birth, duration of OC use, physical activity, study region	
Johnson et al. (2011) Iowa Women's Health Study USA 291 021 person-years	27 791 Women Incidence	Meningioma ICD-9: 192.1, 192.3, 225.2, 225.4, 237.6	BMI 18.5–24.9 25–29.9 30–34.0 ≥ 35 [P_{trend}] WC (in) < 30.25 30.26–33.50 33.51–37.75 > 37.75 [P_{trend}]	 41 36 35 13 22 20 35 44	 1.00 0.92 (0.59–1.44) 2.14 (1.36–3.36) 1.99 (1.06–3.71) [0.0007] 1.00 0.92 (0.50–1.69) 1.56 (0.92–2.67) 2.13 (1.28–3.56) [0.0006]	Age	BMI at age 18 yr and at age 30 yr not associated with risk

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Michaud et al. (2011) EPIC cohort From 1999 (8.4 yr)	380 775 Men and women Incidence	Meningioma	BMI			Age, country, sex, education level	
			< 20	7	1.00 (0.46–2.19)		
			20–24.9	70	1.00		
			25–29.9	87	1.34 (0.97–1.86)		
			≥ 30	39	1.48 (0.98–2.23)		
			[P_{trend}]		[0.05]		
		Meningioma	WC, quartiles			Age, country, sex, education level, height	
			Q1	32	1.00		
			Q2	45	1.18 (0.73–1.88)		
			Q3	41	1.06 (0.65–1.72)		
			Q4	66	1.71 (1.08–2.73)		
			[P_{trend}]		[0.01]		
Wiedmann et al. (2013) Nord-Trøndelag Health Study (HUNT 1 Study) Norway 23.5 yr	74 242 Men and women Incidence	Meningioma ICD-O-3: 9530–9539	BMI			Age, sex	When stratifying by sex, positive associations (borderline significant) observed in women only
			< 20	6	0.82 (0.35–1.92)		
			20–24.9	59	1.00		
			25–29.9	51	1.22 (0.83–1.80)		
			≥ 30	22	1.48 (0.89–2.45)		
			[P_{trend}]		[0.08]		

BMI, body mass index (in kg/m²); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; ICD, International Classification of Diseases; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; OC, oral contraceptive; SES: socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.18b Case–control studies of measures of body fatness and cancers of the brain and central nervous system

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Glioma					
Cabaniols et al. (2011) France 2005	122 Men and women Hospital	BMI in recent past < 25 ≥ 25	 49	 1.00 0.70 (0.41–1.18)	Age, sex
Little et al. (2013) USA 2004–2012	643 Men Population	BMI in adulthood, recent past < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 8 133 311 191	 2.47 (0.63–9.70) 1.00 1.26 (0.94–1.69) 1.26 (0.91–1.75) [0.67]	Age, race, education level, state of residence
	460 Women Population	BMI in adulthood, recent past < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 10 203 136 111	 0.80 (0.34–1.87) 1.00 0.95 (0.70–1.29) 1.11 (0.98–1.03) [0.63]	
	643 Men Population	BMI at age 21 yr < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 34 391 182 29	 0.67 (0.41–1.09) 1.00 1.16 (0.89–1.52) 0.77 (0.45–1.31) [0.054]	
	460 Women Population	BMI at age 21 yr < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 69 324 39 23	 0.68 (0.48–0.96) 1.00 1.39 (0.85–2.27) 1.66 (0.85–3.23) [0.004]	

Table 2.2.18b (continued)

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Meningioma					
Claus et al. (2013) USA 2006–2011	1127 Women Population	BMI < 23.4 23.4–26.6 26.6–30.9 ≥ 30.9 [P_{trend}]	 303 237 269 308	 1.00 1.06 (0.83–1.35) 1.13 (0.89–1.45) 1.29 (1.01–1.65) [0.04]	Race, education level, menopausal status, age at menopause, age at menarche, number of full-term pregnancies, age at first live birth, ever use of OC, ever use of HRT, ever use of fertility medications, smoking, alcohol consumption, breastfeeding, geographical location
Schildkraut et al. (2014) USA 2006–2012	456 Men Population	BMI < 25 25–29.9 30–34.9 ≥ 35	 84 206 102 58	 1.00 1.66 (1.17–2.34) 1.92 (1.28–2.90) 1.64 (1.02–2.64)	Age, race

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; OC, oral contraceptive; yr, year or years

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2.2.19 Cancer of the thyroid

Cancer of the thyroid includes a variety of histological types, ranging from the most common group of differentiated cancers (papillary carcinoma and follicular carcinoma) to medullary carcinoma and anaplastic (undifferentiated) carcinoma. Globally, thyroid cancer incidence has been increasing during the past three decades; incidence rates in women are generally 2–3 times those in men. Known risk factors include exposure to radiation for all thyroid cancers, and iodine deficiency for follicular carcinoma.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and thyroid cancer was *inadequate*. The 2007 WCRF review did not draw any conclusions about body fatness and thyroid cancer risk (WCRF/AICR, 2007).

(a) Cohort studies

The evidence from cohort studies since 2000 includes 15 publications (excluding analyses that were later updated and analyses based on fewer than 100 incident cases), including a large pooled analysis of 22 cohorts (Kitahara et al., 2016). Table 2.2.19a presents results from these studies for BMI at baseline, with comments on findings according to other measures of body fatness, such as weight changes over the life-course, waist circumference, or waist-to-hip ratio.

In general, the evidence from cohort studies supports a positive association between BMI and thyroid cancer, with most studies reporting a significantly increased risk at the highest versus lowest category of BMI and/or a significant dose–response relationship. However, in those studies that provided estimates for women and men separately, inconsistent findings were observed across studies. Almquist et al. (2011) found no association between BMI and thyroid cancer in either sex, but a positive trend across BMI quintiles in women only ($P_{trend} = 0.02$). In a Norwegian population-based cohort, Engeland et al. (2006) observed no association in men, but a positive association in women; the estimated relative risk for BMI ≥ 30 kg/m^2 compared with the reference BMI of 18–24.9 kg/m^2 was 1.29 (95% CI, 1.13–1.46). In the Radiologic Technologists Study in the USA (Meinhold et al. (2010), no association was observed in men, whereas the association in women was also positive (RR, 1.74; 95% CI, 1.03–2.94). A systematic review, including 11 studies, estimated the relative risk of thyroid cancer for obese compared with normal-weight individuals to be 1.53 (95% CI, 0.89–2.64) in men and 1.57 (95% CI, 1.13–2.19) in women (Schmid et al., 2015). Another systematic review (Zhang et al., 2014), including 16 cohort studies, estimated an overall relative risk of thyroid cancer of 1.29 (95% CI, 1.20–1.37) in relation to obesity, with similar risk estimates in men and in women [the Working Group noted that this study provided limited information]. A pooled analysis by Kitahara et al. (2016) of 22 cohorts including 2296 incident cases found a modest positive association between baseline BMI and thyroid cancer risk overall, and the association was stronger in men (RR per 5 kg/m^2, 1.17; 95% CI, 1.06–1.28) than in women (RR per 5 kg/m^2, 1.04; 95% CI, 1.00–1.09).

A total of four studies assessed the association between body fatness and thyroid cancer risk by histological subtype (Engeland et al., 2006; Kabat et al., 2012; Rinaldi et al., 2012; Kitahara et al., 2016). The association with BMI was similar for the papillary and follicular histological subtypes.

In the only study that assessed BMI at younger ages (Kitahara et al., 2016), thyroid cancer risk was similar for BMI in young adulthood (RR per 5 kg/m^2, 1.13; 95% CI, 1.02–1.25) and BMI later in adult life (RR per 5 kg/m^2, 1.06; 95% CI, 1.02–1.10); a positive association was also reported with BMI gain in adult life (RR per 5 kg/m^2, 1.07; 95% CI, 1.00–1.15), after adjustment for BMI.

Two studies assessed anthropometric measures of body fatness other than BMI. In the pooled analysis by Kitahara et al. (2016), a weaker positive association was found with waist circumference (RR per 5 cm, 1.03; 95% CI, 1.01–1.05) than with BMI (RR per 5 kg/m^2, 1.06; 95% CI, 1.02–1.10). In the EPIC cohort (Rinaldi et al., 2012), associations with waist circumference and waist-to-hip ratio were similar to those observed with BMI.

(b) Case–control studies

Six informative case–control studies were identified that evaluated the association between BMI and thyroid cancer, including two larger pooled analyses (Table 2.2.19b). One study (Cléro et al., 2010) that combined two of the five studies but that did not offer additional information was excluded. In two studies, the total number of cases in men was less than 50 (Guignard et al., 2007; Suzuki et al., 2008); therefore, only data for women are reported. Two studies (Guignard et al., 2007; Xu et al., 2014) were restricted to papillary carcinomas.

Overall, there appeared to be an association between elevated current BMI (in adulthood) and the occurrence of thyroid cancer. There was some indication that this relationship was stronger in women than in men. [However, this may reflect small case numbers in the studies, especially in men, related to the low prevalence of the disease.] Two of the studies evaluated the associations between BMI at age 18 years (Brindel et al., 2009) and at age 20 years (Suzuki et al., 2008) and thyroid cancer, and noted some evidence for an association with thyroid cancer occurrence.

Table 2.2.19a Cohort studies of measures of body fatness and cancer of the thyroid

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence or mortality	Obesity Non-obese Obese Non-obese Obese	 White men: 811 64 Black men: 156 13	 1.00 1.40 (1.09–1.81) 1.00 1.92 (1.09–3.40)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0 Cancers diagnosed within 1 yr of obesity diagnoses were excluded from the study In White men only, higher risk of adrenal thyroid cancer
Oh et al. (2005) Korea National Health Insurance Corporation cohort Republic of Korea 1992–2002	781 283 Men	BMI < 18.5 18.5–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 3 72 70 53 28 – 	 0.82 (0.20–3.34) 1.00 1.52 (1.07–2.14) 2.00 (1.38–2.89) 2.23 (1.40–3.55) – [< 0.001]	Age, smoking, alcohol consumption, exercise, family history of cancer, area of residence	
Engeland et al. (2006) Norwegian population-based cohort Norway 1972–2003	963 523 Men Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 2 412 322 42 	 0.47 (0.12–1.87) 1.00 1.12 (0.97–1.30) 1.14 (0.82–1.56) [0.005]	Age	Association was similar for age 50–74 yr
	1 037 424 Women Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 30 1187 710 341 	 0.68 (0.47–0.98) 1.00 1.08 (0.98–1.20) 1.29 (1.13–1.46) [0.001]	Age	Association was similar for age 20–49 yr and stronger for age 50–74 yr (57% increased risk). Somewhat stronger associations for follicular carcinoma vs papillary carcinoma
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 89 73 9 	 1.00 1.24 (0.90–1.71) 0.98 (0.49–1.96) [0.48]	Age, calendar year, smoking	

Table 2.2.19a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Song et al. (2008) Female public servants Republic of Korea 1994–2003	170 481 Women	BMI < 18.5 18.5–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 per 1 kg/m^2	 3 40 89 115 93 59 11	 0.35 (0.11–1.10) 0.78 (0.52–1.16) 1.00 1.05 (0.79–1.41) 1.08 (0.80–1.47) 1.02 (0.72–1.45) 0.70 (0.35–1.40) 1.02 (0.98–1.04)	Age, height, smoking, alcohol consumption, exercise, SES	
Clavel-Chapelon et al. (2010) E3N cohort (female teachers) France 1990–2005	91 909 Women	BMI < 18.5 18.5–22 22–25 25–30 ≥ 30 [P_{trend}]	 3 99 129 62 24	 0.35 (0.11–1.12) 1.00 1.39 (1.07–1.81) 1.18 (0.86–1.63) 1.76 (1.12–2.76) [0.005]	Age, year of birth, history of benign thyroid conditions, smoking, iodine	Large body shape (Sörensen's silhouette) at baseline and at age 35–40 yr, but not at age 20–25 yr, associated with increased risk
Leitzmann et al. (2010) NIH-AARP cohort USA 1995–2003	484 326 Men and women Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 107 153 92	 1.00 1.27 (0.99–1.64) 1.39 (1.05–1.85) [0.007]	Age, sex, physical activity, race/ethnicity, education level, smoking, alcohol consumption, OC use	For WC, positive association in men but not in women. For waist-to-hip ratio, null association in either sex
Meinhold et al. (2010) Radiologic Technologists Study USA 1983–2006	21 207 Men Incidence	BMI 18.5–24.9 25–29.9 30–34.5 ≥ 35 [P_{trend}]	 13 15 9 2	 1.00 0.89 (0.42–1.90) 1.91 (0.80–4.56) 2.14 (0.60–7.67) [0.11]	Year of birth, smoking, radiation exposure, history of benign thyroid conditions	
	69 506 Women Incidence	BMI < 18.5 18.5–24.9 25–29.9 30–34.5 ≥ 35 [P_{trend}]	 6 144 44 26 16	 0.96 (0.42–2.18) 1.00 0.90 (0.64–1.27) 1.41 (0.92–2.16) 1.74 (1.03–2.94) [0.04]		

Table 2.2.19a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Almquist et al. (2011) 7 population-based cohorts Austria, Norway, and Sweden 2006–2016	289 866 Men Incidence	BMI, quintiles			Age, smoking	
		Q1	23	1.00		
		Q2	35	1.41 (0.83–2.39)		
		Q3	20	0.77 (0.42–1.41)		
		Q4	29	1.09 (0.63–1.89)		
		Q5	26	1.00 (0.57–1.77)		
		[P_{trend}]		[0.61]		
	288 834 Women Incidence	BMI, quintiles			Age, smoking	
		Q1	41	1.00		
		Q2	37	0.84 (0.54–1.31)		
		Q3	51	1.10 (0.73–1.68)		
		Q4	59	1.22 (0.81–1.84)		
		Q5	67	1.40 (0.93–2.09)		
		[P_{trend}]		[0.02]		
Kabat et al. (2012) Women's Health Initiative USA 1993–2011	144 319 Women Incidence	BMI			Age, age at first pregnancy, education level, smoking, alcohol consumption, exercise, history of benign thyroid conditions	Waist-to-hip ratio and weight change, null association. Similar associations for papillary carcinoma and follicular carcinoma
		< 25	92	1.00		
		25– < 30	99	1.06 (0.79–1.42)		
		30–35	71	1.40 (1.00–1.94)		
		≥ 35	32	0.97 (0.62–1.50)		
		[P_{trend}]		[0.39]		
Rinaldi et al. (2012) EPIC cohort Europe 1992–2009	343 765 Women Incidence	BMI			Age, centre, smoking	Only 58 incident cases identified in men (results not presented). Similar findings for papillary carcinoma only. WC and waist-to-hip ratio both positively associated with risk
		< 18.5	3	0.27 (0.09–0.84)		
		18.5–24.9	290	1.00		
		25–29.9	145	1.12 (0.91–1.38)		
		≥ 30	66	1.19 (0.89–1.59)		
		[P_{trend}]	4	[0.042]		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5.24 million Men and women Incidence	BMI per 5 kg/m^2	941	1.09 (1.00–1.19)	Age, sex, year, diabetes, alcohol consumption, smoking, SES	Similar association in never-smokers

Table 2.2.19a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kitahara et al. (2016) Pooled analysis of 22 cohorts Asia, Australia, Europe, and North America 1979–2009	578 922 Men Incidence	BMI 15–18.4 18.5–24.9 25–29.9 ≥ 30 per 5 kg/m^2	 2 191 327 129	 0.66 (0.16–2.67) 1.0 1.23 (1.02–1.47) 1.35 (1.07–1.71) 1.17 (1.06–1.28)	Age, alcohol consumption, physical activity, race/ethnicity, marital status, education level, smoking	WC less associated. Similar associations for papillary carcinoma and follicular carcinoma
	774 373 Women Incidence	BMI 15–18.4 18.5–24.9 25–29.9 ≥ 30 per 5 kg/m^2 BMI at baseline per 5 kg/m^2 BMI in young adulthood per 5 kg/m^2 BMI gain in adult life per 5 kg/m^2	 29 995 615 356	 0.86 (0.59–1.24) 1.0 1.02 (0.93–1.14) 1.05 (0.92–1.19) 1.04 (1.00–1.09) 1.06 (1.02–1.10) 1.13 (1.02–1.25) 1.07 (1.00–1.15)		Similar associations for WC. Similar associations for papillary carcinoma and follicular carcinoma

BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; OC, oral contraceptive; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.19b Case–control studies of measures of body fatness and cancer of the thyroid

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Odds ratio (95% CI)	Adjustment for confounding	Comments
Dal Maso et al. (2000) Pooled analysis of 12 case–control studies China, Greece, Italy, Japan, Norway, Sweden, Switzerland, and USA	Men: 417 Women: 2056 Population and hospital	BMI, tertiles T1 T2 T3 [P_{trend}] BMI, tertiles T1 T2 T3 [P_{trend}]	NR NR 	Men: 1.0 0.8 (0.6–1.1) 1.0 (0.8–1.4) [0.71] Women: 1.0 1.0 (0.9–1.2) 1.2 (1.0–1.4) [0.04]	Age, history of radiation exposure	
Guignard et al. (2007) New Caledonia 1993–1999	Women: 279 Population	BMI <18.5 18.5–24.99 25.0–29.9 30.0–34.9 ≥ 35.0 [P_{trend}]	 7 80 87 61 41 	 0.99 (0.35–2.80) 1.00 1.18 (0.75–1.86) 1.92 (1.14–3.22) 1.85 (1.02–3.35) [0.01]	Age, reference year, ethnicity, smoking, number of full-term pregnancies, miscarriages, and irregular menstruations	Papillary and follicular carcinomas only The risk was greater in women aged > 50 yr Data for men NR because of the low number of cases
Suzuki et al. (2008) Japan 2001–2005	Women: 131 Hospital	Current BMI, tertiles 15.4–20.4 20.4–22.9 22.9–37.0 [P_{trend}] BMI at age 20 yr, tertiles 14.9–19.2 19.3–21.1 21.2–33.4 [P_{trend}]	 31 51 49 31 45 50 	 1.00 1.01 (0.59–1.74) 1.48 (0.86–2.57) [0.141] 1.00 1.42 (0.85–2.38) 1.18 (0.69–2.01) [0.526]	Age, smoking habits, drinking habits, regular exercise, family history of thyroid cancer, past history of thyroid diseases, total non-alcohol energy intake, referral pattern to the hospital, menopausal status, age at menarche, parity, HRT use	Papillary and follicular carcinomas only Null associations with BMI or weight change since age 20 yr Data for men NR because of the low number of cases

Table 2.2.19b (continued)

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Odds ratio (95% CI)	Adjustment for confounding	Comments
Brindel et al. (2009) French Polynesia 1979–2004	Men: 23 Women: 177 Population; matched by date of birth and sex	BMI before diagnosis			Height, ethnicity, education level, smoking, interviewer, radiation to head or neck before age 15 yr In women, also adjusted for number of full-term pregnancies, menopausal status	
			Men:			
		< 18.5	0	–		
		18.5–24.9	7	1.0		
		25.0–29.9	11	5.9 (0.8–40.8)		
		30.0–34.9	2	3.1 (0.2–42.1)		
		≥ 35.0	3	3.2 (0.3–39.2)		
			Women:			
		< 18.5	7	0.8 (0.3–2.4)		
		18.5–24.9	74	1.0		
		25.0–29.9	44	3.5 (1.7–7.4)		
		30.0–34.9	25	1.2 (0.6–2.6)		
		≥ 35.0	27	3.0 (1.3–7.1)		
		BMI at age 18 yr				
			Men:			
		< 18.5	1	0.05 (0.0–1.0)		
		18.5–24.9	16	1.0		
		25.0–29.9	3	0.8 (0.1–6.3)		
		≥ 30.0	2	4.8 (0.2–113)		
			Women:			
		< 18.5	26	0.6 (0.3–1.2)		
		18.5–24.9	117	1.0		
		25.0–29.9	32	3.7 (1.6–8.4)		
		≥ 30.0	5	1.2 (0.3–5.2)		
Xu et al. (2014) Pooled analysis Germany, Italy, USA 1993–2013	Men: 557 Women: 1360 Hospital	BMI			Age, sex, race/ethnicity, study centre	Papillary carcinoma only. Body fat percentage (calculated by the formula of Deurenberg) also associated with increased risk, overall and by sex
		< 18.5	35	0.82 (0.52–1.30)		
		18.5–24.9	581	1.00		
		25–29.9	422	1.67 (1.38–2.03)		
		≥ 30	319	3.91 (3.02–5.05)		
		[P_{trend}]		[0.001]		

Table 2.2.19b (continued)

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Odds ratio (95% CI)	Adjustment for confounding	Comments
Xhaard et al. (2015) France 2005–2010	Men and women: 761 Population	BMI	All:		Stratified by sex, region, and age and adjusted for education level, ethnicity, smoking status, family history of thyroid cancer, and number of pregnancies (in women only)	No differences in risk were observed when restricting to papillary carcinomas (n = 676 cases)
		< 18.5	52	1.00		
		18.5–24.9	496	1.15 (0.77–1.71)		
		25–29.9	138	1.23 (0.77–1.96)		
		≥ 30	72	1.56 (0.92–2.66)		
		[P_{trend}]		[0.09]		
		BMI	Women:			
		< 18.5	45	1.00		
		18.5–24.9	384	1.25 (0.82–1.90)		
		25–29.9	102	1.50 (0.89–2.51)		
		≥ 30	65	1.78 (1.01–3.14)		
		[P_{trend}]		[0.03]		

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; NR, not reported; yr, year or years

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2.2.20 *Haematopoietic malignancies of lymphoid origin*

Haematopoietic malignancies are a heterogeneous group of cancers that arise from the blood, the bone marrow, and lymphoid tissue, and the cells of origin are either lymphoid or myeloid. Historically, haematopoietic cancers were grouped into five major categories: Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), multiple myeloma (also referred to as plasma cell myeloma), acute leukaemia, and chronic leukaemia. However, these historical groupings do not reflect the current understanding of etiology and pathogenesis or current clinical practice. In 2001, the World Health Organization (WHO) introduced a new classification system (Jaffe et al., 2001), which was subsequently updated (Swerdlow et al., 2008) and is considered the reference standard for classification of these malignancies. The WHO classification has been adopted worldwide, and the terminology has been incorporated into the third edition of the International Classification of Diseases for Oncology (ICD-O-3) (WHO, 2013).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and cancers of the haematopoietic system (e.g. NHL, multiple myeloma) was *inadequate*. In the current review are included epidemiological studies of BMI, weight, or waist circumference at baseline in relation to risk of the more common types of haematopoietic malignancies for which the body of evidence was substantial enough to review. These include Hodgkin lymphoma, NHL, B-cell lymphoma overall, chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, multiple myeloma, T-cell lymphoma, leukaemia overall, acute myeloid leukaemia (AML), and chronic myeloid leukaemia (CML). Also included are findings from prospective studies with at least 50 cases for any specific subtype, meta-analyses or pooled analyses from prospective and case–control studies, and findings from case–control studies with at least 50 cases that were not included in a meta-analysis or pooled analysis. For malignancies for which there was evidence suggesting a relationship between BMI or weight at baseline and risk, the Working Group also weighed into their evaluation studies that assessed weight change and weight during young adulthood in relation to risk. Not all studies separated the haematopoietic cancers according to the current WHO classification system. Therefore, findings are presented about relationships between BMI and both individual haematological cancers and groups of cancers.

Table 2.2.20a and Table 2.2.20b (both web only, available at: http://publications.iarc.fr/570) present data for cohort and case–control studies, respectively, for subsites with *inadequate* evidence; Table 2.2.20c and Table 2.2.20d present the corresponding studies for subsites with *sufficient* or *limited* evidence.

(a) Hodgkin lymphoma

There are at least four individual prospective studies and one meta-analysis of BMI at baseline in relation to incidence of Hodgkin lymphoma (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570). Results from three prospective studies in men (i.e. the United States Veterans cohort, the NIH-AARP cohort, and the Swedish Construction Worker cohort) showed increased risks (Samanic et al., 2004, 2006; Lim et al., 2007), none of which were statistically significant, whereas a Norwegian cohort study found a positive association in women but not in men (Engeland et al., 2007). [Most studies had limited statistical power, particularly at the high end of the BMI categories.] However, in the meta-analysis of five studies, obesity was

associated with a statistically significant 41% higher risk of Hodgkin lymphoma compared with normal BMI (Larsson & Wolk, 2011).

Only three case–control studies with at least 50 cases have evaluated the relationship between BMI and risk of Hodgkin lymphoma (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570). The largest study, including 618 cases from the Scandinavian Lymphoma Etiology Study and 3187 population controls, did not find a relationship between BMI and risk of Hodgkin lymphoma in individuals younger or older than 45 years, assessed separately because of the bimodal distribution of the disease (Chang et al., 2005). A second large study, including 567 cases and 697 controls, also did not find a relationship between BMI and risk of Hodgkin lymphoma in subgroups defined by sex and age (Li et al., 2013). However, a smaller study of 216 cases and 216 matched controls, which considered BMI 5 years before cancer diagnosis, found an increased risk of Hodgkin lymphoma with BMI ≥ 30 kg/m^2 compared with normal BMI in men, but not in women (Willett & Roman, 2006).

(b) Non-Hodgkin lymphoma

There are at least 21 individual prospective studies and 4 meta-analyses or pooled analyses of BMI and/or weight at baseline in relation to NHL (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570). There were no associations of either BMI or weight with NHL incidence or mortality in 12 individual prospective studies (Samanic et al., 2004, 2006; Fujino et al., 2007; Maskarinec et al., 2008; Song et al., 2008; Andreotti et al., 2010; De Roos et al., 2010; Kanda et al., 2010; Hemminki et al., 2011; Kabat et al., 2012; Bertrand et al., 2013; Bhaskaran et al., 2014). The other nine studies found positive associations in men and/or women (Calle et al., 2003; Oh et al., 2005; Rapp et al., 2005; Chiu et al., 2006; Engeland et al., 2007; Lim et al., 2007; Reeves et al., 2007; Troy et al., 2010; Chu et al., 2011). Three meta-analyses showed a positive association between BMI and NHL incidence and/or mortality (Larsson & Wolk, 2007a, 2011; Renehan et al., 2008), whereas one pooled analysis found no association (Whitlock, et al., 2009). [The inconsistent evidence from individual prospective studies and meta-analyses may be due to the variation in histological subtypes included in a classification of NHL.]

No association between waist circumference and NHL incidence was seen in the Women's Health Initiative in the USA (Kabat et al., 2012). However, in a cohort in Taiwan, China, high abdominal obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women) was associated with an 86% higher risk of fatal NHL compared with lower waist circumference (Chu et al., 2011).

A total of 11 hospital-based or population-based case–control studies have evaluated the relationship between BMI and risk of any NHL (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570). A meta-analysis of six of these reports published in 2004 and 2005 (Pan et al., 2004; Skibola et al., 2004; Bosetti et al., 2005; Cerhan et al., 2005; Chang et al., 2005; Willett et al., 2005) reported a relative risk of NHL of 1.22 (95% CI, 1.00–1.50) in individuals with BMI ≥ 30 kg/m^2 (Larsson & Wolk, 2007a). A subsequent pooled analysis from the InterLymph Consortium included data from 10 000 cases of NHL and 16 000 controls drawn from 18 case–control studies identified through the International Lymphoma Epidemiology Consortium (Willett et al., 2008). That study did not find a relationship between BMI and risk of NHL, with a relative risk of NHL of 0.84 (95% CI, 0.72–0.99) in individuals with BMI of 30–39.9 kg/m^2 and a relative risk of 0.63 (95% CI, 0.40–0.99) in those with BMI ≥ 40 kg/m^2.

(c) B-cell lymphoma

The association between excess body fatness and the incidence of B-cell lymphoma was examined in three individual prospective

studies (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570) [notably, under the current classification, this includes all B-cell malignancies previously included under NHL]. Although no association was found with BMI and/or weight in men or in women in the EPIC cohort (Britton et al., 2008), there were statistically significant positive trends with weight in the California Teachers Study (Lu et al., 2009) and with BMI in the Cancer Prevention Study II Nutrition Cohort (Patel et al., 2013).

In the one study that assessed waist circumference, there was no association with the incidence of B-cell lymphoma in either men or women (Britton et al., 2008).

(d) Subtypes of B-cell lymphoma

(i) Chronic lymphocytic leukaemia/small lymphocytic lymphoma

Most of the individual prospective studies (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570) found no associations of BMI and/or weight at baseline with the incidence of CLL or CLL/SLL (Ross et al., 2004; Samanic et al., 2006; Engeland et al., 2007; Lim et al., 2007; Lu et al., 2009; Pylypchuk et al., 2009; Kabat et al., 2012; Bertrand et al., 2013; Patel et al., 2013; Saberi Hosnijeh et al., 2013). However, in the United States Veterans study, the largest individual prospective study, the risk of CLL was 30% higher in obese White men and 72% higher in obese Black men compared with non-obese men (Samanic et al., 2004). In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial in the USA, baseline weight, but not BMI, was positively associated with risk ($P_{trend} < 0.215$) (Troy et al., 2010). Although an earlier meta-analysis of three cohort studies suggested a 25% higher risk of CLL for obesity versus normal weight (Larsson & Wolk, 2008), an updated meta-analysis of six prospective studies found no association between BMI as a continuous measure and incidence of CLL/SLL (Larsson & Wolk, 2011).

No association between waist circumference and CLL/SLL incidence was found in the three studies that examined this relationship (Ross et al., 2004; Kabat et al., 2012; Saberi Hosnijeh et al., 2013).

Five case–control studies with at least 50 cases assessed the relationship between BMI and risk of CLL/SLL (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570) and found no association between BMI and CLL/SLL risk (Chang et al., 2005; Pan et al., 2005; Morton et al., 2008; Chen et al., 2011; Kelly et al., 2012).

(ii) Diffuse large B-cell lymphoma

Associations of baseline BMI and/or weight with risk of DLBCL have been examined in at least nine individual prospective studies and two meta-analyses (Table 2.2.20c). Most individual prospective studies found no evidence of an association (Lim et al., 2007; Britton et al., 2008; Maskarinec et al., 2008; Lu et al., 2009; Pylypchuk et al., 2009; Kabat et al., 2012; Bertrand et al., 2013). However, two large studies in the USA did report statistically significant trends between baseline weight (Troy et al., 2010) or BMI (Patel et al., 2013) and DLBCL incidence. Both meta-analyses also showed statistically significant positive associations. One meta-analysis reported a relative risk per 5 kg/m^2 increase of 1.13 (95% CI, 1.02–1.26) (Larsson & Wolk, 2011). In the other meta-analysis, both overweight and obesity in men and women were associated with increased risk (Castillo et al., 2014).

Six individual studies assessed the association between BMI or weight in early adulthood and incidence of DLBCL. In the two large studies in the USA, there were statistically significant positive associations of weight at age 20 years ($P_{trend} = 0.013$) (Troy et al., 2010) and of young adult BMI in men and women combined ($P_{trend} = 0.02$) (Bertrand et al., 2013) with risk of DLBCL. However, in none of the four other studies was BMI and/or body weight at age 18 years (Lu et al., 2009; Patel et al., 2013), at

age 20 years (Pylypchuk et al., 2009), or at age 21 years (Maskarinec et al., 2008) associated with DLBCL incidence. Similarly, adult weight gain was not associated with risk of DLBCL in any of the studies that examined this association (Maskarinec et al., 2008; Troy et al., 2010; Patel et al., 2013).

In the EPIC cohort, there was a 2-fold (RR, 2.03; 95% CI, 0.96–4.28) higher incidence of DLBCL for waist circumference ≥ 102 cm versus < 102 cm in men (based on only 21 cases in the group with high waist circumference), and no association in women (Britton et al., 2008). Similarly, there was no association between waist circumference and risk of DLBCL in the Women's Health Initiative in the USA (Kabat et al., 2012).

A pooled analysis of 19 case–control studies from the InterLymph Consortium of 4667 cases of DLBCL and 22 639 controls found a significant positive association between risk of DLBCL and young adult BMI, but not usual adult BMI (Cerhan et al., 2014). A case–control study from the National Enhanced Cancer Surveillance System in Canada, including 419 cases of DLBCL, found an odds ratio for individuals with BMI ≥ 30 kg/m^2 of 1.35 (95% CI, 0.99–1.83) (Pan et al., 2005). Another case–control study, by Chen et al., (2011), including 245 cases of DLBCL, did not find a relationship between BMI and risk of DLBCL (Table 2.2.20d).

(iii) Follicular lymphoma

None of the nine individual prospective studies (Lim et al., 2007; Britton et al., 2008; Maskarinec et al., 2008; Lu et al., 2009; Pylypchuk et al., 2009; Troy et al., 2010; Kabat et al., 2012; Bertrand et al., 2013; Patel et al., 2013) or the one meta-analysis (Larsson & Wolk, 2011) showed any evidence of an association between BMI and/or weight and the incidence of follicular lymphoma (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570).

Waist circumference was also not associated with the incidence of follicular lymphoma in the two studies that examined this relationship (Britton et al., 2008; Kabat et al., 2012).

The largest study evaluating the association between BMI and follicular lymphoma (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570) was a pooled analysis of 3530 cases and 22 639 population controls from 19 case–control studies in the InterLymph Consortium, which found no relationship between BMI and risk of follicular lymphoma (Linet et al., 2014). Two additional case–control studies not included in the pooled analysis also found no association between adult BMI and risk of follicular lymphoma (Pan et al., 2005; Chen et al., 2011).

Therefore, the relationship between BMI and risk of NHL varies by subtype, with a positive association seen in some studies limited to the risk of DLBCL, but not in studies assessing the risk of any NHL or of follicular lymphoma.

(e) Multiple myeloma

In the individual prospective studies that examined the association of baseline BMI and/or weight with multiple myeloma incidence or mortality (Table 2.2.20c), most found positive associations for at least one measure of excess body fatness at baseline (Calle et al., 2003; Samanic et al., 2004; Blair et al., 2005; Birmann et al., 2007; Engeland et al., 2007; Fujino et al., 2007; Reeves et al., 2007; Troy et al., 2010; Hofmann et al., 2013). In particular, a positive association was observed in the largest studies. In the United States Veterans cohort of more than 4 million men, the risk of multiple myeloma was 22% higher in obese White men and 26% higher in obese Black men compared with non-obese men (Samanic et al., 2004). Similarly, the Million Women Study in the United Kingdom found positive associations between BMI and multiple myeloma incidence and mortality (31% and 56% increase, respectively, per 10 kg/m^2) (Reeves et al., 2007). In a Norwegian cohort study of more than 2 million men and women whose height and weight were measured at baseline in 1963, there

were statistically significant dose-related positive associations between BMI and risk of multiple myeloma in men (RR, 1.14 for overweight and 1.28 for obesity vs normal BMI; $P_{trend} < 0.001$) and in women (RR, 1.12 for overweight, 1.23 for grade I, 1.42 for grade II, and 1.57 for grade III obesity vs normal BMI; $P_{trend} < 0.001$) (Engeland et al., 2007). One study found an inverse association (Samanic et al., 2006), and several studies found no association (Oh et al., 2005; Fernberg et al., 2007; Pylypchuk et al., 2009; De Roos et al., 2010; Lu et al., 2010; Kanda et al., 2010; Patel et al., 2013; Bhaskaran et al., 2014).

Several meta-analyses or pooled analyses of excess body fatness in relation to multiple myeloma incidence and/or mortality have been conducted (Larsson & Wolk, 2007b; Renehan et al., 2008; Parr et al., 2010; Wallin & Larsson, 2011; Teras et al., 2014). No association between BMI and multiple myeloma mortality was found in the Asia-Pacific Cohort Study Collaboration (Parr et al., 2010). However, in the meta-analysis by Wallin & Larsson (2011), which included studies worldwide, overweight and obesity were associated with a statistically significantly increased risk of multiple myeloma incidence (RR, 1.12 for overweight and 1.21 for obesity, based on 15 studies) and mortality (RR, 1.15 for overweight and 1.54 for obesity, based on 5 studies). The two earlier meta-analyses (Larsson & Wolk, 2007b; Renehan et al., 2008) found statistically significant positive associations of a similar magnitude. Consistent with these findings, in a pooled analysis of data from 20 prospective studies (Teras et al., 2014), there was a statistically significant positive association between BMI and multiple myeloma mortality (RR per 5 kg/m^2 increase in BMI, 1.09).

Given the observed associations between baseline BMI and risk of multiple myeloma, associations with young adult BMI and with BMI change were also examined. Several studies found no association between young adult BMI and risk of multiple myeloma (Fujino et al., 2007; Pylypchuk et al., 2009; De Roos et al., 2010; Lu et al., 2010; Patel et al., 2013), whereas in two large studies young adult BMI was positively associated with risk (Troy et al., 2010; Hofmann et al., 2013). In the large pooled analysis by Teras et al. (2014) there was a statistically significant positive association between increasing levels of young adult BMI (beginning in the overweight category) and multiple myeloma mortality, although there was no association for change in BMI during adulthood.

High waist circumference was associated with increased multiple myeloma incidence in one prospective study of postmenopausal women (Blair et al., 2005), but not in two other studies (Britton et al., 2008; Lu et al., 2010). In the large pooled analysis by Teras et al. (2014), there was a statistically significant positive association between waist circumference and multiple myeloma mortality in men and women combined (RR per 5 cm increase, 1.06).

Five case–control studies have evaluated the relationship between BMI and the risk of multiple myeloma, four of which were included in a meta-analysis (Larsson & Wolk, 2007b; Table 2.2.20d). An increased risk of multiple myeloma was reported in individuals who were overweight (RR, 1.43; 95% CI, 1.23–1.68) and those who were obese (RR, 1.82; 95% CI, 1.47–2.26). One additional study reported no significant association (Wang et al., 2013).

(f) T-cell lymphoma

In the Cancer Prevention Study II Nutrition Cohort (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570), there was a positive association between BMI and the incidence of T-cell lymphoma ($P_{trend} = 0.013$) (Patel et al., 2013). However, in two European cohort studies there was no association (Lukanova et al., 2006; Lim et al., 2007). In the Cancer Prevention Study II Nutrition Cohort, BMI at age 18 years was not associated with the incidence of T-cell lymphoma (Patel et al., 2013).

Table 2.2.20c Cohort studies of measures of body fatness and haematopoietic malignancies of lymphoid origin with *sufficient* or *limited* evidence

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Diffuse large B-cell lymphoma							
Lim et al. (2007) NIH-AARP cohort USA 1995–2003	473 984 Men and women Incidence	DLBCL ICD-O-2: 9680–9684, 9688, 9710–9712, 9715	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 119 141 61 21	 1.00 0.92 (0.72–1.18) 1.10 (0.81–1.51) 1.17 (0.73–1.88) [0.42]	Age, ethnicity, education level, alcohol intake, cigarette smoking, height, physical activity	
Britton et al. (2008) EPIC cohort 10 European countries 1993–1998	141 425 Men Incidence	DLBCL	BMI < 25 25–29.9 ≥ 30 [P_{trend}] Weight (kg) < 72.7 72.7–79.8 79.9–87.7 ≥ 87.8 [P_{trend}] WC (cm) < 102 ≥ 102	 24 37 10 19 13 20 19 44 21	 1.00 0.83 (0.39–1.76) 0.94 (0.56–1.59) [0.63] 1.00 0.59 (0.29–1.20) 0.90 (0.46–1.74) 0.86 (0.42–1.77) [1.00] 1.00 2.03 (0.96–4.28)	Age, study centre	Also examined height, hip circumference, and waist-to-hip ratio
	230 558 Women Incidence	DLBCL	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 30 31 12	 1.00 1.27 (0.63–2.55) 1.54 (0.92–2.57) [0.28]	Age, study centre	Also examined height, hip circumference, and waist-to-hip ratio

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Britton et al. (2008) (cont.)			Weight (kg)				
			< 72.7	14	1.00		
			72.7–79.8	12	0.78 (0.35–1.69)		
			79.9–87.7	21	1.32 (0.66–2.68)		
			≥ 87.8	26	1.62 (0.81–3.25)		
			[P_{trend}]		[0.06]		
			WC (cm)				
			< 88	47	1.00		
			≥ 88	21	0.88 (0.42–1.85)		
Maskarinec et al. (2008) Multiethnic Cohort 1993–2002	87 079 Men Incidence	DLBCL ICD-O-3: 9675, 9680, 9684	BMI at baseline			Age, ethnicity, education level, alcohol consumption	
			< 22.5	23	0.65 (0.35–1.21)		
			22.5–24.9	44	1.00		
			25.0–29.9	60	0.90 (0.56–1.43)		
			≥ 30.0	23	0.78 (0.40–1.52)		
			[P_{trend}]		[0.69]		
			BMI at age 21 yr				
			< 18.5	14	0.56 (0.27–1.15)		
			18.5–24.9	105	1.00		
			25.0–29.9	17	0.78 (0.41–1.48)		
			≥ 30.0	5	1.03 (0.36–2.91)		
			[P_{trend}]		[0.51]		
			Weight (lb) at baseline				
			< 152.0	47	1.00		
			152.0–170.0	37	1.97 (1.16–3.36)		
			170.1–192.0	32	1.36 (0.75–2.49)		
			> 192.0	35	1.87 (0.95–3.68)		
			[P_{trend}]		[0.12]		
			Weight (lb) at age 21 yr				
			< 130.0	43	1.00		
			130.0–145.0	34	0.87 (0.50–1.53)		
			145.1–165.0	38	1.24 (0.64–2.41)		
			> 165.0	27	1.26 (0.63–2.50)		
			[P_{trend}]		[0.33]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Maskarinec et al. (2008) (cont.)			Annual weight change (lb)				
			0 or loss	32	1.00		
			≤ 1	89	1.07 (0.62–1.86)		
			> 1	31	1.14 (0.56–2.34)		
			[P_{trend}]		[0.69]		
	105 972 Women Incidence	DLBCL ICD-O-3: 9675, 9680, 9684	BMI at baseline			Age, ethnicity, education level, alcohol consumption, age at first birth	
			< 22.5	27	1.41 (0.66–3.00)		
			22.5–24.9	30	1.00		
			25.0–29.9	43	1.06 (0.58–1.96)		
			≥ 30.0	28	1.45 (0.75–2.82)		
			[P_{trend}]		[0.80]		
			BMI at age 21 yr				
			< 18.5	16	1.02 (0.50–2.10)		
			18.5–24.9	91	1.00		
			25.0–29.9	11	1.08 (0.50–2.33)		
			≥ 30.0	4	0.94 (0.25–3.55)		
			[P_{trend}]		[1.00]		
			Weight (lb) at baseline				
			< 125.0	26	1.00		
			125.0–143.0	38	0.74 (0.40–1.38)		
			143.1–167.0	35	1.35 (0.67–2.75)		
			> 167.0	30	1.20 (0.57–2.52)		
			[P_{trend}]		[0.40]		
			Weight (lb) at age 21 yr				
			< 105.0	22	1.00		
			105.0–118.0	34	0.70 (0.35–1.41)		
			118.1–127.0	34	0.97 (0.48–1.96)		
			> 127.0	33	1.10 (0.53–2.29)		
			[P_{trend}]		[0.44]		
			Annual weight change (lb)				
			0 or loss	19	1.00		
			≤ 1	85	0.56 (0.21–1.55)		
			> 1	28	0.93 (0.34–2.54)		
			[P_{trend}]		[0.85]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lu et al. (2009) California Teachers Study USA 1995–2007	121 216 Women Incidence	DLBCL	BMI at baseline			Weight, height, age at menarche, and physical activity	Also included results for height and physical activity
			< 20	17	1.42 (0.83–2.42)		
			20–24.9	64	1.00		
			25–29.9	41	1.07 (0.72–1.59)		
			≥ 30	26	1.37 (0.86–2.16)		
			[P_{trend}]		[0.50]		
			BMI at age 18 yr				
			< 19.5	37	0.98 (0.62–1.56)		
			19.5–20.7	36	1.00		
			20.8–22.4	32	0.90 (0.56–1.45)		
			> 22.4	43	1.23 (0.79–1.92)		
			[P_{trend}]		[0.30]		
			Weight (kg) at baseline				
			< 56.7	33	1.24 (0.76–2.03)		
			56.7– < 63.5	33	1.00		
			63.5– < 73.0	40	0.90 (0.57–1.43)		
			≥ 73.0	42	1.08 (0.68–1.72)		
			[P_{trend}]		[0.81]		
			Weight (kg) at age 18 yr				
			< 52.6	33	0.88 (0.54–1.41)		
			52.6– < 57.2	45	1.00		
			57.2– < 61.7	30	1.16 (0.72–1.84)		
			≥ 61.7	40	1.23 (0.79–1.92)		
			[P_{trend}]		[0.19]		
Pylypchuk et al. (2009) Netherlands Cohort Study on Diet and Cancer The Netherlands 1986–1999	5000 Men and women Incidence	DLBCL ICD-O-3: 9675, 9680, 9684	BMI			Age, sex	Case–cohort design
			< 18.5	3	1.91 (0.58–6.30)		
			18.5–24.9	112	1.00		
			25–29.9	101	1.16 (0.88–1.53)		
			≥ 30	8	0.62 (0.30–1.30)		
			[P_{trend}]		[0.77]		
			per 4 kg/m^2		0.92 (0.77–1.10)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pylypchuk et al. (2009) (cont.)			BMI at age 20 yr				
			< 20	39	0.96 (0.61–1.50)		
			20–21.4	43	1.00		
			21.5–22.9	41	0.99 (0.64–1.54)		
			23–24.9	43	1.35 (0.88–2.10)		
			≥ 25	16	1.29 (0.71–2.35)		
			[P_{trend}]		[0.12]		
			per 4 kg/m²		1.20 (0.98–1.47)		
Troy et al. (2010) PLCO Trial USA 1993–2006	142 982 Men and women Incidence	DLBCL	BMI at baseline			Age, race/ ethnicity, education level	
			< 18.5	4	–		
			18.5–24.9	58	1.00		
			25–29.9	87	1.07 (0.76–1.50)		
			≥ 30	63	1.58 (1.10–2.27)		
			[P_{trend}]		[0.056]		
			BMI at age 20 yr				
			< 18.5	17	1.22 (0.74–2.02)		
			18.5–24.9	157	1.00		
			25–29.9	35	1.19 (0.82–1.73)		
			≥ 30	1	–		
			[P_{trend}]		[0.230]		
			Weight change (kg) per 10 yr				
			Loss	10	0.70 (0.35–1.39)		
			Gain 0–2	53	1.00		
			Gain 2.1–4	66	1.13 (0.78–1.63)		
			Gain 4.1–6	46	1.32 (0.88–1.97)		
			Gain ≥ 6	37	1.41 (0.91–2.18)		
			[P_{trend}]		[0.114]		
			Weight (kg) at baseline, quartiles (sex-specific)				
			Men: Women:				
			< 77.4 < 61.5	51	1.00		
			77.4–85.5 61.5–70.0	46	1.05 (0.71–1.57)		
			85.6–95.5 70.1–80.0	54	1.18 (0.81–1.74)		
			> 95.5 > 80.0	63	1.63 (1.12–2.37)		
			[P_{trend}]		[< 0.01]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Troy et al. (2010) (cont.)			Weight (kg) at age 20 yr, quartiles (sex-specific) Men: / Women: < 64.2 / < 51.9 64.2–72.7 / 51.9–54.5 72.8–79.5 / 54.6–59.1 > 79.5 / > 59.1 [P_{trend}]	 40 41 66 65	 1.00 1.26 (0.81–1.95) 1.46 (0.98–2.17) 1.67 (1.12–2.50) [0.013]		
Larsson & Wolk (2011) Meta-analysis Multiple locations 1999–2010	6 studies Men and women Incidence	DLBCL	BMI per 5 kg/m²	NR	 1.13 (1.02–1.26)		
Kabat et al. (2012) Women's Health Initiative USA 1993–2009	158 975 Women Incidence	DLBCL ICD-O-3: 9678–9680, 9684	BMI at baseline < 25 25– < 30 30– < 35 ≥ 35 [P_{trend}] Weight (kg) at baseline < 62.0 62.0– < 70.4 70.4– < 81.6 ≥ 81.6 [P_{trend}] WC (cm) at baseline < 76.1 76.1– < 84.6 84.6– < 95.0 > 95.0 [P_{trend}]	 99 115 55 33 73 79 80 70 70 80 68 84	 1.00 1.23 (0.93–1.62) 1.11 (0.78–1.58) 1.30 (0.85–1.99) [0.25] 1.00 1.09 (0.78–1.51) 1.11 (0.79–1.56) 1.05 (0.72–1.52) [0.77] 1.00 1.13 (0.82–1.58) 1.02 (0.72–1.44) 1.28 (0.91–1.81) [0.25]	Age, smoking, alcohol consumption, education level, ethnicity, physical activity, energy intake, substudy	Also included estimates for height, hip circumference, waist-to-hip ratio, and weight/BMI at ages 18 yr, 35 yr, and 50 yr

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bertrand et al. (2013) Nurses' Health Study and Health Professionals Follow-up Study USA 1976–2008	163 184 Men and women Incidence	DLBCL	Adult BMI per 5 kg/m^2 [P_{trend}]	[261]	 1.10 (0.91–1.33) [0.31]	Age, height, smoking, physical activity, race	
			Young adult BMI per 5 kg/m^2 [P_{trend}]	[241]	 1.29 (1.05–1.57) [0.02]		
	46 390 Men Incidence	DLBCL	Adult BMI 15–22.9 23–24.9 25–26.9 27–29.9 30–45 per 5 kg/m^2 [P_{trend}]	 11 25 23 17 10	 1.00 1.57 (0.75–3.28) 1.58 (0.75–3.34) 1.65 (0.75–3.64) 2.18 (0.88–5.40) 1.30 (0.92–1.82) [0.14]	Age, height, smoking, physical activity, race	
			Young adult BMI 15–18.4 18.5–22.9 23–24.9 25–29.9 30–45 per 5 kg/m^2 [P_{trend}]	 4 40 19 17 4	 1.36 (0.46–4.02) 1.00 0.94 (0.54–1.64) 1.16 (0.65–2.08) 2.70 (0.93–7.86) 1.29 (0.89–1.88) [0.18]		
	116 794 Women Incidence	DLBCL	Adult BMI 15–22.9 23–24.9 25–26.9 27–29.9 30–45 per 5 kg/m^2 [P_{trend}]	 60 38 31 23 33	 1.00 0.97 (0.64–1.46) 1.06 (0.69–1.65) 0.85 (0.52–1.38) 1.36 (0.88–2.10) 1.04 (0.88–1.23) [0.65]	Age, height, smoking, physical activity, race	

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bertrand et al. (2013) (cont.)			Young adult BMI				
			15–18.4	14	0.71 (0.40–1.24)		
			18.5–22.9	104	1.00		
			23–24.9	18	0.99 (0.60–1.64)		
			25–29.9	17	1.26 (0.75–2.11)		
			30–45	4	1.39 (0.51–3.81)		
			per 5 kg/m^2		1.28 (1.01–1.63)		
			[P_{trend}]		[0.04]		
Patel et al. (2013) Cancer Prevention Study II Nutrition Cohort USA 1992–2007	152 423 Men and women Incidence	DLBCL	BMI at baseline			Age, sex, family history of haematopoietic cancer, education level, smoking status, physical activity, alcohol consumption	
			< 18.5	1	0.28 (0.04–1.97)		
			18.5– < 25	159	1.00		
			25– < 30	199	1.30 (1.05–1.61)		
			≥ 30	85	1.62 (1.23–2.12)		
			[P_{trend}]		[0.0001]		
			BMI at age 18 yr				
			< 18.5	52	0.86 (0.64–1.17)		
			18.5– < 22.5	245	1.00		
			22.5– < 25	88	1.07 (0.83–1.38)		
			25– < 30	44	1.01 (0.72–1.42)		
			≥ 30	7	1.30 (0.60–2.80)		
			[P_{trend}]		[0.32]		
			Adult weight change (lb)				
			Loss > 5	11	0.60 (0.32–1.10)		
			Loss 5 to gain 20	147	1.00		
			Gain 21–40	142	0.97 (0.77–1.22)		
			Gain 41–60	83	0.97 (0.74–1.28)		
			Gain > 60	52	1.11 (0.80–1.54)		
			[P_{trend}]		[0.25]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Castillo et al. (2014) Meta-analysis of 10 cohorts, 6 case–control	NR Men and women Incidence	DLBCL	BMI Overweight Obese		 1.14 (1.04–1.24) 1.29 (1.16–1.43)		
	NR Men Incidence	DLBCL	BMI Overweight Obese		 1.27 (1.09–1.47) 1.40 (1.00–1.95)		
	NR Women Incidence	DLBCL	BMI Overweight Obese		 1.22 (1.07–1.38) 1.34 (1.16–1.54)		
Multiple myeloma							
Calle et al. (2003) Cancer Prevention Study II USA 1982–1998	495 477 Women Mortality	Multiple myeloma	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 341 187 72 20	 1.00 1.12 (0.93–1.34) 1.47 (1.13–1.91) 1.44 (0.91–2.28) [0.004]	Age, race, education level, smoking, physical activity, alcohol consumption, marital status, aspirin use, fat and vegetable consumption	
	404 576 Men Mortality		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 259 368 70 11	 1.00 1.18 (1.01–1.39) 1.44 (1.10–1.89) 1.71 (0.93–3.14) [0.002]		
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Multiple myeloma ICD-9: 203	Obesity Non-obese Obese Non-obese Obese	White men: 2817 204 Black men: 1509 89	 1.00 1.22 (1.05–1.40) 1.00 1.26 (1.02–1.56)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0
Blair et al. (2005) Iowa Women's Health Study USA 1986–2001	37 083 Women Incidence	Multiple myeloma	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 30 37 28	 1.0 1.3 (0.78–2.0) 1.5 (0.92–2.6) [0.10]	Age	Also included analyses of height, waist-to-hip ratio, and hip circumference

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Blair et al. (2005) (cont.)			Weight (lb) < 138 138–160 ≥ 161 [P_{trend}] WC (in) < 31.75 31.76–36.25 ≥ 36.26 [P_{trend}]	 19 40 36 19 37 39 	 1.0 2.0 (1.1–3.4) 1.9 (1.1–3.4) [0.04] 1.0 1.9 (1.1–3.2) 2.0 (1.1–3.5) [0.02]		
Oh et al. (2005) Korea National Health Insurance Corporation Republic of Korea 1992–2001	781 283 Men Incidence	Multiple myeloma	BMI < 18.5 18.5–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 2 36 45 14 6 0 	 1.19 (0.29–4.96) 1.00 1.72 (1.11–2.68) 0.96 (0.51–1.77) 0.98 (0.30–3.32) – [0.61]	Age, smoking, alcohol intake, physical activity, family history of cancer, urban/ rural residence	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Multiple myeloma ICD-7: 203	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 231 201 20 	 1.00 0.96 (0.79–1.16) 0.58 (0.37–0.93) [0.06]	Attained age, calendar year, smoking	
Birmann et al. (2007) Nurses' Health Study and Health Professionals Follow-up Study combined USA 1980–2002	136 623 Men and women Incidence	Multiple myeloma	BMI < 22 22–24.9 25–29.9 ≥ 30 [P_{trend}]	 28 64 84 39 	 1.0 1.2 (0.8–1.9) 1.3 (0.9–2.0) 1.5 (0.9–2.5) [0.11]	Age, sex, physical activity, cohort	

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Birmann et al. (2007) (cont.) Nurses' Health Study	89 663 Women Incidence		BMI < 22 22–24.9 25–29.9 ≥ 30 [P_{trend}]	 21 32 53 23	 1.0 1.1 (0.7–2.0) 1.6 (1.0–2.7) 1.2 (0.7–2.2) [0.43]	Age, physical activity	
Health Professionals Follow-up Study	46 960 Men Incidence		BMI < 22 22–24.9 25–29.9 ≥ 30 [P_{trend}]	 7 32 31 16	 1.0 1.3 (0.5–2.9) 1.0 (0.4–2.2) 2.4 (1.0–6.0) [0.07]	Age, physical activity	
Engeland et al. (2007) Norwegian cohort Norway 1963–2001	963 709 Men Incidence	Plasma cell myeloma	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 11 1596 1417 209	 0.69 (0.38–1.25) 1.00 1.14 (1.06–1.22) 1.28 (1.10–1.47) [< 0.001]	Age, birth cohort	
	1 038 010 Women Incidence		BMI < 18.5 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 24 1161 1125 436 110 26	 0.85 (057–1.27) 1.00 1.12 (1.03–1.22) 1.23 (1.10–1.38) 1.42 (1.17–1.74) 1.57 (1.06–2.31) [< 0.001]		
Fernberg et al. (2007) Swedish construction workers Sweden 1971–2004	336 381 Men Incidence	Multiple myeloma	BMI 18.5–25 25.1–30 > 30	 256 236 27	 1.00 1.04 (0.86–1.24) 0.70 (0.46–1.06)	Attained age, snuff use, daily tobacco smoking	

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Fujino et al. (2007) Japan Collaborative Cohort Study Japan NR	NR Men Mortality	Multiple myeloma	BMI			Age, area of study	[No information provided on follow-up or number of people in study]
			< 18.5	3	0.96 (0.29–3.16)		
			18.5–24	36	1.00		
			25–29	5	0.70 (0.27–1.80)		
			≥ 30	0	N.A		
			Weight (kg)				
			< 55	12	1.00		
			55–62	20	1.51 (0.73–3.11)		
			≥ 63	15	1.41 (0.64–3.12)		
			Weight (kg) at age 20 yr				
			< 55	25	1.00		
			55–60	12	0.91 (0.38–2.14)		
			≥ 61	10	0.98 (0.40–2.42)		
	NR Women Mortality	Multiple myeloma	BMI			Age, area of study	[No information provided on follow-up or number of people in study]
			< 18.5	2	0.59 (0.14–2.48)		
			18.5–24	31	1.00		
			25–29	7	0.77 (0.34–1.77)		
			≥ 30	4	4.34 (1.51–12.5)		
			Weight (kg)				
			< 49	18	1.00		
			49–54	12	0.93 (0.44–1.96)		
			≥ 55	17	1.17 (0.59–2.33)		
			Weight (kg) at age 20 yr				
			< 47	24	1.00		
			47–52	9	0.76 (0.32–1.81)		
			≥ 53	11	0.87 (0.38–1.97)		
Larsson & Wolk (2007b) Meta-analysis Multiple locations 1994–2007	9 cohort studies Men and women Incidence	Multiple myeloma	BMI per 5 kg/m^2	6987 total	1.11 (1.03–1.19)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Larsson & Wolk (2007b) (cont.)	9 cohort studies Men and women Mortality		BMI per 5 kg/m²	1492 total	 1.19 (1.12–1.28)		
	9 cohort studies Men and women Incidence and mortality		BMI Normal Overweight Obese per 5 kg/m²	8479 total	 1.00 1.12 (1.07–1.18) 1.27 (1.15–1.41) 1.14 (1.09–1.20)		Similar values for BMI per 5 kg/m² for men and women separately
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence	Multiple myeloma ICD-10: C90	BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	 76 127 118 73 97	 0.80 (0.64–1.00) 1.00 (0.84–1.19) 1.11 (0.92–1.32) 1.11 (0.88–1.40) 1.16 (0.95–1.42) 1.31 (1.04–1.65)	Age, geographical region, SES, reproductive history, smoking status, alcohol intake, physical activity	
	1 222 630 Women Mortality		BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	 46 63 68 38 69	 0.99 (0.74–1.32) 1.00 (0.78–1.28) 1.26 (0.99–1.59) 1.13 (0.82–1.55) 1.63 (1.28–2.08) 1.56 (1.15–2.10)		
Britton et al. (2008) EPIC cohort 10 European countries 1993–1998	141 425 Men Incidence	Multiple myeloma	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 43 72 24	 1.00 1.33 (0.79–2.23) 1.17 (0.80–1.72) [0.26]	Age, study centre	Also examined height, hip circumference, and waist-to-hip ratio; analyses by weight and WC gave similar results
	230 558 Women Incidence	Multiple myeloma	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 59 49 21	 1.00 0.93 (0.55–1.56) 1.06 (0.72–1.58) [0.89]	Age, study centre	Also examined height, hip circumference, and waist-to-hip ratio; analyses by weight and WC gave similar results

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Renehan et al. (2008) Meta-analysis Multiple locations 1966–2007	7 studies Men Incidence	Multiple myeloma	BMI per 5 kg/m²		1.11 (1.05–1.18)		
	6 studies Women Incidence		BMI per 5 kg/m²		1.11 (1.07–1.15)		
Pylypchuk et al. (2009) Netherlands Cohort Study on Diet and Cancer The Netherlands 1986–1999	5000 Men and women Incidence	Multiple myeloma ICD-O-3: 9731, 9732, 9734	BMI < 25 25–29.9 ≥ 30 [P_{trend}] per 4 kg/m²	 135 126 18 	 1.00 1.23 (0.95–1.58) 1.13 (0.68–1.88) [0.17] 1.13 (0.97–1.31)	Age, sex	Case–cohort design Similar results for BMI at age 20 yr
De Roos et al. (2010) Women's Health Initiative USA 1994–2008	81 219 Women Incidence	Multiple myeloma	BMI at enrolment < 25 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 39 35 10 7 	 1.00 1.03 (0.65–1.63) 0.66 (0.33–1.33) 0.83 (0.37–1.87) [0.37]	Age, minority race, education level, region of the USA, smoking	Similar results for BMI at age 18 yr, age 35 yr, and age 50 yr
Kanda et al. (2010) Japanese men and women Japan 1992–2006	94 547 Men and women Incidence	Plasma cell myeloma ICD-O-3: 9731, 9732	BMI < 18.5 18.5–22.9 23.0–24.9 25–29.9 ≥ 30 per 1 kg/m² Weight (kg), quartiles (sex-specific) Men: / Women: 30–57 / 27–49 58–63 / 50–53 64–69 / 54–59 70–115 / 60–98 per 5 kg	 2 33 29 22 2 22 21 25 20 	 0.56 (0.13–2.36) 0.70 (0.42–1.15) 1.00 0.79 (0.45–1.38) 0.76 (0.18–3.20) 1.01 (0.95–1.09) 1.00 1.05 (0.57–1.93) 1.35 (0.74–2.46) 1.14 (0.59–2.21) 1.06 (0.93–1.22)	Age, sex, study area, pack-years of smoking, alcohol consumption	Also included estimates for height Similar results for weight at baseline and at age 20 yr

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lu et al. (2010) California Teachers Study USA 1995–2007	121 216 Women Incidence	Multiple myeloma	BMI at baseline < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}] Weight (lb) at baseline < 131 131–154 ≥ 155 [P_{trend}]	 9 55 28 14 38 36 32 	 0.92 (0.45–1.86) 1.00 0.83 (0.53–1.31) 0.86 (0.48–1.55) [0.55] 1.00 0.85 (0.54–1.36) 0.71 (0.43–1.16) [0.18]	Height, race	Also included estimates for hip circumference, waist-to-hip ratio, waist-to-height ratio, and height Similar results for BMI at age 18 yr, for weight at age 18 yr, and for WC
Parr et al. (2010) Asia-Pacific Cohort Studies Collaboration 1961–1999 Average follow-up 4 yr	326 387 Men and women Mortality	Myeloma ICD-9: 203 ICD-10: C90	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 5 kg/m² [P_{trend}]	 3 12 19 25 10 	 1.94 (0.57–6.68) 1.00 (0.70–1.43) 0.87 (0.54–1.41) 1.20 (0.59–2.43) 1.05 (0.73–1.50) [0.78]	Age, sex, smoking	
Troy et al. (2010) PLCO Trial USA 1993–2006	142 982 Men and women Incidence	Plasma cell myeloma	BMI at baseline < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}] BMI at age 20 yr < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 2 57 112 66 12 173 41 12 	 – 1.00 1.45 (1.05–2.01) 1.69 (1.18–2.41) [< 0.01] 0.71 (0.40–1.29) 1.00 1.33 (0.94–1.88) 3.08 (1.71–5.54) [< 0.001]	Age, race/ ethnicity, education level	

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Troy et al. (2010) (cont.)			Weight change (kg) per 10 yr				
			Loss	16	1.00 (0.56–1.78)		
			Gain 0–2	52	1.00		
			Gain 2.1–4	78	1.40 (0.98–2.00)		
			Gain 4.1–6	51	1.48 (1.00–2.20)		
			Gain > 6	42	1.55 (1.02–2.36)		
			[P_{trend}]		[0.216]		
Wallin & Larsson (2011) Meta-analysis Multiple locations	15 studies Men and women Incidence	Multiple myeloma ICD-O-3: 9732/3	BMI	NR			
			Overweight		1.12 (1.07–1.18)		
			Obesity		1.21 (1.08–1.35)		
			per 5 kg/m^2		1.12 (1.08–1.16)		
	5 studies Men and women Mortality	Multiple myeloma ICD-O-3: 9732/3	BMI	NR			
			Overweight		1.15 (1.05–1.27)		
			Obesity		1.54 (1.35–1.76)		
			per 5 kg/m^2		1.21 (1.13–1.30)		
Hofmann et al. (2013) NIH-AARP cohort USA 1995–1996	305 618 Men and women Incidence	Multiple myeloma ICD-O-3: 9732	BMI at baseline			Age, sex, race	Analyses also for women and men separately
			< 18.5	1	0.30 (0.04–2.17)		
			18.5–22.49	53	1.0		
			22.5–24.9	99	1.02 (0.73–1.43)		
			25–29.9	207	1.09 (0.80–1.48)		
			30–34.9	82	1.26 (0.89–1.78)		
			≥ 35	34	1.55 (1.01–2.39)		
			[P_{trend}]		[0.008]		
			BMI at age 50 yr				
			< 18.5	3	0.78 (0.25–2.49)		
			18.5–22.49	73	1.00		
			22.5–24.9	129	1.14 (0.85–1.52)		
			25–29.9	193	1.16 (0.88–1.54)		
			30–34.9	45	1.23 (0.84–1.80)		
			≥ 35	18	1.77 (1.05–2.99)		
			[P_{trend}]		[0.04]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Hofmann et al. (2013) (cont.)			BMI at age 35 yr				
			< 18.5	7	0.77 (0.36–1.66)		
			18.5–22.49	136	1.00		
			22.5–24.9	159	1.42 (1.12–1.79)		
			25–29.9	131	1.27 (0.99–1.63)		
			30–34.9	22	1.41 (0.89–2.22)		
			≥ 35	8	2.53 (1.24–5.18)		
			[P_{trend}]		[0.004]		
			BMI at age 18 yr				
			< 18.5	55	0.93 (0.69–1.25)		
			18.5–22.49	237	1.00		
			22.5–24.9	86	1.12 (0.88–1.44)		
			≥ 25	64	1.38 (1.04–1.82)		
			[P_{trend}]		[0.015]		
Patel et al. (2013) Cancer Prevention Study II Nutrition Cohort USA 1992–2007	152 423 Men and women Incidence	Multiple myeloma	BMI at baseline			Age, sex, family history of haematopoietic cancer, education level, smoking status, physical activity, alcohol consumption	
			< 18.5	1	0.32 (0.04–2.30)		
			18.5– < 25	144	1.00		
			25– < 30	149	1.00 (0.79–1.26)		
			≥ 30	58	1.17 (0.86–1.60)		
			[P_{trend}]		[0.25]		
			BMI at age 18 yr				
			< 18.5	44	0.89 (0.64–1.24)		
			18.5–< 22.5	197	1.00		
			22.5–< 25	66	1.01 (0.75–1.34)		
			25– < 30	31	0.92 (0.61–1.37)		
			≥ 30	7	1.77 (0.82–3.84)		
			[P_{trend}]		[0.37]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Patel et al. (2013) (cont.)			Adult weight change (lb)				
			Loss > 5	10	0.77 (0.40–1.47)		
			Loss 5 to gain 20	105	1.00		
			Gain 21–40	133	1.25 (0.96–1.61)		
			Gain 41–60	68	1.08 (0.79–1.47)		
			Gain > 60	28	0.81 (0.53–1.24)		
			[P_{trend}]		[0.85]		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Multiple myeloma ICD-10: C90	BMI per 5 kg/m^2 [P_{trend}]	2969	 1.03 (0.98–1.09) [0.15]	Age, sex, diabetes, smoking, alcohol consumption, SES, calendar year	
Teras et al. (2014) Pooled analysis of 20 cohorts Multiple locations 1970–2002	1 564 218 Men and women Mortality	Multiple myeloma ICD-9: 203; ICD-10: C90	BMI at baseline			Race, sex, education level, marital status, alcohol consumption, physical activity, smoking	
			15.0–18.4	15	1.21 (0.71–2.06)		
			18.5–20.9	85	1.02 (0.79–1.32)		
			21.0–22.9	171	1.00		
			23.0–24.9	302	1.22 (1.01–1.47)		
			25.0–27.4	351	1.15 (0.95–1.38)		
			27.5–29.9	215	1.24 (1.01–1.52)		
			30.0–34.9	178	1.23 (0.99–1.52)		
			≥ 35	71	1.52 (1.15–2.02)		
			per 5 kg/m^2		1.09 (1.03–1.16)		
			Young adult BMI				
			15.0–18.4	121	0.99 (0.80–1.23)		
			18.5–20.9	319	0.91 (0.78–1.07)		
			21.0–22.9	275	1.00		
			23.0–24.9	160	1.04 (0.85–1.26)		
			25.0–27.4	92	1.11 (0.87–1.40)		
			27.5–29.9	31	1.49 (1.03–2.16)		
			≥ 30.0	26	1.82 (1.22–2.73)		
			per 5 kg/m^2		1.22 (1.09–1.35)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories		Exposed cases	Relative risk (95% CI)	Covariates	Comments
Teras et al. (2014) (cont.)			BMI gain					
			≤ –2.5		34	1.12 (0.77–1.64)		
			–2.5 to < 0		67	0.84 (0.64–1.10)		
			0–2.5		221	1.00		
			2.5–4.9		266	1.04 (0.87–1.24)		
			5.0–7.4		220	1.17 (0.96–1.41)		
			7.5–9.9		113	1.10 (0.87–1.38)		
			≥ 10		103	1.17 (0.92–1.50)		
			per 1 kg/m²			1.06 (0.98–1.14)		
	647 478 Men and women Mortality		WC (cm), quartiles (sex-specific)				Race, sex, education level, marital status, alcohol consumption, physical activity, smoking	Also provided estimates for waist-to-hip ratio and height
			Men:	Women:				
			< 90	< 70	112	1.00		
			90–99	70–79	216	1.28 (1.01–1.62)		
			100–109	80–89	153	1.32 (1.02–1.71)		
			≥ 110	≥ 90	108	1.47 (1.10–1.96)		
			per 5 cm			1.06 (1.02–1.10)		
	656 771 Men Mortality		BMI at baseline				Race, education level, marital status, alcohol consumption, physical activity, smoking	Also provided estimates for waist-to-hip ratio and height
			15.0–18.4		1	–		
			18.5–20.9		17	0.97 (0.57–1.67)		
			21.0–22.9		63	1.00		
			23.0–24.9		176	1.37 (1.03–1.83)		
			25.0–27.4		219	1.20 (0.90–1.59)		
			27.5–29.0		130	1.29 (0.95–1.75)		
			30.0–34.9		93	1.28 (0.93–1.78)		
			≥ 35		24	1.48 (0.91–2.38)		
			per 5 kg/m²			1.11 (1.00–1.22)		
			Young adult BMI					
			15.0–18.4		40	0.85 (0.60–1.21)		
			18.5–20.9		136	0.91 (0.73–1.15)		
			21.0–22.9		155	1.00		
			23.0–24.9		92	0.88 (0.68–1.14)		
			25.0–27.4		62	1.00 (0.74–1.34)		
			27.5–29.0		21	1.47 (0.93–2.32)		
			≥ 30.0		10	1.36 (0.72–2.59)		
			per 5 kg/m²			1.15 (0.98–1.35)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Teras et al. (2014) (cont.)			BMI gain				
			≤ –2.5	11	1.04 (0.55–1.97)		
			–2.5 to < 0	33	0.96 (0.65–1.42)		
			0–2.5	117	1.00		
			2.5–4.9	147	1.04 (0.81–1.33)		
			5 0–7.4	108	1.05 (0.80–1.38)		
			7.5–9.9	60	1.18 (0.85–1.64)		
			≥ 10	40	1.20 (0.82–1.76)		
			per 1 kg/m²		1.07 (0.94–1.21)		
			WC (cm)				
			< 90	62	1.00		
			90–99	144	1.25 (0.93–1.69)		
			100–109	83	1.26 (0.90–1.77)		
			≥ 110	38	1.38 (0.91–2.08)		
			per 5 cm		1.06 (1.01–1.12)		
	907 447 Women Mortality		BMI at baseline			Race, education level, marital status, alcohol consumption, physical activity, smoking	Also provided estimates for waist-to-hip ratio and height
			15.0–18.4	14	1.39 (0.79–2.43)		
			18.5–20.9	68	1.01 (0.75–1.38)		
			21.0–22.9	108	1.00		
			23.0–24.9	126	1.08 (0.83–1.39)		
			25.0–27.4	132	1.11 (0.86–1.44)		
			27.5–29.0	85	1.20 (0.90–1.60)		
			30.0–34.9	85	1.18 (0.89–1.58)		
			≥ 35	47	1.51 (1.06–2.15)		
			per 5 kg/m²		1.07 (0.99–1.16)		
			Young adult BMI				
			15.0–18.4	81	1.11 (0.84–1.47)		
			18.5–20.9	183	0.94 (0.75–1.19)		
			21.0–22.9	120	1.00		
			23.0–24.9	68	1.31 (0.97–1.76)		
			25.0–27.4	30	1.28 (0.86–1.91)		
			27.5–29.0	10	1.42 (0.75–2.71)		
			≥ 30.0	16	2.32 (1.37–3.92)		
			per 5 kg/m²		1.27 (1.10–1.47)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Teras et al. (2014) (cont.)			BMI gain				
			≤ –2.5	23	1.16 (0.72–1.89)		
			–2.5 to < 0	34	0.75 (0.51–1.10)		
			0–2.5	104	1.00		
			2.5–4.9	119	1.02 (0.78–1.33)		
			5.0–7.4	112	1.28 (0.98–1.68)		
			7.5–9.9	53	1.00 (0.71–1.40)		
			≥ 10	63	1.12 (0.81–1.56)		
			per 1 kg/m²		1.04 (0.95–1.15)		
			WC (cm)				
			< 70	50	1.00		
			70–79	72	1.32 (0.90–1.94)		
			80–89	70	1.42 (0.94–2.13)		
			≥ 90	70	1.54 (1.00–2.36)		
			per 5 cm		1.05 (1.00–1.11)		

BMI, body mass index (in kg/m²); CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; ICD-O, International Classification of Diseases for Oncology; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; PLCO Trial, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR, relative risk; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.20d Case–control studies of measures of body fatness and haematopoietic malignancies of lymphoid origin with *sufficient* or *limited* evidence

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Diffuse large B-cell lymphoma					
Pan et al. (2005) Canada 1994–1997	419 from National Enhanced Cancer Surveillance System 3106 Population	Adult BMI 2 yr before interview/diagnosis 18.5– < 25 25– < 30 ≥ 30 [P_{trend}]	 162 184 69 	 1.00 1.37 (1.09–1.73) 1.35 (0.99–1.83) [0.015]	Age, province, sex, education level, pack-years of smoking, alcohol consumption, exposure to some chemicals, occupational exposures, physical activity, energy intake
Chen et al. (2011) USA 1996–2000	245 868 Population	Usual adult BMI assessed via interview < 25 25–30 > 30	 77 56 28	 1.0 1.5 (1.0–2.2) 1.1 (0.7–1.8)	Age, race, total energy intake
Cerhan et al. (2014) Pooled analysis from InterLymph Consortium of 19 case–control studies Europe, Japan, North America	4667 22 639	Young adult BMI 15– < 18.5 18.5– < 22.5 22.5– < 25 25– < 30 30–50 [P_{trend}] Usual adult BMI 15– < 18.5 18.5– < 22.5 22.5– < 25 25– < 30 30– < 35 35–50 [P_{trend}]	 64 517 276 226 54 33 722 850 1310 419 175 	 0.93 (0.69–1.24) 1.00 1.11 (0.93–1.31) 1.47 (1.22–1.77) 1.58 (1.12–2.23) [0.002] 0.58 (0.39–0.85) 1.00 0.91 (0.81–1.03) 0.93 (0.83–1.04) 0.95 (0.82–1.10) 1.06 (0.86–1.30) [0.042]	
Multiple myeloma					
Larsson & Wolk (2007b) Meta-analysis of 4 case–control studies Studies published in 1994–2007	1166 total 8247 total	BMI ≤ 25 25–29.9 ≥ 30	 	 1.00 1.43 (1.23–1.68) 1.82 (1.47–2.26)	Note: the reference category was ≤ 25 in all but 3 studies

Table 2.2.20d (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Wang et al. (2013) USA 1985–1992	278 from Los Angeles County Multiple Myeloma Case–Control Study 278 Population	Self-reported BMI 1 yr before cancer diagnosis or at time of interview			Sex, age ± 5 yr, race
			All:		
		< 25	116	1.00	
		25–29.9	98	0.75 (0.51–1.10)	
		30–34.9	43	0.98 (0.59–1.62)	
		≥ 35	21	1.86 (0.84–4.14)	
			Men:		
		< 25	58	1.00	
		25–29.9	65	0.85 (0.52–1.39)	
		30–34.9	19	0.96 (0.46–2.01)	
		≥ 35	8	1.80 (0.51–6.30)	
			Women:		
		< 25	58	1.00	
		25–29.9	33	0.62 (0.34–1.17)	
		30–34.9	24	0.92 (0.45–1.88)	
		≥ 35	11	1.56 (0.55–4.40)	

BMI, body mass index (in kg/m^2); CI, confidence interval; yr, year or years

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2.2.21 Other haematopoietic malignancies

(a) Myeloid leukaemia

(i) Cohort studies

There have been only two prospective studies of BMI and/or weight in relation to total myeloid leukaemia incidence (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570). In the Japan Collaborative Cohort Study, compared with BMI 18.5–24 kg/m^2, BMI ≥ 30 kg/m^2 was associated with a statistically significantly higher risk (Fujino et al., 2007). In the EPIC cohort, BMI was positively associated with risk in women (P_{trend} = 0.04), but no association was found in men (Saberi Hosnijeh et al., 2013).

Statistically significant positive associations between BMI and risk of AML were observed in postmenopausal women in the USA (Ross et al., 2004), in the United States Veterans cohort (Samanic et al., 2004), and in a Norwegian cohort (Engeland et al., 2007). However, there were no associations of BMI or weight with risk in other studies in European men (Samanic et al., 2006; Fernberg et al., 2007; Saberi Hosnijeh et al., 2013) or women (Saberi Hosnijeh et al., 2013). Of six individual prospective studies of BMI and/or weight in relation to CML incidence (Samanic et al., 2004, 2006; Engeland et al., 2007; Fernberg et al., 2007; Kabat et al., 2013; Saberi Hosnijeh et al., 2013), only one (Engeland et al., 2007) found clear evidence of a positive association. In a meta-analysis of prospective studies, obesity was associated with a statistically significant 52% higher risk of AML and a 26% higher risk of CML compared with normal weight (Larsson & Wolk, 2008).

Only two studies have examined associations of abdominal obesity with risk of myeloid leukaemia. In the Iowa Women's Health Study, waist circumference was positively associated with risk of AML (P_{trend} = 0.04) (Ross et al., 2004). Similarly, in the EPIC cohort, there was suggestive evidence for an association of waist circumference with risk of AML in women (P_{trend} = 0.06), but not in men (Saberi Hosnijeh et al., 2013). In that study, there were also no associations of waist circumference with CML incidence in either men or women (Saberi Hosnijeh et al., 2013).

(ii) Case–control studies

Three case–control studies have evaluated the relationship between BMI and the risk of developing various subtypes of leukaemia (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570). In a study of 420 cases of AML from the Minnesota Cancer Surveillance System, Poynter et al. (2016) found a non-significant increase in risk of AML with high BMI in women only. Kasim et al. (2005) found an increased risk of all leukaemia, AML, and CML in obese versus normal-weight individuals in a case–control study of 1068 people with leukaemia from the Canadian Enhanced Survival Surveillance System. Finally, Strom et al. (2009) found a trend towards an increased risk of CML with BMI at age 25 years, at age 40 years, and at diagnosis in a case–control study of 253 cases of CML from MD Anderson Cancer Center in the USA.

(b) Leukaemia not otherwise specified

At least six individual cohort studies found no association between BMI and total leukaemia incidence or mortality (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570; Oh et al., 2005; Samanic et al., 2006; Andreotti et al., 2010; De Roos et al., 2010; Saberi Hosnijeh et al., 2013; Batty et al., 2015). Conversely, positive associations were found in at least eight other studies, conducted in the Republic of Korea, Taiwan, China, the United Kingdom, and the USA (Calle et al., 2003, in men only; Ross et al., 2004; Samanic et al., 2004; Chiu et al., 2006; Reeves et al., 2007; Song et al., 2008; Chu et al., 2011; Bhaskaran et al., 2014). Positive associations in men and in women were found in a meta-analysis of seven

prospective studies (Renehan et al., 2008). In a meta-analysis of 10 studies in men and women combined, there was a 39% increased risk of leukaemia incidence for obese versus normal BMI (Larsson & Wolk, 2008). Similarly, in the Asia-Pacific Cohort Studies Collaboration, there was a positive association between BMI and leukaemia mortality (Parr et al., 2010). However, a pooled analysis of almost 1 million people found no association between BMI and leukaemia mortality (Whitlock et al., 2009).

Although waist circumference was not associated with total leukaemia incidence in the Iowa Women's Health Study (Ross et al., 2004) or in the EPIC cohort (Saberi Hosnijeh et al., 2013), in the MJ Health Screening Center study, in Taiwan, China, abdominal obesity (waist circumference of ≥ 90 cm in men and ≥ 80 cm in women) was associated with an 87% higher risk of death from leukaemia compared with lower waist circumference (Chu et al., 2011).

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2.2.22 Cancers of the head and neck

Head and neck cancer refers to a group of cancers that develop in (i) the oral cavity; (ii) the pharynx, including the nasopharynx, the oropharynx, and the hypopharynx; (iii) the larynx; (iv) the paranasal sinuses and the nasal cavity; and (v) the salivary glands.

Most head and neck cancers are squamous cell carcinomas. Because of the established associations of head and neck cancer with tobacco use, and because BMI is inversely associated with tobacco use, it is important that associations of BMI with risk of head and neck cancers carefully consider potential confounding and/or effect modification by tobacco use. Notably, only prospective studies with at least 50 cases for any specific site were included in this review.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and cancers of the head and neck was *inadequate*.

(a) Cohort studies

See Table 2.2.22a (web only, available at: http://publications.iarc.fr/570).

(i) Cancer of the oral cavity

The association between BMI and risk of cancer of the oral cavity has been examined in two individual prospective studies (Bhaskaran et al., 2014; Etemadi et al., 2014) and in a large pooled analysis of data from 20 prospective studies (Gaudet et al., 2015). All of these studies adjusted for both tobacco use and alcohol consumption. In the United Kingdom data linkage study of more than 5 million men and women, there was a statistically significant inverse association (RR per 5 kg/m^2 increase in BMI, 0.81; 95% CI, 0.74–0.89; $P_{trend} < 0.0001$) (Bhaskaran et al., 2014). No significant association was observed in the NIH-AARP cohort study in the USA (Etemadi et al., 2014) or in the large pooled analysis (Gaudet et al., 2015).

In contrast, quartiles of waist circumference were positively associated with risk (RR for highest vs lowest quartile, 2.00; 95% CI. 1.24–3.23; $P_{trend} < 0.001$) in the NIH-AARP study (Etemadi et al., 2014). Similarly, in the large pooled analysis of 20 prospective studies, there was a 9% increase in risk (95% CI, 1.03–1.16) per 5 cm increase in waist circumference ($P_{trend} = 0.006$) (Gaudet et al., 2015).

(ii) Cancers of the pharynx (nasopharynx, oropharynx, and/or hypopharynx)

There was no association between BMI and risk of nasopharyngeal cancer in the only study that assessed this relationship (Samanic et al., 2004). Similarly, there is no evidence that BMI is associated with risk of oropharyngeal cancer incidence (Gaudet et al., 2012, 2015) or mortality (Gaudet et al., 2012), or with hypopharyngeal cancer incidence (Gaudet et al., 2015). In the NIH-AARP cohort, BMI < 18.5 kg/m^2 was associated with a higher risk of oropharyngeal and hypopharyngeal cancer incidence compared with BMI 18.5– < 25 kg/m^2 (Etemadi et al. 2014). [There were only three cases in the exposed group.]

Waist circumference was not associated with oropharyngeal or hypopharyngeal cancer incidence in the NIH-AARP cohort study (Etemadi et al., 2014) or in the large pooled analysis (Gaudet et al., 2015).

(iii) Cancer of the larynx

Since 2000, there have been two individual prospective studies (Samanic et al., 2004; Etemadi et al., 2014) and one large pooled analysis of 20 prospective studies (Gaudet et al., 2015) of the association between BMI and risk of cancer of the larynx (Table 2.2.22a, web only, available at: http://publications.iarc.fr/570). In the large study of more than 4.5 million United States Veterans, there was a statistically significantly lower risk

of laryngeal cancer for obese compared with non-obese White and Black men (Samanic et al., 2004). [Neither tobacco use nor alcohol consumption was included in the statistical model; therefore, confounding by these factors is likely.] In the NIH-AARP cohort study in the USA, in which both tobacco use and alcohol consumption were adjusted for in the model, BMI was not associated with risk of laryngeal cancer (Etemadi et al., 2014). Conversely, in the pooled analysis, there was a statistically significant positive association between BMI and risk (RR per 5 kg/m^2 increase, 1.42; 95% CI, 1.19–1.70) (Gaudet et al., 2015).

In the NIH-AARP study (Etemadi et al., 2014), there was no evidence of an association between waist circumference and risk of laryngeal cancer, whereas a weak positive association was reported in the pooled analysis (RR per 5 cm increase, 1.10; 95% CI, 0.99–1.22; P_{trend} = 0.08) (Gaudet et al., 2015).

(iv) Cancer of the oral cavity, pharynx, and larynx combined

In two studies, the Asia-Pacific Cohort Studies Collaboration (Parr et al., 2010) and the Cancer Prevention Study II (Gaudet et al., 2012), BMI was inversely associated with death from cancer of the oral cavity, pharynx, and larynx combined. In contrast, in the pooled analysis, an incremental increase in BMI of 5 kg/m^2 was associated with a 36% increase in risk (Gaudet et al., 2015). Results from the Agricultural Health Study (Andreotti et al., 2010) were inconclusive.

The association between waist circumference and the risk of cancer of the oral cavity, pharynx, and larynx combined was examined in the large pooled analysis of 20 prospective studies, and no evidence of association was observed (Gaudet et al., 2015).

(v) Cancer of the salivary glands

There has been only one study of the association between BMI and incidence of salivary gland cancer (Samanic et al., 2004). In that study, being obese was not associated with a higher incidence compared with being non-obese in either White men or Black men.

(vi) Cancer of the head and neck or upper aerodigestive tract

For head and neck cancer incidence overall, in the United States Veterans study there was a significantly lower risk for obese compared with non-obese Black men and White men, without adjustment for tobacco use or alcohol consumption (Samanic et al., 2004). Most other prospective studies found a weak inverse association or no association between BMI at baseline and incidence of head and neck cancer (Wolk et al., 2001; Gaudet et al., 2012; Hashibe et al., 2013; Etemadi et al., 2014). When the pooled analysis of data from 20 prospective studies was stratified by smoking status, BMI was positively associated with risk in never-smokers but was inversely associated with risk in current smokers (Gaudet et al., 2015).

BMI was inversely associated with head and neck cancer mortality ($P_{trend} = 3 \times 10^{-10}$) in the Cancer Prevention Study II in the USA (Gaudet et al., 2012), and in a smaller cohort study in Switzerland a weaker inverse association was found between BMI and death from cancer of the upper aerodigestive tract (Meyer et al., 2015).

In the only study that examined the association between BMI at younger ages and risk of head and neck cancer, no association was found with increased BMI at age 20 years or at age 50 years, or with percentage change in BMI from age 20 years or age 50 years to baseline (Hashibe et al., 2013).

Waist circumference was positively associated with risk of head and neck cancer incidence both in the NIH-AARP cohort study (Etemadi et al., 2014) and in the pooled analysis of 20 prospective studies, in which a 5 cm increase in waist circumference was associated with a 4% increase in risk (95% CI, 1.03–1.05) (Gaudet et al., 2015).

(b) Case–control studies

Since 2000, a total of seven independent case–control studies, conducted in Australia, China, Cuba, India, Europe, Sudan, and the USA, and one large multicentre case–control study (nine countries) have reported on the association of BMI with various combinations of cancers of the head and neck (Table 2.2.22b, web only, available at: http://publications.iarc.fr/570). In addition, Gaudet at al. (2010) and Lubin et al. (2010, 2011) performed pooled reanalyses of 15–17 case–control studies with stratification by smoking status, by alcohol consumption status, and by subsite (Table 2.2.22c, web only, available at: http://publications.iarc.fr/570).

In most studies, BMI was assessed on the basis of self-reported height and body weight, referring to either a recent period (mostly 1 or 2 years) before disease diagnosis or to a period in the more distant past (e.g. at age 30 years). All original studies adjusted for potential confounding by smoking or alcohol consumption, in addition to variable adjustments for other potential confounding factors.

Most of the studies found an inverse association of BMI with cancer risk. In several studies, compared with normal-weight individuals (18.5 kg/m^2 ≤ BMI < 25 kg/m^2), those who were overweight or obese had reduced risks of head and neck cancer (Rajkumar et al., 2003; Rodriguez et al., 2004; Kreimer et al., 2006; Peters et al., 2008; Radoï et al., 2013; Petrick et al., 2014 in African Americans only); being underweight (BMI < 18.5 kg/m^2) was associated with an approximately 2-fold increase in risk in two large-scale studies (French ICARE study, 689 cases and 3481 controls, Radoï et al., 2013; United States CHANCE study, 1289 cases and 1361 controls, Petrick et al., 2014). In the one study that additionally reported recalled body weight at age 30 years (Radoï et al., 2013), this inverse association was also observed for past BMI.

Four case–control studies stratified the analyses by smoking status. In one early study in the USA, the inverse association was more pronounced in current or ever-smokers than in never-smokers (Kabat et al., 1994). In two more recent studies in the USA, a similar pattern was observed in African Americans but not in Whites (Petrick et al., 2014) and in both HPV-positive and HPV-negative individuals (Tan et al., 2015). In contrast, the IARC Multicenter Oral Cancer Study, which included a total of 1670 cases and 1732 controls from nine countries worldwide, found statistically significant inverse associations of BMI (country-specific tertiles) with risk of oral and oropharyngeal squamous cell carcinomas in both tobacco users and never-users, as well as in alcohol consumers and never-drinkers (Kreimer et al., 2006). Similarly, a pooled reanalysis of the data from 17 case–control studies, which included a total of 12 716 cases and 17 438 controls (INHANCE consortium; Gaudet et al., 2010) (see Table 2.2.22c, web only, available at: http://publications.iarc.fr/570), found inverse relationships of BMI with the risk of cancers of the oral cavity, pharynx, and larynx, in men and women combined, in ever-smokers (for BMI ≥ 30 kg/m^2 vs 18.5– < 25 kg/m^2: OR, 0.38; 95% CI, 0.30–0.49) but not in never-smokers. Furthermore, the increase in risk in underweight (BMI < 18.5 kg/m^2) compared with normal-weight (18.5– < 25 kg/m^2) individuals was significant only in the smokers (OR, 2.13; 95% CI, 1.75–2.58) (Gaudet et al., 2010).

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2.2.23 Malignant melanoma

Malignant melanoma is the most lethal of the cancers of the skin. The incidence of melanoma varies between countries and is related to skin colour, with a higher risk for populations with lighter skin. Melanoma is known to be caused by exposure to ultraviolet radiation in people who are susceptible because of family history and/or who have a tendency to burn easily as a result of exposure to sunlight.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and malignant melanoma was *inadequate*.

(a) Cohort studies

The evidence published since 2000 includes eight cohort studies (excluding analyses that were later updated and analyses based on fewer than 100 incident cases) (Table 2.2.23a, web only, available at: http://publications.iarc.fr/570) and one meta-analysis (Table 2.2.23b, web only, available at: http://publications.iarc.fr/570).

In most studies, there was no association between BMI and risk of melanoma (Calle et al., 2003; Rapp et al., 2005; Dennis et al., 2008; Pothiawala et al., 2012; Bhaskaran et al., 2014). However, findings by sex have not been consistent. In two studies in men only, the estimated relative risk for BMI ≥ 30 kg/m^2 was 1.35 (95% CI, 1.06–1.73) in Swedish construction workers (Samanic et al., 2006) and 1.29 (95% CI, 1.14–1.46) in White men in the United States Veterans cohort (Samanic et al., 2004). In the Million Women Study (Reeves et al., 2007), the risk was also significantly increased (RR per 10 kg/m^2, 1.24; 95% CI, 1.03–1.48). In a meta-analysis of cohort studies (Sergentanis et al., 2013), the estimated relative risk of obesity was 1.30 (95% CI, 1.17–1.45) in men (based on 7 studies) and 0.87 (95% CI, 0.70–1.08) in women (based on 6 studies).

Three cohorts have examined weight at earlier ages in relation to risk of melanoma. In both the Nurses' Health Study and the Male Health Professionals Follow-Up Study, BMI at 10 years before baseline was not related to risk (Pothiawala et al., 2012); in the study of agricultural workers in the USA (Dennis et al., 2008), recalled BMI at age 20 years was positively associated, with an estimated relative risk for BMI ≥ 25 kg/m^2 of 2.55 (95% CI, 1.52–4.30).

(b) Case–control studies

The meta-analysis by Sergentanis et al. (2013) included 10 published case–control studies that evaluated the association between BMI and risk of melanoma (Table 2.2.23b, web only, available at: http://publications.iarc.fr/570). The association between BMI and melanoma was significant both in overweight men and in obese men, although there was considerable between-study heterogeneity. No such association was observed in women. When the cohort and case–control studies were combined, the pooled effect estimate was 1.31 (95% CI, 1.18–1.45) in overweight men and 1.31 (95% CI, 1.19–1.44) in obese men. In women, no association was observed in either category (Sergentanis et al., 2013). [There was evidence for confounding by exposure to sunlight in women.]

The pooled analysis of case–control studies (Olsen et al., 2008) assessed BMI in early adulthood and weight change in relation to risk of melanoma in women. There was no association between BMI in early adulthood and melanoma risk, but an elevated risk was associated with a weight gain of 2 kg or more during adult life (pooled OR, 1.5, 95% CI, 1.1–2.0) (see Table 2.2.23b, web only, available at: http://publications.iarc.fr/570).

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2.3. Excess body fatness in early life and subsequent cancer risk

WHO defines children as individuals younger than 19 years (WHO, 2016). The scope of this section includes children and young adults up to age 25 years, the age range collectively referred to as early life.

It is generally held that childhood obesity is strongly associated with obesity in adulthood. According to a recent systematic review (Simmonds et al., 2015), obese children are more than 5 times as likely as non-obese children to be obese as adults. However, childhood BMI is not a good predictor of the occurrence of obesity in adulthood; 80% of people older than 30 years who are obese were not obese in adolescence. Similarly, many obesity-related diseases occur in adults who had a healthy weight in childhood.

Few comprehensive reviews or meta-analyses are available on the topic of body shape and weight in early life and subsequent cancer risk. The literature review for this section identified three categories of studies: (i) prospective studies that directly measured weight and height in childhood and related these parameters with subsequent cancer occurrence; (ii) prospective cohort studies that determined body shape in early adulthood by recall and related these parameters with subsequent cancer occurrence; and (iii) studies that determined trajectories of body shape (from repeated determinations) from childhood to late adulthood and related these parameters with subsequent cancer occurrence.

[The Working Group considered that the relationship between weight at birth and subsequent cancer risk was beyond the scope of this *Handbook*.]

2.3.1 Weight and height measured in childhood

The few prospective studies that directly measured weight and height in childhood and related these parameters with subsequent cancer occurrence have been reviewed recently (Simmonds et al., 2015). These include data from the Helsinki Birth Cohort Study (ages 7 years and 15 years; Hilakivi-Clarke et al., 2001), the 1946 United Kingdom Medical Research Council National Survey of Health and Development (ages 2–15 years; De Stavola et al., 2004), the Copenhagen School Health Records Register (ages 7–15 years; Ahlgren et al., 2006; Aarestrup et al., 2014; Berentzen et al., 2014; Kitahara et al., 2014a, 2014b; Cook et al., 2015), the Norwegian health surveys (ages 14–19 years; Engeland et al., 2003; Bjørge et al., 2004, 2008), the Israeli army (ages 16–19 years; Levi et al., 2011; Leiba et al., 2013), and the Harvard Alumni Health Study (ages 18–21 years; Gray et al., 2012). [These cohorts have the advantage that height and weight were directly measured, but they have relatively small sample sizes. Because the baseline data were collected more than half a century ago, extrapolation to the current childhood and adolescent population may not apply, and it is not always clear whether these cohorts were representative of the general population.] The relationship between weight and height in childhood and subsequent cancer occurrence is presented separately for cancer of the breast (Table 2.3a) and for other cancers (Table 2.3b).

Table 2.3a lists study characteristics and breast cancer risk estimates from three studies (Hilakivi-Clarke et al., 2001; De Stavola et al., 2004; Ahlgren et al., 2006), which included a total of 3576 breast cancer cases. There was no evidence that excess weight directly measured in childhood is associated with subsequent breast cancer risk. Indeed, there is some evidence of an inverse association.

Table 2.3b lists, for boys and/or girls, study characteristics and risk estimates of mortality and incidence for the following types of cancer: colon cancer (Bjørge et al., 2008; Levi et al., 2011), rectal cancer (Levi et al., 2011), oesophageal adenocarcinoma (Cook et al., 2015), gastric non-cardia cancer (Levi et al., 2013), hepatocellular carcinoma (Berentzen et al., 2014), pancreatic cancer (Levi et al., 2012), ovarian cancer (Engeland et al., 2003), prostate cancer (Gray et al., 2012; Aarestrup et al., 2014; Batty et al., 2015), renal cancer (Bjørge et al., 2004; Leiba et al., 2013), urothelial cancer (Leiba et al., 2012), glioma (Kitahara et al., 2014a), and thyroid cancer (Farfel et al., 2014; Kitahara et al., 2014b). Although the number of studies per cancer type is small, for boys, excess weight in childhood and adolescence (generally expressed per increase of 1 or 2 standard deviations in BMI) was generally associated with increased risk of colon cancer (but not rectal cancer), oesophageal adenocarcinoma, hepatocellular carcinoma, pancreatic cancer, renal cancer, or urothelial cancer. There was no association with subsequent prostate cancer occurrence. For girls, there was evidence that excess weight in childhood and adolescence (generally expressed per increase of 1 or 2 standard deviations in BMI) was associated with increased risk of colon cancer (but not rectal cancer), oesophageal adenocarcinoma, hepatocellular carcinoma, and ovarian cancer. The association with renal cancer was uncertain [because of a large confidence interval]. No associations were seen for glioma or thyroid cancer in either sex.

2.3.2 Body shape in early adulthood determined by recall

A larger number of prospective cohort studies have determined body shape in early adulthood (ages 18–25 years) by recall, typically using the Sørensen scale (silhouette drawings), and converting the results to BMI values. [There is a risk of recall bias, but distributions of recalled BMI have been tested against BMI distributions from population data contemporaneous with the respective age strata and were found to be similar (Renehan et al., 2012). It is worth remembering that the mean values of BMI distributions of a cohort at ages 18–25 years are considerably lower than those in later adulthood. For example, in the NIH-AARP cohort, the mean BMI at age 18 years was 21.5 kg/m^2 in men and 20.8 kg/m^2 in women (Renehan et al., 2012). In addition, there is a survival bias, in that individuals have had to survive to baseline age (typically > 50) to participate in the cohort study. Finally, in these studies, risk estimates from multivariate analyses are commonly expressed as those from separate models adjusted for several potential confounders and as those from models adjusted for several potential confounders plus baseline (current-age) BMI. The latter models are of mechanistic relevance; for the purpose of a public health message in this *Handbook*, risk estimates from the former models are reported.]

These studies are dealt with in the individual cancer site-specific sections. Here, specific note is made in relation to breast cancer.

Prospective cohort studies of recalled BMI at ages 18–25 years and subsequent postmenopausal or premenopausal breast cancer risk are presented in Table 2.3c and Table 2.3d, respectively.

For BMI at ages 18–25 years determined by recall, several cohort studies showed no association (van den Brandt et al., 1997; Suzuki et al., 2011; Fagherazzi et al., 2013; Krishnan et al., 2013; Catsburg et al., 2014) or inverse associations (Ahn et al., 2007; Palmer et al., 2007; Baer et al., 2010; Kawai et al., 2010; White et al., 2012) with subsequent breast cancer risk. The same level of association was observed for postmenopausal (Table 2.3c) and premenopausal (Table 2.3d) women.

Some studies additionally evaluated BMI or weight at ages younger than 18 years determined

by recall: age at menarche in the French cohort (Fagherazzi et al., 2013), at age 12 years in the Iowa Women's Health Study (Bardia et al., 2008), and at ages 5 years and 10 years in the Nurses' Health Study (1988–2004) and the Nurses' Health Study II (1989–2005) cohorts (Baer et al., 2010) (data not shown in tables). These studies are consistent in showing that body fatness at ages 5–12 years or age at menarche is independently and inversely associated with subsequent premenopausal (Baer et al., 2010) and postmenopausal breast cancer (Bardia et al., 2008; Baer et al., 2010; Fagherazzi et al., 2013).

2.3.3 *Trajectories of body shape determined from early life*

Additional information may be gained by exploring weight changes with time and cancer risk. Recently, Song et al. (2016) reported combined analyses from the Nurses' Health Study (73 581 women) and the Health Professionals Follow-up Study (32 632 men) for several cancer sites (Table 2.3e). Using a data-driven latent class approach, they identified five distinct trajectories of body shape from age 5 years to age 60 years: maintained a lean body shape (lean-stable), started lean and experienced a moderate increase in body shape (lean-moderate increase), started lean and gained a substantial amount of weight (lean-marked increase), maintained a medium body shape (medium-stable), and started heavy and maintained or gained weight (heavy-stable/increase). Compared with women with the lean-stable trajectory, women with the lean-marked increase and the heavy-stable/increase trajectories had higher risks of colorectal, oesophageal, pancreatic, renal, and endometrial cancers. For postmenopausal breast cancer risk, early-life adiposity with no loss in later life (heavy-stable/increase trajectory) showed no association, whereas late-life adiposity (lean-marked increase trajectory) was positively associated. In men, excess body fatness during any life period was associated with a higher risk of colorectal cancer and oesophageal adenocarcinoma; in addition, the heavy-stable/increase trajectory was associated with a higher risk of pancreatic cancer and a lower risk of advanced prostate cancer.

In the French E3N cohort, Fagherazzi et al. (2013) evaluated the risk of breast cancer associated with body shape (using the Sørensen scale) at ages 8 years, age at menarche, 20–25 years, and 35–40 years. Six lifetime trajectories of body shape were derived, using a finite mixture modelling approach (Jones & Nagin, 2007). In this analysis, from age 8 years and/or at menarche, a constantly elevated body size was associated with a significantly decreased risk of ER-positive and PR-positive postmenopausal breast cancer (approximately 80% of breast cancers). No significant association with other body shape trajectories was found.

Table 2.3a Prospective studies of childhood cohorts where weight and height were directly measured and subsequent risk of cancer of the breast

Reference Cohort Period of study	Number at baseline (Birth cohort)	Number at follow-up	Number of breast cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Hilakivi-Clarke et al. (2001) Helsinki Birth Cohort 1971–1995	3447 (1924–1933)	3447	177	Minimum, 38 (76% > 50)	7 15	0.91 (0.73–1.05) 0.85 (0.70–1.00)
De Stavola et al. (2004) United Kingdom Medical Research Council National Survey of Health and Development 1946–1999	2547 (March 1946)	2187	59	47–53	2 4 7 11 15	1.02 (0.78–1.33) 0.88 (0.67–1.14) 0.87 (0.66–1.15) 0.89 (0.68–1.18) 0.86 (0.65–1.14)
Ahlgren et al. (2006) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register) Until 2001	161 063 (1930–1975)	117 415	3340	NR	14	0.97 (0.96–0.98)

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported; SD, standard deviation

Table 2.3b Prospective studies of childhood cohorts where weight and height were directly measured and subsequent risk of other cancers, by sex and by organ site

Reference Cohort	Number at baseline Period of recruitment	Number at follow-up	Number of cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Boys						
Colon cancer: mortality						
Bjørge et al. (2008) Norwegian Cancer Registry	114 977 (1963–1975)	NR	97	Mean, 40	14–19	≥ 85th percentile vs 25th–75th percentile: 2.1 (1.1–4.1)
Colon cancer: incidence						
Levi et al. (2011) Israeli military cohort	1 109 864 (1947–1966)	NR	445	19–57	16–19	1.21 (1.07–1.38)[b]
Rectal cancer: incidence						
Levi et al. (2011) Israeli military cohort	1 109 864 (1947–1966)	NR	193	19–57	16–19	0.96 (0.88–1.10)[b]
Oesophageal adenocarcinoma: incidence						
Cook et al. (2015) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	188 360 (1930–1989)	128 330	216	> 40	7 8 9 10 11 12 13	1.11 (0.95–1.30) 1.10 (0.94–1.29) 1.15 (0.98–1.35) 1.18 (1.00–1.38) 1.21 (1.03–1.42) 1.25 (1.07–1.47) 1.25 (1.06–1.46)
Gastric non-cardia: incidence						
Levi et al. (2013) Israeli military cohort	1 088 530 (1967/2005–2006)	NR	130	19–57	16–19	vs BMI 18.5–24.9: BMI 25–29.9: 0.98 (0.51–1.89) BMI ≥ 30: 2.62 (0.96–7.15)
Hepatocellular carcinoma: incidence						
Berentzen et al. (2014) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	188 360 (1930–1980)	144 417	229	Median, 59	7 8 9 10 11 12 13	1.18 (1.01–1.37) 1.17 (1.00–1.37) 1.25 (1.07–1.47) 1.29 (1.10–1.51) 1.31 (1.12–1.53) 1.36 (1.16–1.59) 1.36 (1.17–1.60)
Pancreatic cancer: incidence						
Levi et al. (2012) Israeli military cohort	720 927 (1967–1995)	NR	98	29–56	16–19	1.17 (0.96–1.52)[b]

Table 2.3b (continued)

Reference Cohort	Number at baseline Period of recruitment	Number at follow-up	Number of cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Prostate cancer: mortality						
Gray et al. (2012) Harvard Alumni Health Study	19 593 (1914–1952)	NR	NR	NR	Mean, 18.4	1.04 (0.93–1.16)
Prostate cancer: incidence						
Aarestrup et al. (2014) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	188 360 (1930–1969)	133 647	3355	Median, 66.5 (range, 40–81)	7 8 9 10 11 12 13	1.04 (0.98–1.10) 1.04 (0.98–1.11) 1.02 (0.96–1.09) 1.03 (0.97–1.09) 1.02 (0.96–1.08) 1.02 (0.96–1.08) 1.02 (0.96–1.09)
Batty et al. (2015) Scottish Mental Health Survey Scotland, United Kingdom	2332 1947–2014	2332	109	Maximum, 77	11	0.97 (0.80–1.18)
Renal cancer: incidence						
Bjørge et al. (2004) Norwegian Cancer Registry	115 267 (1963–2001)	NR	109	Mean, 45	14–19	≥ 85th percentile vs 25th–75th percentile: 2.64 (1.48–4.70)
Leiba et al. (2013) Israeli military cohort	1 110 835 (1967–2005)	NR	274	Mean, 44	16–19	1.19 (1.04–1.37)[b]
Urothelial cancer:[a] *incidence*						
Leiba et al. (2012) Israeli military cohort	1 110 835 (1967–2005)	NR	661	Mean, 35	16–19	1.21 (1.06–1.38)[b]
Glioma: incidence						
Kitahara et al. (2014a) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	188 360	162 295	355	> 40	7 8 9 10 11 12 13	1.01 (0.86–1.17) 1.04 (0.89–1.22) 1.03 (0.88–1.21) 1.02 (0.87–1.19) 1.02 (0.87–1.19) 1.00 (0.86–1.17) 1.04 (0.89–1.21)

Table 2.3b (continued)

Reference Cohort	Number at baseline Period of recruitment	Number at follow-up	Number of cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Thyroid cancer: incidence						
Farfel et al. (2014) Israeli military cohort	1 145 865 (1967–2005)	NR	425	19–57	16–19	BMI, Q5 vs Q1: 1.19 (0.87–1.63)
Kitahara et al. (2014b) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	165 978	162 632	64	> 40	7 8 9 10 11 12 13	1.22 (0.93–1.60) 1.24 (0.94–1.63) 1.23 (0.93–1.63) 1.21 (0.91–1.60) 1.24 (0.94–1.65) 1.25 (0.94–1.66) 1.25 (0.93–1.66)
Girls						
Colon cancer: mortality						
Bjørge et al. (2008) Norwegian Cancer Registry	111 701 (1963–1975)	NR	108	Mean, 43	14–19	≥ 85th percentile vs 25th–75th percentile: 2.0 (1.2–3.5)
Oesophageal adenocarcinoma: incidence						
Cook et al. (2015) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register)	184 276 (1931–1971)	126 723	38	> 40	7 8 9 10 11 12 13	1.30 (0.90–1.87) 1.41 (0.97–2.06) 1.49 (1.02–2.16) 1.44 (0.99–2.11) 1.63 (1.12–2.36) 1.55 (1.07–2.26) 1.68 (1.15–2.44)
Hepatocellular carcinoma: incidence						
Berentzen et al. (2014) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register)	184 276 (1930–1980)	141 467	62	Median, 60.2	7 8 9 10 11 12 13	1.20 (0.90–1.60) 1.12 (0.84–1.50) 1.12 (0.83–1.51) 1.03 (0.77–1.39) 1.05 (0.78–1.40) 1.15 (0.85–1.54) 1.23 (0.93–1.65)
Ovarian cancer						
Engeland et al. (2003) Norwegian Cancer Registry	NR (1963–1999)	111 883	7882	Mean, 41	14–19	1.22 (1.01–1.49)[b]

Table 2.3b (continued)

Reference Cohort	Number at baseline Period of recruitment	Number at follow-up	Number of cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Renal cancer: incidence						
Bjørge et al. (2004) Norwegian Cancer Registry	111 954 (1963–2001)	NR	45	Mean, 45	14–19	≥ 85th percentile vs 25th–75th percentile: 1.48 (0.57–3.85)
Glioma: incidence						
Kitahara et al. (2014a) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register)	184 276	158 130	253	> 40	7 8 9 10 11 12 13	0.96 (0.79–1.16) 0.95 (0.79–1.16) 0.95 (0.79–1.16) 0.87 (0.72–1.06) 0.93 (0.76–1.13) 0.91 (0.75–1.10) 1.01 (0.83–1.22)
Thyroid cancer: incidence						
Farfel et al. (2014) Israeli military cohort	478 445 (1989–2005)	NR	323	19–57	16–19	BMI, Q5 vs Q1: 1.14 (0.81–1.60)
Kitahara et al. (2014b) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register)	161 262	158 453	171	> 40	7 8 9 10 11 12 13	1.13 (0.96–1.33) 1.12 (0.95–1.32) 1.18 (1.00–1.39) 1.14 (0.96–1.35) 1.11 (0.94–1.31) 1.09 (0.92–1.29) 1.13 (0.96–1.34)

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported; SD, standard deviation.

[a] Bladder, ureter, and renal pelvis.

[b] Taken from the systematic review and meta-analysis by Simmonds et al. (2015).

Table 2.3c Prospective cohort studies of BMI at ages 18–25 years determined by recall and subsequent risk of cancer of the breast in postmenopausal women

Reference Cohort Country	Total number in cohort	Follow-up period (years)	Baseline age (years)	Recall age (years)	Number of cases	Relative risk (95% CI)
van den Brandt et al. (1997) Netherlands Cohort Study The Netherlands	62 573	4.3	55–69	20	626	Per 8 kg/m²: 0.79 (0.58–1.08)
Ahn et al. (2007) NIH-AARP Diet and Health Study USA	99 039	3.9	50–71 All postmenopausal	18	2111	BMI ≥ 30.0 vs 18.5–22.4: HRT non-users 0.48 (0.27–0.86) HRT current users 0.65 (0.35–1.23)
Palmer et al. (2007) Black Women's Health Study USA	9542	10	21–69	18	442	BMI ≥ 25.0 vs < 20.0: 0.55 (0.37–0.82)
Baer et al. (2010) Nurses' Health Study (NHS) and NHS II USA	188 860	16	NHS, 30–55 NHS II, 25–42	20	4974	Per 1 kg/m²: 0.93 (0.90–0.95)
Kawai et al. (2010) Miyagi Cohort Study Japan	10 106	12.8	40–64	20	108	BMI ≥ 23.8 vs < 20.5: 0.44 (0.24–0.81)
Suzuki et al. (2011) Japan Public Health Cohort Study Japan	41 594	10	40–59	20	232	Per 5 kg/m²: 0.77 (0.59–1.02)
White et al. (2012) Multiethnic Cohort USA	82 971	NR	45–75	21	3030	BMI ≥ 30.0 vs < 20.0–24.9: 0.63 (0.43–0.91)
Fagherazzi et al. (2013) French E3N cohort France	81 089	NR	40–64	20–25	2828	Level ≥ 4 vs level 1:[a] 0.86 (0.74–1.00)
Krishnan et al. (2013) Melbourne Collaborative Cohort Study Australia	14 441	16.5	27–76 (99% 40–69)	18–21	668	Per 5 kg/m²: 0.90 (0.79–1.04)

Table 2.3c (continued)

Reference Cohort Country	Total number in cohort	Follow-up period (years)	Baseline age (years)	Recall age (years)	Number of cases	Relative risk (95% CI)
Catsburg et al. (2014) Canadian Study of Diet, Lifestyle and Health Canada	2210	12	67	20	541	BMI ≥ 30.0 vs 18.5–24.9: 0.21 (0.03–1.59)

BMI, body mass index (in kg/m^2); CI, confidence interval; HRT, hormone replacement therapy; NR, not reported

[a] Participants were asked to recall their body fatness by using a 9-level figure drawing, where level 1 represents the most lean and level 9 represents the most overweight.

Table 2.3d Prospective cohort studies of BMI at ages 18–25 years determined by recall and subsequent risk of cancer of the breast in premenopausal women

Reference Cohort Country	Total number in cohort	Follow-up period (years)	Baseline age (years)	Recall age (years)	Number of cancers	Relative risk (95% CI)
Palmer et al. (2007) Black Women's Health Study USA	42 538	10	21–69	18	491	BMI ≥ 25.0 vs < 20.0: 0.63 (0.46–0.87)
Baer et al. (2010); Michels et al. (2012) Nurses' Health Study (NHS) and NHS II USA	188 860	16	NHS, 30–55 NHS II, 25–42	20	2188	Per 1 kg/m^2: 0.89 (0.86–0.93)
Suzuki et al. (2011) Japan Public Health Cohort Study Japan	41 594	10	40–59	20	220	Per 5 kg/m^2: 0.78 (0.57–1.06)
Fagherazzi et al. (2013) French E3N cohort France	81 089	NR	40–64	20–25	745	Level ≥ 4 vs level 1:[a] 1.22 (0.88–1.69)
Catsburg et al. (2014) Canadian Study of Diet, Lifestyle and Health Canada	1110	14	45	20	556	BMI ≥ 30.0 vs 18.5–24.9: 0.96 (0.33–2.81)

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported

[a] Participants were asked to recall their body fatness by using a 9-level figure drawing, where level 1 represents the most lean and level 9 represents the most overweight.

Table 2.3e Relative risk of selected cancers according to trajectories of body shape from age 5 years to age 60 years in women and in men

Cancer type	Category of body shape trajectory[a]				
	Lean-stable	Lean-moderate increase	Lean-marked increase	Medium-stable	Heavy-stable/increase
Women					
Number of participants	13 183	18 405	18 217	23 288	11 699
Colorectal cancer	1.00	0.97 (0.80–1.17)	1.22 (1.00–1.49)	1.02 (0.85–1.22)	1.40 (1.13–1.74)
Oesophageal adenocarcinoma	1.00	1.02 (0.29–3.63)	2.56 (0.82–8.03)	1.04 (0.30–3.57)	2.19 (0.63–7.70)
Pancreatic cancer	1.00	1.18 (0.82–1.69)	1.36 (0.93–1.98)	1.15 (0.81–1.63)	1.39 (0.91–2.12)
Kidney cancer	1.00	1.26 (0.78–2.04)	1.89 (1.19–3.03)	1.05 (0.65–1.69)	1.92 (1.15–3.21)
Postmenopausal breast cancer	1.00	1.30 (1.17–1.45)	1.41 (1.26–1.58)	1.05 (0.94–1.17)	1.11 (0.97–1.28)
Endometrial cancer	1.00	0.99 (0.75–1.29)	1.57 (1.21–2.03)	0.94 (0.73–1.22)	2.08 (1.59–2.73)
Ovarian cancer	1.00	0.88 (0.66–1.16)	0.93 (0.70–1.25)	0.88 (0.67–1.15)	0.84 (0.59–1.19)
Men					
Number of participants	5946	6881	14 225	5725	4929
Colorectal cancer	1.00	1.36 (1.03–1.80)	1.23 (0.95–1.60)	1.26 (0.92–1.72)	1.47 (1.05–2.05)
Oesophageal adenocarcinoma	1.00	1.90 (0.67–5.34)	2.09 (0.80–5.48)	1.53 (0.48–4.84)	3.01 (1.04–9.13)
Pancreatic cancer	1.00	0.85 (0.54–1.35)	1.20 (0.81–1.78)	1.12 (0.70–1.80)	1.50 (0.92–2.46)
Kidney cancer	1.00	1.05 (0.67–1.64)	0.94 (0.63–1.43)	1.07 (0.66–1.74)	0.93 (0.53–1.64)
Advanced prostate cancer	1.00	1.16 (0.91–1.47)	0.97 (0.78–1.21)	1.00 (0.76–1.32)	0.67 (0.47–0.95)

[a] Trajectories of body shape: maintained a lean body shape (lean-stable); started lean and experienced a moderate increase in body shape (lean-moderate increase); started lean and gained a substantial amount of weight (lean-marked increase); maintained a medium body shape (medium-stable); started heavy and maintained or gained weight (heavy-stable/increase).

Source: Song et al. (2016). Data for women are from the Nurses' Health Study, and data for men are from the Health Professionals Follow-up Study.

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2.4 Excess body fatness in cancer survivors

2.4.1 Studies of weight at diagnosis and cancer outcomes

An increasing number of observational studies are focusing on the association between excess body fatness and prognosis in cancer survivors. Specifically, more than 100 individual reports have evaluated the relationship between BMI or body weight at the time of diagnosis of early-stage breast cancer and the risk of breast cancer recurrence, breast cancer-related mortality, and all-cause mortality.

A meta-analysis of 82 reports on this topic (all but 8 of which had a median follow-up of at least 5 years) incorporated data from 213 075 women (Chan et al., 2014). Women who were obese (BMI > 30.0 kg/m^2) at the time of diagnosis of breast cancer had a 35% increased risk (RR, 1.35; 95% CI, 1.24–1.47) of breast cancer-related mortality and a 41% increased risk of all-cause mortality compared with women who were of normal weight at the time of breast cancer diagnosis. The association between obesity and poor outcomes was seen in both postmenopausal and premenopausal breast cancer survivors, with summary relative risks for all-cause mortality in obese versus normal-weight women of 1.75 (95% CI, 1.26–2.41) in women with premenopausal breast cancer and 1.34 (95% CI, 1.18–1.53) in women with postmenopausal breast cancer.

In another study, the WCRF Continuous Update Project reviewed data on the association in female breast cancer survivors between weight and the risk of dying of breast cancer, second cancers, or any cause (WCRF/AICR, 2014). The report stressed the importance of taking into account the timing of weight measurement, focusing on three main time points: (i) before diagnosis; (ii) less than 12 months after diagnosis; and (iii) more than 12 months after diagnosis. Associations were observed between measures of adiposity and prognosis, but there were many pitfalls to interpretations, biases, and confounding. The evidence linking obesity to cancer survival was rated as "limited-suggestive", primarily because of concerns about the timing of baseline BMI analysis in relation to cancer diagnosis in some studies.

Fewer studies have evaluated the association between body fatness and cancer prognosis in other malignancies. A meta-analysis that evaluated the relationship between obesity and colorectal cancer outcomes included 16 reports that encompassed 58 917 individuals followed up for a median of 9.9 years (Lee et al., 2015). Obesity before diagnosis of colorectal cancer was associated with an increased risk of colorectal cancer-specific mortality (RR, 1.22; 95% CI, 1.00–1.35) and all-cause mortality (RR, 1.25; 95% CI, 1.14–1.36). Obesity after diagnosis of colorectal cancer was also associated with an increased risk of all-cause mortality (RR, 1.08; 95% CI, 1.03–1.13).

Excess body fatness has also been linked with biochemical recurrence of cancer (rising levels of prostate-specific antigen [PSA]) in men with early-stage prostate cancer treated with radical prostatectomy or external beam radiation. A meta-analysis of 26 studies, including 36 927 men, estimated a 16% increase in the risk of elevated PSA levels with each 5 kg/m^2 increase in BMI (RR, 1.16; 95% CI, 1.08–1.24) (Hu et al., 2014).

A meta-analysis of 14 studies that assessed BMI before or shortly after diagnosis in women with ovarian cancer estimated a hazard ratio for all-cause mortality of 1.17 (95% CI, 1.03–1.34) for obese versus non-obese patients (Protani et al., 2012). Another meta-analysis of 13 cohort studies of individuals with pancreatic cancer reported an adjusted hazard ratio for pancreatic cancer-related mortality of 1.06 (95% CI, 1.02–1.11) in overweight patients and of 1.31 (95%

CI, 1.20–1.42) in obese patients versus normal-weight patients (Majumder et al., 2015).

Meta-analyses and/or systematic reviews on obesity and cancer survival have also been conducted in patients with endometrial cancer (Arem & Irwin, 2013; Nakao et al., 2014) and with childhood leukaemia (Amankwah et al., 2015).

[It is unclear whether the relationship between obesity and increased risk of cancer-related mortality stems from differences in the biological aggressiveness or subtypes of cancers that develop in obese versus non-obese patients. Some studies have suggested that obese individuals are more likely to develop biologically aggressive cancers with poorer outcomes, or to have more advanced disease at the time of diagnosis. For example, studies have shown that obese individuals are at increased risk of developing biologically aggressive prostate cancers, but not of developing lower-grade prostate cancers (see Section 2.2.14). Some reports suggest that obese women are more likely to develop poorly differentiated and hormone receptor-negative breast cancers (Stark et al., 2010; Abdel-Maksoud et al., 2012), although other reports suggest that obese women are more likely to develop slower-growing hormone receptor-positive breast cancers (Borgquist et al., 2009; Canchola et al., 2012; Biglia et al., 2013). A few recent studies that have used genomic profiling techniques have suggested that obese women who develop hormone receptor-positive cancers are more likely to have luminal B cancers, which have been shown to have a worse prognosis, compared with luminal A cancers (Kwan et al., 2015; Ligibel et al., 2015). See Section 2.2.9 for more detailed data on risk estimates by subtype of breast cancer.]

2.4.2 Studies of weight change after cancer diagnosis and cancer outcomes

Fewer studies have investigated the association between weight change after cancer diagnosis and recurrence-free or overall survival.

A recent meta-analysis of 12 studies examined the association between weight gain after diagnosis of breast cancer and prognosis (Playdon et al., 2015). High weight gain after breast cancer diagnosis (> 10% of body weight at diagnosis) increased the risk of both all-cause mortality and breast cancer-specific mortality, whereas moderate weight gain (5–10%) did not (HR, 0.98; 95% CI, 0.83–1.15). The increased risk was observed among women with a BMI at diagnosis of less than 25 kg/m^2 and of 25 kg/m^2 or more. In an earlier analysis of a prospective cohort study of 5204 non-smoking women with early-stage breast cancer, those who gained more than 2 kg/m^2 had a significantly increased risk of death from breast cancer compared with women who maintained a stable weight; the relative risk of death from breast cancer was 1.35 (95% CI, 0.93–1.95) for weight gain of 0.5–2 kg/m^2 and 1.64 (95% CI, 1.07–2.51) for weight gain of more than 2 kg/m^2 (Kroenke et al., 2005). In contrast, in another study of 1692 women with early-stage breast cancer, no association was observed between weight gain and breast cancer recurrence or all-cause mortality, even among women who gained more than 10% of their baseline body weight (Caan et al., 2006).

2.4.3 Intervention trials of weight-loss intervention and dietary modification

No data were available to the Working Group about the impact of a weight-loss intervention on cancer recurrence, cancer-related mortality, or all-cause mortality in cancer survivors.

Two randomized trials assessed the impact of dietary modification on disease-free and overall survival in women with early-stage breast cancer.

The Women's Intervention Nutrition Study randomized 2400 women to a low-fat dietary intervention or usual care (control group) (Chlebowski et al., 2008). Patients assigned to the intervention group reduced their dietary fat intake for the duration of the 5-year intervention.

Intervention participants experienced an average weight loss of 6 lb (2.7 kg). An initial analysis of study results demonstrated a 24% reduction in breast cancer recurrence compared with the control group (HR, 0.76; 95% CI, 0.60–0.98) (Chlebowski et al., 2006), although the difference lost statistical significance with further follow-up (Chlebowski et al., 2008). Unplanned subset analysis suggested that the impact of the intervention differed in women with ER-positive cancers versus those with ER-negative cancers, with a hazard ratio for recurrence in the intervention group versus controls of 0.58 (95% CI, 0.37–0.91) in women with ER-negative cancers and 0.85 (95% CI, 0.63–1.14) in women with ER-positive cancers ($P_{interaction} = 0.15$). [The weight loss experienced by participants in the Women's Intervention Nutrition Study may have contributed to the reduced risk of cancer recurrence in intervention participants in that study.]

In contrast, the Women's Healthy Eating and Living study randomized 3088 women to a counselling programme for a diet very high in fruits and vegetables and low in fat or printed guidelines (Pierce et al., 2007). Adherence to the dietary intervention was good, with intervention participants increasing their daily intake of vegetables by 65% and of fruits by 25%, and reducing their daily intake of fat by 13%. [Of note, participants consumed on average seven servings of fruits and vegetables per day at baseline.] Participants randomized to the dietary intervention group did not lose weight compared with controls. The dietary intervention had no impact on rates of recurrence (HR for recurrence in intervention group vs controls, 0.96; 95% CI, 0.80–1.14).

[There were several differences between the trials, including in the degree of reduction in dietary fat intake achieved by intervention participants, the baseline diets, the delivery method of the dietary intervention, the timing of enrolment relative to breast cancer diagnosis, and the study population.]

Several ongoing studies are testing the hypothesis that weight loss after cancer diagnosis reduces the risk of cancer recurrence or progression in individuals with early-stage cancer (Courneya et al., 2008; Rack et al., 2010; Villarini et al., 2012; Crane et al., 2014; Parsons et al., 2014).

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2.5 Sustained weight loss and cancer risk: illustrative examples

Studies investigating whether weight loss protects against cancer occurrence are limited to a few observational studies on weight reduction in relation to breast cancer incidence and on the impact of intentional weight loss after bariatric surgery on cancer risk in morbidly obese patients.

2.5.1 Studies of weight loss and cancer risk

Few observational studies have been able to assess the impact of weight loss on cancer risk. Women from the Nurses' Health Study who had never used postmenopausal HRT and had lost 10 kg or more sustainably since menopause [duration not reported] had a lower risk of postmenopausal breast cancer than those who maintained their weight since menopause (RR, 0.43; 95% CI, 0.21–0.86) (Eliassen et al., 2006). However, no association was found between short-term (4-year) weight loss and subsequent cancer risk in the same cohort (Rosner et al., 2015). In contrast, regardless of use of postmenopausal HRT, adult weight loss was unrelated to postmenopausal breast cancer risk compared with stable weight in the NIH-AARP study (Ahn et al., 2007), the EPIC-PANACEA study (Emaus et al., 2014), and the Cancer Prevention Study II for the first 5 years of follow-up (Teras et al., 2011); however, in the Cancer Prevention Study II an inverse association was suggested in women who maintained a weight loss of 10 lb [4.5 kg] or more for the next 4 years. Similarly, in the Women's Health Initiative Dietary Intervention Trial, no effect of weight loss on postmenopausal breast cancer risk was found in overweight or obese women (Neuhouser et al., 2015).

[It is important to note that many of the published trials and observational studies were not designed to document weight loss, and weight change may reflect both intentional weight loss (with uncertainty about what exactly the intervention was) and unintentional weight loss (which is potentially illness-induced).]

2.5.2 Studies of bariatric surgery and cancer risk

Several prospective intervention trials or retrospective cohort studies (Christou et al., 2008; Adams et al., 2009; Sjöström et al., 2009; Ward et al., 2014) and reviews (Tee et al., 2013; Maestro et al., 2015) have evaluated the effect of bariatric surgery on cancer risk, comparing the risk of cancer in patients who underwent bariatric surgery with that in an obese control group who did not undergo surgery (Table 2.5). Overall, in most studies the risk of cancer at all sites in obese patients was significantly reduced after bariatric surgery. A 45% decrease in risk of all cancers combined was estimated in a recent meta-analysis (RR, 0.55; 95% CI, 0.41–0.73) (Tee et al., 2013). The extent of the cancer-protective effect of bariatric surgery seems to be more pronounced in women than in men: in the Swedish Obese Subjects study, after a median follow-up of more than 10 years, the relative risk was 0.58 (95% CI, 0.44–0.77) in women and 0.97 (95% CI, 0.62–1.52) in men (Sjöström et al., 2009). Also, there are broadly consistent inverse associations with the subsequent risk of female sex hormone-sensitive cancers, notably endometrial cancer and breast cancer (Adams et al., 2009; Tee et al., 2013; Ward et al., 2014). [However, there were methodological problems in the study designs because of confounding by indication, and failure to adequately capture the extent of body weight reduction after bariatric surgery.]

Studies using population-level registry data (i.e. standardized population cohorts) for comparison purposes have reported an increased incidence of colorectal cancer in obese men who underwent bariatric surgery compared with the expected risk in the general population (Östlund et al., 2010; Derogar et al., 2013). [Because the general population was used as comparator, the median BMI (not reported) would have been considerably less than that for the treatment group, and the observed increase in incidence might reflect the effect of the premature morbidly obese status rather than of the surgery itself. Therefore, any comparison with the general population may be misleading in the evaluation of the effects of bariatric surgery on subsequent cancer risk in obese patients.]

Table 2.5 Studies of obese patients who underwent bariatric surgery and subsequent cancer risk

Reference Location	Study design Mean follow-up (years)	Surgery group	Control group	Cancer site	Surgery cases (cohort) Control cases (cohort)	Relative risk (95% CI)	Adjustments Comments
Men and women							
Christou et al. (2008) Canada	Retrospective hospital-based Maximum, 5.0	Bariatric patients in regional database BMI not available	Diagnosis of "morbid obesity" from hospital records or prescription BMI unknown	All sites[a]	21 (1035) 487 (5746)	0.22 (0.14–0.35)	Age, sex, BMI
Adams et al. (2009) Utah, USA	Retrospective registry 12.5	Roux-en-Y gastric bypass Mean BMI, 44.9	State document applicants with a self-reported BMI > 35 Mean BMI, 47.4	All sites[b]	254 (6596) 477 (9442)	0.76 (0.65–0.89)	Age, sex, BMI Data also reported for the 31 individual cancer sites
				"Obesity-related sites"[c]	104 (6596) 253 (9442)	0.62 (0.49–0.78)	
				Colorectum	25 (6596) 52 (9442)	0.70 (0.43–1.15)	
Women							
Adams et al. (2009) Utah, USA	Retrospective registry Median, 12.5	Roux-en-Y gastric bypass Mean BMI, 44.9	State document applicants with a self-reported BMI > 35 Mean BMI, 47.4	All sites[b]	215 (5654) 412 (7872)	0.73 (0.62–0.87)	Age, BMI
				Breast	25 (5654) 52 (7872)	0.91 (0.67–1.24)	
				Premenopausal breast	49 (5654) 65 (7872)	0.93 (0.63–1.37)	
				Postmenopausal breast	24 (5654) 40 (7872)	0.96 (0.57–1.63)	
				Corpus uteri	14 (5654) 98 (7872)	0.22 (0.13–0.40)	
Sjöström et al. (2009) Sweden	Prospective intervention trial 10.9	Mean BMI, 42.2	Matched using 18 anthropometric, cardiovascular, and biochemical indices Mean BMI, 41.6	All sites[d]	79 (1420) 130 (1447)	0.58 (0.44–0.77)	Age, smoking, weight change, energy intake, and matching Also significantly reduced for melanoma and haematopoietic cancers
Ward et al. (2014) USA	Retrospective clinical data repository Unknown	All female patients with a history of bariatric surgery BMI unknown	All female admissions with an associated diagnosis of obesity BMI unknown	Corpus uteri	424 (103 797) 43 921 (7 328 061)	0.29 (0.26–0.32)	None

Table 2.5 (continued)

Reference Location	Study design Mean follow-up (years)	Surgery group	Control group	Cancer site	Surgery cases (cohort) Control cases (cohort)	Relative risk (95% CI)	Adjustments Comments
Men							
Adams et al. (2009) Utah, USA	Retrospective registry 12.5	Roux-en-Y gastric bypass Mean BMI, 44.9	State document applicants with a self-reported BMI > 35 Mean BMI, 47.4	All sites[b]	39 (942) 65 (1570)	1.02 (0.69–1.51)	Age, BMI
Sjöström et al. (2009) Sweden	Prospective intervention trial 10.9	Mean BMI, 40.6	Matched using 18 anthropometric, cardiovascular, and biochemical indices Mean BMI, 39.2	All sites[d]	39 (590) 39 (590)	0.97 (0.62–1.52)	Age, smoking, weight change, energy intake, and matching Results were not statistically significant for any of the individual cancer sites

[a] Includes colorectum, pancreas, breast, endometrium, kidney, melanoma, myeloma, and non-Hodgkin lymphoma.
[b] Includes 31 cancer sites and "other".
[c] Includes colorectum, oesophagus (adenocarcinoma), liver, gall bladder, pancreas, postmenopausal breast, corpus and uterus, kidney, non-Hodgkin lymphoma, leukaemia, and multiple myeloma.
[d] Includes colorectum, stomach, liver, pancreas, kidney, bladder, lung and bronchia, haematopoietic system, and melanoma for both sexes, and breast, cervix, and endometrium in women and prostate in men.
BMI, body mass index (in kg/m^2); CI, confidence interval

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3. CANCER-PREVENTIVE EFFECTS IN EXPERIMENTAL ANIMALS

3.1 Methodological considerations

3.1.1 Definition of dietary/calorie restriction

Dietary/calorie restriction involves altering food intake qualitatively or quantitatively to control body weight gain and presumably maintain body composition. Several terms have been used to describe the different methodological approaches in which amount, nutrient, calorie, or energy intake is restricted or modulated to control body weight (Thompson et al., 2002, 2003; Thompson, 2015). These terms are not synonyms, and it is important to be aware of the methodological distinctions between the approaches when designing experiments.

Dietary restriction protocols refer to feeding a reduced amount of a complete diet, such that less total nutrients and dietary factors are ingested. If excessive, this approach can lead to an intake of micronutrients and/or macrocomponents that is incompatible with optimal health and survival. In early studies, this was the most commonly used approach to study cancer prevention. These studies have provided valuable insights, but the results should be interpreted with caution, because this approach does not allow the detection of effects that are specifically due to dietary modulation. Terms used to describe this approach include dietary restriction, food restriction, and total dietary restriction.

In energy restriction protocols, diets are formulated so that animals fed different amounts of calories still receive the same levels of other nutrients, such that the only variable is energy intake (Thompson et al., 2002, 2003; Thompson, 2015). In other words, there is selective reduction in energy intake (nutrient density) while feeding the same level of micronutrients as those of the control group. Nutrient density is altered in a manner that facilitates investigation of the effects of energy restriction without changing the amounts of nutrients and other dietary factors. These studies may provide information most relevant to understanding the mechanisms involved. Terms used to describe this approach include calorie restriction (CR), caloric restriction, dietary energy restriction, and energy restriction. In this section, the term dietary restriction (DR) will be used to include both dietary and calorie restriction.

3.1.2 Design issues in studies of dietary restriction

DR has been one of the most widely used methods for studying cancer prevention in experimental models. In DR protocols, control and carcinogen-treated animals are diet-restricted by amounts that result in lower body weights relative to those of controls fed ad libitum (AL), without weight loss. Also, diet-restricted animals

generally survive longer (Maeda et al., 1985; Yu et al., 1985).

However, inherent within DR protocols are factors that could confound the assessment of tumorigenesis. An important factor in carcinogenesis studies is that the sensitivity of bioassays to detect xenobiotics-induced carcinogenic responses may be altered by DR. A chemical that is observed to be toxic or carcinogenic in animals fed AL might not produce the same effects in diet-restricted or otherwise leaner animals, i.e. carcinogenic activity might be underestimated in the diet-restricted animals. In addition, DR may induce a variety of pleiotropic responses that affect metabolism, distribution, and disposition of xenobiotics. Furthermore, because diet-restricted animals live longer than those fed AL, evaluations performed at age 2 years result in comparisons at disproportionate times in the respective lifespans (NTP, 1997).

(a) Experimental systems

Animal models have been used to study how DR modulates the development and/or progression of cancer in humans. Typically, animals are fed diets that result in 20–40% reduction in daily food/calorie intake relative to controls fed AL while maintaining adequate nutrition (Klurfeld et al., 1989a; Kritchevsky, 1999; Hursting et al., 2010, 2013). The animals have lower body weight, proportionately smaller skeletal size, lower percentage of total body fat, and decreased weight of most internal organs (with the exception of the brain and testes) compared with animals fed AL, indicating that malnutrition is not involved (Keenan et al., 2013). DR models are designed to directly parallel and model conditions in humans. The range of DR controls body weight and is intended to resemble the range of energy balances that occur in healthy people.

(b) Selection of model

Characteristics that should be considered when choosing a model to study cancer in humans include the similarity of tumour morphology and biological traits (e.g. hormonal responsiveness) to those observed in humans. Such models are available for many organ sites. For example, in rat models for breast cancer, not only are the tumours in the rat morphologically similar to tumours in humans, but the majority are ovarian steroid-responsive. *N*-nitrosobis(2-oxopropyl) amine (BOP)-induced ductular pancreatic cancer in the Syrian hamster is a model that has been useful in studying aspects of pancreatic cancer in humans (Pour et al., 1993), whereas other carcinogen-induced pancreatic tumours are acinar cell carcinomas, which are not a common lesion in humans. There is a variety of animal models for cancers of the mammary gland, colon, liver, prostate, pancreas, skin, and pituitary gland, and cancers of the haematopoietic system, including lymphoma and leukaemia. In earlier studies, spontaneous tumour models were used. Increasingly in recent decades, researchers have used transgenic mice to model cancer in humans and to determine whether dietary interventions can prevent cancer development driven by genes known to be mutated in human cancer (Hursting et al., 2011). These models are described in the subsequent sections.

(c) Selection of intervention protocol

When a chemical carcinogen is used in DR models, the timing of carcinogen administration and dietary intervention needs to be taken into consideration. The intervention should generally be separate from the administration of the chemical carcinogen. However, it is important to assess the impact of the intervention both on the cancer induction phase (before and at the time of treatment with the carcinogen) and on the promotion/progression (development) of the cancer (after treatment with the carcinogen).

Models involving a short induction phase provide the ability to assess the impact of diet on early or late stages of promotion. If tumours are allowed to develop before the intervention, it is possible to assess the impact of the intervention on the regression or progression of the lesions. When spontaneous or genetically modified models are used, the dietary intervention can be applied at different ages, depending on the individual model (Thompson et al., 2002; Everitt & Alder, 2013).

(d) Selection of diet

Laboratory rodents can be fed three types of diets: (i) non-purified, (ii) purified or semi-purified, and (iii) chemically defined (Everitt & Alder, 2013; Lipman & Leary, 2015). Purified diets are the most widely used in cancer-related studies in rodents. These diets should meet and label the minimum requirements for protein and fat and maximum levels of fibre and ash; however, the percentages of the various macronutrients can vary. Purified diets (previously known as semi-synthetic or semi-purified diets) are formulated using refined ingredients, including sugars, proteins, carbohydrates, and fats, with added mineral and vitamin mixtures.

Non-purified and purified diets have been used in studies of dietary impact on tumorigenesis. In these types of studies, it is very important that the diet of both the intervention and the control group be adequate in all nutrients. Non-purified diets have the advantage that they are formulated using whole food ingredients. Purified diets have the advantage that each component can be changed independently of other constituents in a highly controlled fashion.

In most rodent models, DR administered throughout life appears to be more effective in controlling body weight than regimens started in adult animals (Ross & Bras, 1971; Hursting et al., 2010, 2013). There are three commonly used animal DR regimens that model approaches to and patterns of body weight regulation in adult humans. In the first regimen, animals are fed a restricted amount of energy (i.e. energy restriction to various extents) and continue to gain weight, but at a slower rate than animals fed AL. This DR does not usually cause weight loss, because restriction is started shortly after weaning. In the second regimen, when DR is started in older animals, restriction initially causes weight loss, but then diet-restricted animals maintain a body weight that is lower than that of animals that consume food AL. The third regimen mimics a cyclic pattern of dieting. Animals are subjected to intermittent and repetitive periods of DR or total fasting that result in alternating patterns of weight loss and weight gain (Thompson et al., 2002; Cleary & Grossmann, 2011).

3.2 Overview of the effects of excess body weight

3.2.1 Obesity models

The use of rodent models to study excess body weight and associated diseases in humans has steadily increased (Kanasaki & Koya, 2011). These models have several modulating factors that include species, strain, age of animals, type of diet, level of fat, and type of control diet; inflammation, metabolic status, and endocrine status may be associated confounding factors. Ray & Cleary (2013) and Cleary (2013) have published comprehensive reviews on the use of such animal models.

Most mouse models used to study obesity and cancer are genetically manipulated (transgenic) animals: animals are either genetically modified to induce carcinogenicity and fed a modified diet to induce obesity, or genetically modified to induce obesity and administered chemicals to induce cancer. There are several genetic mutations that result in obesity. One common disturbance is in the function of leptin, a critical anorexigenic adipokine that conveys information about adipose status; leptin levels

in serum/plasma are elevated in proportion to adipose tissue mass. Genetically obese mice include A^{vy} yellow obese mice, leptin-deficient C57BL/6L-*Lep*^{ob}*Lep*^{ob} (originally termed *ob/ob*) mice, and leptin receptor-deficient *Lepr*^{db}*Lepr*^{db} (originally termed *db/db*) mice. *Lep*^{ob}*Lep*^{ob} mice are homozygous recessive and do not produce leptin (Zhang et al., 1994), whereas *Lepr*^{db}*Lepr*^{db} mice have a defect in the leptin receptor (OB-R) and manifest high circulating levels of leptin (Frederich et al., 1995). Both strains are obese at a young age, and develop hyperinsulinaemia and insulin resistance. The A^{vy} yellow obese mouse has mutations in the *agouti* gene that cause ubiquitous expression of the agouti protein, which results in appetite stimulation, leading to hyperinsulinaemia (Wolff et al., 1999).

Genetically obese rat strains, such as the Zucker and Corpulent strains that have leptin receptor defects, have also been used in cancer studies. The Zucker "fatty" rat carries a mutation on the *Lepr* gene for obesity, which is inherited as a Mendelian recessive trait and leads to extreme, early-onset obesity by age 3 weeks (Zucker & Zucker, 1961).

The diet-induced obesity (DIO) model is also used to study the interplay between cancer and increased body weight in mice and rats. Although this model is generally considered to be closest to the development of obesity in humans, the utility of the model is limited by the fact that humans do not normally consume extremely high quantities of fat in their diets. In DIO studies, the fat content of the diets is increased from 10% of total calories to 30–60% of total calories. High-fat diets (HFDs) also contain higher calorie density than control or standard rodent chow, and therefore are in fact high-fat, high-calorie diets. Although the response is species- and strain-dependent, the animals gain weight rapidly and develop other health complications, such as glucose intolerance and insulin resistance or diabetes. This response may be species- and strain-specific, because not all species gain weight when placed on a HFD.

Other methods for inducing obesity in rodents include surgical removal of the ovaries to induce weight gain and a postmenopausal-like state (Nkhata et al., 2009), or damaging the hypothalamus by injection of gold thioglucose (GTG), which results in overeating, rapid weight gain, and subsequent obesity (Bergen et al., 1998). These models have been used to study mammary tumorigenesis (see Section 3.2.2).

3.2.2 Cancer of the mammary gland

See Table 3.1.

Various rodent models have been used to assess the association between obesity and cancer of the mammary gland, including genetic, diet-induced, and GTG-induced obesity models. The A^{vy} yellow obese mouse model was one of the first genetic obesity models used to study both spontaneous and chemically induced cancer of the mammary gland. In an early study, the time to tumour detection (latency period) for spontaneous mammary tumours initiated by the mouse mammary tumour virus (MMTV) was determined in breeding and virgin A^{vy} mice. The incidence of spontaneous mammary tumours was 96–100% by 8 months in virgin obese mice, whereas it reached 100% at 15 months in virgin lean mice (Heston & Vlahakis, 1961, 1962). The difference disappeared in the breeding mice, with approximately 100% incidence at 8 months in both lean and obese mice. In another study using A^{vy} mice, the time course of appearance of hyperplastic alveolar nodules and mammary tumours was determined in virgin "viable yellow" (A^{vy}/A) [obese] and non-yellow (A/a) (C3H/HeNIcrWf × VY/Wf)F_1 [lean] female mice. Hyperplastic alveolar mammary nodules occurred by age 16 weeks in virgin yellow obese mice compared with age 19 weeks in their non-yellow lean counterparts. In addition, the incidence of hyperplastic alveolar nodules was increased among yellow obese females compared with non-yellow lean females by age 36 weeks. Mammary adenocarcinomas

Table 3.1 Effect of obesity on the development of mammary tumours in mice and rats

Species	Obesity model	Cancer etiology	Results (obese vs lean animals)	Reference
Mouse	A^{vy} yellow obese	MMTV	Shortened latency until 100% incidence of tumours	Heston & Vlahakis (1961, 1962)
Mouse	A^{vy} yellow obese	Spontaneous	Shortened latency for hyperplastic alveolar nodules and adenocarcinomas	Wolff et al. (1979)
Mouse	A^{vy} yellow obese	DMBA	Shortened latency and increased incidence of tumours	Wolff et al. (1982)
Mouse	$Lep^{ob}Lep^{ob}$	Spontaneous	Shortened latency but decreased incidence of tumours	Heston & Vlahakis (1962)
Mouse	$Lep^{ob}Lep^{ob}$	Transgenic MMTV-TGF-α	No tumours; increased incidence of tumours in wild-type and heterozygous mice (see text)	Cleary et al. (2004c)
Rat	Zucker rat	MNU	No effect on latency of tumours; decreased incidence of carcinomas	Lee et al. (2001)
Rat	Zucker *fa/fa* rat; LA/Ncp corpulent rat	DMBA	Shortened latency and increased incidence of tumours	Klurfeld et al. (1991); Hakkak et al. (2005)
Rat	Zucker rat, ovariectomized	DMBA	Shortened latency and increased incidence of tumours (no tumours in lean animals)	Hakkak et al. (2007)
Mouse	GTG-induced	Spontaneous (C3H)	Shortened latency until 50% incidence of tumours	Waxler et al. (1953)
Mouse	GTG-induced	Implantation of T47-D human breast cancer cells	Increased incidence of tumours	Nkhata et al. (2009)
Mouse	Diet-induced (33% fat diet; mice divided into groups based on weight gain)	Transgenic MMTV-TGF-α (C57BL/6)	Shortened latency and increased incidence of palpable tumours; some high-grade adenocarcinomas	Cleary et al. (2004a); Dogan et al. (2007)
Mouse	Diet-induced (33% fat diet; mice divided into groups based on weight gain)	Transgenic MMTV-neu (FVB/N)	No effect on latency or incidence of tumours; earlier onset of second tumours, increased multiplicity	Cleary et al. (2004b); Khalid et al. (2010)
Mouse	Diet-induced (5.2 kcal/g or 3.8 kcal/g)	Implantation of mammary tumour cells from Wnt-1 transgenic mice	Significantly increased tumour volume and growth rate	Nuñez et al. (2008)
Mouse	Diet-induced, ovariectomized	Implantation of mammary tumour cells from Wnt-1 transgenic mice	Increased tumour volume	Rossi et al. (2016)
Rat	Obesity-prone Sprague-Dawley	MNU	Shortened latency; increased tumour incidence and tumour weight	Matthews et al. (2014)

DMBA, 7,12-dimethylbenz[*a*]anthracene; GTG, gold thioglucose; MMTV, mouse mammary tumour virus; MNU, *N*-methyl-*N*-nitrosourea; TGF-α, transforming growth factor alpha.

were first observed at an earlier age in yellow obese mice than in non-yellow lean mice (Wolff et al., 1979).

In a study of chemically induced mammary tumours, obese A^{vy} (BALB/c) mice aged 8 weeks treated with 1.5 mg/kg of 7,12-dimethylbenz[*a*] anthracene (DMBA) weekly for 2 weeks or with 6.0 mg/kg of DMBA weekly for 6 weeks had higher incidences of mammary tumours compared with the lean mice at both doses. In addition, the latency period was shorter for the A^{vy} mice than for the lean mice at both doses of DMBA (Wolff et al., 1982).

The $Lep^{ob}Lep^{ob}$ mouse is another model that has been used to study obesity and cancer. In an early study, obese $Lep^{ob}Lep^{ob}$ female mice had decreased incidences of spontaneous mammary tumours compared with lean mice; however, tumours were first detected at an earlier age, 10.7 months for obese mice versus 17.6 months for lean mice (Heston & Vlahakis, 1962).

In another study, obese $Lep^{ob}Lep^{ob}$ female mice crossed with transgenic mice overexpressing human transforming growth factor alpha (MMTV-TGF-α) were used as a model for postmenopausal mammary tumorigenesis. The MMTV-TGF-α strain develops 30% incidence of mammary tumours by age 16 weeks and is useful in assessing tumour incidence and latency. MMTV-TGF-α/$Lep^{ob}Lep^{ob}$ mice did not develop mammary tumours by age 2 years. However, the incidence was 50% for wild-type mice and 67% for heterozygous mice (Cleary et al., 2004c). Similar results were obtained with the leptin receptor-deficient ($Lepr^{db}Lepr^{db}$) model (Cleary et al., 2004d). [The lack of development of mammary tumours in these two genetically obese mouse strains has been attributed to problems with basic mammary gland development as well as the now-known involvement of leptin signalling in tumorigenesis.]

The Zucker rat is another genetic obesity model that has been used to study mammary tumours. Zucker rats developed fewer mammary tumours when treated with *N*-methyl-*N*-nitrosourea (MNU) compared with lean rats (Lee et al., 2001). However, two strains of genetically obese rats, the LA/Ncp Corpulent rat and the Zucker *fa/fa* rat, administered DMBA had higher incidences and significantly shorter latency of mammary tumours by approximately 112 days and 150 days after administration, respectively, compared with lean rats. Whereas multiplicity and tumour size were increased in Corpulent rats, such effects were not observed in Zucker *fa/fa* rats (Klurfeld et al., 1991; Hakkak et al., 2005).

Lean and obese ovariectomized Zucker rats were treated with DMBA at 50 days and killed at 135 days after DMBA treatment. Obese rats had higher incidences and shorter latency of mammary tumours compared with lean rats, which did not develop any mammary tumours (Hakkak et al., 2007).

Chemically induced obesity has been another approach to study increased body weight and cancer of the mammary gland. Injection of GTG to destroy the hypothalamus results in overeating and obesity (Bergen et al., 1998). Obese C3H mice injected with 10 mg of GTG at age 2–3 months to induce obesity developed 50% incidence of spontaneous mammary tumours by 295 days, whereas the incidence was only 19% in lean control mice (Waxler et al., 1953). In another study, ovariectomized mice aged 6 weeks were treated with GTG, followed 4 weeks later by implantation of the T47-D human breast cancer estrogen-positive cell line with and without estrogen implants. When assessed at 30 weeks, GTG-obese mice without estrogen implants had 100% tumour incidence, compared with 50% for GTG-lean controls, 20% for lean vehicle controls, and 0% for GTG-obese mice with estrogen implants (Nkhata et al., 2009).

HFDs have also been used to investigate mammary tumour development in rats and mice (Cleary, 2013; Ray & Cleary, 2013). In one approach, tumour-prone MMTV-TGF-α transgenic C57BL/6 mice aged 10 weeks were fed the

same HFDs and then divided into groups based on whether they gained weight (obesity-prone) or did not gain weight (obesity-resistant). All groups had incidences of mammary tumours between 72% and 82%; however, obesity-prone mice developed mammary tumours at an earlier age than obesity-resistant or control (low-fat) mice. In addition, some obesity-prone mice developed a more malignant variant of mammary adenocarcinoma (Cleary et al., 2004a; Dogan et al., 2007). In MMTV-neu mice, tumour latency was similar in mice fed a HFD compared with a low-fat diet (LFD) (Cleary et al., 2004b; Khalid et al., 2010); however, twice as many HFD mice developed a second tumour, compared with LFD mice (Khalid et al., 2010). In another study, C57BL/6 mice were fed either a high-calorie diet with 5.2 kcal/g (obese) or 3.8 kcal/g (overweight) or a 30% CR diet (lean). The mice were inoculated with mammary tumour cells from Wnt-1 transgenic mice. Tumour volume and growth rate were higher in obese mice and overweight mice than in lean animals (Nuñez et al., 2008).

Ovariectomized female C57BL/6 mice were fed a control diet or a DIO regimen, resulting in a normal weight or an obese phenotype, respectively. At week 24, mice were injected with MMTV-Wnt-1 mouse mammary tumour cells. At 36 months, mean tumour volumes were higher in DIO mice than in control animals (Rossi et al., 2016).

Matthews et al. (2014) used a somewhat different approach, with administration of MNU. Sprague-Dawley rats that had been bred to be obesity-resistant or obesity-prone were fed a moderately HFD from age 20 days and followed up for development of mammary tumours. Tumour incidence was significantly higher in the obesity-prone rats (91.1%) than in the obesity-resistant rats (65.1%). In addition, tumour weight was increased and latency was shortened in obesity-prone rats, compared with obesity-resistant rats.

3.2.3 Cancer of the colon

See Table 3.2.

Elevated body weight and obesity in association with cancers of the colon and intestine have been investigated in several transgenic and DIO rodent models. Genetically obese *Lep*^{ob}*Lep*^{ob} and *Lepr*^{db}*Lepr*^{db} mice treated with azoxymethane (AOM) or MNU to induce cancer of the colon had increases in the multiplicity of pre-neoplastic aberrant crypt foci in the colon compared with control lean mice (Hirose et al., 2004; Hayashi et al., 2007; Bobe et al., 2008; Ealey et al., 2008). Similar effects were observed in studies with obese gastrin gene knockout (GAS-KO) mice (Cowey et al., 2005), KK-*A*^{y} mice (derived from *A*^{vy} yellow obese mice) (Teraoka et al., 2011), and Zucker rats (Raju & Bird, 2003) administered AOM. In studies with Zucker obese (*fa/fa*) and lean (*Fa/Fa*) rats, tumours of the colon induced by administration of AOM or MNU were observed in the obese rats, whereas none occurred in the lean rats (Weber et al., 2000; Lee et al., 2001; Ray & Cleary, 2013).

Mice harbouring mutations in the adenomatous polyposis coli (*Apc*) gene develop tumours of the intestine and colorectum and have also been used to study the association between obesity and colorectal cancer. When *Apc*$^{1638N/+}$ mice were crossed with genetically obese *Lepr*^{db} mice, the resulting obese mice developed increased numbers of colon adenomas by age 6 months, compared with non-obese *Apc* mice, which did not develop tumours (Gravaghi et al., 2008).

In male and female C57BL/6 mice fed a high-calorie diet followed by subcutaneous injection of the MC38 colon carcinoma cell line, obese mice had increased numbers of palpable tumours and significantly higher average tumour size compared with non-obese mice (Yakar et al., 2006; Algire et al., 2010).

Table 3.2 Effect of obesity on the development of colon tumours and pre-neoplastic lesions in mice and rats

Species	Obesity model	Cancer etiology	Results (obese vs lean animals)	Reference
Mouse	*Lep*^{ob}*Lep*^{ob}	AOM	Increased multiplicity of ACF	Hirose et al. (2004); Hayashi et al. (2007); Bobe et al. (2008); Ealey et al. (2008)
Mouse	*Lepr*^{db}*Lepr*^{db}	AOM	Increased multiplicity of ACF	Hirose et al. (2004); Hayashi et al. (2007); Ealey et al. (2008)
Mouse	*Lepr*^{db}*Lepr*^{db}	MNU	Increased multiplicity of ACF	Ealey et al. (2008)
Mouse	Gastrin gene knockout (GAS-KO)	AOM	Increased multiplicity of ACF	Cowey et al. (2005)
Mouse	KK-*A*^{y}	AOM	Increased multiplicity of ACF at age 13 wk; increased tumour incidence at age 19 wk	Teraoka et al. (2011)
Mouse	*Lepr*^{db}*Lepr*^{db}	*Apc*$^{1638N/-}$	Increased incidence of colon tumours at age 6 mo (no tumours in lean animals)	Gravaghi et al. (2008)
Rat	Zucker	AOM	Increased multiplicity of ACF	Raju & Bird (2003)
Rat	Zucker (*fa/fa*)	AOM	Increased multiplicity of ACF and incidence of colon tumours	Weber et al. (2000)
Rat	Zucker (*fa/fa*)	MNU	Increased incidence of colon tumours	Lee et al. (2001)
Mouse	Diet-induced	s.c. injection of MC38 colon carcinoma cell line	Increased number and size of colon tumours	Yakar et al. (2006); Algire et al. (2010)

ACF, aberrant crypt foci; AOM, azoxymethane; mo, month or months; MNU, *N*-methyl-*N*-nitrosourea; s.c., subcutaneous; wk, week or weeks.
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3.2.4 Cancer of the liver

See Table 3.3.

Several genetically modified animal models have been used to study the link between obesity and cancer of the liver. For example, genetically obese yellow *agouti* (*A*^{vy}) mice and *Lep*^{ob}*Lep*^{ob} mice had increased incidences of liver tumours, which also developed at a younger age in obese mice compared with lean mice (Heston & Vlahakis, 1961, 1962).

The genetically obese *Lep*^{ob}*Lep*^{ob} mouse is often used as an animal model for non-alcoholic fatty liver disease in humans. These mice have increased incidences of hepatocellular carcinoma (HCC) and of focal hepatocyte hyperplasia (considered to be a pre-neoplastic lesion) at an earlier age compared with lean littermates (Yang et al., 2001). The fatty liver Shionogi (FLS)-*Lep*^{ob}/*Lep*^{ob} mouse is a congenic obese strain that develops spontaneous hepatocellular adenomas and carcinomas at a younger age and a higher incidence than either parental strain (FLS and *Lep*^{ob}/*Lep*^{ob}) (Soga et al., 2010).

The outbred obese, diabetic, male Swiss-Webster mouse is another model for studying the link between obesity and cancer of the liver. These mice are polyuric, polydipsic, glucosuric, and hyperglycaemic. Compared with their lean counterparts, they develop a high incidence of late-onset HCC (Lemke et al., 2008). Strain–diet interactions are another important consideration for genetically controlled, diet-induced HCC. For example, male C57BL/6J mice made obese by feeding a HFD developed HCC, compared with none in mice fed a LFD; in contrast, a HFD had little effect on A/J mice similarly treated (Hill-Baskin et al., 2009).

Table 3.3 Effect of obesity on the development of liver tumours and pre-neoplastic lesions in mice and rats

Species	Obesity model	Cancer etiology	Results (obese vs lean animals)	Reference
Mouse	*A*^{vy}	Spontaneous	Shortened latency and increased incidence of tumours	Heston & Vlahakis (1961)
Mouse	*Lep*^{ob}*Lep*^{ob}	Spontaneous	Shortened latency and increased incidence of tumours	Heston & Vlahakis (1962)
Mouse	*Lep*^{ob}*Lep*^{ob}	Spontaneous	Shortened latency and increased incidence of tumours and of focal hepatocyte hyperplasia	Yang et al. (2001)
Mouse	*Lep*^{ob}*Lep*^{ob} crossed with fatty liver Shionogi (FLS)	Spontaneous	Increased incidence of hepatocellular adenoma and carcinoma at age 12 mo	Soga et al. (2010)
Rat	Obese, diabetic Swiss-Webster	Spontaneous	Increased incidence of late-onset hepatocellular carcinoma (male mice only)	Lemke et al. (2008)
Mouse	Diet-induced C57BL/6 (58% fat)	Spontaneous	Increased incidence of hepatocellular carcinoma (none in lean mice)	Hill-Baskin et al. (2009)
Mouse	Diet-induced A/J (58% fat)	Spontaneous	No effect	Hill-Baskin et al. (2009)
Mouse	*Lep*^{ob}*Lep*^{ob}	DEN	Increased incidence and number and size of tumours	Park et al. (2010)
Mouse	Diet-induced C57BL/6 (58% fat)	DEN	Increased incidence and number and size of tumours	Park et al. (2010)
Mouse	Diet-induced *IL6*$^{-/-}$; *TNFR1*$^{-/-}$ (59% fat)	DEN + phenobarbital promotion	Induction of hepatocellular carcinoma without phenobarbital promotion in mice fed high-fat diet but not in mice fed low-fat diet	Park et al. (2010)

DEN, diethylnitrosamine; mo, month or months.
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Carcinogen-induced protocols involve induction of hepatocellular tumours by administration of diethylnitrosamine (DEN). After administration of DEN, DIO C57BL6 mice and genetically obese *Lep*^{ob}*Lep*^{ob} mice had increased incidence, numbers, and size of hepatocellular tumours, compared with lean mice fed a LFD. When IL-6-deficient (*IL6*$^{-/-}$) and tumour necrosis factor receptor-deficient (*TNFR1*$^{-/-}$) mice were fed either a LFD or a HFD and treated with DEN, the majority of the mice fed the HFD developed HCC without phenobarbital promotion. In contrast, DEN-treated mice fed the LFD did not develop HCC unless treated with phenobarbital (Park et al., 2010).

3.2.5 Cancer of the prostate

See Table 3.4.

There has been a lack of suitable experimental animal models that mimic the development and progression of cancer of the prostate in humans. Therefore, few published studies have reported the long-term effects of a HFD and/or obesity on the development of prostate cancer. In recent years, several genetically engineered mouse models of prostate cancer have been developed (Parisotto & Metzger, 2013). The model that is most commonly used is the transgenic adenocarcinoma of the mouse prostate (TRAMP) mouse model. When maintained on a C57BL/6 genetic background, male TRAMP mice develop prostatic intraepithelial neoplasia (PIN) (pre-neoplastic lesions) in all lobes between age

Table 3.4 Effect of obesity on the development of prostate tumours and pre-neoplastic lesions in mice

Obesity model	Cancer etiology	Results (obese vs lean animals)	Reference
Diet-induced, "Western diet" (40% fat vs chow)	TRAMP mice	More advanced disease; increased percentage of metastasis	Llaverias et al. (2010)
Diet-induced (33% fat)	TRAMP mice	More advanced disease; higher incidence of metastasis (see text for comment)	Bonorden et al. (2012)
GTG-induced	TRAMP mice	Less advanced disease; lower percentage of metastasis	Bonorden et al. (2012)
Diet-induced in C57BL/6	Implantation of TRAMP-C2 cells	Faster tumour growth	Bonorden et al. (2012)
Diet-induced (60% fat)	Transgenic Hi-Myc mice	More advanced disease	Blando et al. (2011)
Diet-induced	s.c. injection of RM1 prostate carcinoma cell line	Larger tumours	Ribeiro et al. (2010)
Lep^{ob}*Lep*^{ob}	s.c. injection of RM1 prostate carcinoma cell line	Larger tumours	Ribeiro et al. (2010)
Lepr^{db}*Lepr*^{db}	s.c. injection of RM1 prostate carcinoma cell line	Smaller tumours	Ribeiro et al. (2010)

GTG, gold thioglucose; s.c., subcutaneous; TRAMP, transgenic adenocarcinoma of the mouse prostate.
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2 months and age 3 months, and progression to poorly differentiated neuroendocrine carcinoma occurs by age 4–7 months.

When fed a "Western-type" diet, enriched in both fat and cholesterol, TRAMP-C57BL6 mice had accelerated tumour incidence and burden compared with mice fed a control chow diet. Mice fed the Western-type diet had more advanced disease, characterized by highly invasive and less well differentiated tumours and fewer high-grade PIN, in contrast to the chow-fed mice, which had only high-grade PIN. Increased incidences of metastasis to the lung (67% vs 43%) were also observed in mice fed the Western-type diet (Llaverias et al., 2010).

In another study, TRAMP mice were fed a moderately HFD (33% of calories from fat) from age 7 weeks, and at age 18 weeks they were divided into obesity-resistant, overweight, and obesity-prone groups and were then followed up until age 50 weeks (Bonorden et al., 2012). An LFD group was also included. Obesity-prone mice tended to have more severe lesions, including a higher incidence of moderate and poorly differentiated tumours, than mice that weighed less, and a higher incidence of metastasis. [It should be noted that these results were not statistically significant and also that the aggressiveness of the development of prostate cancer in the TRAMP mouse affects its usefulness in this type of study.]

Implantation of TRAMP-C2 cells into diet-induced obese mice showed similar effects. In contrast, GTG-induced obesity in TRAMP mice led to a reduction in disease progression and metastasis (Bonorden et al., 2012).

The Hi-Myc transgenic mouse model of prostate cancer was used to study the effect of modulating dietary energy balance on the development and progression of prostate cancer. The mice were placed on one of three diets: 30% CR; a modified AIN-76A diet with 10% of calories from fat (overweight); or a DIO diet with 60% of calories from fat (obese). All three groups had similar incidences of hyperplasia and low-grade PIN at age 3 months and 6 months. The CR group had significantly reduced incidence of in situ adenocarcinomas at 3 months compared with the DIO

Table 3.5 Effect of obesity on the development of skin tumours in mice

Obesity model	Cancer etiology	Results (obese vs lean animals)	Reference
Lep^{ob}*Lep*^{ob}	s.c. injection of B16BL6 mouse melanoma cells	Increased number of metastatic tumour foci in the lung	Mori et al. (2006)
Lepr^{db}*Lepr*^{db}	s.c. injection of B16BL6 mouse melanoma cells	Increased number of metastatic tumour foci in the lung	Mori et al. (2006)
Lep^{ob}*Lep*^{ob}	s.c. injection of B16F10 melanoma cells	Significantly larger tumours	Brandon et al. (2009)
MC4R$^{-/-}$	s.c. injection of B16F10 melanoma cells	Significantly larger tumours	Brandon et al. (2009)
Diet-induced: HFD	s.c. injection of B16F10 mouse melanoma cells	Time to tumour formation similar, but tumours progressed more rapidly; increased tumour weight and volume	Pandey et al. (2012)
Diet-induced: pelleted + powdered (overweight) or powdered (obese)	SKH-1 hairless mice + UV radiation	Shortened latency and increased multiplicity: obese > overweight > lean	Dinkova-Kostova et al. (2008)

HFD, high-fat diet; s.c., subcutaneous; UV, ultraviolet.
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group, and at 6 months compared with both the overweight group and the DIO group. The DIO regimen also significantly increased (P = 0.02) the incidence of invasive adenocarcinoma (95%), compared with the overweight group (65%) and with the 30% CR group (no invasive adenocarcinomas) (Blando et al., 2011).

Cancer cell lines have also been used to study the induction and progression of prostate cancer. Obese *Lep*^{ob}*Lep*^{ob} and *Lepr*^{db}*Lepr*^{db} mice, DIO mice, and control C57BL/6J mice were injected subcutaneously with RM1, a murine androgen-insensitive prostate carcinoma cell line, and evaluated 14 days after inoculation. The tumours induced in the obese *Lep*^{ob}*Lep*^{ob} mice and the DIO mice were significantly larger (P < 0.001), and those induced in the *Lepr*^{db}*Lepr*^{db} mice were significantly smaller (P = 0.047) than those in the controls (Ribeiro et al., 2010).

3.2.6 Cancer of the skin (melanoma)

See Table 3.5.

Several studies have been performed to assess the effect of obesity on the progression and metastasis of skin tumours. In one study, B16BL6 melanoma cells were injected into the tail vein of male genetically obese *Lep*^{ob}*Lep*^{ob} and *Lepr*^{db}*Lepr*^{db} mice to assess the effects of obesity on metastasis. At 14 days after injection, the number of metastatic tumour foci was significantly increased in the lungs of both obese strains compared with control C57BL/6 mice (Mori et al., 2006).

In another study, obese *Lep*^{ob}*Lep*^{ob} mice, obese melanocortin receptor 4 knockout MC4R$^{-/-}$ mice, lean wild-type mice, and pair-fed lean *Lep*$^{ob-/-}$ mice were injected subcutaneously with B16F10 melanoma cells. The resulting tumours were significantly larger in the obese *Lep*^{ob}*Lep*^{ob} (5.1 ± 0.9 g) and MC4R$^{-/-}$ mice (5.1 ± 0.7 g) than in the lean wild-type mice (1.9 ± 0.3 g) or the pair-fed *Lep*$^{ob-/-}$ mice (0.95 ± 0.2 g) (Brandon et al., 2009).

Table 3.6 Effect of obesity on the development of pancreatic tumours and pre-neoplastic lesions in mice

Obesity model	Cancer etiology	Results (obese vs lean animals)	Reference
Lep^{ob}*Lep*^{ob} and *Lepr*^{db}*Lepr*^{db}	s.c. injection of PAN02 pancreatic tumour cells	Larger tumours; increased incidence of metastases	Zyromski et al. (2009)
Diet-induced (60% fat)	s.c. injection of PAN02 pancreatic tumour cells	Larger tumours and increased tumour weight	White et al. (2010)
Diet-induced (HFHC diet)	*Kras*^{G12D}	More advanced PanIN lesions	Dawson et al. (2013)
Diet-induced (HFHC diet)	*Kras*^{G12D} + Ink4a deficiency: LSL-Kras/Pdx-1-Cre/Ink4a/Arf	Increased number of PanIN, more advanced PanIN, increased number of PDAC, and increased number of pancreatic desmoplastic (fibrotic) stroma	Lashinger et al. (2013)
Diet-induced (HFHC diet)	*Kras*^{G12D} with or without COX conditional knockout: LSL-Kras/Ela-CreERT; COXKO/LSL-Kras/Ela-CreERT and LSL-Kras/Pdx-1-Cre	Increased numbers of PanIN and PDAC in all 3 models	Philip et al. (2013)

HFHC, high-fat, high-calorie; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; s.c., subcutaneous.
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In another study, male C57BL/6J mice made obese by feeding a HFD for 6 months and subsequently injected subcutaneously with B16F10 murine melanoma cells developed significantly larger tumours compared with LFD control mice (Pandey et al., 2012). Although there was no noticeable difference in the time of initiation of tumour formation between the two groups, tumours in HFD mice progressed more rapidly than those in controls. The average tumour weight was 3.52 g in HFD mice and 0.92 g in control mice, and the average tumour volume was 1920 mm^3 in HFD mice and 924 mm^3 in control mice.

One study involved the induction of skin cancer by whole-body exposure to ultraviolet radiation. SKH-1 hairless mice made obese by feeding a powdered AIN-76A diet exclusively from age 5 weeks to age 30 weeks, or made overweight by feeding a pelleted diet followed by a powdered diet, were exposed to ultraviolet radiation twice a week for 17 weeks (Dinkova-Kostova et al., 2008). A control group received the pelleted diet only. The obese group had a shortened tumour latency and an increased multiplicity of squamous cell carcinoma/papilloma compared with the control group; the overweight group had intermediate values.

3.2.7 Cancer of the pancreas

See Table 3.6.

After BOP treatment, increased incidence and multiplicity of cancer of the pancreas was reported in an early study in Syrian hamsters fed a HFD compared with those fed a LFD (Birt et al., 1981). More recent studies assessing the link between obesity and pancreatic cancer have used inoculation of cell lines and have examined progression rather than the induction and development of pancreatic tumours. Obese *Lep*^{ob}*Lep*^{ob} and *Lepr*^{db}*Lepr*^{db} mice injected subcutaneously with PAN02 murine pancreatic adenocarcinoma cells developed larger tumours, and a significantly greater number of them developed metastases compared with lean mice. Tumour weights at 5 weeks after inoculation were highest in the *Lep*^{ob}*Lep*^{ob} mice, intermediate in the

Table 3.7 Effect of obesity on the development of endometrial tumours in mice

Obesity model	Cancer etiology	Results (obese vs lean animals)	Reference
Diet-induced (AIN-93G-based; 58% fat)	Transgenic *Pten*$^{+/-}$	Increased incidence of glandular hyperplasia with atypia; 1 adenocarcinoma (0 in lean animals)	Yu et al. (2010)

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Table 3.8 Effect of obesity on the development of acute lymphoblastic leukaemia in mice

Obesity model	Cancer etiology	Results (obese vs lean animals)	Reference
Diet-induced (60% fat)	Transgenic BCR/ABL	Shortened latency for development of B-cell-derived and T-cell-derived ALL	Yun et al. (2010)
Diet-induced (60% fat)	AKR/J	Shortened latency for development of B-cell-derived and T-cell-derived ALL	Yun et al. (2010)

ALL, acute lymphoblastic leukaemia.
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Lepr^{db}*Lepr*^{db} mice, and lowest in the lean mice. Tumour weights were also positively correlated with body weights, and tumours from both obese groups exhibited higher proliferation rates than those from lean mice (Zyromski et al., 2009). DIO C57BL/6 mice injected with PAN02 murine pancreatic tumour cells also had significantly larger tumours compared with control mice, and tumour weights were positively correlated with body weights (White et al., 2010).

In mice, the *Kras* mutation combined with Ink4a/Arf deficiency induces development of pre-neoplastic pancreatic intraepithelial neoplasia (PanIN) lesions and their progression to invasive pancreatic ductal adenocarcinoma (PDAC). The association between obesity and pancreatic cancer was tested in three DIO studies using mice with acinar cell-specific expression of *Kras*^{G12D} alone, or mice crossed with the COX2 conditional knockout or with Ink4a deficiency. The mice were fed a control diet (12% of calories from fat), or a high-fat, high-calorie diet (40–60% of calories from fat) for 4–14 weeks. In all three studies, mice fed the high-fat, high-calorie diet had increased numbers of PanIN lesions, more advanced PanIN, increased numbers of PDAC, and shorter survival time than control mice (Dawson et al., 2013; Lashinger et al., 2013; Philip et al., 2013).

3.2.8 Cancer of the endometrium of the uterus

See Table 3.7.

Heterozygous phosphatase and tensin homologue deleted on chromosome 10 *Pten*$^{+/-}$ mice develop spontaneous multifocal glandular hyperplasia and endometrial cancer between age 28 weeks and age 52 weeks. Feeding *Pten*$^{+/-}$ mice a HFD increased the incidence of focal atypical glandular hyperplasia and malignant lesions from 58% in the *Pten*$^{+/-}$ mice fed a control diet to 78% in the obese *Pten*$^{+/-}$ mice (Yu et al., 2010).

3.2.9 Leukaemia

See Table 3.8.

Genetically modified models to study the link between obesity and haematological malignancies such as leukaemia and lymphoma are limited. The progression of acute lymphoblastic leukaemia (ALL) was tested in two animal models (transgenic BCR/ABL and AKR/J mice)

fed a HFD (60% of calories from fat). In both models, the obese mice developed both B-cell-derived and T-cell-derived acute lymphoblastic leukaemia significantly earlier than control mice (Yun et al., 2010).

3.3 Preventive effects of dietary/calorie restriction

3.3.1 Cancer of the mammary gland

The effect of dietary/calorie restriction on mammary tumorigenesis has been studied extensively over many decades. In the *IARC Handbook* on weight control and physical activity (IARC, 2002), the Working Group concluded that there was "*sufficient evidence* in experimental animals for a cancer-preventive effect of avoidance of weight gain by restriction of dietary energy intake" on tumours of the mammary gland. The models used for these initial investigations were primarily rats with carcinogen-induced mammary tumours or mice with spontaneous tumour development. Studies on the prevention of mammary tumours by dietary/calorie restriction are presented in Table 3.9 for mice and in Table 3.10 for rats, in chronological order. The text presents the key studies, by type of model and/or intervention.

(a) Mice

Tannenbaum (1945a) studied the effect of overall moderate CR, carbohydrate restriction, and DR with increased fat intake – all in the range of about 17% DR – in virgin DBA female mice from age 10 weeks until age 136 weeks. The mammary tumour incidence was lowest (47%) in the carbohydrate-restricted group, compared with 74% in the group fed AL, whereas the incidence was 65% in mice with overall CR and 87% in the high-fat group. In addition, tumour latency was extended for the carbohydrate-restricted group compared with the other three groups. [The basic diet had only 2% fat; no statistics were presented.]

In another study using the same mouse strain, a 27% DR or 36% DR compared with the AL mice was used (Tannenbaum, 1945b). No mice in the 36% DR group developed spontaneous mammary tumours, compared with 54% in the AL group and 12% in the 27% DR group. [No statistics were provided, and the diets fed were very low in fat (2–3%).] In a second study, parous DBA female mice were subjected to DR at various degrees (12–31% DR) beginning at age 21–25 weeks. A 50% reduction in incidence of spontaneous mammary tumours was observed for the 31% DR group. [No statistics were presented.]

Engelman et al. (1990) studied the effects of DR and/or increased fat levels in the diet on the development of spontaneous mammary tumours associated with MMTV in C3H/HeOu female mice. The mice were assigned to one of five experimental groups between age 6 weeks and age 8 weeks. This included four groups fed purified diets (AL LFD, 40% DR LFD, AL HFD, and 40% DR HFD) and an AL group fed regular laboratory chow. Mice were followed up until age 60 weeks. The chow-fed mice reached 100% incidence of spontaneous mammary tumours by age 46 weeks, whereas the AL HFD mice and the AL LFD mice did so by age 58 weeks and 64 weeks, respectively. At termination of the study, the incidence was 15% for the 40% DR HFD mice and 0% for the 40% DR LFD mice. Body weights were significantly reduced in the 40% DR groups compared with the AL groups ($P < 0.001$).

Engelman et al. (1994) also tried to identify potential critical periods for the impact of DR on the development of spontaneous mammary tumours in C3H/HeOu mice. Mice were separated into three groups: (i) fed AL, (ii) continuously 40% DR, or (iii) 40% DR only from age 4 weeks to age 12 weeks (40% DR4–12), after which they were fed a HFD AL [this was not described]. Mice were followed up until age 60 weeks; the incidence of mammary tumours was 83% in the

Table 3.9 Studies on the prevention of mammary tumours by dietary/calorie restriction in female mice

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen[a], and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance vs AL, unless otherwise specified	Comments
DBA 9–10 wk *n* = 200 126 wk Tannenbaum (1945a)	Spontaneous tumours	Cereal-based (fox chow), 2% fat 16% DR-CHO restricted 16% DR-all components 23% DR-18% fat	Mammary tumours: AL, 74% 16% DR-CHO restricted, 47% 16% DR-all components, 65% 23% DR-18% fat, 87%	NR	Diets low in fat; bw reduced in all DR groups Latency extended for the 16% DR-CHO restricted group
DBA 4 wk *n* = 150 96 wk Tannenbaum (1945b)	Spontaneous tumours	Cereal-based (fox chow) diluted with cornstarch, 2–3% fat DR: 27% or 36%, cornstarch removed	Mammary tumours [no indication of pathology]: AL, 54% 27% DR, 12% 36% DR, 0%	NR	Diets low in fat; bw of DR groups reduced Latency extended
DBA parous 21–25 wk *n* = 140 134–138 wk Tannenbaum (1945b)	Spontaneous tumours	Cereal-based (fox chow) diluted with cornstarch, 2–3% fat DR: 12%, 18%, 24%, or 31%, cornstarch removed	Mammary tumours [no indication of pathology]: AL, 73% 12% DR, 57% 18% DR, 63% 24% DR, 68% 31% DR, 36%	NR	Diets low in fat; bw reduced to 76% and 69% of AL DR started in adult animals
C3H/HeOu 6–8 wk *n* = 215 60 wk Engelman et al. (1990)	Spontaneous tumours (with MMTV)	Purified diets, either high-CHO (sucrose), low-fat (4.5%) or high-fat (60%), no-CHO, AL or 40% DR Chow-fed control	Mammary adenocarcinoma: Chow, 100% AL low-fat, 100% 40% DR low-fat, 0%* AL high-fat, 100% 40% DR high-fat, 15%**	Weibull distribution by survival analysis (*P* values NR) [*Significant vs AL low-fat] [**Significant vs AL high-fat]	Tumour latency: chow < AL high-fat < AL low-fat << 40% DR high-fat ≈ 40% DR low-fat Bw significantly reduced in DR groups vs AL groups ($P < 0.001$)
C3H/HeOu 4 wk *n* = 144 age 60 wk Engelman et al. (1994)	Spontaneous tumours	Purified diets 40% DR 40% DR age 4–12 wk	Mammary tumours: AL, 83% 40% DR, 13%*,** 40% DR 4–12 wk, 50%***	*$P < 0.000\,001$ **$P = 0.009$ vs 40% DR 4–12 wk ***$P = 0.004$	

Table 3.9 (continued)

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen[a], and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance vs AL, unless otherwise specified	Comments
$B6C3F_1$ 4 wk *n* = 102 Lifetime Sheldon et al. (1996)	Spontaneous tumours	NIH-31 diet 40% DR from age 14 wk	Mammary tumours (benign and malignant combined): AL, 27% 40% DR, 4%	NR	
C57BL6 4 wk *n* = 102 Lifetime Sheldon et al. (1996)	Spontaneous tumours	NIH-31 diet 40% DR from age 14 wk	Mammary tumours (benign and malignant combined): AL, 14% 40% DR, 0%	NR	
$B6D2F_1$ 4 wk *n* = 102 Lifetime Sheldon et al. (1996)	Spontaneous tumours	NIH-31 diet 40% DR from age 14 wk	Mammary tumours (benign and malignant combined): AL, 27% 40% DR, 0%	NR	
MMTV-TGF-α C57BL6 10 wk *n* = 93 age 79–80 wk Cleary et al. (2002)	Human TGF-α	AIN-93M CDR, mice pair-fed to IDR (21% DR) IDR, mice fed 3 wk of 50% DR + 3 wk of AL for 11 cycles (21% DR)	Mammary adenocarcinoma: AL, 77% CDR, 44%* IDR, 3%*	[*Significant, χ^2 test] (*P* values NR)	Final bw similar in all 3 groups, although IDR mice lost bw during the 50% DR periods Latency shorter in AL vs DR Only 1 tumour detected at necropsy for IDR (*n* = 1, hence no statistics)
HER2/neu 9 wk *n* = 96 age 80 wk Pape-Ansorge et al. (2002)	Transgene-heterozygous for HER2/neu	AIN-93M with 10% fat CDR, 25% CHO restriction IDR, mice fed 3 wk of 50% DR + 3 wk of AL for 11 cycles (~25% DR)	Mammary adenocarcinoma: AL, 37.5% CDR, 33.3% IDR, 22.5%	NS	Bw reduced in CDR and IDR vs AL

Table 3.9 (continued)

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen[a], and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance vs AL, unless otherwise specified	Comments
MMTV-TGF-α C57BL6 10 wk *n* = 76 age 85 wk Cleary et al. (2004a)	Human TGF-α	Chow, 33% fat; at age 34 wk, divided (based on weight status) into obesity-prone, overweight, and obesity-resistant groups; 1 group chow-fed, lean	Histologically confirmed mammary adenocarcinoma: AL, 72% Obesity-resistant, 82% Obesity-prone, 76%	NS	Latency shorter for obesity-prone mice ($P < 0.0001$); higher multiplicity per tumour-bearing animal ($P < 0.015$)
HER2/neu 8 wk *n* = 106 10 mo Anisimov et al. (2005)	Transgene	Diet NR AL AL-metformin (100 mg/kg bw in drinking-water 5 d/wk)	Mammary adenocarcinoma: 100% incidence in both groups Mean latency: 187 d vs 178 d Mean tumour size: 1.71 cm vs 1.59 cm	 NS $P < 0.05$ $P < 0.05$	Metformin used as a CR mimetic No effect on bw
MMTV-TGF-α C57BL6 10 wk *n* = 100 age 79–80 wk Cleary et al. (2007)	Human TGF-α	AIN-93M CDR, mice pair-fed to IDR (14% DR) IDR, mice fed 3 wk of 50% DR + 3 wk of AL for 11 cycles (11% DR)	Mammary adenocarcinoma: AL, 84% CDR, 27%* IDR, 15%*	*$P < 0.001$, χ^2 test	Final bw similar for AL and IDR (within 1 wk of refeeding); significantly higher than for CDR mice
MMTV-TGF-α C57BL6 10 wk *n* = 200 age 79–82 wk Rogozina et al. (2009)	Human TGF-α	AIN-93M CDR, mice pair-fed to IDR (27% DR) IDR, mice fed 3 wk of 50% DR + 3 wk pair-fed to AL for 11 cycles (25% DR)	Mammary adenocarcinoma: AL, 71% CDR, 35.4%* IDR, 9.1%*	*Significant, χ^2 test (*P* values NR)	Final bw for IDR and CDR significantly lower ($P < 0.001$) than for AL IDR mice limited to intake of AL mice during refeeding, thus higher DR; latency extended for both CDR and IDR vs AL
HER2/neu 8 wk *n* = 75 Lifetime Anisimov et al. (2010)	Transgene	Diet NR AL AL-metformin (100 mg/kg bw in drinking-water 5 d/wk)	Mammary adenocarcinoma: > 90% incidence in both groups Slower kinetic of tumour incidence with metformin Latency: 223 d vs 197 d	 NS $P < 0.001$ $P < 0.05$	No effect on bw

Table 3.9 (continued)

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen[a], and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance vs AL, unless otherwise specified	Comments
C57BL6 (OVX) 6–8 wk *n* = 120 14 wk Dunlap et al. (2012)	M-Wnt or E-Wnt cells implanted 8 wk after diets started, and mice followed up for 6 wk	AIN-76A, AL 30% DR HFD (60% fat)	Allograft: Tumour growth (area in mm^2) reduced by 30% DR for both cell lines	$P < 0.02$	Tumour growth enhanced by HFD for M-Wnt cells but not for E-Wnt cells
C57BL6 (OVX) 6 wk *n* = 45 4 wk Nogueira et al. (2012)	Wnt-1 cells implanted and mice followed up for 4 wk	AIN-76A 30% DR	Allograft: Tumour weight: 0.045 g vs 0.39 g Latency: 16.3 wk vs 15.6 wk	$P = 0.0002$ NS	Bw reduced in 30% DR vs AL
HER2/neu 10 wk *n* = 178 age 60 wk Mizuno et al. (2013)	Transgene-homozygous for HER2/neu	AL-CON, AIN-93M with 10% fat calories from soy oil CDR-CON, 25% CHO restriction IDR-CON, 3 wk of 50% DR + 3 wk pair-fed to AL for 11 cycles (25% DR) Same groups with EPA substituted for some of the soy oil	Mammary adenocarcinoma: AL-CON, 87% CDR-CON, 47%* IDR-CON, 59%* AL-EPA, 63% CDR-EPA, 40% IDR-EPA, 15%**	*$P < 0.05$ vs AL-CON **$P < 0.05$ vs CDR-EPA and AL-EPA	Bw reduced in CDR and IDR vs AL
MMTV-TGF-α C57BL6 10 wk *n* = 135 age 79–82 wk Rogozina et al. (2013) See Rogozina et al. (2009)	Human TGF-α	AIN-93M based diet with 22.7% fat CDR, mice matched to IDR (22% DR) IDR, mice fed 3 wk of 50% DR + 3 wk pair-fed to AL for 11 cycles (22% DR)	Mammary adenocarcinoma: AL, 66.7% CDR, 52.3%* IDR, 4.4%* Latency: AL < CDR* < IDR*	*$P < 0.0001$, χ^2 test *$P < 0.0001$, Kaplan–Meier	Bw of AL mice greater than CDR and IDR. IDR mice lost and regained weight with each cycle to values similar to those of CDR

Table 3.9 (continued)

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen[a], and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance vs AL, unless otherwise specified	Comments
C3(1)-TAg FVB/N 3 wk *n* = 40 27 wk Sundaram et al. (2014)	Transgenic C3(1)-TAg	LFD (10% fat) HFD (60% fat) HFD for 7 wk, switched to LFD for ~17 wk	Basal-like mammary tumours: Tumour volume: ~3-fold higher in HFD vs LFD HFD-7 vs LFD	 *P* = 0.0024 NS	Bw of HFD-7 decreased and remained at level of LFD mice; both significantly lower than in HFD mice (*P* = 0.019); latency and multiplicity not affected [Not clear whether effect due to weight loss or to change in diet composition]
HER2/neu/p53KO 60 d NR 11 mo Thompson et al. (2015)	Transgene	Teklad 4% mash AL AL-metformin (150 mg/kg)	Mammary adenocarcinoma: Tumour multiplicity Tumour weight	 NS NS	Metformin used as a CR mimetic [No bw data] Survival not affected

AL, ad libitum; bw, body weight; CDR, chronic dietary restriction; CHO, carbohydrate; d, day or days; CON, control; CR, calorie restriction; DR, dietary restriction; EPA, eicosapentaenoic acid; HFD, high-fat diet; IDR, intermittent dietary restriction; LFD, low-fat diet; mo, month or months; MMTV, mouse mammary tumour virus; NR, not reported; NS, not significant; OVX, ovariectomized; TGF-α, transforming growth factor alpha; vs, versus; wk, week or weeks.

[a] The (%) indicates the percentage of calories from fat.

Table 3.10 Studies on the prevention of mammary tumours by dietary/calorie restriction in female rats

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention as appropriate	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Wistar NR ~50/group 24 mo Tucker (1979)	Spontaneous tumours	AL, 20% DR after 1 mo for 23 mo	Mammary tumours: 17%, 3%	$P < 0.001$	
Sprague-Dawley 57 d $n = 104$ 26 wk Sylvester et al. (1981)	DMBA, 5 mg, once	Rat chow, 50% DR for 7 d before and for 30 d after injection of DMBA. One 50% DR group received various hormone treatments (e.g. E2)	Palpable mammary tumours: AL, 76% 50% DR, 29%* 50% DR+E2, 71%	*$P < 0.05$ vs AL or 50% DR+E2	Latency extended in 50% DR rats
Sprague-Dawley 57 d $n = 101$ 22 wk Sylvester et al. (1982)	DMBA, 5 mg, once	Rat chow: AL; 50% DR for 1 wk before and for 1 wk after DMBA; 50% DR for 2 wk starting 1 wk after DMBA; 50% DR for 2 wk starting 3 wk after DMBA; 50% DR for 4 wk starting 5 wk after DMBA	Palpable mammary tumours: 80.9%, 27.8%*, 76.2%, 75.0%, 75.0%	*$P < 0.05$	No significant effect on latency or tumour multiplicity
F344 52 d $n = 45$ 24 wk Boissonneault et al. (1986)	DMBA, 65 mg/kg bw, once	Purified diet, dextrose reduced in 30% fat diets, 1 d after DMBA: AL 30% fat, AL 5% fat, 14% DR 30% fat	Mammary tumours: 73%, 43%, 7%	NR	
Sprague-Dawley 50 d $n = 100$ 20 wk Klurfeld et al. (1989a)	DMBA, 5 mg, once	AIN-76A, sucrose reduced in DR diets, 1 wk after DMBA: AL, 10% DR, 20% DR, 30% DR, 40% DR	Histologically verified mammary tumours: 60%, 60%, 40%*, 35%*, 5%*	*$P < 0.005$	Tumour latency extended in 30% DR and 40% DR groups. Tumour multiplicity reduced in 40% DR group

Table 3.10 (continued)

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention as appropriate	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Sprague-Dawley 50 d n = 100 20 wk Klurfeld et al. (1989b)	DMBA, 5 mg, once	AIN-76A, sucrose reduced in DR diets, 1 wk after DMBA: AL 5% fat, AL 15% fat, AL 20% fat, 25% DR 20% fat, 25% DR 26.7% fat	Mammary tumours: 65%*, 85%, 80%, 60%*, 30%**	*P < 0.01 vs AL 15% fat and AL 20% fat **P < 0.0001 vs AL groups	Tumour multiplicity reduced to similar levels in both 25% DR groups
Sprague-Dawley 50 d n = 120 16 wk Kritchevsky et al. (1989)	DMBA, 5 mg, once	AIN-76A, sucrose reduced in DR diets, 1 wk after DMBA. 6 groups: (A) AL; (B) 25% DR, wk 1–16; (C) 25% DR, wk 1–4; (D) 25% DR, wk 1–8; (E) 25% DR, wk 5–12; (F) 25% DR, wk 9–16	Palpable mammary tumours: 50%, 20%*, 60%, 40%, 45%, 30%	*P < 0.001, group B vs A and group B vs C	Weight gain correlated with tumour incidence (r = 0.96) and with total calorie intake (r = 0.83)
Sprague-Dawley 50 d n = 110 20 wk Ruggeri et al. (1989a, b)	DMBA, 5 mg, once	AIN-76A, sucrose reduced in DR diets, 1 wk after DMBA: AL, 25% DR, 40% DR	Mammary tumours: 90%, 61%*, 20%*	*P = 0.007, χ^2 test	Multiplicity of palpable tumours reduced in 40% DR rats (P < 0.05)
LA/N 65 d n = 49 17 wk Klurfeld et al. (1991)	DMBA, 5 mg, once	AIN-76A, sucrose reduced in DR diets, 1 wk after DMBA: obese AL, obese 25% DR, lean AL	Mammary tumours: 100%, 27%, 21%	NR	Tumour multiplicity reduced in obese 25% DR rats; bw in DR significantly lower than in obese AL rats
Sprague-Dawley 50 d n = 83 30 wk Zhu et al. (1991)	MNU, 25 mg/kg bw, at age 50 d, once	Purified diet, 45% fat diet for ~10 wk (until tumour of 1 cm^3), then divided into 4 groups: AL 45% fat, 30% DR 45% fat, AL 25% fat, 30% DR 25% fat	Mammary tumours: Multiplicity: 2.43, 1.74*, 2.35, 0.95* Tumour/bw (%): 3.8, 2.2*, 2.5, 1.3*	*P < 0.05 vs corresponding AL group	100% incidence of mammary tumours; bw reduced by 10% in DR groups

Table 3.10 (continued)

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention as appropriate	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
F344 14 wk *n* = 54/group (exp. 1); *n* = 114–116/group (exp. 2) Lifetime Thurman et al. (1994)	Spontaneous tumours	NIH-31; AL, 40% DR	Mammary adenocarcinoma: Exp. 1: 8%, 2% Exp. 2: 5%, 0% Mammary fibroadenoma: Exp. 1: 36%, 2% Exp. 2: 35%, 1%	[NS] [$P = 0.048$] [$P < 0.0001$] [$P < 0.0001$]	Extended survival; reduced bw; reduced tumour multiplicity [Low incidence of tumours in AL animals]
F344 50 d *n* = 132 20 wk Gillette et al. (1997)	MNU, 50 mg/kg bw, at age 50 d and 57 d, once	AIN-76A with cornstarch + cerelose; AL, 20% DR	Mammary adenocarcinoma: 23.3%, 6.7%*	*$P < 0.05$	Tumour multiplicity reduced in AL vs 20% DR; exercise by treadmill running not effective in any group
Sprague-Dawley 21 d *n* = 75 35 d Zhu et al. (1997)	MNU, 50 mg/kg bw, once	AIN-93G with cornstarch + cerelose, fed AL, 10% DR, 20% DR, 40% DR	Mammary carcinoma: 100%, 80%, 60%, 25%	$P_{trend} < 0.01$, dose-dependent reduction	Dose-dependent increased latency for DR Additional results presented (Zhu et al., 1999a, b)
ACI 49 d *n* = 84 220 d Harvell et al. (2002)	E2 treatment from age 59 d	Purified diet, 5% fat; AL, 40% DR in controls or mice treated with E2	Mammary tumours: AL, 0% 40% DR, 0% AL+E2, 100% 40% DR+E2, 59%*	*$P < 0.001$ vs AL+E2	Latency of palpable tumour: 69 d after E2 for AL+E2 vs 104 d for 40% DR+E2 Bw reduced in 40% DR groups
Sprague-Dawley 3 wk *n* = 66 90 d Zhu et al. (2002)	MNU, 50 mg, once	AIN-93G; AL, 40% DR (CHO reduced) for 6 wk, and then fed AL (DR-AL)	Mammary adenocarcinoma: Detectable tumour incidence at day 42 after MNU: AL, 61%; DR, 11%*	*$P < 0.001$, χ^2 test	Bw similar; incidence of tumours in DR-AL similar to AL by end of experiment

Table 3.10 (continued)

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention as appropriate	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Sprague-Dawley 3 wk *n* = 108 54 d Thompson et al. (2004a)	MNU, 50 mg, once	AIN-93G; 40% DR; 40% DR for 6 wk, and then fed AL (DR-AL)	Mammary adenocarcinoma: Tumour volume of DR rats significantly smaller than AL or DR-AL rats	$P < 0.001$	Bw reduced in DR rats 2 meals daily
Sprague-Dawley 3 wk *n* = 78 77–78 d Thompson et al. (2004b)	MNU, 50 mg, once	AIN-93G; 40% DR (CHO reduced) from age ~4 wk	Mammary adenocarcinoma: 96%, 59%* Multiplicity: 4.3, 1.0**	*$P < 0.01$ **$P < 0.001$	2 meals daily
Wistar 7 wk *n* = 90 50 wk Buison et al. (2005)	DMBA, 2 mg, once	AL, HFD (60% fat) IDR-HFD (50% DR CHO reduction), first cycle at age 15 wk to loss of 20% – 4 cycles	Mammary tumours: HFD, 17.6% IDR-HFD, 8.8%	NS	Bw significantly lower in IDR-HFD rats
Sprague-Dawley 3 wk *n* = 99 57–58 d Zhu et al. (2005)	MNU, 50 mg/kg bw, at age 21 d	AIN-93G; AL, 40% DR (CHO) at age 30 d for 6 wk, then divided into DR, DR-AL, DR+IGF-1	Mammary adenocarcinoma: AL, 96.6% DR, 56.7%* DR-AL, 80% DR+IGF-1, 60%	*$P < 0.0006$	
Sprague-Dawley 3 wk *n* = 60 7 wk Jiang et al. (2008a)	MNU, 50 mg/kg bw, at age 21 d	AIN-93G: AL, AL+0.03% 2-deoxyglucose	Mammary adenocarcinoma: 86.7%, 53.3% Multiplicity: 2.03, 1.37	$P < 0.005$ $P = 0.018$	2-deoxyglucose used as a CR mimetic No difference in bw

Table 3.10 (continued)

Strain Age at start Number of animals Duration of study Reference	Dose and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention as appropriate	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Sprague-Dawley 21 d *n* = 90 52 d Jiang et al. (2008b)	MNU, 50 mg/kg bw, at age 21 d	AIN-93G: AL, 20% DR, 40% DR	Mammary adenocarcinoma: 96%, 60%*, 23%* Multiplicity: 2.1, 1.1*, 0.3*	*$P < 0.001$	Bw reduced in DR rats
Sprague-Dawley 21 d *n* = 103, 101 60 d Matthews et al. (2014)	MNU, 50 mg/kg bw, at age 21 d	SUMO32 diet (32% HFD corn oil-9.4% saturated fat) Obesity-prone (OP) Obesity-resistant (OR)	Mammary adenocarcinoma: OP, 91%; OR, 65%*	*$P < 0.01$	OP rats weighed 15% more than OR rats at study termination Tumour weight reduction of 80% for OR vs OP; tumour latency extended for OR vs OP
Sprague-Dawley 50 d NR 126 d Thompson et al. (2015)	MNU, 75 mg/kg bw, at age 50 d	Teklad standard diet (8% fat) Control; metformin, 50 mg/kg/d; metformin, 150 mg/kg/d	ER^+ mammary tumours: Tumour latency Tumour weight	 NS NS	Metformin used as a CR mimetic 2 meals daily Bw NR
Sprague-Dawley 21 d *n* = 120 (30/group) 51 d Zhu et al. (2015)	MNU, 50 mg/kg bw, once	AIN-93G Control; metformin, buformin, or phenformin	Mammary adenocarcinoma: 83.3%, 93.3%, 43.3%*, 76.7%	*$P < 0.003$	Compounds studied as CR mimetics Bw reportedly measured, but no data presented

AL, ad libitum; bw, body weight; d, day or days; CHO, carbohydrate; CR, calorie restriction; DMBA, 7,12-dimethylbenz[*a*]anthracene; DR, dietary restriction; E2, 17β-estradiol; ER, estrogen receptor; exp., experiment; F344, Fischer 344; HFD, high-fat diet; IDR, intermittent dietary restriction; IGF-1, insulin-like growth factor 1; MNU, *N*-methyl-*N*-nitrosourea; mo, month or months; NR, not reported; NS, not significant; OP, obesity-prone; OR, obesity-resistant; vs, versus; wk, week or weeks.

AL group, 13% in the 40% DR group, and 50% in the 40% DR4–12 group.

The effect of 40% DR on ageing and longevity in three different mouse strains was reported by Sheldon et al. (1996). DR was initiated at age 14 weeks and extended to 48 months in $B6C3F_1$, C57BL6, and $B6D2F_1$ mice. AL mice in the $B6C3F_1$, C57BL6, and $B6D2F_1$ groups had incidences of spontaneous mammary tumours of 27%, 14%, and 27%, respectively, compared with 4%, 0%, and 0% for the corresponding 40% DR groups.

More recently, transgenic mice have been used to evaluate the effect of DR on development of mammary tumours. Several studies were conducted using mice that overexpress human TGF-α, in which two modes of DR were compared (Cleary et al., 2002, 2007; Rogozina et al., 2009, 2013). In the initial experiments, mice received either intermittent DR (IDR) or chronic DR (CDR). IDR mice were subjected to 50% DR for 3-week intervals, followed by 3 weeks of refeeding AL. This resulted in an overall DR of 21%, because of overconsumption during refeeding compared with what the AL mice consumed. CDR mice were matched for calorie intake for each 6-week cycle of 50% DR/refeeding. The IDR mice had significantly lower mammary tumour incidence compared with the CDR mice, i.e. mammary tumour incidences of 3% and 15% in the two reports, compared with 77% and 84% for AL mice and 44% and 27% for the CDR mice (Cleary et al., 2002, 2007). In subsequent studies, IDR mice were pair-fed to the AL group during the refeeding phases, resulting in significantly lower body weights in both DR groups, with fluctuating body weights in the IDR group; both the CDR and IDR groups had lower tumour incidence than the AL mice (Rogozina et al., 2009, 2013). This was also observed when the fat content of the diets was moderately increased (Rogozina et al., 2013). IDR compared with CDR was also examined in the transgenic mouse strain HER2/neu. IDR resulted in lower tumour incidence than in CDR, although not significantly so (Pape-Ansorge et al., 2002; Mizuno et al., 2013).

In another transgenic mouse strain, C3(1)-TAg mice were fed either a LFD (10% of calories from fat) or a HFD (60% of calories from fat) from age 3 weeks (Sundaram et al., 2014), and a group of the HFD mice was switched to the LFD after 7 weeks on the HFD. The switch to the LFD from the HFD resulted in weight loss to the level of the LFD mice. The tumour volume in the HFD mice was 3 times that in the LFD mice, and switching from the HFD to the LFD resulted in tumour volumes similar to those in the LFD mice. [It is not clear whether the findings are due to weight loss or to the change in diet composition.]

Allograft models were also used to assess tumour progression in response to dietary intervention. For example, ovariectomized C57BL6 mice were fed AL, 30% DR, or a HFD (60% of calories from fat) for 8 weeks, before two types of Wnt cells (M-Wnt or E-Wnt cells) were implanted; the mice then continued on their diets for 6 weeks while tumour growth was monitored. DR reduced tumour growth for both cell lines compared with AL, whereas tumour growth was enhanced by the HFD only for the M-Wnt cells (Dunlap et al., 2012). In another study, Wnt-1 cells were implanted in AL or 30% DR mice. Tumour weight was lower in DR mice than in AL mice, but latency was not affected (Nogueira et al., 2012).

Another approach to assess the effects of body weight independent of diet is to use mouse or rat strains that respond to HFD feeding with a range of body weights. Cleary et al. (2004a) fed MMTV-TGF-α mice on a C57BL6 background a LFD or a moderately HFD (33% of calories from fat) and then divided the mice into three groups (obesity-prone, overweight, and obesity-resistant), based on body weight status at age 34 weeks. The heaviest group, obesity-prone, had the shortest mammary tumour latency, compared with obesity-resistant mice fed the

same diet, i.e. with body weights similar to those of the LFD mice. Furthermore, the heavier mice had more palpable tumours than mice that weighed less, although this was not statistically significant.

A murine model of basal-like breast cancer was used to assess whether the obesity-induced pro-tumour effects are reversed by weight normalization. Ovariectomized female C57BL/6 mice were fed a control diet or a DIO regimen for 17 weeks, resulting in a normal weight or an obese phenotype, respectively. After 17 weeks, mice on the DIO regimen were randomized to continue the DIO diet or switched to the control diet. The resulting formerly obese mice had body weights comparable to those of the controls. At week 24, the mammary pads of all mice were injected with MMTV-Wnt-1 mouse mammary tumour cells, and tumour growth was then measured twice per week until 36 months. Mean tumour volumes in the DIO and formerly obese mice were similar, and were higher than those in the controls (Rossi et al., 2016).

(b) Rats

In a longevity study, the incidence of mammary tumours was significantly lower in 20% DR Wistar rats (3%) than in the AL group (17%) (Tucker, 1979).

In one study (Thurman et al., 1994), groups of female Fischer 344 (F344) rats were fed AL or subjected to 40% DR from age 14 weeks and followed up for their lifetime in two experiments with a similar study design. In general, survival was extended by DR [the increase was modest, and no statistics were presented]. Incidence of spontaneous mammary adenocarcinoma was 8% and 5% in the AL rats and 2% and 0% [$P = 0.048$] in the 40% DR rats in the first and second experiment, respectively. Reductions in the incidence of mammary fibroadenoma were also reported, from 36% and 35% in the AL rats to 2% [$P < 0.0001$] and 1% [$P < 0.0001$] in the 40% DR rats. Reduced body weight was associated with extended survival and reduced multiplicity.

Female Sprague-Dawley rats were administered 5 mg of DMBA dissolved in corn oil at age 50 days (Klurfeld et al., 1989a). The rats treated with DMBA were then subjected to 10%, 20%, 30%, or 40% DR from age 57 days and followed up for 20 weeks. The 10% DR had no effect on tumour incidence, but the 20%, 30%, and 40% DR resulted in incidences of 40%, 35%, and 5%, respectively. Tumour multiplicity was significantly reduced in the 40% DR group, and latency was extended in the 30% DR and 40% DR groups.

In another study also using DMBA (Ruggeri et al., 1989a, b), only three groups of rats were included: AL, 25% DR, and 40% DR. The incidence of mammary tumours in these groups was 90%, 61%, and 20% ($P = 0.007$), respectively. In the 40% DR group, the majority of the tumours were small and non-palpable ($P < 0.05$). The authors also used rats treated with DMBA and fed diets combining increased fat levels with DR and determined effects on development of mammary tumours (Klurfeld et al., 1989b). The experimental groups included AL rats fed diets with 5%, 15%, and 20% of calories from fat, as well as 25% DR rats fed diets with 20% and 26.7% of calories from fat. The incidence of mammary tumours was significantly lower in the 25% DR, 26.7% fat group than in the other groups, for which the incidences were in the range of 60–85%. Although there was only a slight reduction in incidence for the 25% DR, 20% fat group, tumour weight and tumour multiplicity were reduced to similar levels as in the other DR group (i.e. 25% DR, 26.7% fat).

A similar study was reported by Boissonneault et al. (1986) using female F344 rats that were switched to experimental diets 1 day after DMBA treatment (at age 52 days); these groups included AL 30% fat, AL 5% fat, and 14% DR 30% fat. The groups were then followed up for 24 weeks after DMBA treatment. The incidence of mammary tumours was 73% for the AL 30% fat group

and 43% for the AL 5% fat group but only 7% for the 14% DR 30% fat group [no statistics were reported].

Klurfeld et al. (1991) also investigated the effects of DR on the development of DMBA-induced mammary tumours in genetically obese rats. After administration of DMBA at age 65 days, female LA/N Corpulent rats were fed purified diets either AL or 40% DR, and an AL lean group was also included. The body weight of the obese 40% DR rats remained at a level substantially lower than that of the AL obese rats but higher than that of the AL lean rats. The incidence of mammary tumours was 100% in the AL obese rats, compared with 27% in the obese 40% DR rats and 21% in the AL lean rats. [The Working Group noted that this study assessed DR in obese rats.]

Several investigations have focused on timing of DR interventions and development of mammary tumours.

One study examined the impact of 25% DR imposed at different times relative to the administration of DMBA (Kritchevsky et al., 1989). There were a total of six groups in the 16-week experiment: fed AL throughout (group A), fed 25% DR throughout (group B), fed 25% DR for the first 4 weeks (group C), fed 25% DR for the first 8 weeks (group D), fed 25% DR for the 8 weeks (weeks 5–12) in the middle of the experiment (group E), and fed 25% DR for the last 8 weeks (group F). The incidence of mammary tumours was 50% in the AL rats and 20% in the rats fed 25% DR throughout the study. The other groups had incidences of 30–60%; the incidence was 30% in the group fed 25% DR for the last 8 weeks (group F).

Sylvester et al. (1981, 1982) also investigated the effect of timing of DR in Sprague-Dawley rats treated with DMBA. In their first study, a 50% DR was imposed 1 week before and continued until 30 days after DMBA injection (Sylvester et al., 1981). After 26 weeks, the incidence of mammary tumours was 76% in the AL group and 29% in the 50% DR group. In the follow-up study, five groups of rats were used (Sylvester et al., 1982): AL control rats, 50% DR 1 week before and 1 week after DMBA treatment, 50% DR for 2-week periods starting 1 week or 3 weeks after DMBA treatment, and 50% DR for 4 weeks starting 5 weeks after DMBA treatment. All groups had similar incidences of mammary tumours (75.0–80.9%), except for the group subjected to 50% DR for 1 week before and 1 week after DMBA treatment, in which the incidence was only 27.8%. [The Working Group noted that DR started before administration of DMBA, and hence the effect of DR on DMBA metabolism is unknown and might have been partly responsible for the observed effect.]

Zhu et al. (1991) used Sprague-Dawley rats administered MNU at age 50 days to induce mammary tumours. The rats were then fed a 45% fat diet and followed up until the tumours reached a volume of 1 cm^3, which was 10 ± 2 weeks after administration of MNU. The rats were then divided into four groups: AL 45% fat (group 1), 30% DR 45% fat (group 2), AL 25% fat (group 3), and 30% DR 25% fat (group 4). The rats were then followed up for an additional 30 weeks, after which tumour progression was assessed. DR reduced the number of tumours per animal, the tumour weight, and the tumour weight per body weight, compared with AL. Body weight was reduced by 10%. [No statistics were reported.]

A rapidly developing carcinogen-induced mammary tumour model was developed in Sprague-Dawley rats to investigate the effect of DR on mammary tumorigenesis (Gillette et al., 1997; Zhu et al., 1997, 1999a, b, 2002, 2005; Thompson et al., 2004a, b). In this model, rats are administered MNU at age 21 days and then followed up until age 100 days or more as the tumours develop; they are subjected to 40% DR through carbohydrate restriction. This degree of DR consistently and significantly reduced body weight as well as mammary tumour development, as reflected by incidence and tumour volume.

In an additional study (Jiang et al., 2008b), 20% DR led to an incidence of 60%, compared with 96% in AL rats and 23% in the 40% DR rats. Multiplicity was also significantly reduced. [The Working Group noted that in this study model, tumours develop in pre-pubertal animals.]

Buison et al. (2005) used the DMBA mammary tumour model with the carcinogen administered at age 50 days and the rats followed up for 50 weeks. The intervention consisted of feeding the rats a 60% HFD followed by 50% DR (with carbohydrate restriction) for 4 cycles of 20% weight loss, followed by refeeding; this resulted in a 50% reduction in mammary tumour incidence, from 17.6% to 8.8% [not significant]. The body weight of the IDR rats fluctuated and at termination of the study was significantly lower than that of the HFD control rats. [The Working Group noted that a control group with chronic DR is missing.]

In another model (Matthews et al., 2014), ovary-intact female Sprague-Dawley rats were injected with 50 mg/kg of MNU at age 21 days. Obesity-resistant or obesity-prone animals were fed a purified diet containing 32% of calories from fat. At termination of the study, obesity-prone rats were approximately 15.5% heavier than obesity-resistant rats. Obesity-resistant rats had lower incidence, multiplicity, and burden of mammary carcinomas, with a concomitant increase in cancer latency compared with obesity-prone rats ($P < 0.01$ for all analyses).

Another model for breast cancer is the ACI rat; when supplementary estrogen is given to ovary-intact animals, this leads to development of mammary tumours (Shull et al., 1997). Harvell et al. (2002) determined the impact of 40% DR starting at age 7 weeks on mammary tumorigenesis in this model. By 216 days of estrogen treatment, 100% of the AL rats had at least one palpable mammary tumour, with the first tumour detected at 69 days. In contrast, the first palpable mammary tumour in the 40% DR group was not detected until 104 days of estrogen treatment, and at termination of the study, mammary tumour incidence was 59%. As expected, body weight was reduced for the 40% DR rats. No tumours were detected in ACI rats not treated with estrogen, whether they were fed AL or subjected to 40% DR.

(c) Calorie restriction mimetics

An additional approach to study the effect of CR on mammary tumour development has been the use of CR mimetics. Metformin, the most common CR mimetic, did not have an effect on mammary tumour development in the MNU rat model, when MNU was administered at age 50 days, or in transgenic HER2/neu/p53KO mice (Thompson et al., 2015). Several earlier studies using the HER2 mouse model of breast cancer had reported some effects of metformin on latency, but tumour incidence was not affected (Anisimov et al., 2005, 2010).

In the rapidly emerging tumour model in rats, treatment with 2-deoxyglucose (Jiang et al., 2008a) but not with metformin (Thompson et al., 2015; Zhu et al., 2015) decreased the incidence of mammary tumours; buformin and phenformin both reduced tumour incidence.

3.3.2 Cancer of the colon

See Table 3.11.

The early studies of the effect of DR on cancer of the colon used carcinogen-induced models in rats, whereas more recent studies used mouse models.

In one of the early studies, male Lobund Sprague-Dawley rats were administered methylazoxymethanol at 30 mg/kg at weaning, and about 25% DR started either 10 days or 63 days after and continued until 140 days after administration of methylazoxymethanol (Pollard et al., 1984). [It is not clear what the natural ingredient diet contained.] The long-term DR significantly reduced tumour incidence and multiplicity, whereas there was no effect when DR was initiated

Table 3.11 Studies on the prevention of colon tumours by dietary/calorie restriction in rats and mice

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Rat					
Lobund Sprague-Dawley (M) Weanling *n* = 76 20 wk Pollard et al. (1984)	MAM, s.c., 30 mg/kg bw	Natural ingredient diet L-485; AL or 25% DR, starting at either 10 d or 63 d after MAM, or ADF from 8 d or 31 d after MAM (each intervention own AL group)	Tumours of colon and small intestine: AL, 90%; 25% DR-10, 30% AL, 85%; 25% DR-63, 100% AL, 60%; ADF-8, 60% AL, 90%; ADF-31, 67%	 $P < 0.0001$ NS NS NS	Small group sizes may have affected findings, and possibly components of diet had protective effect
F344 (M) 5 wk *n* = 60 32 wk Reddy et al. (1987)	AOM, 15 mg/kg bw, once a wk from age 7 wk for 2 wk	Semi-purified diet (23% fat); AL or 30% DR from 4 d after AOM, followed up for 32 wk	Colon adenoma or adenocarcinoma (combined): AL, 83%; 30% DR, 33% Colon adenocarcinoma: AL, 30%; 30% DR, 0%	$P < 0.05$ $P < 0.05$	Tumour multiplicity significantly reduced by DR
Sprague-Dawley (F, M) Neonatal *n* = 179 32 wk Newberne et al. (1990)	DMH, s.c., 10 mg/kg bw, once a wk for 10 wk from 1 mo after weaning	Two groups: pups raised 4/litter or 8/litter; weaned to semi-purified diet (20% fat) AL Third group: 4/litter pair-fed to 8/litter after weaning	Colon tumours: 8/litter: M, 48%; F, 42% 4/litter: M, 85%*; F, 60%* 4/litter pair-fed: M, 76%**; F, 52%	*$P < 0.01$ vs respective 8/litter M or F **$P < 0.01$ vs 8/litter M	[The Working Group considered that using litter size as an indicator of early-life access to nutrition made it difficult to evaluate the effect of DR on colon tumour development]
Zucker lean and obese (*fa/fa*) (F) 6 wk *n* = 32 obese, *n* = 16 lean 15 wk Raju & Bird (2003)	AOM, 10 mg/kg bw, at age 6 wk, once a wk for 2 wk	Lean rats, AL Obese rats, AL Obese rats, 20–25% DR	Multiplicity of ACF: All ACF Advanced ACF (≥ 7 crypts)	 NS $P < 0.001$ for DR vs obese AL	100% incidence of ACF in all groups; bw not affected by DR [Small *n* values; effect seen only when distinguishing between advanced and early foci, which is questionable]
Mouse					
C57BL6 *Apc*^{Min} (M) 10 wk 28–30/group 9 wk Mai et al. (2003)	Transgenic	AIN-76A 25% DR (CHO restriction)	Colon polyps: Mean number/mouse: AL, 5; 25% DR, 7	NS	Bw reduced in DR vs AL (19.4 g vs 25.9 g). No effect of feeding a HFD (30% of calories from corn oil) [Values reported in graph]

Table 3.11 (continued)

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
C57BL6 (M) 6 wk *n* = 80 (20/group) 23 wk Wheatley et al. (2008)	MC38 murine adenocarcinoma cells injected at wk 15	HFD (60% fat) for 7 wk, then divided into 4 groups: HFD (60% fat + 20% protein + 20% CHO) LCD (60% fat + 35% protein + 5% CHO) HCD (10% fat + 20% protein + 70% CHO) 30% DR (10% fat + 20% protein + 70% CHO)	Allograft tumour: Tumour latency: HFD, 11.2 d; LCD, 11.4 d; 30% DR, 20.1 d Tumour size : HFD, 397.2 mm^2; LCD, 351.6 mm^2; HCD, 474.6 mm^2; 30% DR, 162.4 mm^2*	NS *$P < 0.001$ vs all the other groups	Bw of HFD and LCD mice higher than other groups; HCD mice maintained bw; 30% DR mice lost bw and then maintained it
BALB/c (M) 4 wk 21/group 24 wk Park et al. (2012)	CT26 murine colon carcinoma cells inoculated at age 20 wk, and tumours harvested after 31 d	LFD (10% fat) for 16 wk HFD (60% fat) for 16 wk	Allograft tumour: Tumour volume increase from 3 wk after cell injection (measured in situ) Tumour weight (g): LFD, 1.2; HFD, 1.5	$P < 0.05$ $P < 0.05$	Metastasis to lung [number of tumour nodules] higher in HFD vs LFD ($P < 0.05$) Bw slightly higher, by 5.9%, in HFD vs LFD [BALB/c mice resistant to HFD]
C57BL6 (F) 7 wk 15/group 25 wk Harvey et al. (2013)	MC38 murine adenocarcinoma cells inoculated at age 29 wk, and tumours harvested after 24 d	AIN-76A 30% DR (CHO restriction) for 25 wk	Allograft tumour: Tumour volume: AL, 2286 mm^3; 30% DR, 515 mm^3	$P < 0.001$	Bw of DR mice remained stable over the 22 wk of restriction, whereas AL mice gained bw ($P < 0.05$)
FVB (M) 10 wk 12/group up to 20 wk Olivo-Marston et al. (2014)	AOM, 10 mg/kg bw, once a wk for 5 wk	AIN-76A 30% DR (CHO restriction) for 5, 10, or 20 wk HFD (45% fat)	Colon tumours: Multiplicity after 20 wk: AL, 9.5; 30% DR, 7.2*	*$P < 0.05$ vs AL	30% DR mice lost bw and then maintained it; increase in bw and tumour number in HFD group [Values read from graph]

ACF, aberrant crypt foci; ADF, alternate-day fasting; AL, ad libitum; AOM, azoxymethane; bw, body weight; CHO, carbohydrate; d, day or days; DMH, dimethylhydrazine; DR, dietary restriction; F, female; F344, Fischer 344; HCD, high-carbohydrate diet; HFD, high-fat diet; LCD, low-carbohydrate diet; LFD, low-fat diet; M, male; MAM, methylazoxymethanol; mo, month or months; NS, not significant; s.c., subcutaneous; vs, versus; wk, week or weeks.

in the older rats. Alternate-day fasting was also initiated at either 8 days or 31 days after administration of methylazoxymethanol, but there was no effect of this intervention. [The low number of animals per group in this experiment may have affected the study conclusions.]

Several other studies used the carcinogen AOM to induce cancer of the colon. For example, Reddy et al. (1987) fed F344 male rats a HFD AL or 30% DR from age 5 weeks. They were treated with an AOM regimen beginning at age 7 weeks and followed up until age 32 weeks. No adenocarcinomas were detected in the 30% DR group, compared with a 30% incidence in the AL rats. In a study with Zucker rats, AL lean and AL obese rats were used, as well as a 20–25% DR obese group, fed 75–80% of the consumption of the AL lean rats. After 8 weeks of DR, there was no effect on the multiplicity of total aberrant crypt foci in the colon (Raju & Bird, 2003). [The Working Group noted the small *n* values; an effect was seen when distinguishing between advanced and early foci, which is questionable.]

Another approach by Newberne et al. (1990) to study the effect of body weight on development of colon cancer was to use pups obtained from litter sizes adjusted to either four or eight. Dimethylhydrazine was administered from 1 month after weaning for 10 weeks. In addition to rats raised in litter sizes of four or eight, some pups from the litters of four were pair-fed to the pups from the litters of eight. Tumour incidence was significantly higher in male and female rats raised in the smaller litters when fed AL compared with the corresponding groups raised in the larger litters. Pair-fed male rats from litters of four had a higher incidence of colon tumours than the male rats from litters of eight. [The Working Group considered that the use of litter size as an indicator of food intake made interpretation difficult for the evaluation of the effect of DR on colon tumour development.]

More recent studies on the effect of DR on colon cancer development have focused on mice models. Transgenic *Apc*^{Min} mice that develop "spontaneous" tumours were subjected to 25% DR for 9 weeks and compared with AL mice (fed AIN-76A-based diets). DR had no effect on the number of colon polyps. In addition, feeding a HFD (30% of calories from fat) had no effect (Mai et al., 2003). In another study, AOM was used to induce colon tumours in FVB male mice. AL mice were fed the AIN-76A diet and compared with mice subjected to 30% DR (with carbohydrate restriction). Mean numbers of colon tumours were significantly reduced after 20 weeks of 30% DR (Olivo-Marston et al., 2014).

Allograft implants of colon cancer cell lines have also been used to assess the effects of DR on tumour growth. MC38 cells were used in two different studies (Wheatley et al., 2008; Harvey et al., 2013). In one study, female C57BL6 mice were fed the AIN-76A diet or were subjected to 30% DR (with carbohydrate restriction) from age 7 weeks (Harvey et al., 2013); the cells were implanted at age 29 weeks, and tumours were harvested 24 days later. Tumour volume was reduced significantly in the 30% DR mice compared with the AL mice (515 mm^3 vs 2286 mm^3). In the other study (Wheatley et al., 2008), male C57BL6 mice were fed a HFD (60% of calories from fat) for 7 weeks and then divided into four experimental groups, including a group subjected to 30% DR (10% of calories from fat). MC38 cells were injected at week 15. Tumour size was reduced in the 30% DR group compared with all the other experimental groups. [The Working Group noted that this study assessed DR in obese mice.]

The CT26 murine carcinoma cell line, which was developed from BALB/c mice, was used to evaluate tumour growth in LFD versus HFD mice (Park et al., 2012). The HFD group was fed from age 4–20 weeks; the cells were inoculated at age 20 weeks, and the mice continued on their respective diets for an additional 31 days. Body weight was only slightly higher in the HFD mice than in the LFD mice, whereas tumour volume

and weight were significantly higher in the HFD group. Metastasis to the lungs, as determined by the number of tumour nodules, was significantly higher in the HFD mice. [This study is of interest because – although it did not use DR – the BALB/c mice were resistant to the HFD.]

3.3.3 Cancer of the liver

See Table 3.12.

Comprehensive studies of nutrition and ageing, conducted in collaboration with the United States Food and Drug Administration's National Center for Toxicological Research and the United States National Institute on Aging provided pathological data on mice subjected to 40% DR (Blackwell et al., 1995; Sheldon et al., 1995, 1996). In scheduled-sacrificed female $B6C3F_1$ mice, no liver tumours were found in DR mice until age 30 months, whereas in AL mice, 4.9% (2 of 41 mice) had liver tumours at 24 months and 13.3% (2 of 15 mice) had liver tumours at 30 months (Sheldon et al., 1995). At 36 months, the incidences were similar between female AL and DR mice, at 42.9% (6 of 14 mice) and 33.3% (5 of 15 mice), respectively. In male $B6C3F_1$ mice, the incidence increased with advancing age in the AL group, and the incidence was significantly lower in the DR group than in the AL group at 24 months and 36 months. Necropsy data from mice that died spontaneously or were killed when moribund also showed that the incidence of liver tumours was lower in female and male DR mice, compared with the respective control AL mice. In C57BL6 mice, the incidence of liver tumours in scheduled-sacrificed male and female AL mice was less than 5%, and no tumours were found in the DR group (Blackwell et al., 1995). The incidence of liver tumours in male mice at necropsy was also lower in the DR group than in the AL group; there was no significant difference in female mice between the AL group and the DR group at necropsy.

In a study by the United States National Toxicology Program (NTP, 1997), administration of salicylazosulfapyridine (SASP) in the feed decreased the body weights of male $B6C3F_1$ mice by 15% in the 2-year bioassay. To eliminate a possible effect of the weight reduction by SASP on the occurrence of neoplasms, a weight-matched control group was included, in which the food intake was restricted by 13–22% to reduce the body weight to the level of AL mice treated with SASP (15% less than for the untreated AL group). The incidence of hepatocellular adenomas or of carcinomas was lower in the weight-matched control group, although this difference was not statistically significant. However, the incidence of adenoma and carcinoma combined was significantly lower in the weight-matched control group compared with the untreated AL group. Although the DR level in the 40% DR group was double (i.e. 40%), and therefore body weight was lower in the 40% DR group than in the weight-matched controls, the incidences of adenoma, of carcinoma, and of adenoma and carcinoma combined were not significantly lower even when compared with the untreated AL group. In contrast, in the animals treated with SASP, the 40% DR group had a significantly lower incidence of hepatocellular adenoma ($P < 0.001$), of carcinoma ($P < 0.05$), and of adenoma and carcinoma combined ($P < 0.001$), compared with the SASP AL controls.

In the National Toxicology Program feeding study of scopolamine hydrobromide trihydrate (SHT), the untreated weight-matched group (20% lower body weight compared with the AL group) and the DR group had lower incidences of hepatocellular adenoma, and of adenoma and carcinoma combined, although for carcinoma the difference was not statistically significant (NTP, 1997). In animals treated with SHT, the 40% DR group had a significantly lower incidence of hepatocellular adenoma ($P < 0.05$), of carcinoma ($P < 0.05$), and of adenoma and carcinoma combined ($P < 0.01$), compared with

Table 3.12 Studies on the prevention of tumours of the liver by dietary/calorie restriction in mice

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration, duration of study	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Swiss OF1 (M) Weanling (21 d) 14–20/group 48 wk Lagopoulos et al. (1991)	NDEA, 0.4 µmol/g bw, i.p., at birth	Nafag 857 diet, fed AL or 30% DR, from age 12 wk, killed at 24, 36, 48 wk	Liver G6Pd foci; adenoma; carcinoma; adenoma or carcinoma (combined):		
		Control (AL):			
		12 wk	17/20, 0/20, 0/20, 0/20		
		24 wk	17/20, 16/20, 0/20, 16/20		
		36 wk	11/18, 18/18, 5/18, 18/18		
		48 wk	2/14, 9/14, 6/14, 14/14		
		30% DR:			
		12 wk	7/19*, 0/19, 0/19, 0/19	*$P < 0.05$ vs AL group, χ^2 test	
		24 wk	16/20, 0/20*, 0/20, 0/20*	*$P < 0.001$ vs AL group, Fisher exact test	
		36 wk	16/17*, 12/17, 1/17, 12/17*	*$P < 0.05$ vs AL group, χ^2 test	
		48 wk	15/16*, 10/16, 0/16**, 10/16***	*$P < 0.001$, **$P < 0.01$, ***$P < 0.05$ vs AL group, χ^2 test or Fisher exact test	
C57BL6 (F, M) 4 wk 266/group SS at 12–36 mo, or lifelong Blackwell et al. (1995)	Spontaneous neoplasms	NIH-31 diet, fed AL or 40% DR, from age 14 wk	Hepatocellular tumours, mostly adenoma or carcinoma (%) (0–33 mo):	*$P < 0.01$ vs controls, Fisher exact test	Incidence of liver tumours was small; therefore, data of 0–27 mo and 28–33 mo were combined
		Control (AL)	**F:** 4/115 (*3.5%*), **M:** 18/156 (*11.5%*)		
		40% DR	**F:** 2/100 (*2%*), **M:** 2/106 (*1.9%*)*		

Table 3.12 (continued)

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration, duration of study	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
$B6C3F_1$ (F, M) 4 wk 266/group SS at 12–42 mo, or lifelong Sheldon et al. (1995)	Spontaneous neoplasms	NIH-31 diet, fed AL or 40% DR; DR increased gradually: 10% at 14 wk, 25% at 15 wk, and 40% at age 16 wk	Hepatocellular tumours, mostly adenoma or carcinoma (%): 0–27 mo, 28–40 mo	*$P < 0.05$, **$P < 0.001$ vs controls, Fisher exact test	Data of necropsied mice from the SS group and the lifespan study group were combined AL: 31 hepatocellular neoplasms, 13 of them carcinomas; 7 metastasized to the lungs 40% DR: 18 hepatocellular neoplasms, 9 of them carcinomas; 1 metastasized to the lungs
		Control (AL)	**F:** 7/56 (*12.5%*), 14/131 (*10.7%*) **M:** 13/39 (*33.3%*), 48/118 (*40.7%*)		
		40% DR	**F:** 0/10 (*0%*), 1/72 (*1.4%*)* **M:** 0/7 (*0%*), 1/45 (*2.2%*)**		
$B6D2F_1$ (F, M) 4 wk 56/group Lifelong Sheldon et al. (1996)	Spontaneous neoplasms	NIH-31 diet, fed AL or 40% DR	Benign and malignant liver tumours:	*[NS]; **[$P < 0.001$]	
		Control (AL)	**F:** 13%, **M:** 24%		
		40% DR	**F:** 4%*, **M:** 2%**		
$B6C3F_1$ (M) 6 wk 50 or 52/group 104 wk NTP (1997)	SASP, 2700 mg/kg bw in corn oil by gavage, once a day, 5 d/wk	NIH-07 diet, fed AL or (on average) 15% DR (weight-matched to SASP group), or 40% DR	Hepatocellular adenoma; carcinoma; adenoma or carcinoma (combined):		
		Untreated, AL	13/50, 13/50, 24/50	*$P < 0.05$ vs untreated AL group, χ^2 test	
		Untreated, 15% DR	8/50, 6/50, 14/50*		
		Untreated, 40% DR	13/52, 7/52, 18/52	*$P < 0.001$, **$P < 0.05$ vs SASP AL group, χ^2 test or Fisher exact test	
		SASP, AL	42/50, 8/50, 44/50		
		SASP, 40% DR	9/50*, 1/50**, 9/50*		

Table 3.12 (continued)

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration, duration of study	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
$B6C3F_1$ (M) 6 wk 70/group 104 wk NTP (1997)	SHT, 25 mg/kg bw in corn oil by gavage, once a day, 5 d/wk	NIH-07 diet, fed AL or (on average) 15% DR (weight-matched to SHT group), or 40% DR	Hepatocellular adenoma; carcinoma; adenoma or carcinoma (combined):		Untreated weight-matched group had 20% lower bw compared with AL group
		Untreated, AL	26/50, 6/50, 30/50	*$P < 0.001$ vs untreated AL group, χ^2 test	
		Untreated, 15% DR	5/50*, 5/50, 10/50*		
		Untreated, DR	3/50*, 2/50, 5/50*	*$P < 0.001$ vs untreated AL group, χ^2 test or Fisher exact test	
		SHT, AL	8/50*, 7/50, 15/50**	*$P < 0.001$, **$P < 0.01$ vs untreated AL group, χ^2 test	
		SHT, 40% DR	0/50*, 1/50*, 1/50**	*$P < 0.05$, **$P < 0.001$ vs SHT AL group, Fisher exact test	

AL, ad libitum; bw, body weight; d, day or days; DR, dietary restriction; F, female; G6Pd, glucose-6-phosphatase-deficient; i.p., intraperitoneal; M, male; mo, month or months; NDEA, *N*-nitrosodiethylamine; NS, not significant; NTP, National Toxicology Program; SASP, salicylazosulfapyridine; SHT, scopolamine hydrobromide trihydrate; SS, scheduled-sacrificed; vs, versus; wk, week or weeks.

the SHT AL controls. [The protective effect on adenoma development may have been due to decreased food intake and was not a direct effect of administration of SHT.]

In male Swiss OF1 mice treated with *N*-nitrosodiethylamine, the incidence of glucose-6-phosphatase-deficient pre-neoplastic foci was significantly lower in the 30% DR group compared with the AL group at age 12 weeks. In the AL group, 80% of the mice had hepatocellular adenoma or carcinoma at 24 weeks, and 100% at 36 weeks and 48 weeks. The incidence of hepatocellular neoplasms (adenoma and carcinoma combined) was significantly lower in the 30% DR group than in the AL group at 24 weeks, 36 weeks, and 48 weeks (Lagopoulos et al., 1991).

3.3.4 Cancer of the pancreas

See Table 3.13.

The incidence of spontaneous pancreatic tumours is very low in mice, on both C57BL6 and B6C3F$_1$ backgrounds (Blackwell et al., 1995; Sheldon et al., 1995). LSL-*Kras*^{G12D}; Pdx-1/Cre mice, a genetic model, develop pancreatic precursor lesions such as PanIN, which progress to PDAC. In one study (Lanza-Jacoby et al., 2013), two regimens for 25% DR were used with this model. One was CDR at 25% less than the AL average intake; the other was IDR, i.e. 50% restriction for 1 week after 100% provision of AL intake for 1 week, and therefore IDR also reduced the calorie intake by 25% over the 2-week interval. The body weight of the IDR mice fluctuated according to calorie intake. In the 100% feeding week, body weights were similar to those in the AL group; in the 50% restriction week, body weights were lower than those in the CDR mice. The incidence of PanIN was lower in both the CDR and IDR groups than in the AL group, with a greater effect of DR in the IDR regimen than in the CDR regimen. PDAC was found in the AL group, whereas no PDAC was observed in the CDR and IDR groups at age 44 weeks.

Another genetic model uses FVB-Tg (BK5. COX-2) mice and calculates a composite score for pancreatic dysplasia. In the study of Lashinger et al. (2011), formation of severe dysplasia in pancreatic ducts was lower in the 30% DR group than in the AL group. When tumour cells were injected into wild-type mice, tumour weight at 4 weeks after injection was significantly lower in 30% DR mice. Lashinger et al. (2013) used *Kras*^{G12D}/*Ink4a*$^{+/-}$ male mice and observed longer median survival in 30% DR mice than in AL mice, and no PDAC in 30% DR mice compared with 3 PDAC in AL mice.

In Sprague-Dawley rats, 4–6% of the AL group rats spontaneously developed pancreatic islet adenomas or carcinomas (Keenan et al., 1995). The overall incidence of pancreatic islet neoplasms over a 2-year study seemed to be lower in the 35% DR group. [The baseline incidence was low, and therefore the effect of 35% DR on spontaneous islet neoplasms could not be evaluated.] In another study in Sprague-Dawley rats (Molon-Noblot et al., 2001), the incidence of adenomas was 24% and 18% in female and male AL groups, respectively. The inhibition of adenomas by three different levels of DR was significant in female rats, whereas the effect of DR was modest in male rats. In a third study in male Sprague-Dawley rats (Duffy et al., 2008), the incidence of islet adenomas was lower in the 31% DR group than in the AL group, but this difference was not statistically significant.

In male Lewis rats, the effect of DR on the post-initiation phase of pancreatic carcinoma induced by azaserine was assessed (Roebuck et al., 1993). Feeding AL for a limited time (5–6 hours per day), designated as a "meal-fed" regimen, reduced the food intake to an equivalent of 10–15% DR relative to AL. The meal-fed regimen significantly reduced the incidence of adenomas and carcinomas 14 months after azaserine initiation.

In male Syrian golden hamsters, the incidence of pancreatic carcinoma, induced by BOP, did not differ among control AL, 20% CR, and 40% CR groups (Birt et al., 1997). However, the

Table 3.13 Studies on the prevention of tumours of the pancreas by dietary/calorie restriction in experimental animals

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration, duration of study	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Mouse					
FVB-Tg (BK5.COX-2) (F, M) 6 wk 24/group 20 wk Lashinger et al. (2011)	Genetic model for dysplastic lesions	Control diet (Research Diets, Inc., New Brunswick, NJ, #D12450B), fed AL or 30% DR	Composite score for pancreatic dysplasia: AL: 10 ± 4 30% DR: 5 ± 4**	$^{**}P < 0.01$	
FVB-WT (F, M) 6 wk 24/group 20 wk Lashinger et al. (2011)	JC101 pancreatic tumour cell injection at age 13–15 wk	Control diet (Research Diets, Inc., New Brunswick, NJ, #D12450B), fed AL or 30% DR	Tumour weight 4 wk after s.c. transplantation: AL: 1.05 ± 0.38 g 30% DR: 0.47 ± 0.30 g*	$^{*}P < 0.05$	
LSL-*Kras*^{G12D}; Pdx-1/Cre (M) 6 wk 31/group 44 wk Lanza-Jacoby et al. (2013)	Genetic model for PDAC	Modified AIN-93 diets, fed AL or 25% DR (CDR) or IDR, 6–44 wk	PanIN (PanIN-2 or greater); PDAC: Control (AL): 70%, 27% (n = 11) CDR: 40%*, 0% (n = 15) IDR: 27%*/#, 0% (n = 16)	$^{*}P < 0.05$ vs AL control group, exact Poisson regression analysis $^{*}P < 0.05$ vs AL control group, $^{\#}P < 0.05$ vs CDR group, exact Poisson regression analysis	IDR: 50% DR for 1 wk, then 100% of AL intake for 1 wk
Kras^{G12D}/*Ink4a*$^{+/-}$ (M) 6 wk 42–43/group 10 wk or 56 wk Lashinger et al. (2013)	Genetic model for PanIN-2 or PDAC	Control diet (Research Diets, Inc., New Brunswick, NJ, #D12450B), fed AL or 30% DR, from age 6–9 wk	PanIN (PanIN-2 or greater); PDAC: 10 wk study: AL: 7/15 (46.7%), 3/15 (20%) 30% DR: 9/15 (60%), 0/15 (0%) 56 wk study, median survival: AL: 20.0 wk 30% DR: 30.0 wk*	NS $^{*}P < 0.001$, log-rank test	

Table 3.13 (continued)

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration, duration of study	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Rat					
Lewis (M) 2 wk 22–23/group 14 mo Roebuck et al. (1993)	Azaserine, 30 mg/kg bw, i.p., once, at age 2 wk	AIN-76A diet, fed AL or 10–15% DR by meal-feeding Control	Pancreatic adenoma (%); carcinoma (%); adenoma multiplicity; carcinoma multiplicity: AL: 23/23 (100%), 15/23 (65%), 8.04 ± 0.99, 1.60 ± 0.214 10–15% DR: 5/22 (23%)*, 0/22 (0%)*, 1.00 ± 0#, 0	*$P < 0.05$ vs control group, χ^2 test or Fisher exact test #$P < 0.05$ vs AL group, ANOVA with Bonferroni test	
Sprague-Dawley [Crl:CD® (SD) BR] (F, M) 36 d 70/group 106 wk Keenan et al. (1995)	Spontaneous neoplasms	Purina Certified Rodent Chow 5002 or 5002-9 at various regimens Chow 5002: Control (AL) DR 6.5 h (AL for 6.5 h) 35% DR Chow 5002-9: Control (AL) DR (fed at the same calorie intake as rats fed 35% DR chow 5002)	Pancreatic islet adenoma (%); islet carcinoma (%): **F:** 3/70 (*4.3%*), 0/70 (*0%*) **M:** 4/70 (*6.2%*), 4/70 (*6.2%*) **F:** 1/70 (*1.4%*), 1/70 (*1.4%*) **M:** 2/70 (*2.9%*), 7/70 (*10%*) **F:** 1/70 (*1.4%*), 0/70 (*0%*) **M:** 5/70 (*7.1%*), 1/70 (*1.4%*) **F:** 3/70 (*4.3%*), 0/70 (0%) **M:** 3/70 (*4.3%*), 5/70 (*7.1%*) **F:** 1/70 (*1.4%*), 2/70 (*2.9%*) **M:** 3/70 (*4.3%*), 0/70 (*0%*)	 — NS NS NS NS — NS NS	Chow 5002: 21.4% protein, 5.7% fat, 4.1% crude fibre, energy value 3.07 kcal/g; Chow 5002-9: 13.6% protein, 4.6% fat, 15.7% crude fibre, energy value 2.36 kcal/g Baseline incidence was low, so that the effect of DR could not be evaluated

Table 3.13 (continued)

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration, duration of study	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Sprague-Dawley [Crl:CD® (SD) IGS BR] (F, M) 7 wk 15/group 100 wk Molon-Noblot et al. (2001)	Spontaneous neoplasms	Purina Certified Rodent Diet, 21–28% DR, 28–32% DR, 52–53% DR	Pancreatic islet adenoma (%); islet carcinoma (%):	*$P < 0.05$ vs AL group, Fisher exact test	
		Control (AL)	**F:** 12/50 (24%), 2/50 (4%) **M:** 9/50 (18%), 3/50 (6%)		
		21–28% DR	**F:** 3/52* (5.8%), 0/52 (0%) **M:** 16/50 (32%), 5/50 (10%)		
		28–32% DR	**F:** 3/52* (5.8%), 0/52 (0%) **M:** 12/50 (24%), 0/50* (0%)		
		52–53% DR	**F:** 1/51* (2%), 0/51 (0%) **M:** 4/50 (8%), 3/50 (6%)		
Sprague-Dawley [Crl:CD® (SD) BR] (M) 6 wk 40 or 60/group 108 wk Duffy et al. (2008)	Spontaneous neoplasms	AIN-93M diet, fed AL or 31% DR from age 6–114 wk	Pancreatic islet adenoma: AL: 11.8% ($n = 57$) 31% DR: 6.7% ($n = 38$)	NS (poly-3 test)	
Hamster					
Syrian golden (M) 8 wk 25–35/group Up to 44 wk Birt et al. (1997)	BOP, 20 mg/kg bw, 3 weekly s.c. injections	Control diet, fed AL or 20% CR or 40% CR for 42–44 wk	Pancreatic carcinoma; multiplicity: AL: 17/29, 0.9 ± 0.2 20% CR: 19/29, 1.2 ± 0.2 40% CR: 17/26, 1.7 ± 0.3*	Incidence: NS Multiplicity: *$P < 0.02$ vs control	

AL, ad libitum; ANOVA, analysis of variance; BOP, *N*-nitrosobis(2-oxopropyl)amine; bw, body weight; CDR, chronic dietary restriction; CR, calorie restriction; d, day or days; DR, dietary restriction; F, female; h, hour or hours; IDR, intermittent dietary restriction; i.p., intraperitoneal; M, male; mo, month or months; NS, not significant; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; s.c., subcutaneous; vs, versus; wk, week or weeks; WT, wild-type.

multiplicity of pancreatic carcinoma was greater in the 40% CR group than in the AL group.

3.3.5 Cancer of the skin and subcutaneous tissue

See Table 3.14.

Lifespan studies using mice and rats have indicated the low incidence of spontaneous skin tumours (Blackwell et al., 1995; Sheldon et al., 1995). In one study, less than 2% of scheduled-sacrificed male B6C3F$_1$ mice had skin or subcutaneous tumours (Sheldon et al., 1995). In contrast, female mice had relatively high incidences of skin or subcutaneous tumours. However, there was no statistical difference between the AL and DR groups for either sex (Sheldon et al., 1995). [The occurrence of skin tumours could be delayed in the DR group.]

Topical application of benzo[*a*]pyrene is one of the models used to induce skin tumours in rodents. Boutwell et al. (1949) demonstrated that 50% DR reduced the incidence of skin carcinoma induced by benzo[*a*]pyrene.

Birt et al. (1991) reported the effect of DR on either the initiation or the promotion phase of a chemically induced skin carcinoma model in female SENCAR mice. They used two regimens for 40% DR: one was a total DR of the control diet (TDR), and the other involved CR using a diet that was low in fat and glucose but high in protein and fibre. Mice that were subjected to 40% TDR or CR at the initiation phase had reduced weight gain, and the subsequent AL regimen led to recovery of the weight gain within 4 weeks. Mice that were subjected to 40% TDR and CR starting at the promotion phase had significantly lower body weight according to the energy restriction levels. Neither 40% TDR nor CR at the initiation phase affected the incidence or multiplicity of skin papilloma or the incidence of skin carcinoma. Mice that were subjected to 40% TDR and CR starting at the promotion phase had significantly lower incidence of skin papilloma and skin carcinoma.

Birt et al. (1993) tested the effect of 35% CR from fat or carbohydrate in the chemically induced DMBA skin tumour model in female SENCAR mice. The incidence of skin carcinoma was significantly lower in the groups subjected to CR from either fat or carbohydrate, and there was no difference in incidence between the two CR regimens, although papilloma multiplicity was greater in the carbohydrate-restricted (and thus HFD) group, compared with the fat-restricted group [no statistics were reported]. A subsequent study indicated that moderate (i.e. 20%) CR of a HFD or a LFD was ineffective, suggesting the importance of the level of CR (Birt et al., 1996).

Birt et al. (1994) also tested the effect of 40% DR in the two-stage promotion protocol, which comprised early-stage treatment with DMBA at age 9 weeks, promotion by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) for 2 weeks, and subsequent late-stage promotion by mezerein for 15 weeks. The individual effect of DR on the promotion phase by either TPA or mezerein was evaluated. Mice subjected to DR at age 10–27 weeks recovered their weight loss once they returned to AL feeding with a control diet at age 28 weeks. However, those mice subjected to DR during the period of treatment with TPA and/or mezerein had a reduction of approximately 10% in body weight compared with the control AL mice at age 71 weeks. DR during the entire period of promotion, i.e. at age 10–27 weeks (DR/DR group), and DR during the period of treatment with mezerein, at age 12–27 weeks (AL/DR group), significantly reduced the incidence and multiplicity of skin papilloma at 28 weeks; the cumulative incidence of skin carcinoma was also reduced (not significantly) in the DR/DR group and the AL/DR group. However, 2-week DR feeding during TPA treatment was insufficient to produce an inhibitory effect of DR on skin tumorigenesis.

Table 3.14 Studies on the prevention of tumours of the skin and subcutaneous tissue by dietary/calorie restriction in mice

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Rockland (F) ~2–3 mo 48/group 173 d Boutwell et al. (1949)	60 µg of benzo[*a*]pyrene (skin application), twice a wk for 19 wk from 26 d after beginning of DR	High-calorie, low-fat (AL), or low-calorie, low-fat (50% DR) Control (AL) 50% DR	Skin carcinoma: 32/39 8/44**	$^{**}P < 0.01$, χ^2 test	
C57BL/6 (M) 4.5 mo 7–10/group 5–6 wk Ershler et al. (1986)	10^5 B16 melanoma cells injected s.c., 2 wk after beginning of DR	Purina Laboratory Chow, fed AL or 40% DR Control (AL) 40% DR	Tumour volume (mm^3)/1000 (mean ± SE): 7.9 ± 1.5 2.3 ± 0.5*	$^{*}P < 0.05$, Student *t* test	
SENCAR (F) 6 wk or 10 wk 15–30/group Up to 56 wk Birt et al. (1991)	10 nmol of DMBA (skin application), once at age 9 wk; 3.2 nmol of TPA (skin application), twice a wk for 20 wk from age 10 wk	AIN; fed AL or 40% DR by TDR or CR, from 6–9 wk or 10–56 wk Control (AL) 40% TDR, 6–9 wk 40% TDR, 10–56 wk 40% CR, 6–9 wk 40% CR, 10–56 wk	Skin papilloma (%) at age 30 wk; papilloma multiplicity at age 34 wk (mean ± SE); skin carcinoma (%) until age 56 wk 27/30 (90%), 5.7 ± 0.4, 15/24 (71%) 24/30 (80%), 4.9 ± 0.9, 14/24 (58%) 11/20 (55%)***, 2.2 ± 0.4***, 7/17 (41%)* 25/29 (89%), 6.6 ± 0.9, 11/17 (69%) 13/23 (56%)***, 1.8 ± 0.4***, 5/15 (28%)*	— NS $^{***}P < 0.001$, $^{*}P < 0.05$ vs AL, χ^2 test or ANOVA NS $^{***}P < 0.001$, $^{*}P < 0.05$ vs AL, χ^2 test or ANOVA	Both TDR and CR from 10–56 wk lowered bw by 30% No significant difference in tumour incidence and multiplicity between TDR and CR groups [Multiplicity at age 34 wk read from figure]

Table 3.14 (continued)

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
CD-1 (F) ~6–7 wk 42–59/group 100 d Pashko & Schwartz (1992)	51.2 µg of DMBA (skin application), once at age 6 wk or 7 wk; 2 µg of TPA (skin application), twice a wk for 82 d from 1 wk after beginning of DR	Purina 5015 chow, fed AL or ~35% DR from age 8–9 wk Control (AL) DR	Number of skin papillomas/mouse: 5.5 0.9*	*$P < 0.01$, Wilcoxon Mann–Whitney sum test	
SENCAR (F) 6 wk 38–42/group Up to 68 wk Birt et al. (1993)	10 nmol of DMBA (skin application), once at age 9 wk; 2.0 µg of TPA (skin application), twice a wk for 20 wk from age 10 wk	AIN diet fed AL, balanced high fat (BHD) AL, 35% CR with high carbohydrate (HCD), 35% CR with high fat (HFD), from age 10 wk Control AL BHD AL 35% CR HCD 35% CR HFD	Number of papillomas/mouse at 28 wk after DMBA; time to carcinoma at 50% incidence 6.5, ~40 wk 6.2, ~44 wk 1.5*, > 59 wk# 3.2*, > 59 wk#	*$P < 0.05$ vs control and BHD AL #$P < 0.01$ vs control and BHD AL, log-rank test	Bw reduced in HCD and HFD vs control AL and BHD AL groups; no difference between HCD and HFD, or between control AL and BHD AL
SENCAR (F) 7 wk 30–52/group Up to 62 wk Birt et al. (1994)	10 nmol of DMBA (skin application), once at age 9 wk; 3.2 nmol of TPA (skin application), twice a wk at 10–11 wk, and 10 nmol of MEZ twice a wk at age 12–27 wk	Ingredient diet, fed AL or 40% DR at various regimens Control (AL), age 7–71 wk 40% DR, 10–27 wk; AL, 28–71 wk 40% DR, 10–11 wk; AL, 12–71 wk AL, 10–11 wk; DR, 12–27 wk; AL, 28–71 wk	Skin papilloma; papilloma multiplicity at age 28 wk; skin carcinoma (%) at age 71 wk: 42%, 0.9, 14/48 (29%) 17%*, 0.3*, 3/31# (10%) 54%, 0.9, 10/30 (33%) 17%*, 0.2*, 5/33 (15%)	— *$P < 0.05$, #NS vs AL, χ^2 test or Fisher exact test NS *$P < 0.05$ vs AL	Bw loss of ~10% in DR mice vs AL at age 71 wk Multiplicity was tested by a Poisson random variable, using the generalized estimating equation approach of Liang and Zeger, and the estimation of regression coefficients

Table 3.14 (continued)

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
$B6C3F_1$ (F, M) 4 wk 245–266/group SS at 12–42 mo, or lifelong Sheldon et al. (1995)	Spontaneous neoplasms	NIH-31 diet, fed AL or 40% DR; DR increased gradually: 10% at 14 wk, 25% at 15 wk, and 40% at age 16 wk; SS at age 12, 18, 24, 30, 36, 42 mo	Skin tumours (%): 0–27 mo, 28–33 mo, 34–39 mo, 40–51 mo:	NS	Incidence of spontaneous skin tumours was low even in the AL groups
		Control (AL)	**M:** 1/72 (1.4%), 1/83 (1.2%), 0/65 (0%), 0/15 (0%) **F:** 4/97 (4.1%), 10/110 (9.1%), 1/50 (2%), 0/1 (0%)		
		40% DR	**M:** 0/49 (0%), 0/27 (0%), 0/48 (0%), 0/138 (0%) **F:** 1/52 (1.9%), 2/38 (5.3%), 6/64 (9.4%), 3/111 (2.7%)		
SENCAR (F) 9 wk 35/group 45 wk Birt et al. (1996)	10 nmol of DMBA (skin application), once at age 9 wk; 3.2 nmol of TPA (skin application), twice a wk for 18 wk from age 10 wk	Fed AL, 20% or 40% CR from fat or carbohydrate using LFD (10% fat) or HFD (42% fat), from age 10 wk	Skin carcinoma (%):		
		Control: LFD AL 20% CR of LFD 40% CR of LFD HFD AL 20% CR of HFD 40% CR of HFD	35% 20% 15%* 35% 35% 0%*	*$P < 0.05$ vs LFD AL, HFD AL, and 20% CR of HFD	
ICR (M), *Nrf2* gene knockout 10 wk 10–15/group up to 42 wk Pearson et al. (2008)	25 µg of DMBA (skin application), once at age 15 wk or 16 wk; 4 µg of TPA (skin application), twice a wk, from 2 wk after DMBA until appearance of first papilloma	Teklad 2018 diet, fed AL or 20% DR, 30% DR, or 40% DR for 5–6 wk	Skin tumour: time at 25% and 50% incidence:		Kaplan–Meier survival analysis was performed to compare the 2 curves of papilloma occurrence Time of appearance of tumour was recorded when at least 1 papilloma with a radius > 1 mm was identified
		Control (AL) 20% DR 30% DR 40% DR	13 wk, 15 wk 18 wk, 25 wk (< 50% incidence) 18 wk, 20 wk 42 wk, 42 wk	— $P < 0.05$	

Table 3.14 (continued)

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
129S1/SvImJ (M) 3–5 mo 11–13/group 18 wk Minor et al. (2011)	25 µg of DMBA (skin application), once; 4 µg of TPA (skin application), twice a wk, from 2 wk after DMBA until appearance of first papilloma	AIN-93G diet, fed AL or 30% DR	Skin papilloma (%); multiplicity ± SD	*$P < 0.0083$ vs WT AL, Bonferroni *t* tests	[Values read from graph]
		Control (AL)	100%, 4.0 ± 2.7	—	
		30% DR	58%, 1.0 ± 1.1*		
ICR (F) 7 wk 30/group 58 wk Moore et al. (2012)	25 nmol of DMBA (skin application), once at age 7 wk; 3.4 nmol of TPA, twice a wk (skin application), from age 15 wk for 50 wk	AIN-76A diet, fed AL,15% DR, or 30% DR from age 11 wk	Skin papilloma (%) at age 30 wk; multiplicity at age 39 wk; skin carcinoma (%) at age 65 wk; multiplicity at age 65 wk:		Bw lower in both DR groups
		Control (AL)	81%, 8.2, 92%, 1.6	—	
		15% DR	81%, 6.2*, 69%#, 1.6	*$P < 0.05$ vs AL, Mann–Whitney *U* test #$P < 0.05$ vs AL, χ^2 test	
		30% DR	68%, 4.3*, 58%#, 1.0*	*$P < 0.05$ vs AL, Mann–Whitney *U* test #$P < 0.05$ vs AL, χ^2 test	

AL, ad libitum; ANOVA, analysis of variance; BHD, balanced high-fat diet; bw, body weight; CR, calorie restriction; d, day or days; DMBA, 7,12-dimethylbenz[*a*]anthracene; DR, dietary restriction; F, female; HCD, high-carbohydrate diet; HFD, high-fat diet; LFD, low-fat diet; M, male; MEZ, mezerein; mo, month or months; NS, not significant; s.c., subcutaneous; SD, standard deviation; SE, standard error; SS, scheduled-sacrificed; TDR, total dietary restriction; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; vs, versus; wk, week or weeks; WT, wild-type.

Moore et al. (2012) used female ICR mice to assess the effect of 15% DR or 30% DR on the promotion of skin tumours. At the end of the experiment, the body weights were 36% lower in the 30% DR group and 15% lower in the 15% DR group, compared with the control AL group. The cumulative incidences of skin papilloma in the experimental groups did not differ significantly among these groups. However, the multiplicity of skin papilloma was significantly lower in the 15% DR and 30% DR groups compared with the AL group. The incidences of skin carcinoma were also significantly lower in the 15% DR and 30% DR groups; the multiplicity of skin carcinoma was significantly lower only in the 30% DR group (Moore et al., 2012).

In the B16 melanoma cell injection model, the tumour volume was significantly lower in C57BL/6 mice subjected to 40% DR compared with AL mice (Ershler et al., 1986).

Using the two-stage skin tumorigenesis model in CD-1 mice treated with DMBA, Pashko & Schwartz (1992) reported that DR suppressed TPA promotion of skin papillomas.

The preventive effect of 40% DR on DMBA-TPA-induced skin tumours was diminished in ICR mice (Pearson et al., 2008) and in 129S mice (Minor et al., 2011).

3.3.6 Cancer of the pituitary gland

See Table 3.15.

In lifespan studies in mice, the incidence of pituitary tumours is very low in males (Blackwell et al., 1995; Sheldon et al., 1995, 1996).

The incidence in female scheduled-sacrificed C57BL6 control mice was reported to be 14% at 24 months and 64% at 30 months. In DR mice, no pituitary tumours were found at 24 months and 30 months. Necropsies of mice that died spontaneously or were killed when moribund also indicated a significant reduction in the incidence of pituitary tumours in the female DR group compared with the AL group (Blackwell et al., 1995). In female B6C3F$_1$ and B6D2F$_1$ mice, the incidence of spontaneously occurring pituitary tumours was also lower in the DR group than in the AL group (Sheldon et al., 1995, 1996).

In a 2-year study in Sprague-Dawley rats fed 35% DR with either a standard diet or a low-protein, high-fibre diet, incidences of spontaneous pituitary adenomas were very high in both male and female AL rats (Keenan et al., 1995). In male rats, both 35% DR groups had lower incidences of pituitary adenomas. In contrast, in female rats the preventive effect of 35% DR was observed only in the 35% DR group fed the low-protein, high-fibre diet and not in the 35% DR group fed the standard diet.

In a lifespan study in F344 rats (Thurman et al., 1994), the incidence of pituitary tumours in the 40% DR group was significantly lower than in the AL group in both female and male rats. The mean age at death of rats bearing pituitary tumours was also higher in the 40% DR group compared with the AL group in both male and female rats.

Estrogen stimulates the proliferation of prolactin-producing lactotrophs, and therefore continuous administration of estrogen promotes the development of prolactin-producing tumours in the rat. Pituitary weight can be measured as a quantitative indicator of estrogen-induced pituitary tumour development, because increased weight correlates with increases in pituitary cell number and DNA content. Several studies (Shull et al., 1998; Spady et al., 1998, 1999; Harvell et al., 2001) have used this model to study pituitary tumour development, and some have shown a reduction of tumour development with 40% DR. [In this model, response to DR for the inhibition of tumours depends on the strain of rat used. These results are confounded by the fact that body weight was reduced by estrogen administration in the AL group, whereas it was not significantly reduced in the DR group. In addition, there was no indication of histopathology or of tumour incidence. Therefore, these studies are regarded

Table 3.15 Studies on the prevention of tumours of the pituitary gland by dietary/calorie restriction in mice and rats

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Mouse					
C57BL6 (F) Weanling 266/group SS at 12–36 mo, or lifelong Blackwell et al. (1995)	Spontaneous neoplasms	NIH-31 open formula diet, fed AL or 40% DR from age 4 wk; SS at 12, 18, 24, 30, 36 mo	Pituitary tumours (%): Mice SS at 0–24 mo, 30 mo:	[*$P < 0.05$, **$P < 0.0005$ vs controls, Fisher exact test]	
		Control (AL)	6/43 (14%), 9/14 (64%)		
		40% DR	0/44 (0%)*, 0/15 (0%)**		
			Pituitary tumours (%): Mice that died spontaneously or were killed when moribund in the SS and the lifespan study groups (0–27 mo, 28–33 mo):	*$P < 0.001$ vs controls, Fisher exact test	
		Control (AL)	17/75 (22.7%), 31/40 (77.5%)		
		40% DR	0/50 (0%)*, 2/50 (4%)*		
$B6C3F_1$ (F) Weanling 266/group SS at 12–36 mo, or lifelong Sheldon et al. (1995)	Spontaneous neoplasms	NIH-31 open formula diet, fed AL or 40% DR from age 4 wk; SS at 12, 18, 24, 30, 36 mo	Pituitary tumours: Mice SS at 24 mo, 30 mo, 36 mo:	NS	
		Control (AL)	0/41, 4/15, 3/14		
		40% DR	0/42, 1/15, 0/15		
			Pituitary tumours (%): Mice that died spontaneously or were killed when moribund in the SS and the lifespan study groups (0–27 mo, 28–33 mo, 34–39 mo):	*$P < 0.001$ vs controls, Fisher exact test	
		Control (AL)	3/56 (5.4%), 13/95 (13.7%), 15/36 (41.7%)		
		40% DR	0/10 (0%), 0/23 (0%)*, 1/49 (2.0%)*		

Table 3.15 (continued)

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
$B6D2F_1$ (F) Weanling 4 wk 56/group Lifelong Sheldon et al. (1996)	Spontaneous neoplasms	NIH-31 open formula diet, fed AL or 40% DR Control (AL) 40% DR	Pituitary tumours: 17% 0%	NR	
Rat					
F344 (F, M) 4 wk 54/group SS at 18–30 mo, or lifelong Thurman et al. (1994)	Spontaneous neoplasms	NIH-31 open formula diet, fed AL or 40% DR, from age 14 wk Control (AL) 40% DR Control (AL) 40% DR	Pituitary tumours: Mice SS at 18 mo, 24 mo, 30 mo: **F:** 3/10, 11/12, 11/12 **M:** 6/10, 9/11, 9/9 **F:** 0/10, 4/12*, 4/12* **M:** 2/12, 3/12**, 7/12 Pituitary tumours: Mice that died spontaneously or were killed when moribund: **F:** 118/160, **M:** 92/128 **F:** 60/137*, **M:** 55/152*	*$P < 0.01$, **$P < 0.05$ vs controls, Fisher exact test *$P < 0.01$ vs controls, χ^2 test	Mean age at death of 40% DR rats bearing pituitary tumours was higher compared with AL rats in both sexes

Table 3.15 (continued)

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Sprague-Dawley [Crl:CD® (SD) BR] (F, M) 36 d 70/group 106 wk Keenan et al. (1995)	Spontaneous neoplasms	Purina Certified Rodent Chow 5002 (energy value: 3.07 kcal/g) or 5002-9 (energy value: 2.36 kcal/g), fed at various regimens Chow 5002: Control (AL) DR 6.5 h (AL for 6.5 h) 35% DR Chow 5002-9: Control (AL) DR (fed at the same calorie intake as rats fed 65% DR chow 5002)	Pituitary adenoma: **F:** 50/70, **M:** 40/70 **F:** 49/70, **M:** 32/70 **F:** 47/70, **M:** 28/70* **F:** 55/70, **M:** 37/70 **F:** 31/70*, **M:** 19/70**	 — NS *$P < 0.05$ vs controls, χ^2 test NS *$P < 0.001$, **$P < 0.01$ vs controls, χ^2 test	No difference in incidence of pituitary focal hyperplasia between groups
F344 (M) 32 d 6–8/group 9 wk Shull et al. (1998)	Silastic tubing implants containing 5 mg of DES, s.c. at age 39 d; animals killed 8 wk after DES	Ingredient diet, fed AL or 40% DR Control (AL) 40% DR	Prolactin-producing pituitary tumour: Fold increase of the weight vs DES-untreated counterparts; pituitary-to-bw ratio (bw ± SD): 11.2-fold, 55.8×10^{-5} (125 ± 7 g) 3.5-fold*, 18.4×10^{-5} (80 ± 3 g)	*$P < 0.05$ vs controls	Pituitary weight was measured as a quantitative indicator of estrogen-induced pituitary development DES treatment reduced the food intake and thus bw by ~50% in both AL and DR groups

Table 3.15 (continued)

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Holtzman (M) 32 d 6–8/group 9 wk Shull et al. (1998)	Silastic tubing implants containing 5 mg of DES, s.c. at age 39 d; animals killed 8 wk after DES	Ingredient diet, fed AL or 40% DR Control (AL) 40% DR	Prolactin-producing pituitary tumour: Fold increase of the weight vs DES-untreated counterparts; pituitary-to-bw ratio (bw ± SD): 5.3-fold, 31.6×10^{-5} (263 ± 10 g) 4.1-fold, 30.2×10^{-5} (175 ± 5 g)	NS	Pituitary weight was measured as a quantitative indicator of estrogen-induced pituitary development DES treatment reduced the food intake and thus the bw by ~40% in both AL and DR groups
F344 (F-OVX) 57 d 5–8/group 11 wk Spady et al. (1998)	Silastic tubing implants containing 27.5 mg of E2, by s.c. injection at age 63 d; animals killed 10 wk after E2	Ingredient diet, fed AL, 25% DR, or 40% DR Control (AL) 25% DR 40% DR	Prolactin-producing pituitary tumour: Fold increase of the weight vs E2-untreated counterparts: 4.9-fold 4.1-fold 2.0-fold*	*$P < 0.05$ vs controls	Pituitary weight was measured as a quantitative indicator of estrogen-induced pituitary development
ACI (F-OVX) 35 d 12/group 22 wk Spady et al. (1999)	Silastic tubing implants containing 27.5 mg of E2, s.c. at age 45 d; animals killed 20 wk after E2	Ingredient diet, fed AL or 40% DR Control (AL) 40% DR	Prolactin-producing pituitary tumour: Fold increase of the weight vs E2-untreated counterparts; pituitary-to-bw ratio (bw): 5.3-fold, 31.6×10^{-5} (160 g) 4.1-fold, 30.2×10^{-5} (85 g)	NS	Pituitary weight was measured as a quantitative indicator of estrogen-induced pituitary development E2 treatment reduced the bw by 22% in AL rats and 21% in DR rats, vs respective untreated groups

Table 3.15 (continued)

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention (if not until termination of study)	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
COP (F-OVX) or ACI (F-OVX) 35 d 12/group 13 wk Harvell et al. (2001)	Silastic tubing implants containing 27.5 mg of E2, s.c. at age 45 d; animals killed 12 wk after E2	Ingredient diet, fed AL or 40% DR	Prolactin-producing pituitary tumour: Fold increase of the weight vs E2-untreated counterparts:	NR	Pituitary weight was measured as a quantitative indicator of estrogen-induced pituitary development
		COP			
		Control (AL)	2.4-fold		
		40% DR	1.5-fold		
		ACI			
		Control (AL)	3.4-fold		
		40% DR	4.5-fold		

AL, ad libitum; bw, body weight; d, day or days; DES, diethylstilbestrol; DR, dietary restriction; E2, 17β-estradiol; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; NS, not significant; OVX, ovariectomized; s.c.; subcutaneous; SD, standard deviation; SS, scheduled-sacrificed; vs, versus; wk, week or weeks.

as less informative and are considered to provide only supporting evidence.]

3.3.7 Cancer of the prostate

See Table 3.16.

Several rat models have been used to evaluate the effects of DR on prostate cancer development. Only one early study reported the effect of DR on spontaneous prostate cancer development in rats. Lobund-Wistar rats raised in conventional or germ-free conditions were followed up for up to 41 months. Rats subjected to 30% DR and raised in conventional conditions had reduced incidence of prostate adenocarcinoma compared with the AL rats (6% vs 26%), but among rats raised in germ-free conditions, the incidence was higher in the 30% DR rats than in the AL rats (10% vs 5%), although the overall incidence of prostate cancer was reduced for rats raised in germ-free conditions compared with those raised in conventional conditions (Pollard et al., 1989).

In a carcinogen-induced prostate cancer model, Wistar-Unilever rats were treated with the luteinizing hormone-releasing antagonist cyproterone, followed by treatment with testosterone, followed by administration of MNU to induce prostate cancer. Rats subjected to 20% DR had longer prostate cancer-free survival compared with AL rats, and this was accompanied by reduced body weight (Boileau et al., 2003). However, in a similar study, no effect of 15% DR or 30% DR on incidence of prostate cancer was reported, and DR did not reduce body weight gain (McCormick et al., 2007).

Transgenic models have also been used to determine the effect of DR on the development of prostate cancer in rodents. In the probasin/SV40 T antigen transgenic rat model, 30% DR had no effect on incidence of PIN or of adenocarcinoma but significantly reduced the percentage ratio of the epithelial area to the whole prostate area (which included PIN and tumour cells) (Kandori et al., 2005). There was reduced weight gain due to DR. [The Working Group noted the difficulty in performing morphometric measures in the prostate gland.]

Another model has been the TRAMP mouse. When TRAMP mice were subjected to 20% DR from age 7 weeks for 4 weeks or 13 weeks, lesions of a lower grade were reported compared with AL mice [no body weight information was provided] (Suttie et al., 2003). In a second study from the same group, 20% DR was not implemented until age 20 weeks and had no effect on survival or lesion severity [body weight data were not presented] (Suttie et al., 2005). In an additional study using TRAMP mice, two different modes of DR were used, with the same overall degree of restriction, i.e. 25% DR (Bonorden et al., 2009a, b). Mice that received IDR – 2 weeks of 50% DR with 2 weeks of AL feeding, for 11 cycles – had delayed time to prostate tumour detection, compared with both AL and 25% DR mice. Body weights were lower in the 25% DR mice than in the AL mice. [Although the findings are of interest, the Working Group noted the strong influence of the transgene as the mice age, thus possibly limiting the model's usefulness for evaluating the effect of DR on prostate cancer development.]

The Hi-Myc mouse model was also used to assess the effects of 30% DR or a HFD (60% fat) implemented at age 6 weeks compared with an AL group. At age 26 weeks, the incidence of prostate adenocarcinomas was 62% in the AL mice, compared with no tumours observed in the 30% DR group (Blando et al., 2011).

3.3.8 Cancers of the haematopoietic system

(a) Lymphoma

See Table 3.17.

Two lifespan studies in male B10C3F$_1$ (Weindruch & Walford, 1982) and C57BL/6 mice (Volk et al., 1994) started DR at age 45–50 weeks and assessed incidence of malignant lymphoma. DR (44% DR or 25% DR) significantly increased

Table 3.16 Studies on the prevention of tumours of the prostate by dietary/calorie restriction in rats and mice

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Rat					
Lobund-Wistar (M) Weanling *n* = 100 up to 41 mo Pollard et al. (1989)	Spontaneous tumours in either conventional or germ-free housing	Cereal-based L-485 30% DR for 6, 18, 30 mo or > 30 mo	Prostate adenocarcinoma: Conventional AL, 26%; 30% DR, 6%* Germ-free AL, 5%; 30% DR, 10%	[*$P < 0.008$, Fisher exact test, 2-tailed]	A second study (Snyder et al., 1990), with the same design, reported similar results: 22%, 7% [NS], 7%, 6%
Wistar-Unilever (M) 6 wk *n* = 194 age 73 wk Boileau et al. (2003)	Cyproterone, 4 weekly i.p. injections; then testosterone, daily i.p. injection; then MNU, 50 mg/kg bw, at age 9 wk	AIN-93M for 4 wk; then half of all rats given 20% DR	Prostate adenocarcinoma: Cancer-free survival at 50 wk: AL, 35%; 20% DR, 52%	$P = 0.03$	Lower bw in DR rats than in AL rats Additional groups fed lycopene or tomato supplements AL or at 20% DR
Probasin/SV40 T antigen transgenic on Sprague-Dawley background (M) 6 wk *n* = 40 13 wk Kandori et al. (2005)	Probasin/SV40 T antigen	NIH-07 (soybean-free) 30% DR	Adenocarcinoma: Ratio of epithelial area to whole prostate area	NS $P < 0.01$ for ventral, lateral, or dorsal prostate	100% incidence of PIN in all groups Small *n* values; bw significantly lower in 30% DR group vs controls
Wistar-Unilever (M) 7–8 wk *n* = 159 52 wk McCormick et al. (2007)	Cyproterone, oral gavage for 21 d; then testosterone, daily s.c. for 3 d; then MNU, 30 mg/kg bw, at age ~12 wk	Purina 5001 laboratory chow 15% DR 30% DR	Prostate adenocarcinoma: Control, 74% 15% DR, 64% 30% DR, 72%	NS	30% DR had no effect on bw
Mouse					
TRAMP on C57BL6 background (M) 7 wk *n* = 10 13 wk Suttie et al. (2003)	TRAMP mice	NTP-2000 20% DR for 4 wk or 13 wk	Lower grade of lesions: 11 wk: ventral***, lateral***, dorsal***, and anterior** lobes 20 wk: ventral, lateral**, dorsal***, and anterior* lobes	*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, Mann–Whitney *U* test	

Table 3.16 (continued)

Species, strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
TRAMP on C57BL6 background (M) 20 wk *n* = 10 19 wk Suttie et al. (2005)	TRAMP mice	NTP-2000 20% DR for 4 wk, 12 wk, or 19 wk	No effect on grade of lesions Survival at 19 wk: AL, 75%; DR, 90%	NS NS	[Model not adequate for studying prostate cancer at later age]
TRAMP on C57BL6 background (M) 5 wk *n* = 130 48–50 wk Bonorden et al. (2009a)	TRAMP mice	Ain-93M fed AL, 25% DR, or 25% IDR (50% DR for 2 wk, then AL for 2 wk for 11 cycles)	Adenocarcinoma: Latency to detection: AL, 33 wk; 25% DR, 35 wk; IDR, 38 wk	$P < 0.006$, IDR vs AL $P = 0.39$, DR vs AL	Bw of DR mice fairly constant, whereas that of IDR mice fluctuated See also cross-sectional study by Bonorden et al. (2009b)
Hi-Myc FVB/N (M) 6–8 wk *n* = 36 age 26 wk Blando et al. (2011)	Transgenic Hi-Myc mice	AIN76A, fed AL, 30% DR, or HFD (60% fat)	Prostate invasive adenocarcinoma: AL, 62%; DR, 0%*; HFD, 97% Prostate in situ carcinoma: AL, 100%; DR, 38%*; HFD, 100%	*$P = 0.0001$, DR vs AL or HFD	[Values read from graph]

AL, ad libitum; bw, body weight; d, day or days; DR, dietary restriction; F, female; HFD, high-fat diet; IDR, intermittent dietary restriction; i.p., intraperitoneal; M, male; mo, month or months; MNU, *N*-methyl-*N*-nitrosourea; NR, not reported; NS, not significant; PIN, prostatic intraepithelial neoplasia; TRAMP, transgenic adenocarcinoma of the mouse prostate; vs, versus; wk, week or weeks.

Table 3.17 Studies on the prevention of lymphomas by dietary/calorie restriction in mice

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
B10C3F$_1$ (M) 45–50 wk 67–68/group Lifelong Weindruch & Walford (1982)	Spontaneous neoplasms	Semi-purified diet, fed AL or 44% DR with supplementation, from age 12–13 mo Control (160 kcal/wk) 44% DR (90 kcal/wk)	Lymphoma (%); mean lifespan with lymphoma: 47%, 31.9 mo 31%#, 36.2 mo*	#NS ($P < 0.08$) *$P < 0.01$, *t* test	Animals were killed when moribund
C57BL/6 (M) 45 wk 60–72/group Age 25 mo Volk et al. (1994)	Spontaneous neoplasms	AL or 25% DR, from age 12 mo Control (AL) 25% DR	Lymphoma (%): 14/72 (19%) 3/60 (5%)*	*$P < 0.05$, χ^2 test	
C57BL6 (F, M) 4 wk 266/group SS at 12–36 mo, or lifelong Blackwell et al. (1995)	Spontaneous neoplasms	NIH-31 open formula diet, fed AL or 40% DR. Mice were SS at 12, 18, 24, 30, and 36 mo, or necropsied when died spontaneously or were killed when moribund Control (AL) 40% DR	Lymphoma: Mice SS at 0–24 mo, 30 mo: **F:** 11/43, 5/14 **M:** 2/43, 2/14 **F:** 3/44*, 0/15 **M:** 2/44, 0/15	*$P < 0.05$ vs controls, Fisher exact test	SS mice were combined because of the low incidence of lymphoma
			Lymphoma (%): Mice that died spontaneously or were killed when moribund in the SS and the lifespan study groups (0–33 mo): Control (AL) 40% DR	*$P < 0.01$ vs controls, χ^2 test **F:** 35/115 (29.6%) **M:** 12/156 (7.7%) **F:** 13/100 (13%)* **M:** 9/106 (8.5%)	

Table 3.17 (continued)

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Blackwell et al. (1995) (cont.)			Histiocytic sarcoma: SS at 0–24 mo, 30 mo:	NS	
		Control (AL)	**F:** 1/43, 5/14 **M:** 1/43, 4/14		
		40% DR	**F:** 3/44, 3/15 **M:** 1/44, 5/15		
			Histiocytic sarcoma (%): Mice that died spontaneously or were killed when moribund in the SS and the lifespan study groups (0–27 mo, 28–33 mo):	*$P < 0.001$ vs controls, Mantel–Haenszel χ^2 test	
		Control (AL)	**F:** 19/75 (25%), 18/40 (45%) **M:** 34/83 (41%), 54/73 (74%)		
		40% DR	**F:** 20/50 (40%), 27/50 (54%) **M:** 9/32 (28.1%), 31/74 (41.9%)*		
$B6C3F_1$ (F, M) 4 wk 266/group SS at 12–36 mo, or lifelong Sheldon et al. (1995)	Spontaneous neoplasms	NIH-31 open formula diet, fed AL or 40% DR. Mice were SS at 12, 18, 24, 30, and 36 mo, or necropsied when died spontaneously or were killed when moribund	Lymphoma (%): SS at 30 mo, 36 mo:	NS	Incidence of malignant lymphoma during the period 0–24 mo was < 3% in F and M mice of AL and DR groups
		Control (AL)	**F:** 4/15 (26.7%), 9/14 (64.3%) **M:** 3/15 (20.0%), 6/15 (40.0%)		
		40% DR	**F:** 0/15 (0%), 1/15 (6.7%) **M:** 0/15 (0%), 0/15 (0%)		
			Lymphoma (%): Mice that died spontaneously or were killed when moribund in the SS and the lifespan study groups (0–27 mo, 28–40 mo):	NS	
		Control (AL)	**F:** 24/56 (42.9%), 84/161 (52.2%) **M:** 8/39 (20.5%), 46/118 (39%)		

Table 3.17 (continued)

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
Sheldon et al. (1995) (cont.)		40% DR	**F:** 2/10 (20%), 28/72 (38.9%) **M:** 0/7 (0%), 13/45 (28.9%)		
			Histiocytic sarcoma (%): Mice that died spontaneously or were killed when moribund in the SS and the lifespan study groups (27–33 mo, 28–40 mo):	NS	
		Control (AL)	**F:** 7/95 (7.4%), 4/36 (11.1%) **M:** 9/68 (13.2%), 5/50 (10%)		
		40% DR	**F:** 3/23 (13%), 3/49 (6.1%) **M:** 4/12 (33%), 5/33 (15%)		
$p53^{-/-}$, $p53^{+/+}$ [94% C57BL/6, 6% 129/Sv] (M) 4–7 wk 28–30/group Lifelong Hursting et al. (1997)	Spontaneous neoplasms	AIN-76A diet, fed AL or 40% DR from 6–9 wk, lifelong	Lymphoma; mean time to death by lymphoma (*n*):	*$P < 0.05$ vs controls	Median time to death: 16 wk in $p53^{-/-}$ AL, 25 wk in $p53^{-/-}$ DR; 68 wk in $p53^{+/+}$ AL, 102 wk in $p53^{+/+}$ DR
		Control (AL)	$p53^{-/-}$: 17/30, 110 ± 50 d (16) $p53^{+/+}$: 4/30, 384 ± 187 d (4)		
		40% DR	$p53^{-/-}$: 19/28, 162 ± 59 d (16) $p53^{+/+}$: 6/30, 679 ± 198 d* (6)		
$p53^{+/-}$ C57BL6 (M) 10.5 mo 31–32/group 12.5 mo Berrigan et al. (2002)	Spontaneous neoplasms	AIN-76A diet, fed AL or 40% DR, or 1 d/wk fast (14% DR)	Number of mice that died from lymphoma/effective number of mice; mean lifespan:	*$P = 0.001$, **$P = 0.039$ vs AL group, Cox proportional hazards analysis (1-tailed)	Mean bw: ~50 g in AL, 27 g in 40% DR, 38 g in 1 d/wk fast
		Control (AL) 40% DR 1 d/wk fast (14% DR)	17/32, 313 ± 17 d 15/31, 388 ± 23 d* 15/31, 357 ± 23 d**		

AL, ad libitum; bw, body weight; d, day or days; DR, dietary restriction; F, female; M, male; mo, month or months; NS, not significant; SS, scheduled-sacrificed; vs, versus; wk, week or weeks.

the mean lifespan of mice with lymphoma or reduced the incidence of lymphoma.

In another study (Blackwell et al., 1995), the incidence of spontaneous malignant lymphoma was significantly lower in the female 40% DR group than the female AL group at 24 months and 30 months; however, there was no difference between the male 40% DR and AL groups. [Lymphoma incidence in male AL mice was substantially lower than that in female AL mice.]

In the same study, the incidence of histiocytic sarcoma [diffuse large B-cell lymphoma] in scheduled-sacrificed mice did not differ significantly between the 40% DR and AL groups in either male or female mice. However, the incidence of histiocytic sarcoma in mice that died spontaneously or were killed when moribund was significantly lower in the male DR group compared with the male AL group (Blackwell et al., 1995). [The Working Group noted that the study provided separate results for scheduled-sacrificed and moribund animals, which makes evaluation of the effect difficult.]

In another study in male and female $B6C3F_1$ mice, the incidence of malignant lymphoma was lower than 3% up to 24 months in both AL and 40% DR groups (Sheldon et al., 1995). At age 30 months and 36 months, the incidence was greater than 20% in both female and male AL mice, whereas it remained at mostly 0% in 40% DR mice. In mice that died spontaneously or were killed when moribund during the periods of 0–27 months and 28–40 months, the incidence was lower in the DR groups than in the AL groups of male and female mice, although the difference was not statistically significant. No difference was observed for histiocytic sarcomas.

Tp53-deleted mice display earlier occurrence of spontaneous neoplasms, including malignant lymphoma (Hursting et al., 1994). The incidence of malignant lymphoma in necropsied *Tp53*$^{-/-}$ mice subjected to 40% DR did not differ from that in their AL counterparts, but the mean time to death by lymphoma was longer in the 40% DR group than in the AL group (Hursting et al., 1997). In another study, p53$^{+/-}$ mice prone to malignant tumours including lymphoma (mostly histiocytic sarcoma) were subjected to adult-onset 40% DR (Berrigan et al., 2002). The mean lifespan was longer in the 40% DR group than in the AL group. Even with 1 day of fasting per week followed by AL feeding, the regimen reduced the body weight to 76% of that of the AL group and extended the lifespan, although the effect was modest ($P = 0.039$) compared with that observed in the 40% DR group.

(b) Leukaemia

See Table 3.18.

In long-term studies, F344 rats (particularly F344/N) often develop leukaemia, mostly mononuclear (large granular) cell leukaemia.

The incidence of leukaemia in rats killed at 24 months and 30 months did not differ between AL and 40% DR groups of male and female rats (Thurman et al., 1994). The proportion of rats bearing leukaemia that died spontaneously or were killed when moribund seemed to be greater in the 40% DR groups of male and female rats. However, the mean ages at death in rats found dead or killed when moribund were higher in the 40% DR groups of male and female rats than in the AL groups. [The number of animals may have been too small to allow relevant statistics; also, leukaemia incidence may have been increased in the DR rats because they lived longer.]

Peto et al. (1980) and Gart et al. (1986) have addressed the biases inherent to long-term animal studies in which lifespan is extended by an intervention such as DR, and have described statistical analyses to circumvent the problem. By following their statistical procedures, Shimokawa et al. (1996) estimated that the onset rate of leukaemia in F344 rats was reduced by 20% in the 40% DR rats compared with the AL animals.

Pathological data of F344/N rats generated in the National Toxicology Program study of butyl benzyl phthalate (NTP, 1997) indicated

Table 3.18 Studies on the prevention of leukaemia by dietary/calorie restriction in rats

Strain (sex) Age at start Number of animals Duration of study Reference	Route, dose, and duration of carcinogen administration	Type of diet, dosing regimen, and duration of intervention	Type of tumours: Tumour incidence (number of tumours/effective number of animals, and/or percentage), multiplicity, or other outcomes as specified	Statistical significance	Comments
F344 (F, M) 4 wk 54/group Lifelong Thurman et al. (1994)	Spontaneous neoplasms	NIH-31 open formula diet, fed AL or 40% DR gradually implemented over 2 wk from age 14 wk Control (AL) 40% DR	Leukaemia (%) at 24 mo, 30 mo: **F:** 1/12 (8.3%), 7/12 (58.3%) **M:** 6/12 (50%), 5/9 (55.6%) **F:** 4/12 (33.3%), 3/12 (25%) **M:** 7/12 (58.3%), 6/12 (50%)	NS	
F344 (M) 6 wk 153 or 155/group Shimokawa et al. (1996)	Spontaneous neoplasms	Semi-synthetic diet, fed AL or 40% DR Control (AL) 40% DR	Leukaemia (%); relative onset rate: 38/111 (34.2%), 1.00 39/89 (43.8%), 0.80*	*$P < 0.05$, Peto test	The relative onset rate, defined by Peto et al. (1980), is a descriptive index useful in determining whether a dietary modulation influences the occurrence of a neoplasm. The expected number of rats with leukaemia/lymphoma was calculated by analysing the death rate and the prevalence rate separately.
F344/N (F, M) 6 wk 60/group 104 wk NTP (1997)	Spontaneous neoplasms	NIH-07 open formula diet, fed AL; **M:** 20% DR between 14 wk and 52 wk and 7% DR between 53 wk and 101 wk; **F:** 25% DR between 14 wk and 52 wk and 30% DR between 53 wk and 104 wk Control (AL) Weight-matched control of a carcinogen testing protocol (7–30% DR) from 14 wk to 104 wk	Leukaemia (mostly mononuclear cell leukaemia); adjusted rate: **F:** 21/50, 51.7% **M:** 31/50, 71.8% **F:** 13/50, 28.6% **M:** 15/50*, 34.9%	*$P < 0.01$	Adjusted rate: Kaplan–Meier-estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

AL, ad libitum; DR, dietary restriction; F, female; F344, Fischer 344; M, male; mo, month or months; NS, not significant; NTP, National Toxicology Program; wk, week or weeks.

a reduction in the incidence of leukaemia in F344 rats in which daily feed allocations were restricted to 7–30% less than that of untreated AL rats, to weight-match the animals. When the rates were adjusted for intercurrent mortality, the Kaplan–Meier-estimated incidences of leukaemia were approximately 50% less than those in AL animals.

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4. MECHANISTIC AND OTHER RELEVANT DATA

4.1 Introduction

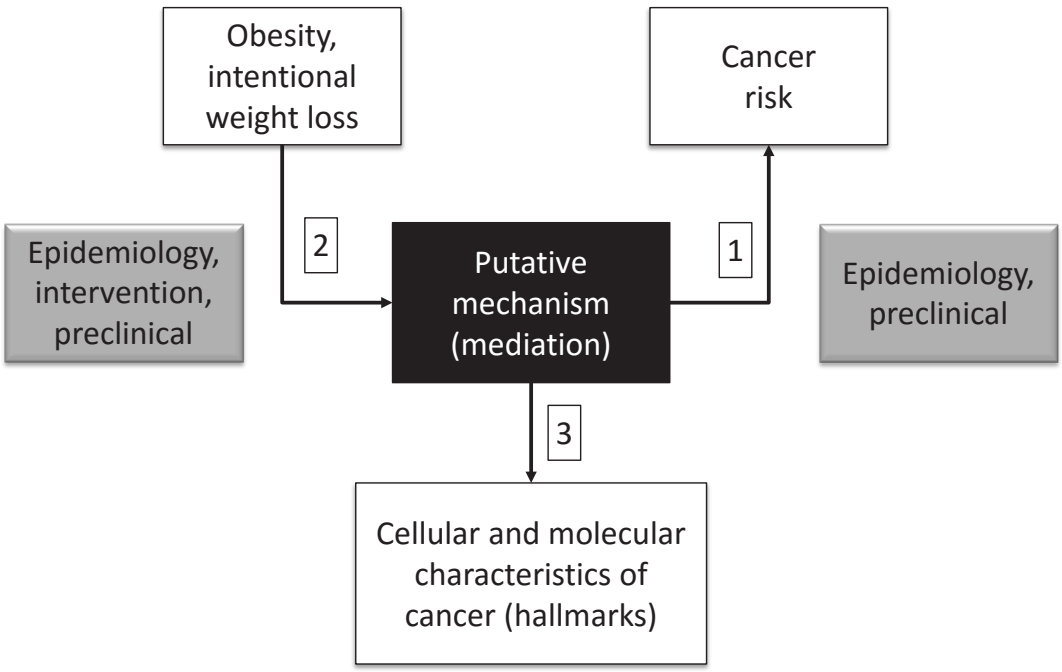
The goal of this section is to assess which cellular and molecular processes known to be dysregulated during the carcinogenesis process are causally linked with obesity and, when sufficient data are available, to identify the organ sites for which cancer risk is increased. This assessment, based primarily on data on obesity, was extended to consider whether the dysregulation observed in obesity was reversed by intentional weight loss (IWL). With evidence of resolution, the argument for a causal association was considered to be strengthened. There are two approaches to IWL with demonstrated efficacy in reducing body mass in obese individuals, i.e. dietary/energy restriction and bariatric surgery. For the purposes of this assessment, the term dietary restriction (DR) will be adopted to include both dietary and energy (calorie) restriction.

The framework for this evaluation resulted from the integration of the key characteristics of carcinogenic agents used for identifying and evaluating carcinogenic mechanisms in the IARC Monographs (Smith et al., 2016), the concepts arising from genome projects (Vogelstein et al., 2013), and the characteristics of cancer referred to as cancer hallmarks (Hanahan & Weinberg, 2000, 2011).

The approach used to evaluate the evidence that a particular factor mediates the effects of obesity on cancer development is shown in Fig. 4.1. Briefly, evidence must exist (i) that the factor plays a significant role in the carcinogenic process (arrow 1 in Fig. 4.1), (ii) that obesity exerts an effect on that factor (arrow 2), and (iii) that the factor affects the processes that regulate cell proliferation, cell death, and/or angiogenesis with an identifiable molecular basis for the observed changes in those processes (arrow 3). Although this approach is based on the traditional concept of mediation, it distinguishes itself by extending the assessment to hallmarks of cancer and their molecular underpinnings.

Factors were grouped as being operative within the target cell (i.e. intracellular factors) or as external factors to which target cells are exposed (i.e. host factors). Within the intracellular category, the key characteristics related to electrophilic and metabolically activated carcinogens of exogenous and endogenous origin, the damage they cause, and the mutations induced (Smith et al., 2016) are considered not individually but rather from the perspective of those mutations that confer a selective growth advantage to a cell (i.e. driver mutations) versus those that do not (i.e. passenger mutations) (Vogelstein et al., 2013); also considered within the intracellular category are other key characteristics (Smith et al., 2016) that contribute to the emergence of driver mutations and their expression, including oxidative stress, epigenetic alterations and various aspects of DNA repair. This assessment emphasized the cancer hallmarks related

Fig. 4.1 Diagram of the paradigm used to establish the mechanisms that mediate the effects of obesity on cancer risk



Compiled by the Working Group.

to the dysregulation of the balance between cell proliferation and cell death, clonal expansion, and angiogenesis.

The host factors considered in this section are related to small molecules involved in energy metabolism and macromolecular synthesis, mediators involved in inflammation, and those factors that exert their effects via cell surface receptors (growth factors, sex hormones, and cytokines) (receptor-mediated effects). With regard to the small molecules, many of which can be considered as energy substrates, the approach was inclusive of the microbiome and of the intracellular energy sensors that integrate extracellular and intracellular signals by affecting the processes that drive clonal expansion and selection and disease progression. Most of the factors considered are shown in Fig. 4.2.

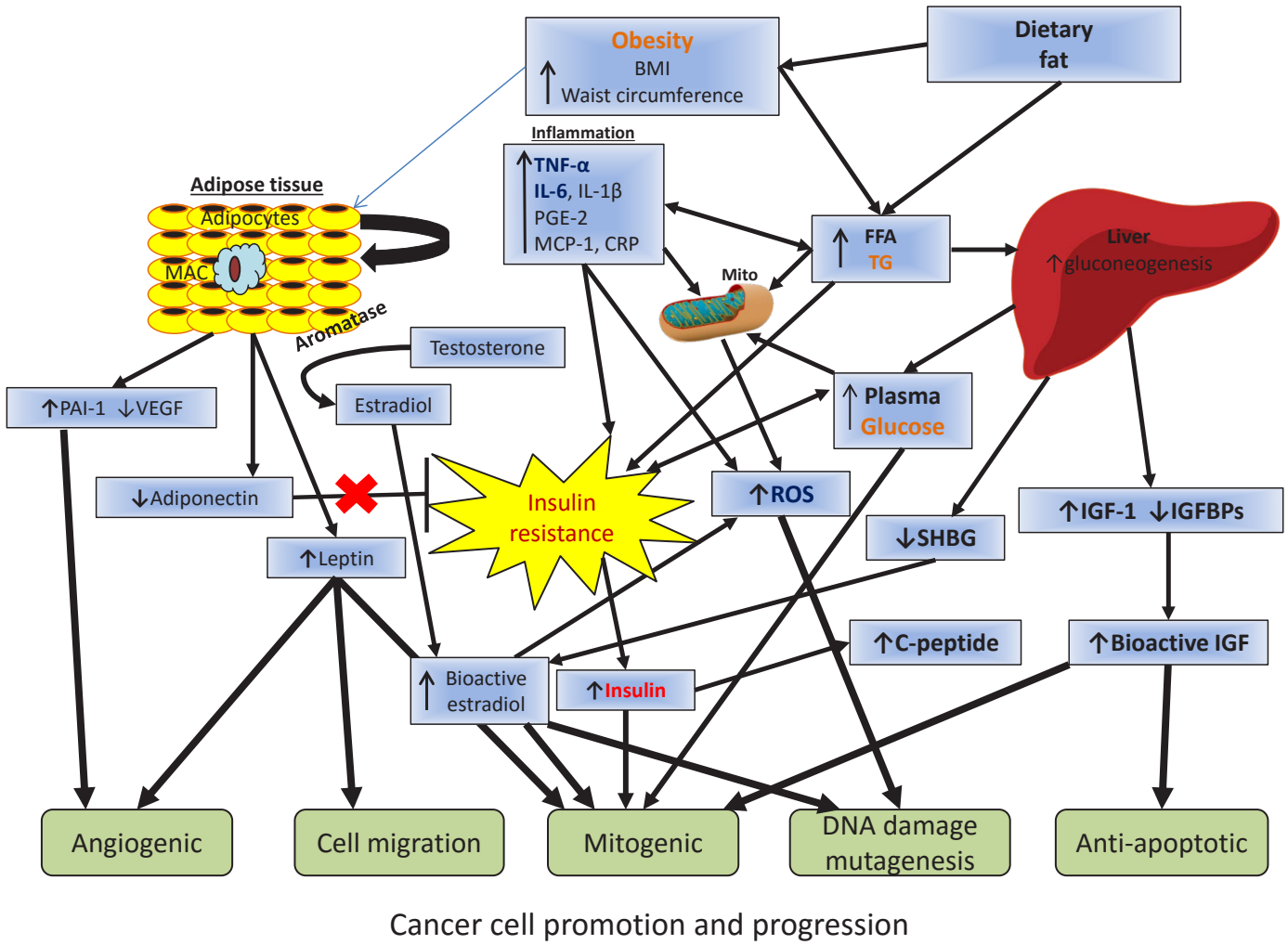
4.2 Intracellular factors

Within the approach outlined in Section 4.1, the findings are presented by the strength of the evidence of an effect of obesity or IWL on those factors.

4.2.1 Cell proliferation, apoptosis, and angiogenesis

Because the time frame for the development of obesity and cancer is long and the imbalance between cell proliferation and cell death is small at any snapshot in time (Bozic et al., 2010), evaluation of the impact of obesity on these factors is problematic, even though their involvement in obesity-induced carcinogenesis is obligatory. The impact of IWL, particularly via bariatric surgery, provides an opportunity to gain insight into how these processes are regulated in the situation of negative energy balance.

Fig. 4.2 Summary of mechanisms underlying the obesity–cancer link



Factors denoted in bold red text are established features of the obesity–cancer connection. Factors denoted in bold blue text are emerging features.
BMI, body mass index; CRP, C-reactive protein; FFA, free fatty acids; IGF, insulin-like growth factor; IGFBP, IGF binding protein; IL, interleukin; MAC, macrophage; MCP-1, monocyte chemoattractant protein 1; Mito, mitochondria; PAI-1, plasminogen activator inhibitor 1; PGE2, prostaglandin E2; ROS, reactive oxygen species; SHBG, sex hormone-binding globulin; TG, triglycerides; TNF-α, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.
Compiled by the Working Group.

(a) Cell proliferation

The effect of IWL on neoplasia-associated cell proliferation has received little attention in intervention studies, and the evidence is limited to effects of bariatric surgery. Whereas IWL via bariatric surgery, including the Roux-en-Y gastric bypass, resulted in a reduction in endometrial hyperplasia (Argenta et al., 2013; Modesitt et al., 2015), proliferation was reported to be increased after Roux-en-Y gastric bypass or jejunoileal bypass surgery in the rectum (Appleton et al., 1988; Sainsbury et al., 2008; Kant et al., 2011); however, when a sleeve gastrectomy was used, hyperproliferation was not observed in the rectal mucosa (Kant et al., 2014). Although the reduction in endometrial hyperplasia is consistent with reduced risk of endometrial cancer, the question of how the hyperproliferative state would affect the risk of cancer of the colon and rectum has been identified as a concern (Appleton et al., 1988; Sainsbury et al., 2008; Kant et al., 2011).

Another question of interest is how the regulation of cell cycle machinery, which ultimately accounts for effects on the magnitude of cell proliferation observed in a tissue, is affected by IWL; however, that specific question has not been addressed in IWL intervention studies in humans or rodents. What has been done in experiments in rodents is to investigate the effects of DR, which is protective against cancer (see Section 3) and has been reported to decrease cell proliferation in mammary tumours (Zhu et al., 1999b; Jiang et al., 2003). Briefly, the studies focused on factors that regulate the G1/S transition, which appears to be a target when energy availability is limited by DR (Jiang et al., 2003). Observed effects included reductions in levels of phosphorylated retinoblastoma protein and the transcription factor E2F1, decreased activity of cyclin-dependent kinase 2 (CDK2) and CDK4, increased concentrations of the CDK inhibitors Cip1/p21 and Kip1/p27, increased levels of these proteins complexed with CDK2, and increased binding of p16 and p19 to CDK4 (Zhu et al., 1999a; Jiang et al., 2003). In addition, DR reduced epidermal proliferation during tumour promotion in mice (Azrad et al., 2011), and endometrial cancer cells grown in sera obtained from women randomized to calorie restriction were less mitogenic than cells grown in sera obtained from overweight women (Moore et al., 2012).

(b) Apoptosis

Intervention studies of IWL that evaluated apoptosis end-points in cancer were not identified. Therefore, studies in rat and mouse models with cancer-related end-points were reviewed. A dose-dependent relationship between DR and elevated rates of apoptosis has been reported (Zhu et al., 1999b; Thompson et al., 2004a; Tomita, 2012; Olivo-Marston et al., 2014). DR induced a pro-apoptotic state via the coordinated regulation of pro- and anti-apoptotic factors involved in the mitochondrial pathway of caspase activation (Thompson et al., 2004a). Specifically, complementary DNA (cDNA) microarray analysis identified the *Bcl-2*, *CARD*, and *IAP* functional gene groupings as being involved in induction of apoptosis. Consistent with the microarray data, the activities of caspases 9 and 3 were observed to be 2-fold higher in carcinomas from DR rats, whereas the activity of caspase 8 was similar in carcinomas from DR animals and those fed ad libitum. Collectively, this evidence indicated that DR-induced apoptosis is mediated by the mitochondrial pathway.

(c) Angiogenesis

Studies of the effects of IWL on angiogenesis in the context of cancer in humans were not identified. However, studies have reported the effects of IWL via DR (Rizkalla et al., 2012; Cullberg et al., 2013) or bariatric surgery (Lemoine et al., 2012; Moreno-Castellanos et al., 2015) on circulating factors that reflect angiogenic drive and on gene and protein expression profiles in adipose tissue sampled before and after weight

loss. For either intervention approach, levels of circulating factors associated with angiogenesis, for example vascular endothelial growth factor A (VEGF-A) and angiopoietin 1 (ANG-1), are reduced by IWL, whereas the level of angiopoietin-like 4 (ANGPTL-4) is increased and the pattern of gene or protein expression in adipose tissue in response to IWL has been characterized as anti-angiogenic (Cullberg et al., 2013).

Reduction in tumour vascularization in response to DR has been reported in rodent models of cancer (Mukherjee et al., 2004; Thompson et al., 2004a; Higami et al., 2006; Powolny et al., 2008; Zhu et al., 2009; De Lorenzo et al., 2011; Kurki et al., 2012), and this has been shown to involve many of the same factors identified in the clinical studies. These factors play roles at different stages of the angiogenic process, which can be divided into endothelial proliferation and migration, blood coagulation, fibrinolysis, and the degradation of basement membranes and the extracellular matrix.

(d) Synthesis

Alteration of cell proliferation, apoptosis, and angiogenesis are key characteristics of carcinogenesis, and their necessary involvement in the development of cancer is established. Available studies of IWL in humans and rodents, although limited in number, support the view that obesity dysregulates one or more of these processes, and that IWL can reverse these changes.

4.2.2 The mTOR network and other energy-sensor networks

Blood levels of amino acids, carbohydrates, and lipids – the primary substrates that are interconverted and metabolized to produce energy – are generally altered in obesity, and are reduced during IWL, whether it is achieved via bariatric surgery or DR (Thompson et al., 2012; Fabian et al., 2013; Modesitt et al., 2015). In addition, IWL exerts systemic effects by altering circulating concentrations of growth factors and hormones that affect cell function as well as the mechanisms that drive the carcinogenic process. These IWL-mediated intracellular and systemic effects are transduced to signalling pathways that regulate tissue growth and endothelial homeostasis via intracellular nutrient and energy sensors. Prominent among these pathways are those regulated by adenosine monophosphate (AMP)-activated protein kinase (AMPK)–mammalian target of rapamycin (mTOR)–protein kinase B (AKT), sirtuins, peroxisome proliferator-activated receptors (PPARs), and soluble guanylyl cyclase (sGC). Most of this discussion focuses on AMPK–mTOR–AKT (i.e. the mTOR network); the other pathways are briefly discussed, recognizing their likely involvement in mediating the effects of IWL.

(a) The mTOR network

IWL can inhibit tumour growth by suppressing the activation of the mTOR signalling network. In this network, mTOR plays a key role in integrating information received from the extracellular environment via the binding of growth factors and hormones with their cognate receptor tyrosine kinases (Gwinn et al., 2008). Suppression is mediated through the effects of restricted energy availability on concentrations of the circulating growth factors and hormones and of the substrates used in intermediary metabolism to synthesize high-energy phosphates and reducing equivalents. As a consequence, the drive for cell proliferation is reduced (Zhu et al., 1999a; Jiang et al., 2003; Moore et al., 2008; Lashinger et al., 2011; De Angel et al., 2013), a pro-apoptotic environment is maintained (Zhu et al., 1999b; Thompson et al., 2004a), and the stimulus for formation of new blood vessels is suppressed (Thompson et al., 2004b). One or more elements of the mTOR network are dysregulated in the majority of human cancers (Wood et al., 2007).

AMPK serves as a metabolic checkpoint, downregulating cell growth and cell division

in the absence of an adequate supply of biosynthetic and energy substrates (Gwinn et al., 2008). AMPK has been shown to be an exquisitely sensitive detector of small changes in the intracellular ratio of AMP to adenosine triphosphate (ATP), and some investigators have even proposed that AMPK plays a central role in homeostatic regulation of whole-body energy metabolism (Hardie, 2004).

IWL by bariatric surgery (Peng et al., 2010) and DR (Jiang et al., 2008, 2009) results in AMPK activation. This suggests that either energy availability alters substrate availability (the fuel mixture presented to tissues throughout the body) or activation is being induced via a mechanism independent of the AMP-to-ATP ratio. In this regard, it is clear that additional factors control the activation of AMPK, including various cytokines such as adiponectin (Kahn et al., 2005).

Limiting energy availability, for example by DR, has been reported to decrease circulating levels of insulin and insulin-like growth factor 1 (IGF-1) (Zhu et al., 2005; Jiang et al., 2008; Nogueira et al., 2012; Ford et al., 2013; Lashinger et al., 2013; Harvey et al., 2014; Olivo-Marston et al., 2014). Lower levels of these growth factors downregulate signalling via the pathway of which IGF-1 receptor (IGF-1R), phosphoinositide 3-kinase (PI3K), and AKT are components. Of these proteins, activated Akt, a serine/threonine kinase, is the critical effector molecule (Hursting et al., 2003).

(b) Sirtuins

Studies of the effects of IWL on histone deacetylase activity in the context of cancer in humans have not been identified. However, it is widely recognized that the activity of SIRT1 is lower in obesity and that sirtuins are activated by IWL in liver and adipose tissue (Moschen et al., 2013; Xu et al., 2013; Jukarainen et al., 2016; Rappou et al., 2016). Sirtuins play a significant role in altering gene expression, and recent studies have shown that activation or inhibition of histone deacetylases can alter the carcinogenic process (Ahmad et al., 2012; Guo & Zhang, 2012; Jiang et al., 2013; Ravillah et al., 2014; Busch et al., 2015).

(c) Peroxisome proliferator-activated receptors

PPARs are transcription factors that are activated by long-chain fatty acids and their oxidized metabolites, the oxylipins. There are three isoforms of PPARs (α, β/δ, and γ), each of which has tissue-specific distribution and activity (Georgiadi & Kersten, 2012; Janani & Ranjitha Kumari, 2015). Because the intracellular concentrations of PPARs are affected by obesity and IWL, they are considered to be energy sensors, and their activation or lack thereof regulates not only energy metabolism (lipid metabolism as well as glucose homeostasis) but also cell growth and differentiation (Cantó et al., 2015; Cetrullo et al., 2015; Cao et al., 2016).

Studies of the effects of IWL on PPAR expression in the context of cancer in humans were not identified. The expression of PPARγ1, which has been reported to be suppressed in subcutaneous adipose tissue in obesity, is restored by IWL induced by bariatric surgery (Leyvraz et al., 2012). Many reports in humans and rodents indicate that suppression of PPAR-related signalling constitutes a link between obesity and cancer and that pharmacological activation of PPARs is protective against cancer (Georgiadi & Kersten, 2012; Laplante & Sabatini, 2013; Janani & Ranjitha Kumari, 2015; Kim et al., 2015; Mishra et al., 2016; Polvani et al., 2016).

(d) Soluble guanylyl cyclase

sGC is the receptor for nitric oxide, which is synthesized and released by various cell types as a paracrine–autocrine mechanism that coordinates energy production with consumption, in part by improving the delivery of substrates and oxygen via the vascular system (Bellamy et al., 2002; Nossaman et al., 2012). Nitric oxide-mediated

signalling has been reported to be suppressed in obesity and restored by IWL induced by bariatric surgery (Felipo et al., 2013; Blum et al., 2015). Although the activation of sGC by nitric oxide induces tissue-specific responses, its link with energy metabolism and cancer is attributed to endothelial homeostasis, to induction of angiogenesis, and to the downstream effects of cyclic guanosine monophosphate (cGMP), the product of sGC; cGMP activates protein kinase GI, which in turn inhibits RhoA, resulting in the release of the RhoA/Rho-associated protein kinase (ROCK)-dependent inhibition of the insulin–insulin receptor substrate 1 (IRS-1)–PI3K–Akt pathway (Furukawa et al., 2005; Huang et al., 2013). Of additional interest is a recent report that sGC agonists induce brown adipose tissue differentiation and the browning of white adipose tissue in obese mice, effects that result in increased energy expenditure and weight loss (Hoffmann et al., 2015). Therefore, this little-studied energy-sensing cascade provides direct links between energy metabolism, vascular supply, and tumour progression.

(e) Synthesis

The role of the mTOR network in obesity and cancer is well established and illustrates the complex nature of the regulatory cascades that underlie this relationship. There are suggestions that other energy-sensing networks, such as sirtuins, PPARs, and sGC, are involved in the association between obesity and cancer; however, direct evidence of an effect of IWL is lacking.

4.2.3 Epigenetics, oxidative stress, DNA repair, and telomeres

(a) Epigenetics

(i) Epigenetics and obesity

Unlike in cancer research, epigenetic investigations are relatively new in the field of obesity research (van Dijk et al., 2015). In the general population, the more than 100 identified loci associated with body mass index (BMI) account for only 3% of the inter-individual variation of BMI, and genome-wide estimates suggest that common variation accounts for more than 20% of BMI variation (Speliotes et al., 2010; Locke et al., 2015; Shungin et al., 2015). It is hypothesized that epigenetic mechanisms may be a missing link between the obesity-associated genes and the phenotype, and evidence is beginning to emerge in this area. Despite the different types of epigenetic alterations, studies in humans have largely been limited to examining DNA methylation. In a few small genome-wide studies, associations between DNA methylation and BMI or other indices of obesity were investigated, but the findings were generally inconclusive (Feinberg et al., 2010; Wang et al., 2010; Almén et al., 2012; Relton et al., 2012).

An epigenome-wide association study investigated associations between methylation patterns in whole blood from 459 European individuals and BMI. Samples were typed using the Infinium HumanMethylation450 array. BMI was associated with differential methylation at sites cg22891070, cg27146050, and cg16672562 located in the intron 1 region of *HIF3A* (Dick et al., 2014). A subanalysis of methylation patterns in adipose tissue found a similar association, thus suggesting that this is a BMI-related modification of the epigenome. In a subsequent investigation conducted in 991 individuals in the USA, with replication sets from other cohorts in the USA, associations between DNA methylation and BMI and waist circumference were assessed (Aslibekyan et al., 2015). Differentially methylated loci in *CPT1A* and *PHGDH* (genes involved in energy metabolism) and *CD38* were found to be associated with BMI and waist circumference.

(ii) Epigenetics and intentional weight loss

Emerging evidence in humans suggests that IWL is associated with changes in DNA methylation patterns. A small study showed that DNA

methylation in adipose tissue after a 6-month DR were higher in 7 women who lost 3% or more of their body fat than in 7 women who lost less than 3% of their body fat (Bouchard et al., 2010). Results from other studies using shorter-term dietary interventions also suggest that diet-induced weight loss causes differential DNA methylation patterns (Milagro et al., 2011; Mansego et al., 2015).

(iii) Epidemiological evidence of the epigenetic mediation between obesity and cancer risk

Evidence supporting an epigenetic mediation in the link between obesity and cancer risk is sparse and fragmented, and was identified only for breast cancer and colorectal cancer (CRC).

In a study of 803 premenopausal and postmenopausal women with breast cancer, associations between BMI and waist-to-hip ratio (WHR) with methylation at the *E-cadherin*, *p16*, and *RAR-β2* genes were examined in breast tumour tissue (Tao et al., 2011). Promoter methylation was assessed by using real-time methylation-specific polymerase chain reaction (PCR). Compared with women in the lowest quartile of WHR, those in the highest quartile were more likely to have methylation at one or more of the promoter regions that were assessed (odds ratio [OR], 1.85; 95% confidence interval [CI], 1.10–3.11). No significant differences were found in similar case–case comparisons of BMI, or weight change (from age 20 years to 1 year before study enrolment), nor were significant trends detected for these indicators of body size and body size history.

In another study of 532 postmenopausal women with breast cancer in the USA, one arm of the investigation examined whether BMI was associated with promoter methylation status in 13 breast cancer-related genes (*APC*, *BRCA1*, *CCND2*, *CDH1*, *DAPK1*, *ESR1*, *GSTP1*, *HIN1*, *CDKN2A*, *PGR*, *RARβ*, *RASSF1A*, and *TWIST1*) (McCullough et al., 2015). Promoter methylation status was assessed by methylation-specific PCR or the MethyLight assay. Compared with 209 normal-weight women (BMI, 18.5–24.9 kg/m^2), 167 overweight women (BMI ≥ 25.0 kg/m^2) were more likely to have methylated promoter regions for *HIN1* (OR, 1.57; 95% CI, 1.03–2.39). No significant associations were detected for the 12 other genes that were investigated.

A subsequent study examined methylation at 1505 genes with known relevance to cancer using breast tumour tissue from women with breast cancer (Hair et al., 2015). Methylation status of the tissue was assessed using the Cancer Panel 1 platform. Although 30 CpG sites were differentially methylated among 195 normal-weight women with breast cancer compared with 150 obese women with breast cancer in unadjusted analyses, only two sites (on the *SH3BP2* and *XIST* genes) remained statistically significant in the final adjusted models (false discovery rate $q < 0.05$). In analyses limited to estrogen receptor (ER)-positive tumours, differential methylation at CpG sites was statistically significant on the *SH3BP2*, *IGFBP6*, *DNMT3B*, and *ERCC6* genes.

In a case–case study, associations between BMI and the CpG island methylator phenotype (CIMP) in CRC were investigated using data from 3119 patients from the Colon Cancer Family Registry (Weisenberger et al., 2015). CIMP CRC was more common in women (16.8%) than in men (9.3%) ($P = 0.0001$). However, only among women were positive associations between BMI and CIMP CRC observed. Compared with normal-weight women, overweight and obese women were more likely to have CIMP CRC (OR, 1.42; 95% CI, 1.09–1.86 for overweight women and OR, 1.93; 95% CI, 1.09–2.56 for obese women).

Evidence on IWL is limited to experimental studies. One study used a diet-induced obesity (DIO) rodent model followed by DR to investigate the epigenetic effects of DIO and DR on mammary tissue (Rossi et al., 2016). C57BL/6 mice were fed a control diet or a DIO regimen, and mice on the DIO regimen were then randomized

to continue the DIO diet or switch to the control diet, resulting in formerly obese mice with weights comparable to those of the control mice. Comparisons among control, DIO mice, and formerly obese mice both showed that there was a persistent effect of obesity on hypermethylation patterns in mammary tumours, even after DR.

(iv) Synthesis

Data on the epigenetics of obesity are emerging. Although epigenetic links between obesity and cancer risk are biologically plausible, to date the evidence in support of them is sparse and fragmented, and most of the studies have investigated only DNA methylation. Epidemiological studies of breast cancer (Tao et al., 2011; Hair et al., 2015; McCullough et al., 2015) and CRC (Weisenberger et al., 2015) have used DNA methylation at known cancer-related genes to investigate associations of BMI with epigenetic tumour characteristics. Taken together, these studies suggest that obesity may contribute to carcinogenesis via epigenetic mechanisms, but to date few associations have been detected and there has been almost no replication of findings among the different investigations.

(b) Oxidative stress

Oxidative stress is a well-established mechanism of the carcinogenic process and is one of the key characteristics as defined by Smith et al. (2016). To date, multiple biomarkers have been developed that measure oxidative damage. A commonly measured marker for whole-body oxidative stress is the isoprostane 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$), which can be measured in blood and/or urine (Morrow & Roberts, 1997; Czerska et al., 2015). The activity of antioxidant enzymes and their products (e.g. glutathione peroxidase, catalase) and 8-hydroxydeoxyguanosine (8-oxo-dG) can also provide some information about oxidative stress processes in humans (Roszkowski, 2014).

(i) Oxidative stress and obesity

In obesity, adipose tissue is characterized by chronic, low-grade inflammation, which promotes oxidative stress. Adipokines can also induce the production of reactive oxygen species (ROS), resulting in oxidative stress and, in turn, causing production of other adipokines (Marseglia et al., 2015). Many activated immune cells generate free radicals, and the synthesis of ROS further promotes inflammation (Marseglia et al., 2015). Obesity-induced oxidative stress may elicit or exacerbate insulin resistance (Marseglia et al., 2015). In addition, increased ROS production may promote calcium mishandling by affecting the redox state of key proteins implicated in this process. Levels of ROS are frequently increased in obesity, and obesity induced by a high-fat diet has been shown to increase oxidative stress in animal models (e.g. Dobrian et al., 2001; Vincent et al., 2007; Matsuda & Shimomura, 2013; Cerdá et al., 2014).

(ii) Oxidative stress and dietary restriction/ weight loss

One important and consistent effect of DR is the ability to reduce oxidative stress and its resulting damage to macromolecules. Three possible mechanisms have been identified for the antioxidant effects of DR: DR may (i) reduce the production of ROS, (ii) directly increase the activity of antioxidant enzymes, or (iii) increase the turnover of oxidized macromolecules, such as oxidized lipids or DNA, which are commonly measured as biomarkers. These effects are complicated and are thought to be influenced by several factors, including sex, species, or tissue studied, types of ROS or biomarkers and antioxidant enzymes examined, and duration of DR (Merry, 2000; Skrha, 2009).

Five recent studies were identified that investigated the effect of weight-loss interventions on an individual's oxidative stress level: three randomized controlled trials (RCTs) (Meydani et al., 2011; Buchowski et al., 2012; Wegman et

al., 2015) and two non-randomized intervention studies (Gutierrez-Lopez et al., 2012; Chae et al., 2013). All of these studies measured oxidative stress by identifying markers (e.g. activity of enzymes, 8-epi-$PGF_{2\alpha}$, 8-oxo-dG) in blood (plasma or serum) or urine samples.

Buchowski et al. (2012) conducted an RCT comparing a 25% calorie-restricted diet and a control (habitual) diet in 40 overweight or obese women, with direct observation for 28 days and follow-up for the next 90 days. The initial (baseline) serum F_2-isoprostane concentration in the calorie-restricted group (median, 57.0 pg/mL; interquartile range, 40.5–79.5 pg/mL) was 1.75 times the average concentration in normal-weight women (32.5 pg/mL). During calorie restriction (which resulted in a 3.2% reduction in body weight after 29 days), F_2-isoprostane levels fell rapidly, resulting in statistically significant differences from the control group by day 5 (median, 33.5 pg/mL; interquartile range, 26.0–48.0 pg/mL; $P < 0.001$). F_2-isoprostane levels remained low while the study participants continued on the calorie-restricted diet, but returned to the higher baseline concentrations in about 80% of the women after 3 months on a habitual diet.

In an intervention study of 16 normal-weight and 32 obese individuals (BMI, 30–34.9 kg/m^2), Gutierrez-Lopez et al. (2012) studied the effects of a hypocaloric diet and a hypocaloric diet plus regular moderate aerobic exercise on oxidative stress. Over 90 days, an average weight loss of 7.6% was achieved. Higher levels of oxidative stress markers and increased molecular damage and polymerization of insulin were observed in the blood from obese individuals at baseline. Treatment with a hypocaloric diet significantly decreased oxidative stress and molecular damage to values similar to those of normal-weight individuals.

As part of a controlled feeding study, Meydani et al. (2011) studied 46 moderately overweight volunteers (BMI, 25–30 kg/m^2) aged 20–42 years who were randomized to either a high glycaemic load or a low glycaemic load regimen with either 10% ($n = 12$) or 30% ($n = 34$) reduction in calorie intake for 6 months. Overall, independently of the type of calorie-restriction regimen, body weight decreased, plasma glutathione peroxidase activity increased ($P = 0.04$), and plasma protein carbonyl levels decreased ($P = 0.02$), with a concurrent nonsignificant decrease in plasma 8-epi-$PGF_{2\alpha}$ levels ($P = 0.09$) and no changes in superoxide dismutase and catalase activity.

Wegman et al. (2015) recruited a cohort of 24 healthy individuals in a double-crossover, double-blinded RCT of intermittent fasting. Study participants underwent two 3-week treatment periods: intermittent fasting and intermittent fasting with antioxidant (vitamins C and E) supplementation. Despite strict adherence to study-provided diets, no change in expression of oxidative stress markers was observed. Body weight remained stable over the entire trial period.

Chae et al. (2013) investigated overweight or obese participants (BMI, 25–34 kg/m^2, $n = 122$, aged 30–59 years) who joined a clinical intervention lasting 3 years and involving daily calorie deficits of 100 kcal. Body weight changed by 5.4% (−4.16 ± 0.31 kg) in the group with successful mild weight loss ($n = 50$) compared with 0.05 ± 0.14 kg in the unsuccessful group ($n = 49$). Successful mild weight loss was coupled with significantly reduced serum levels of insulin, IL-6 (30% decrease; $P = 0.031$), IL-1β (45% decrease; $P < 0.001$), and tumour necrosis factor alpha (TNF-α) ($P < 0.001$), as well as urinary 8-epi-$PGF_{2\alpha}$ (14% decrease; $P = 0.036$). A positive correlation was reported between IL-1β and urinary 8-epi-$PGF_{2\alpha}$ ($r = 0.435$, $P < 0.001$) and between the corresponding changes in IL-6 and urinary 8-epi-$PGF_{2\alpha}$ ($r = 0.393$, $P < 0.001$).

(iii) Synthesis

Oxidative stress is well established as a cellular mechanism that can affect DNA integrity and has been linked to cancer, metabolic syndrome, and obesity. Evidence of the involvement of oxidative stress in obesity-induced cancer in humans is limited by methodological issues. Results from weight-loss intervention trials indicate that oxidative stress can be rapidly reduced and the lower level sustained through a modest reduction in calorie intake.

(c) DNA repair

(i) DNA repair mediation in obesity and cancer

Elevated BMI is consistently associated with CRC (see Section 2.2.1). To assess the role of DNA repair in this association, several studies have investigated associations between BMI and CRC stratified by tumour microsatellite status (Campbell et al., 2010; Hoffmeister et al., 2013). In a population-based study, CRC cases were divided into those with high-level microsatellite instability (MSI-high) tumours and microsatellite-stable (MSS) tumours (Hoffmeister et al., 2013). Among the 1215 cases, 67% were overweight or obese, and 115 (9.5%) had MSI-high tumours. BMI was weakly associated with MSS tumours in women (OR, 1.15; 95% CI, 0.97–1.35 per 5 kg/m^2) and in men (OR, 1.25; 95% CI, 1.08–1.45 per 5 kg/m^2); in contrast, the association between BMI and MSI-high CRC was significant only in women (OR, 2.04; 95% CI, 1.50–2.77 per 5 kg/m^2). When the analysis was limited to case–case comparisons, BMI was more strongly associated with MSI-high than with MSS tumours in women (OR, 1.84; 95% CI, 1.34–2.52 per 5 kg/m^2), but not in men.

Elevated BMI is consistently associated with increased risk of endometrial cancer (see Section 2.2.9). Endometrial cancer is also commonly observed in women with Lynch syndrome (hereditary non-polyposis CRC due to a defect in the DNA mismatch repair system), and in about 30% of endometrial cancer cases, sporadic MSI occurs (Mills & Longacre, 2016). Furthermore, the positive associations observed between BMI and endometrial cancer are significantly stronger among carriers of germline mutations in the DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2* than among non-carriers (Win et al., 2011).

In a clinical study of 446 women with endometrial cancer (McCourt et al., 2007), women with MSS tumours were significantly heavier (median BMI, 32.7 kg/m^2) than those with MSI tumours (median BMI, 30.3 kg/m^2) ($P = 0.02$). A larger, population-based case–control study of 524 cases and 1032 controls investigated associations between obesity and endometrial cancer by microsatellite status (Amankwah et al., 2013). Unlike in the previous study, the association between BMI and MSI tumours was stronger than that between BMI and MSS tumours ($P_{heterogeneity} = 0.05$ for overweight and 0.02 for obesity).

(ii) DNA repair and dietary restriction/weight loss

One recent RCT investigated the effect of weight loss on DNA repair capacity. The Nutrition and Exercise for Women RCT recruited 439 women, who were randomized to one of four groups: (i) dietary intervention, (ii) aerobic exercise, (iii) diet plus exercise, or (iv) control (Habermann et al., 2015). The diet intervention was a group-based programme with a goal of 10% weight loss. The exercise intervention consisted of moderate to vigorous aerobic activity for 45 minutes per day, 5 days per week. DNA repair capacity was measured in fasting blood samples taken at baseline and after 12 months in a subset of 226 women, using a modified comet assay conducted in pre- and post-intervention cryopreserved lymphocytes, analysed within the same batch. DNA repair capacity did not change significantly with any of

the diet or exercise interventions compared with the control group. Similarly, there were no significant changes when the analysis was stratified by changes in body composition or aerobic fitness (maximal oxygen consumption, VO_{2max}).

(iii) Synthesis

The role of DNA repair function in cancer risk is unequivocal and is particularly well established for cancers of the colorectum, breast, endometrium, and skin. However, there have been few studies investigating functional assays of DNA repair in the context of obesity or weight reduction. One well-designed RCT showed no effects, but assay limitations were present. Several studies point towards a link between BMI and DNA mismatch repair deficiencies. Overall, a causal link of obesity and weight control with DNA repair is still lacking.

(d) Telomeres

Multiple studies have reported that obesity is associated with shorter telomere length in different cell types. A recent systematic review and meta-analysis comprising 119 439 individuals reported that 39 studies showed weak to moderate correlations between obesity and telomere length (Mundstock et al., 2015). However, there was significant heterogeneity, which suggests that this relationship is still incompletely understood.

In the Nutrition and Exercise for Women RCT of 439 postmenopausal women randomized to diet, exercise, diet plus exercise, or control groups for 1 year (see Section 4.2.3c(ii)), DNA was extracted from isolated leukocytes, and telomere length was measured by quantitative PCR (Mason et al., 2013a). Baseline telomere length was correlated inversely with age ($r = -0.12$, $P < 0.01$) and positively with VO_{2max} ($r = 0.11$, $P = 0.03$), but was not correlated with BMI or body fat percentage. The change in telomere length was inversely associated with the telomere length at baseline ($r = -0.47$, $P < 0.0001$). None of the interventions resulted in any significant group differences in leukocyte telomere length compared with controls, and there were no differences in telomere length by the degree of weight loss.

García-Calzón et al. (2014) reported that a 2-month energy-restricted diet (30% of energy from fat, 15% from proteins, and 55% from carbohydrates) among overweight or obese adolescents aged 12–16 years resulted in increased telomere length, with a greater effect in those who had the shortest telomeres at baseline ($r = 0.96$, $P < 0.001$).

4.3 Receptor-mediated effects

Adiposity and overweight/obesity are associated with significant metabolic and endocrinological changes that are included as key characteristics of the carcinogenesis process, in particular (i) alterations in sex hormone metabolism, (ii) changes in insulin levels and IGF signalling, and (iii) chronic inflammation (see Table 4.1; for a review, see Pischon & Nimptsch, 2016). A large and growing number of epidemiological and experimental studies have measured biomarkers of these pathways in relation to cancer at different sites. Data in the tables are presented by type of cancer (Tables 4.2–4.11), whereas the text summarizes the studies by mechanistic pathway.

4.3.1 Sex hormones

Sex hormones are involved in specific cancers, exemplified by the implications of estrogen in breast and endometrial cancers and of androgen in prostate cancer. In postmenopausal women, estrogens are synthesized almost exclusively in adipose tissue stromal cells, and consequently obese postmenopausal women have elevated levels of estrogens compared with leaner postmenopausal women (Key et al., 2003).

(a) Cancer of the breast

See Table 4.2.

Estrogens stimulate the proliferation of normal breast tissue and neoplastic breast epithelial cells directly and can promote the development of ER-positive, estrogen-dependent breast cancer by both endocrine and paracrine mechanisms (Vona-Davis & Rose, 2007; Bulun et al., 2012).

Elevated levels of circulating estrogens have been linked to breast cancer risk in numerous epidemiological studies (Hankinson et al., 1998a; Kaaks et al., 2005; Tworoger et al., 2011; Zhang et al., 2013). The Endogenous Hormones and Breast Cancer Collaborative Group, which pooled data from nine prospective investigations of sex hormone levels and breast cancer comprising individual data from 663 incident breast cancer cases and 1765 controls, reported that risk of postmenopausal breast cancer is 2-fold higher among women in the highest versus the lowest quintile of estradiol and testosterone levels, as well as for other related sex hormones such as estrone, dehydroepiandrosterone (DHEA), DHEA sulfate, and androstenedione (Key et al., 2002). Furthermore, in a subsequent analysis, the positive association between BMI and risk of postmenopausal breast cancer was almost entirely explained by levels of estradiol (Key et al., 2003). For premenopausal breast cancer, the risk of breast cancer was 40% higher among women in the highest versus the lowest quintile of estradiol level. Levels of androstenedione, DHEA sulfate, and testosterone were also significantly positively associated with risk of breast cancer in multivariate models that included established breast cancer risk factors (Key et al., 2013).

(b) Cancer of the endometrium

See Table 4.3.

Estrogens play a critical role in the normal proliferation of endometrial tissue during the menstrual cycle (Barile et al., 1979; Klotz et al., 2002; Zhu & Pollard, 2007). In premenopausal endometrial tissue, the actions of estrogen are opposed by those of progesterone (Gao & Tseng, 1997). Consistent with these mechanistic data, use of unopposed estrogen postmenopausal hormone therapy is associated with a significantly higher risk of endometrial cancer, whereas use of the combined estrogen plus progestogen formulation appears to have a protective effect (Beral et al., 2005).

There are consistent epidemiological data linking higher circulating estrogen levels with increased risk of endometrial cancer. Five prospective investigations of estradiol concentrations and endometrial cancer have all reported relative risks between 2 and 4 for the comparison of high versus low estradiol levels in multivariate models that controlled for adiposity and other established endometrial cancer risk factors (Zeleniuch-Jacquotte et al., 2001; Lukanova et al., 2004a; Allen et al., 2008; Gunter et al., 2008a; Brinton et al., 2016). In addition, higher circulating levels of sex hormone-binding globulin (SHBG) were associated with significantly lower risk of endometrial cancer in three of these prospective studies (Zeleniuch-Jacquotte et al., 2001; Lukanova et al., 2004a; Allen et al., 2008).

(c) Cancer of the colorectum

See Table 4.4.

The role of sex hormones in CRC development is unclear and is likely to be complex. The Women's Health Initiative Clinical Trial reported a significant reduction in CRC incidence among women assigned to the combined estrogen plus progestogen intervention arm (Chlebowski et al., 2004); however, with additional follow-up of the trial participants, it was later suggested that this effect may be a consequence of diagnostic delay (Simon et al., 2012). Experimental data also suggest that estrogens may have protective effects on CRC development. ERβ has been demonstrated to play an important role in the anti-

proliferative effects of estrogens on colonic tissue (Hartman et al., 2009). Furthermore, expression of ERβ is low in human CRC cells (Waliszewski et al., 1997) and is inversely associated with the stage of colon cancer (Castiglione et al., 2008), suggesting a possible role in disease progression.

However, investigations of the relationship between endogenous circulating estrogens and CRC have produced inconsistent results. Of the five prospective studies published to date, all of which were mainly of postmenopausal women, three reported null associations between circulating estrogens and CRC risk (Clendenen et al., 2009; Lin et al., 2013; Falk et al., 2015) and a fourth reported a borderline significant positive association (Gunter et al., 2008b). More recently, in a case–control study nested within the non-intervention arms of the Women's Health Initiative Clinical Trial that included only postmenopausal women, higher endogenous levels of free estradiol were inversely associated with CRC risk (OR for highest vs lowest quartile, 0.43; 95% CI, 0.27–0.69) in a multivariate model that included established CRC risk factors as well as other obesity-related hormones such as insulin and IGF-1 (Murphy et al., 2015). Higher levels of SHBG were positively associated with CRC development (OR for highest vs lowest quartile, 2.30; 95% CI, 1.51–3.51), and this relationship strengthened after statistical adjustment for levels of circulating estradiol, estrone, insulin, IGF-1, and C-reactive protein (CRP) (OR for highest vs lowest quartile, 2.50; 95% CI, 1.59–3.92). Interestingly, the link between obesity and CRC is weaker in women than in men (see Section 2.2.1). Furthermore, in the study by Murphy et al. (2015) of postmenopausal women who were non-users of hormone replacement therapy (HRT), the inclusion of estradiol in the waist circumference–CRC model strengthened the risk estimate.

(d) Cancer of the prostate

See Table 4.5.

Sex steroids, and specifically androgens such as testosterone, play critical roles in the development and function of the prostate gland, and their involvement in prostate tumorigenesis has long been hypothesized (Hsing, 2001). However, testosterone levels tend to be lower in obese men than in men of normal weight.

Prospective studies that have investigated androgen levels and prostate cancer development have reported inconsistent findings. The Endogenous Hormones and Prostate Cancer Collaborative Group, which pooled data from 18 prospective studies evaluating individual data from 3886 incident prostate cancers and 6438 men without prostate cancer, reported null associations between testosterone, DHEA sulfate, androstenedione, or estradiol and incident prostate cancer (Roddam et al., 2008). It has been hypothesized that a hypoandrogenic environment promotes the development of higher-grade prostate tumours. At least two prospective studies have reported inverse relationships between serological testosterone levels and high-grade prostate cancer (Platz et al., 2005a; Severi et al., 2006a). Furthermore, in the Prostate Cancer Prevention Trial, finasteride, which lowers testosterone levels, reduced the risk of low-grade prostate cancer by 25% but led to a higher incidence of high-grade disease (Thompson et al., 2003). Interestingly, the association between obesity and prostate cancer is stronger for high-grade (fatal) tumours (see Section 2.2.14).

Collectively, these data point to a complex relationship between androgen levels and prostate cancer, with an indication of tumour subtype specificity, but offer limited insight into the mechanisms underlying the link between obesity and prostate cancer.

(e) Cancer at other sites

Sex hormones have been hypothesized to play a role in ovarian cancer development. Use of oral contraceptives confers a reduced risk of ovarian cancer, whereas use of postmenopausal HRT

is associated with increased risk (Beral et al., 2008, 2015). However, epidemiological studies that have investigated circulating estrogen and SHBG levels in relation to risk of ovarian cancer were generally null (Table 4.6; Helzlsouer et al., 1995; Lukanova et al., 2003a; Rinaldi et al., 2007; Trabert et al., 2016). [It is plausible that the associations may be specific to particular ovarian cancer subtypes, but to date individual studies have been of insufficient size to address this hypothesis with precision.]

For other cancer types, there are intriguing data that point to possible sex hormone-mediated mechanisms. In a case–control study, SHBG levels were strongly associated with risk of hepatocellular carcinoma (HCC) even after adjusting for all established risk factors (Lukanova et al., 2014; Table 4.7). Also, there are distinct sex differences in the incidence of cancers of the oesophagus, liver, pancreas, and kidney, all of which occur more frequently in men than in women (see Sections 2.2.2, 2.2.4, 2.2.7, and 2.2.16, respectively). However, to date there are no published data on the association of endogenous sex hormones with these cancers. Experimental data, mainly from studies of cell lines, indicate possible anti-proliferative and anti-tumorigenic effects of estrogen in renal cells (Yu et al., 2013).

(f) Impact of weight loss on sex hormones

Investigations of the effects of IWL on sex steroid levels are relatively consistent; however, these studies have largely been restricted to postmenopausal women. A comprehensive overview of the available literature until 2011 concluded that IWL reduces levels of sex steroid hormones in postmenopausal women and increases SHBG levels in premenopausal and postmenopausal women (Byers & Sedjo, 2011). In the Nutrition and Exercise for Women RCT, 439 overweight or obese postmenopausal women were randomized to one of four groups: control, dietary intervention only, exercise intervention only, or diet plus exercise (Foster-Schubert et al., 2012). Over a 12-month period, women in the diet group and the diet plus exercise group lost on average 8.5% and 10.8%, respectively, of their pre-intervention weight (Campbell et al., 2012). Compared with the control group, women in these two groups had statistically significant reductions in estrone and estradiol levels. SHBG levels increased significantly in the diet group and the diet plus exercise group, and decreased slightly in the control group and the exercise group.

Results from an analysis of overweight postmenopausal women enrolled in the Diabetes Prevention Program who underwent moderate weight loss did not reveal significant effects on estradiol or testosterone levels, although DHEA levels were reduced and there was a statistically significant increase in SHBG concentrations (Kim et al., 2012).

(g) Synthesis

Estrogen levels correlate with amount of body fat in postmenopausal women. Overall, data from observational and experimental studies support clear associations between higher levels of estrogens and increased risk of breast cancer and endometrial cancer. In addition, IWL affects sex steroid hormones and SHBG levels in postmenopausal women in a direction that would favour reducing their risk of breast cancer and endometrial cancer. For CRC, estradiol may be anti-tumorigenic and may in fact lessen the impact of adiposity on CRC development. For cancers of the prostate and ovary, the data are much less consistent and the associations are likely to be more complex. For other tumours, the role of sex hormones in their development is largely unknown.

4.3.2 Insulin resistance

Insulin resistance indicates the presence of an impaired physiological response to insulin, and is manifested by decreased insulin-stimulated

glucose transport. Hyperinsulinaemia, which is a consequence of insulin resistance, is more common in obese individuals than in those of normal weight, and metabolic indicators of hyperinsulinaemia, such as C-peptide levels, are positively associated with BMI and waist circumference (Bezemer et al., 2005).

Insulin, in addition to its metabolic effects, has mitogenic and anti-apoptotic activity and appears to play a significant role in normal organogenesis. Insulin has been shown to stimulate cell proliferation in normal tissues such as breast tissue and in human cancer cell lines (Ish-Shalom et al., 1997; Chappell et al., 2001), and administration of exogenous insulin promotes tumour growth in animal models (Heuson & Legros, 1972; Shafie & Grantham, 1981; Shafie & Hilf, 1981).

(a) Cancer of the breast

See Table 4.2.

A number of epidemiological studies have investigated the association of fasting insulin levels in women with higher BMI with incidence of breast cancer, with variable results. One study found a positive association between hyperinsulinaemia and postmenopausal breast cancer among women with BMI > 26 kg/m^2, but not among women with BMI ≤ 26 kg/m^2 (Muti et al., 2002). In an analysis conducted in the Women's Health Initiative Observational Study, fasting insulin levels were positively associated with postmenopausal breast cancer among women who were non-users of HRT, in a multivariate model that controlled for multiple breast cancer risk factors, including estradiol and BMI (hazard ratio for highest vs lowest quartile of insulin level [HR_{q4-q1}], 2.40; 95% CI, 1.30–4.41; $P_{trend} < 0.001$) (Gunter et al., 2009, 2015a). In a subsequent formal mediation analysis, it was demonstrated that insulin, rather than estradiol, explained the majority of the association between obesity and breast cancer risk in this population (Hvidtfeldt et al., 2012).

(b) Cancer of the endometrium

See Table 4.3.

Hyperinsulinaemia, whether assessed by fasting insulin levels or C-peptide levels, has been associated with increased incidence of endometrial cancer in several prospective investigations (Lukanova et al., 2004b; Cust et al., 2007a; Gunter et al., 2008a). In an analysis in the Women's Health Initiative cohort, baseline fasting insulin levels among women who were non-users of HRT were positively associated with risk of endometrioid adenocarcinoma after adjusting for estradiol levels and other factors (HR_{q4-q1}, 2.33; 95% CI, 1.13–4.82), and this association was stronger among women with BMI ≥ 25 kg/m^2 (HR_{q4-q1}, 4.30; 95% CI, 1.62–11.43) (Gunter et al., 2008a). Two additional studies that measured C-peptide concentrations also reported significant positive associations with endometrial cancer risk (Lukanova et al., 2004b; Cust et al., 2007a). An analysis from the European Prospective Investigation into Cancer and Nutrition (EPIC) study reported an increased risk of endometrial cancer among women with high C-peptide levels compared with those with low levels; this association was independent of obesity, but the risk estimate was attenuated after adjustment for estradiol (Cust et al., 2007a). Recently, further support for a causal role of insulin in endometrial cancer development came from a Mendelian randomization analysis conducted in 1287 endometrial cancer cases and 8273 controls, which identified a robust positive association between genetically determined insulin levels and endometrial cancer (Nead et al., 2015).

(c) Cancer of the colorectum

See Table 4.4.

In laboratory models, high insulin levels have been shown to promote the development of

aberrant crypt foci in the colon (which are posited to be CRC precursors), as well as the growth of colon cancer cells (Koohestani et al., 1997; Tran et al., 2006). Furthermore, overexpression of the insulin receptor can induce cell transformation in vitro (Giorgino et al., 1991), and human colorectal adenocarcinomas have been shown to express the insulin receptor at high levels, indicating that these cells may be sensitive to the growth effects of insulin (Kiunga et al., 2004).

Epidemiological data on the association of hyperinsulinaemia with CRC are somewhat inconsistent. Of the five published studies to date that directly measured fasting insulin levels (Schoen et al., 1999; Palmqvist et al., 2003; Saydah et al., 2003; Limburg et al., 2006; Gunter et al., 2008b), three reported positive associations between hyperinsulinaemia and CRC (Schoen et al., 1999; Limburg et al., 2006; Gunter et al., 2008b), but the associations were attenuated after adjustment for other risk factors. In the largest of such studies, which was conducted in the Women's Health Initiative cohort, insulin levels were significantly associated with CRC ($HR_{q4–q1}$, 1.89; 95% CI, 1.33–2.69; P_{trend} = 0.0005); however, adjustment for waist circumference weakened the association ($HR_{q4–q1}$, 1.42; 95% CI, 0.91–2.23; P_{trend} = 0.11), just as adjustment for insulin also attenuated the relationship between obesity and CRC (Gunter et al., 2008b). The remaining two studies found no association between insulin and CRC [insulin was measured in non-fasting blood specimens, which complicates the interpretation] (Palmqvist et al., 2003; Saydah et al., 2003). Other prospective studies have assessed C-peptide concentrations in relation to CRC and have generally reported positive associations (Kaaks et al., 2000; Ma et al., 2004; Wei et al., 2005a; Jenab et al., 2007; Otani et al., 2007). Most recently, an analysis in the EPIC study demonstrated that individuals with a normal BMI but elevated C-peptide levels were at higher risk of CRC compared with those with a normal BMI and without elevated C-peptide levels, and were at equivalent risk of CRC as overweight and obese individuals with higher C-peptide levels. In contrast, overweight or obese participants without raised C-peptide levels were not at increased risk of CRC. These findings support an association of hyperinsulinaemia with CRC independent of obesity status (Murphy et al., 2016).

(d) Cancer at other sites

A number of prospective studies have investigated the association of insulin with prostate cancer development (Table 4.5), and the majority reported null associations (Stattin et al., 2000; Hubbard et al., 2004; Stocks et al., 2007; Parekh et al., 2013; Lai et al., 2014). A study nested within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study reported a 2-fold higher risk of prostate cancer when men in the highest quartile of insulin level were compared with those in the lowest quartile (Albanes et al., 2009).

A null association was also reported in the single study of ovarian cancer (Table 4.6; Lukanova et al., 2003b).

Hyperinsulinaemia has also been linked to development of liver cancer in a small number of prospective studies (Table 4.7). An investigation nested within the EPIC cohort demonstrated a more than 3-fold greater risk of HCC and an almost 10-fold greater risk of intrahepatic bile duct tumour among participants in the highest tertile of C-peptide level compared with the lowest tertile (Aleksandrova et al., 2014). Similarly, in a study of men chronically infected with hepatitis B virus, individuals with fasting insulin levels higher than 6.1 μU/mL were at more than 2-fold higher risk of HCC compared with those with insulin levels in the range 2.75–4.10 μU/mL (Chao et al., 2011).

For pancreatic cancer (Table 4.8), two studies that measured insulin levels in pre-diagnostic samples both reported statistically significant positive associations between insulin levels and risk of pancreatic cancer (Stolzenberg-Solomon

et al., 2005; Wolpin et al., 2013), whereas an investigation nested within the EPIC cohort reported no association between C-peptide levels and pancreatic cancer (Grote et al., 2011).

A single nested case–control study reported statistically significant associations between both insulin and C-peptide levels (highest vs lowest tertiles) and risk of stomach cancer (Table 4.9; Hidaka et al., 2015).

(e) Synthesis

Hyperinsulinaemia and insulin resistance are metabolic disturbances commonly observed in obesity. Insulin, in addition to indirectly raising free estrogen levels by suppression of SHBG expression, can directly activate cellular pathways that confer growth and survival advantages to the cell and therefore may promote cancer development. Experimental data in in vitro and animal models generally support a protumorigenic effect of insulin; studies in humans generally only support a positive association between hyperinsulinaemia and cancers of the endometrium and colorectum, whereas findings for breast cancer and prostate cancer are more heterogeneous. There are few data for cancer at other sites.

4.3.3 Insulin-like growth factors

The IGF system comprises two ligands, IGF-1 and IGF-2, as well as at least six binding proteins (IGFBPs) that sequester IGF-1 and IGF-2 and regulate their bioavailability and activity. IGF-1 and IGF-2 are growth factors that share significant structural similarities with insulin but have much stronger mitogenic and anti-apoptotic effects.

A substantial body of epidemiological literature has now accumulated on the association of circulating IGF-1 levels with cancer development, and several meta-analyses and pooled studies have demonstrated robust associations of systemic IGF-1 concentrations with breast cancer (Table 4.2), CRC (Table 4.4), and prostate cancer (Table 4.5). However, the evidence that the IGF axis is dysregulated in obesity and is modified by IWL, although convincing in studies in animals, is less convincing in humans, at least in part due to current challenges in measuring bioavailable IGF-1 in human biospecimens. Although insulin levels generally rise with increasing BMI and waist circumference, most large, population-based studies have reported a non-linear relationship between measures of adiposity and IGF-1 levels. One study found the highest IGF-1 levels among those with a BMI in the range 26–27.9 kg/m^2 (Allen et al., 2003), and other studies suggest decreasing levels of IGF-1 as BMI rises above 25 kg/m^2 (Lukanova et al., 2004c). The non-linearity hypothesis relating circulating IGF-1 levels to adiposity is also supported by findings among women enrolled in the EPIC study, which reported a positive trend in IGF-1 levels as BMI and waist circumference increased, with levels peaking at a BMI of 24.6–26.6 kg/m^2, and then declining among participants with BMI > 26.6 kg/m^2 (Gram et al., 2006). In contrast, linear regression analysis of data from the United States National Health and Nutrition Examination Survey (NHANES) suggested an overall inverse relationship between circulating total IGF-1 levels and BMI (Faupel-Badger et al., 2009). This phenomenon may, in part, be explained by obesity-induced hyperinsulinaemia and growth hormone effects. Insulin inhibits the synthesis of IGFBP-1 and IGFBP-2, leading to an increase in unbound IGF-1 (Nam et al., 1997). Thus, as adiposity increases over time, IGF-1 levels rise, but with the development of obesity, elevated free IGF-1 levels exert a negative feedback effect on pituitary secretion of growth hormone, with subsequent attenuation of hepatic IGF-1 synthesis (Tannenbaum et al., 1983).

A comprehensive review of the literature on IGF-1 and IGFBPs presents an inconsistent portrait of how IWL affects IGF-1 and IGFBPs (Byers & Sedjo, 2011). In the Nutrition and

Exercise for Women RCT, published afterwards (Mason et al., 2013b), weight loss was positively associated with change in circulating IGF-1 and in the molar ratio of IGF-1 to IGFBP-3 in the diet group.

The IGF axis plays a major role in the regulation of cell growth and survival, and increased signalling through the IGF system can exert a pro-tumorigenic effect. Studies in humans support a role for systemic IGF-1 levels in determining risk of breast, prostate, and colorectal cancer, whereas for other malignancies the relationship is much less clear. However, the relationship between IGF-1/IGFBPs and obesity is uncertain and is still being investigated.

4.3.4 Chronic inflammation

Chronic inflammation, a key characteristic of carcinogenesis (Hanahan & Weinberg, 2000, 2011; Smith et al., 2016), has been associated with obesity in a large number of epidemiological and experimental studies. Obesity is considered a chronic pro-inflammatory state associated with progressive infiltration of adipose tissue by macrophages and other immune cells that secrete pro-inflammatory cytokines (including TNF-α, IL-1β, and IL-6) and other chemical mediators of a persistent, subacute (often referred to as smouldering) inflammatory response (Renehan et al., 2008). In addition, several clinical and experimental studies suggest that IWL – by behavioural interventions, bariatric surgery, or pharmacological approaches – can reverse some of the obesity-associated changes in certain inflammatory factors, particularly CRP. However, it is also clear from this literature that the underlying causes, cellular contributors, and molecular and metabolic factors involved in the obesity–inflammation–cancer triad are extremely complex.

The increase in white adipose tissue mass associated with obesity drives chronic inflammation through at least three established and interacting mechanisms, which are each discussed here: (i) altered production of inflammatory factors secreted from adipose and other tissues, (ii) increased adipose tissue inflammation (as measured by crown-like structures and other measures of infiltration by immune cells), and (iii) adipose tissue remodelling. In addition, several emerging contributors to the obesity-associated pro-inflammatory state, including the cyclooxygenase-2 (COX-2)/prostaglandin pathway, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, and inflammation-related molecules from the microbiome, are briefly discussed.

(a) Established markers and mechanisms

(i) Changes in inflammatory markers

Leptin, a peptide hormone produced by adipocytes (and thus referred to as an adipokine), is positively correlated with adipose storage and nutritional status, and functions as an energy sensor. Leptin interacts directly with peripheral tissues, interacts indirectly with hypothalamic pathways, and modulates immune function, cytokine production, angiogenesis, and many other biological processes (Münzberg & Morrison, 2015). At the high levels found with obesity, leptin also has pro-inflammatory activity and upregulates the secretion of TNF-α and IL-6 (Park & Ahima, 2015).

The leptin receptor is structurally and functionally similar to class I cytokine receptors and acts through the signal transducer and activator of transcription (STAT) family of transcription factors (Villanueva & Myers, 2008). STATs induce signalling pathways for several cellular processes, including cell growth, proliferation, survival, migration, and differentiation. The activity of STATs is commonly dysregulated in cancer (Yu et al., 2014).

Adiponectin is the most abundant hormone secreted from adipose tissue. In contrast with leptin, levels of adiponectin correlate negatively with adiposity. Adiponectin can reduce pro-

inflammatory cytokine expression and induce anti-inflammatory cytokine expression via inhibition of NF-κB (discussed below) (Fantuzzi, 2013; Park & Ahima, 2015).

CRP is a non-glycosylated circulating acute-phase reactant protein of the pentraxin family (Thiele et al., 2015). CRP has long been used as a marker of inflammation in studies in humans (see Section 4.3.4c), and data are accumulating that CRP (particularly the monomeric form that results from dissociation from the pentameric form on activated macrophages and platelets) may be a mediator of inflammation (Thiele et al., 2015).

In addition to adiponectin, leptin, and CRP, many other adipokines, cytokines, and acute-phase reactant proteins can be produced by adipocytes, by other cells in adipose tissue (e.g. macrophages, dendritic cells, fibroblasts, B and T lymphocytes), or by other tissues (e.g. stomach, skeletal muscle, liver) (Blüher & Mantzoros, 2015). With increased adiposity, the secretome (the conglomerate of secreted factors) can become dysregulated and have significant biological impacts on insulin sensitivity, inflammatory response, vascular endothelial function, estrogen metabolism, and cell proliferation.

At the intracellular level, inflammatory signals are transduced through multiple pathways to drive cellular responses. For example, NF-κB is a transcription factor activated in response to various stimuli, including cytokines and other inflammatory molecules, and is responsible for inducing gene expression associated with cell proliferation, apoptosis, angiogenesis, cytokine secretion, and other responses to inflammatory signals (Xia et al., 2014). Activation of NF-κB has been observed in many types of tumour cells (Karin, 2006). There is considerable cross-talk between growth factor signalling pathways and NF-κB signalling, and obesity and energy restriction modulate NF-κB activation, possibly through alterations in systemic cytokines, growth factors, and Akt signalling (Hursting et al., 2013). Activation of NF-κB by cytokines or Akt can lead to the translocation of the active NF-κB subunit, p65, from the cytoplasm to the nucleus (Adli & Baldwin, 2006), inducing multiple genes associated with inflammation and cancer, including IL-6, COX-2, and IL-1β (Karin, 2006).

(ii) Increased adipose tissue inflammation

A new role of adipose tissue inflammation in obesity and its connection to cancer has been proposed. Subclinical inflammation in visceral and subcutaneous white adipose tissue is characterized by rings of activated macrophages surrounding engorged or necrotic adipocytes and referred to as crown-like structures. Macrophages, T cells, and other immune cells infiltrate adipose tissue at the onset of weight gain. This adipocyte–macrophage interaction results in the production of a pro-inflammatory secretome from both cell types, which activates the cellular transcription factor NF-κB, increases levels of cytokines and other inflammatory factors, and triggers inflammation. Chronic inflammation eventually leads to systemic insulin resistance and altered levels of circulating adipokines, cytokines, and other factors that promote the development of obesity, and also plays a role in obesity-associated cancers (Wellen & Hotamisligil, 2003; Neels & Olefsky, 2006; Subbaramaiah et al., 2011).

(iii) Adipose tissue remodelling

Stored triacylglycerides undergo lipolysis within the cytoplasm of adipocytes and are released into the bloodstream as free fatty acids during times of low substrate availability or heightened energy requirements (Duncan et al., 2007). Once in the circulation, free fatty acids can be used to generate energy. In a state of obesity, white adipose tissue does not respond appropriately to changes in energy requirements, resulting in elevated production of adipokines and cytokines (Jung & Choi, 2014).

When lipid storage capacity in adipose tissue is exceeded, surplus lipids often accumulate

within muscle, liver, and pancreatic tissue, leading to impairment of lipid processing and clearance within these tissues (Henry et al., 2012; Suganami et al., 2012). As a result, lipid intermediates impair the function of cellular organelles and cause further release of cytokines, which foster inflammation as well as insulin resistance.

(b) Emerging markers and mechanisms

(i) COX-2, prostaglandins, and other lipid mediators

COX-2 can be highly induced in several tissue types as part of the inflammatory response; COX-2 levels are increased in many obesity-associated cancers, including breast, ovarian, and colorectal tumours, and are associated with a poor clinical outcome (Eberhart et al., 1994; Howe, 2007; Lee et al., 2013).

In addition, the increased lipolysis that occurs with obesity results in a higher concentration of circulating free fatty acids (Björntorp et al., 1969; Jensen et al., 1989; Nicklas et al., 1996), and saturated fatty acids can stimulate expression of COX-2 and secretion of prostaglandin E2 in cultured macrophages via activation of Toll-like receptor 4 and subsequent NF-κB signalling (Lee et al., 2001; Hellmann et al., 2013). This may be another contributor to obesity-associated adipose tissue inflammation. Also, serum concentrations of IL-6 and TNF-α are generally increased with obesity (Fain, 2006), and these cytokines have been shown to stimulate COX-2 expression and to promote production of prostaglandin E2 (Geng et al., 1995; Maihöfner et al., 2003).

(ii) Inflammatory contributions from the microbiome

An emerging field of research is the influence of the microbiome – the community of commensal, symbiotic, and pathogenic microorganisms that inhabit an individual – on obesity, inflammation, and related chronic diseases (discussed in Section 4.3.6a).

(c) Epidemiological evidence for the mediation of inflammatory factors between obesity and cancer

(i) Cancer of the breast

See Table 4.2.

Epidemiological studies on the association of adipokines and inflammatory factors with breast cancer have generally yielded inconsistent results. Adiponectin levels have been reported to be inversely associated with breast cancer incidence in several prospective investigations (Tworoger et al., 2007b; Gross et al., 2013) but not in others (Cust et al., 2009; Gaudet et al., 2013); three recent meta-analyses that included both prospective cohort and case–control studies reported an overall inverse relationship between adiponectin levels and breast cancer risk (Liu et al., 2013; Macis et al., 2014; Ye et al., 2014). Most recently, data from the Women's Health Initiative demonstrated an inverse association between adiponectin levels and postmenopausal breast cancer, but this relationship was attenuated after adjustment for insulin (Gunter et al., 2015b). Data on the association of other adipokines, such as leptin, plasminogen activator inhibitor 1 (PAI-1), and resistin, with breast cancer risk are also mixed (Gaudet et al., 2013; Gross et al., 2013; Gunter et al., 2015b).

CRP, a sensitive but nonspecific marker of the inflammatory response, has been investigated in relation to breast cancer risk in a large number of prospective studies. A recent meta-analysis that summarized data from 12 prospective studies concluded that moderately elevated CRP levels were associated with higher risk of breast cancer such that for every doubling in CRP concentration, the risk of breast cancer increased by 7% (Chan et al., 2015). An additional study not included in the meta-analysis also reported that higher circulating CRP levels were associated with increased incidence of breast cancer (Gunter et al., 2015b). Specifically, the breast cancer incidence in women in the upper two quartiles of

CRP levels was twice that of those in the lowest quartile of CRP levels among women who were non-users of HRT, even after controlling for estradiol, insulin, BMI, and established breast cancer risk factors. Furthermore, in that analysis CRP appeared to be a significant mediator of the relationship between BMI and breast cancer, along with insulin and estradiol.

(ii) Cancer of the endometrium

See Table 4.3.

A number of prospective studies have investigated the association of circulating inflammatory factors and adipokines with endometrial cancer. Within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, leptin levels were positively associated with endometrial cancer development (OR_{t3-t1}, 2.77; 95% CI, 1.60–4.79), whereas adiponectin levels were inversely related to risk (OR_{t3-t1}, 0.48; 95% CI, 0.29–0.80); both associations strengthened when analyses were restricted to women who were non-users of HRT (Luhn et al., 2013). Leptin levels were also positively associated with endometrial cancer risk in the B~FIT study, although this relationship was no longer significant after adjustment for BMI (Dallal et al., 2013). Within the EPIC study, adiponectin concentrations were significantly inversely associated with endometrial cancer risk, even after controlling for BMI (OR_{q4-q1}, 0.56; 95% CI. 0.36–0.86) (Cust et al., 2007a); however, other studies did not report significant inverse associations between adiponectin and endometrial cancer after adjustment for BMI (Soliman et al., 2011; Dallal et al., 2013).

Data from the Women's Health Initiative indicated a significant positive association between CRP levels and endometrial cancer; however, this relationship was attenuated and lost statistical significance after adjustment for insulin and estradiol levels (Wang et al., 2011). A case–control study nested within the EPIC cohort found levels of CRP and IL-6 to be positively associated with endometrial cancer, but the risk estimates were no longer significant after adjusting for BMI (Dossus et al., 2010). However, a subsequent study in the same population reported significant positive associations between circulating TNF-α levels and endometrial cancer, even after controlling for BMI and other endometrial cancer risk factors (Dossus et al., 2011), and a factor analysis of all metabolic and inflammatory markers revealed a distinct inflammatory pattern of markers that was predictive of endometrial cancer development (Dossus et al., 2013).

(iii) Cancer of the colorectum

See Table 4.4.

Several prospective studies have investigated the association of adipokines and inflammatory markers with CRC risk. In general, most studies have reported an inverse association between adiponectin levels and CRC (Wei et al., 2005b; Aleksandrova et al., 2012a; Song et al., 2013). In a nested case–control study of CRC in Norway, leptin levels were positively associated with colon cancer (OR_{q4-q1}, 2.72; 95% CI, 1.44–5.12) but not with rectal cancer (Stattin et al., 2004b). In the Women's Health Initiative Observational Study, a panel of pro-inflammatory adipokines, namely leptin, IL-6, and PAI-1, were associated with higher incidence of CRC, whereas adiponectin levels were inversely related to CRC risk (Ho et al., 2012). However, the associations were attenuated, and only leptin remained significant, after adjusting for insulin, suggesting that their effects on CRC risk may be attributed partly to insulin. A follow-up study conducted in the same population reported that higher levels of the soluble IL-1 receptor were associated with significantly lower risk of CRC, suggesting that regulators of cytokine signalling and availability may modify CRC development (Ho et al., 2014).

A substantial number of studies have investigated the link between circulating CRP levels and CRC, and the majority have reported positive associations. In a recent meta-analysis that

captured data from more than 4500 CRC cases, risk of CRC was increased by 12% for every unit change in the natural logarithm of CRP concentration (Zhou et al., 2014).

(iv) Cancer of the ovary

See Table 4.6.

A potential role for inflammation in ovarian cancer development was hypothesized several decades ago, but until recently, data from prospective cohort studies were sparse. In the EPIC cohort, CRP levels above 10 mg/L were indicative of higher risk of epithelial ovarian cancer compared with levels of 1 mg/L or below (OR, 1.67; 95% CI, 1.03–2.70), and this relationship was more pronounced among overweight and obese women (Ose et al., 2015). Similar findings were reported from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, the Nurses' Health Study, and a combined analysis in the New York University Women's Health Study, the Northern Sweden Health and Disease Study, and ORDET Cohort, which all reported statistically significant positive associations between CRP levels and ovarian cancer risk when comparing levels above 10 mg/L with levels of 1 mg/L or below (Lundin et al., 2009; Poole et al., 2013; Trabert et al., 2014).

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial also identified significant associations between specific pro-inflammatory cytokines, namely TNF-α and IL-1α, and ovarian cancer risk (Trabert et al., 2014), and a case–control study nested within three prospective cohorts also found a significant link between specific cytokines related to a pro-inflammatory phenotype and ovarian cancer (Clendenen et al., 2011).

(v) Cancer at other sites

For cancer at other sites, studies of circulating inflammatory markers and adipokines are more sparse. Overall, there are inconsistent data for the association of leptin levels with prostate cancer risk (Table 4.5); one study reported a significant inverse relationship (Stocks et al., 2007), whereas other investigations generally reported null associations for both leptin and adiponectin (Hsing et al., 2001; Li et al., 2010; Lai et al., 2014).

Combined data from five cohorts in the USA yielded a significant inverse association between adiponectin levels and pancreatic cancer (OR_{q5-q1}, 0.63; 95% CI, 0.43–0.92) (Bao et al., 2013b). In the EPIC cohort, adiponectin was inversely related to pancreatic cancer risk, but only among never-smokers (Grote et al., 2012b).

Interestingly, data from a Japanese cohort and from the EPIC study reported a consistent positive association between circulating IL-6 levels and HCC development (Aleksandrova et al., 2014; Ohishi et al., 2014), with relative risks between 3 and 5. Levels of other cytokines and CRP were not associated with HCC in these studies.

(vi) Weight loss

Although the obesity–inflammation–cancer link is established for some cancers, namely CRC, the impact of IWL on inflammation and cancer risk has been much less studied. However, a consistent picture is emerging that IWL, particularly if more than 10%, can reverse some of the pro-inflammatory effects of obesity.

Most of the studies in humans that addressed weight loss and inflammation assessed systemic markers of inflammation, including CRP (the most consistently changed inflammatory marker with weight loss), IL-6, and TNF-α. One review included about 30 observational cohort studies or RCTs that used various modes of weight loss, including surgical, dietary, physical activity, or pharmacological interventions, and encompassed a large range of weight-loss attainment (Byers & Sedjo, 2011). Consistent decreases in circulating levels of CRP, TNF-α, and IL-6 were observed in studies that reported weight loss of more than 10%; the findings are less clear with more moderate (and more achievable and sustainable)

levels of weight loss achieved through diet and/or exercise interventions.

In the Nutrition and Exercise for Women RCT, high-sensitivity CRP, serum amyloid A (another acute-phase reactant protein that can stimulate CRP), IL-6, and neutrophil counts decreased statistically significantly in both the diet group and the diet plus exercise group. The intervention reduced high-sensitivity CRP by 36% in the diet group and by 42% in the diet plus exercise group. Women who lost more body weight (> 5%) experienced the largest reductions (e.g. 50% and 49% for high-sensitivity CRP with diet and diet plus exercise, respectively) (Imayama et al., 2012). In another study (Fabian et al., 2013), obese women who lost more than 10% of their body weight had reductions of about 30–50% in the leptin-to-adiponectin ratio, IL-6, and CRP levels in their serum, whereas women who lost less than 10% of their body weight had little or no change in systemic biomarkers. [There appears to be a threshold below which inflammatory markers fail to respond to weight loss; this may be due partly to sensitivity in the analytical methods and partly to limitations of statistical power, as well as the heterogeneity in marker levels before weight loss is initiated.]

Few studies investigated weight loss and changes in tissue-specific biomarkers of inflammation. Campbell et al. (2013) reported that in overweight or obese postmenopausal women, weight loss through a 6-month dietary intervention, exercise, or the combination of the two resulted in significant changes in adipose tissue gene expression; in addition to significant reductions in leptin mRNA expression, steroid hormone metabolism, inflammatory genes, and IGF signalling also appeared to be altered. In overweight or obese postmenopausal women who underwent a weight-loss intervention (Fabian et al., 2013), the adiponectin-to-leptin ratio in fine-needle aspirate of breast tissue increased in response to weight loss.

(vii) Synthesis

Obesity is associated with a state of chronic, low-grade inflammation triggered by adipose tissue remodelling and reflected in several local and systemic changes in the levels of adipokines (e.g. increased leptin; decreased adiponectin released from hypertrophied adipocytes), cytokines (e.g. increased IL-6, TNF-α, secreted from adipocytes and macrophages), and acute-phase reactant proteins (e.g. CRP, secreted primarily from the liver). These secretome changes are accompanied by changes in tissue markers of inflammation (such as crown-like structures) and cancer-associated intracellular signals (such as activation of the NF-κB pathway).

Emerging contributors to the obesity–inflammation–cancer relationship include (i) the COX-2/prostaglandin pathway, which can be particularly activated in adipocytes and macrophages in response to an obesity-associated abundance of free fatty acids (catalysed to inflammatory prostaglandins and other lipid intermediates); (ii) the microbiome, particularly the community of organisms residing in the gut that can release short-chain fatty acids and other metabolites that have pro-inflammatory activity.

Data from epidemiological studies of inflammatory markers and cancer development have generally shown consistent positive associations between circulating levels of CRP, a highly sensitive but nonspecific marker of the inflammatory response, and cancers of the breast and colorectum, and suggestive positive associations for cancers of the ovary and endometrium. However, the specific inflammatory pathways that mediate this relationship, and the extent to which it might be specific to certain ovarian cancer subtypes, remain unknown. In weight-loss intervention trials, CRP concentrations were generally reduced in the individuals who lost more than 5–10% of their initial body weight. Data on the associations of specific circulating cytokines and adipokines with obesity-related

cancers are generally more limited, possibly because of technical challenges in measuring these proteins, which typically circulate at very low concentrations. A number of studies have investigated these markers in relation to endometrial cancer, with inconsistent results.

4.3.5 Vitamin D

(a) Vitamin D and cancer

Vitamin D can induce cell differentiation and apoptosis and can also inhibit proliferation, inflammation, and angiogenesis, as well as invasion and metastasis (Fleet et al., 2012; Feldman et al., 2014; Castronovo et al., 2015; Davis-Yadley & Malafa, 2015; Christakos et al., 2016; Meeker et al., 2016) and thus may have cancer-preventive effects. Despite these strong experimental data, the epidemiological data on Vitamin D levels and cancer risk have been limited and heterogeneous. Cohort studies that measure the biomarker 25-hydroxyvitamin D (25(OH)D) pre-diagnostically have shown a consistent reduction of CRC risk in the range of 30–40% among individuals with high versus low levels (Feldman et al., 2014). However, a large RCT of vitamin D supplementation showed no effects in preventing the recurrence of colorectal adenoma (Baron et al., 2015). Similarly, a meta-analysis of prospective studies of prostate cancer showed no inverse association (Gilbert et al., 2011), and one study even suggested an increased risk with higher vitamin D levels (Brändstedt et al., 2012). For breast cancer, only some studies observed inverse associations, and these were not linear and were limited to postmenopausal women (Chlebowski et al., 2008; Bauer et al., 2013). [This pattern of cancer risk – preventive for colon cancer and, to some extent, postmenopausal breast cancer – mimics the associations of physical activity with cancer risk (IARC, 2002), and 25(OH)D is strongly associated with physical activity. Therefore, a direct interrelation or residual confounding by physical activity (particularly levels of outdoor physical activity, which tend to be poorly measured) cannot be excluded.] Further background information about vitamin D and cancer can be found in the IARC Working Group Report on vitamin D and cancer (IARC, 2008).

(b) Vitamin D and obesity

Increasing BMI has been consistently associated with lower serum 25(OH)D concentrations and higher parathyroid hormone concentrations (Vanlint, 2013; Pereira-Santos et al., 2015). Moreover, body fat content is inversely associated with serum 25(OH)D concentrations, and this association may be stronger than that with BMI and body weight alone (Arunabh et al., 2003; Vanlint, 2013).

In a recent meta-analysis, the prevalence of vitamin D deficiency was 35% higher in obese individuals compared with a normal-weight group, and 24% higher compared with overweight individuals. There were no significant differences in this proportion between children and adults; however, there was a significant degree of heterogeneity between studies overall (Pereira-Santos et al., 2015). [A challenge of this meta-analysis was the change in the definitions of vitamin D deficiency over time, although the results appeared to be consistent independent of the cut-off points used.]

There are multiple potential reasons for the inverse associations between obesity and vitamin D (Soares et al., 2012; Pereira-Santos et al., 2015). One theory is that because of issues of low social acceptance, obese individuals reduce their exposure to sunlight, cover up their bodies more, and are less active outdoors. Nevertheless, in the Framingham Heart Study cohort, adjustment for outdoor physical activity did not entirely attenuate this association (Cheng et al., 2010).

It has also been proposed that vitamin D metabolites are retained by excess body fat, and that cholecalciferol that is synthesized in the skin or taken up through the diet is in part sequestered by the body fat before transport to the

liver for hydroxylation (Wortsman et al., 2000). Adipocytes of obese individuals show significant levels of 1-α-hydroxylase, which activates vitamin D; this could explain the greater local use of vitamin D. This hypothesis is consistent with the observation that after exposure to sunlight, obese individuals have shown a 53% lower increase in 25(OH)D compared with non-obese individuals, independent of the amount of the cutaneous precursor of vitamin D (Pereira-Santos et al., 2015).

Alternatively, some experimental data suggest that vitamin D deficiency may facilitate adiposity by causing higher parathyroid hormone levels and greater influx of calcium into adipocytes, thereby increasing lipogenesis (Pereira-Santos et al., 2015). There are several additional mechanisms, investigated mainly in experiments in animals, that link vitamin D, through vitamin D receptor-mediated activity, directly to energy regulation and effects in adipocytes (Martini & Wood, 2006).

Finally, there is increasing experimental evidence that vitamin D may also have anti-inflammatory properties, presumably via effects on the state of low-grade chronic inflammation in adipose tissues (Fleet et al., 2012; Song & Sergeev, 2012; Feldman et al., 2014). In an RCT of 218 postmenopausal women with BMI ≥ 25 kg/m^2 who underwent 12 months of weight-loss intervention plus either 2000 IU/day of oral vitamin D_3 or daily placebo, significantly decreased circulating levels of IL-6 were reported with vitamin D in an analysis stratified by weight loss ($P = 0.004$) (Duggan et al., 2015).

(c) Vitamin D and weight loss

Several studies have demonstrated effects of weight loss on improving vitamin D biomarker status in obese individuals.

Tzotzas et al. (2010) investigated changes of 25(OH)D at 4 weeks and 20 weeks after introduction of a weight-loss programme (low-calorie diet of ~1000 kcal/day) among 44 obese women. At baseline, 25(OH)D levels were lower in the obese women than in 25 normal-weight controls ($P < 0.001$). The 20-week low-calorie diet (26 completers) resulted in reductions of body weight and BMI by 10% and an increase in 25(OH)D (15.4 ± 6.0 ng/mL vs 18.3 ± 5.1 ng/mL, $P < 0.05$), compared with baseline. This increase was also associated with improvement in insulin resistance and the homeostasis model assessment index.

Rock et al. (2012) prospectively examined the effects of weight loss on serum 25(OH)D concentrations in 383 overweight or obese women who participated in a 2-year clinical trial of a weight-loss programme and recommendation to increase physical activity. More than half of the women lost at least 5% of baseline weight by 24 months, and serum 25(OH)D levels increased at the end of the intervention period, with a linear trend towards greater increases in women who lost more weight; 25(OH)D increased by 5.0 ng/mL for those who lost more than 10% of baseline weight ($P = 0.014$). [Although the programme included some increase in physical activity, this was not a major component of the intervention, and the resulting greater sun exposure during outdoor activity is unlikely to explain the observed effect.]

In 192 obese patients with knee osteoarthritis, Christensen et al. (2012) tested an 8-week formula weight-loss diet of 415–810 kcal/day, followed by 8 weeks on a hypo-energetic 1200 kcal/day diet combining normal food and formula products. They reported that this intensive programme increased bone mineral density and improved 25(OH)D concentrations. [It is not clear whether this increase in 25(OH)D was attributable to the effects of the calorie restriction or the supplementation with vitamin D as part of the formula.]

Several studies have also investigated the effects of bariatric surgery on vitamin D status, and suggest decreases in vitamin D status with surgery (Karefylakis et al., 2014; Costa et al., 2015; Luger et al., 2015). [This type of weight-loss

intervention can alter the resorption of dietary vitamin D, and therefore is not considered informative.]

(d) Synthesis

Vitamin D status can directly affect many cellular processes relevant to cancer prevention. Prospective studies of the blood biomarker 25(OH)D have found consistent inverse associations with CRC, and to a lesser extent with postmenopausal breast cancer. There is a clear inverse relationship between obesity and vitamin D status, but the causes for this association are not well defined and may range from societal factors and links via physical activity to physiological changes in the adipose tissue that result in a sequestering of vitamin D metabolites; weight loss appears to improve 25(OH)D status. The experimental data are limited and do not further inform the role of vitamin D as a mediator in the effect of obesity on cancer risk.

4.3.6 Other factors

This section summarizes factors that may play a role in mediating the obesity–cancer connection but for which there are limited data.

(a) The gut microbiome

Obesity is associated with an overall reduction in bacterial diversity in the gut microbiota (Turnbaugh et al., 2009) (see Section 1.3.8), and decreased bacterial richness has been linked to elevated systemic inflammation, measured by plasma CRP levels and white blood cell counts (Le Chatelier et al., 2013). Furthermore, weight loss does not significantly improve CRP levels in obese individuals with low microbiome richness (Cotillard et al., 2013), suggesting that resistance to the inflammation-reducing effects of weight loss may be mediated by differences in microbiome richness. Feeding mice a high-fat diet is accompanied by impairments in gut barrier function, including increased plasma levels of lipopolysaccharide, a component of the outer membrane of Gram-negative bacteria (Cani et al., 2008); lipopolysaccharide induces metabolic endotoxaemia, characterized by elevated infiltration of adipose tissue by macrophages and elevated expression of pro-inflammatory cytokines (Cani et al., 2007), thus inducing chronic systemic and adipose tissue inflammation. These effects were completely prevented by treatment with a broad-spectrum antibiotic (Cani et al., 2008). Given the known role that this type of inflammation plays in the progression of many cancer types (see Section 4.3.4), it is plausible that obesity-induced perturbations of the gut microbiota are a contributing factor in the obesity–cancer link.

(b) Gut hormones

The role of gut hormones and appetite regulatory factors in cancer development is an emerging area of research, and may be a mechanism linking obesity with cancer. Ghrelin, a hormone produced in the gastric fundic glands, is known to mediate appetite and fatty acid metabolism and to promote fat storage (Higgins et al., 2007). Ghrelin can also inhibit the expression and/or production of pro-inflammatory cytokines, and ghrelin treatment increases anti-inflammatory cytokines (Gonzalez-Rey et al., 2006; Baatar et al., 2011) (see Section 1.3.1).

In the three small prospective studies of the association of ghrelin with gastrointestinal cancer development, individuals in the lowest quartile of serum ghrelin at baseline, compared with those in the highest quartile, had an increased risk of oesophageal adenocarcinoma (31 cases; OR, 5.55; 95% CI, 1.28–25.0) (de Martel et al., 2007), oesophageal squamous cell carcinoma (82 cases; OR, 6.83; 95% CI, 1.46–31.84) (Murphy et al., 2012), gastric cardia cancer (98 cases; OR, 4.90; 95% CI, 2.11–11.35), and gastric non-cardia cancer (261 cases; OR, 5.63; 95% CI, 3.16–10.03) (Murphy et al., 2011). There is considerable cross-talk between ghrelin and other hormones

involved in energy metabolism, such as leptin, adiponectin, and insulin, and as more data become available on the association of ghrelin with cancer development, the gut hormones may emerge as an important pathway linking obesity with cancer development.

(c) *Non-alcoholic fatty liver and pancreatic diseases*

Obesity is the most common cause of non-alcoholic fatty liver disease (NAFLD), a spectrum of diseases including variable degrees of simple steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis (Papandreou & Andreou, 2015). Simple steatosis is benign, whereas NASH is characterized by hepatocyte injury, inflammation, and/or fibrosis, which can lead to cirrhosis, liver failure, and HCC (Hui et al., 2003). About 80% of cases of cryptogenic cirrhosis [end-stage liver disease of unknown etiology] present with NASH, and 0.5% of these cases will progress to HCC, a percentage that increases significantly with hepatitis C-associated cirrhosis (White et al., 2012). The prevalence of NAFLD has increased concomitantly with the increase in childhood obesity over the past 30 years (Berardis & Sokal, 2014).

Adipocyte infiltration and fat accumulation in the pancreas appear to be early events in obesity-associated pancreatic endocrine dysfunction, and can trigger pancreatic steatosis, non-alcoholic fatty pancreatic disease (NAFPD), and subclinical pancreatitis. In addition, "fatty pancreas" has been positively associated with visceral white adipose tissue mass and systemic insulin resistance (van Geenen et al., 2010; Smits & van Geenen, 2011). Together, pancreatic steatosis and NAFPD contribute to the already complex metabolic and inflammatory perturbations associated with obesity and metabolic syndrome.

(d) *Immune function*

The major mechanisms relating immunity to obesity focus on the inflammatory response that originates in the adipose tissue (see Section 4.3.4). For a description of the innate immune response to obesity, see Lumeng (2013).

Studies investigating immune competence in relation to calorie restriction or IWL are few. One cross-sectional study in 114 overweight or obese postmenopausal women reported that natural killer cell cytotoxicity (assessed by flow cytometry at four effector-to-target ratios) was inversely associated with increasing frequency of prior IWL (P_{trend} = 0.003) (Shade et al., 2004). Conversely, longer duration of recent weight stability was associated with significantly greater natural killer cell cytotoxicity (21.6% ± 11.9%, 24.4% ± 11.0%, and 31.9% ± 14.4% for ≤ 2, > 2 to ≤ 5, and > 5 years of weight stability, respectively; P_{trend} = 0.0002).

In one RCT, 91 obese women were randomized to control (n = 22), exercise (n = 21), diet (n = 26), or exercise plus diet (n = 22) groups. After 12 weeks of calorie restriction (1200–1300 kcal/day) with weight loss of about 9%, mitogen-stimulated lymphocyte proliferation was significantly reduced, whereas no changes were observed in natural killer cell cytotoxicity, monocyte and granulocyte phagocytosis and oxidative burst activity, or the number of days with upper respiratory tract infections (Nieman et al., 1998).

(e) *Cancer stem cells*

A link between obesity and cancer stem cells has been identified by Zheng et al. (2011), who showed that spontaneous tumours derived from mouse mammary tumour virus (MMTV)-Wnt-1 transgenic mice, when transplanted, were highly dependent on leptin for growth. Thus, when these tumours were transplanted into obese, leptin receptor-deficient ($Lepr^{db}/Lepr^{db}$) mice with high leptin concentrations, they grew to 8

times the volume of those tumours transplanted into wild-type mice, whereas in leptin-deficient (*Lep*^{ob}/*Lep*^{ob}) mice, tumour growth was impaired. The residual tumours in *Lep*^{ob}/*Lep*^{ob} mice were found to have fewer "cancer stem cells", and these cells were characterized by flow cytometry to express leptin receptor. When isolated by leptin receptor expression, these cells exhibited stem cell properties based on the ability to form tumourspheres in vitro, and their survival was regulated by leptin. Dunlap et al. (2012) used two types of cells – mesenchymal (M-Wnt) or epithelial (E-Wnt) – derived from spontaneous mammary tumours in MMTV-Wnt-1 mice, transplanted into ovariectomized C57BL/6 mice to emulate human claudin-low and basal-like breast tumours, respectively. They reported that M-Wnt, but not E-Wnt, mammary tumour cells were stably enriched in breast cancer cell markers, and exhibited stem cell properties. In addition, M-Wnt cells orthotopically injected into mice rapidly formed claudin-low tumours that were highly responsive to the tumour-enhancing effects of obesity, as well as the anti-cancer effects of DR.

(f) Synthesis

Emerging factors that are likely to contribute to the obesity–cancer link, but for which there is currently insufficient data, include the gut microbiome, gut hormones (such as ghrelin produced by the stomach), NAFLD (which drives secretion of CRP and other inflammation-related factors), the immune function, and cancer stem cells.

Table 4.1 Effect of obesity and weight reduction on selected serological factors involved in the carcinogenesis process

Serological factor	Obesity	Weight reduction
Sex hormones		
Estradiol	Increase	Decrease
Sex hormone-binding globulin	Decrease	Increase
Testosterone	Decrease (men) Increase (women)	Increase (men) Decrease (women)
Insulin and IGF-1		
Insulin	Increase	Decrease
IGF-1	Increase (overweight) Decrease (obese)	Decrease
IGFBP-1	Decrease	Increase
IGFBP-3	—	—
Inflammation		
Adiponectin	Decrease	Increase
Leptin	Increase	Decrease
C-reactive protein	Increase	Decrease

IGF-1, insulin-like growth factor 1; IGFBP, IGF binding protein.
Compiled by the Working Group.

Table 4.2 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the breast

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Hankinson et al. (1998b); USA; Nurses' Health Study	Nested case–control; 156, 312	Steroids: extraction, separation by column chromatography, radioimmunoassay Estrone sulfate: enzyme hydrolysis, organic extraction, separation by column chromatography, radioimmunoassay DHEAS: radioimmunoassay	Estradiol, quartiles RR = 1.91 (1.06–3.46), P_{trend} = 0.03 Estrone, quartiles RR = 1.96 (1.05–3.65), P_{trend} = 0.01 Estrone sulfate, quartiles RR = 2.25 (1.23–4.12), P_{trend} = 0.01 DHEAS, quartiles RR = 2.15 (1.11–4.17), P_{trend} = 0.01 Percentage free or percentage bioavailable estradiol, androstenedione, testosterone, DHEAS: NS
Key et al. (2002); USA, Japan, Italy; 9 prospective studies	Pooled analysis; 663, 1765; postmenopausal	NR	Estradiol, quintiles RR = 2.00 (1.47–2.71), P_{trend} < 0.001 Free estradiol, quintiles RR = 2.58 (1.76–3.78), P_{trend} < 0.001 Estrone, quintiles RR = 2.19 (1.48–3.22), P_{trend} < 0.001 Estrone sulfate RR = 2.00 (1.26–3.16), P_{trend} < 0.001 DHEA, quintiles RR = 2.04 (1.21–3.45), P_{trend} = 0.18 DHEAS, quintiles RR = 1.75 (1.26–2.43), P_{trend} = 0.002 Testosterone, quintiles RR = 2.22 (1.59–3.10), P_{trend} < 0.001 SHBG, quintiles RR = 0.66 (0.43–1.00), P_{trend} = 0.041
Kaaks et al. (2005); several European countries; EPIC	Nested case–control; 677, 1309; postmenopausal	DHEAS and testosterone: radioimmunoassay Androstenedione, estrone, estradiol, and SHBG: double-antibody radioimmunoassay	Estradiol, quintiles RR = 2.28 (1.61–3.23), P_{trend} < 0.0001 Free estradiol, quintiles RR = 2.13 (1.52–2.98), P_{trend} < 0.0001 Estrone, quintiles RR = 2.07 (1.42–3.02), P_{trend} = 0.0001 SHBG, quintiles RR = 0.61 (0.44–0.84), P_{trend} = 0.004 Testosterone, quintiles RR = 1.85 (1.33–2.57), P_{trend} < 0.0001 Free testosterone, quintiles RR = 2.50 (1.76–3.55), P_{trend} < 0.0001 Androstenedione, quintiles RR = 1.94 (1.40–2.69), P_{trend} < 0.0001 DHEAS, quintiles RR = 1.69 (1.23–2.33), P_{trend} = 0.0002
Gunter et al. (2009); USA; Women's Health Initiative Observational Study	Case–cohort; 835, 816	Vitros ECi immunodiagnostic assay	Estradiol, tertiles All, HR = 1.59 (1.00–2.55), P_{trend} = 0.04 Non-HRT users, HR = 1.59 (1.00–2.55), P_{trend} = 0.04 Further adjustments, HR = 1.87 (1.11–3.15), P_{trend} = 0.03

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Baglietto et al. (2010); Australia; Melbourne Collaborative Cohort Study	Case–cohort; 197, 857; postmenopausal	Estradiol and testosterone: electrochemiluminescence immunoassay Estrone sulfate: radioimmunoassay DHEAS: competitive immunoassay Androstenedione: radioimmunoassay SHBG: immunometric assay	Total estradiol, quartiles HR = 1.44 (0.89–2.35), P_{trend} = 0.12 Free estradiol, quartiles HR = 1.75 (1.06–2.89), P_{trend} = 0.01 Estrone sulfate, quartiles HR = 2.05 (1.24–3.37), P_{trend} < 0.01 Testosterone, quartiles HR = 1.25 (0.78–2.01), P_{trend} = 0.37 DHEAS, quartiles HR = 1.41 (0.88–2.27), P_{trend} = 0.17 Androstenedione, quartiles HR = 1.49 (0.91–2.44), P_{trend} = 0.08 SHBG, quartiles HR = 0.33 (0.19–0.55), P_{trend} < 0.01
Farhat et al. (2011); USA; Women's Health Initiative Observational Study	Case–cohort; 317, 594; postmenopausal	Radioimmunoassay	Estradiol, quartiles ER+, HR = 1.86 (1.00–3.45), P_{trend} = 0.08 ER–, HR = 0.83 (0.43–1.61), P_{trend} = 0.60 Testosterone, quartiles ER+, HR = 1.55 (0.92–1.61), P_{trend} = 0.04 ER–, HR = 0.51 (0.28–0.94), P_{trend} = 0.03
James et al. (2011); several European countries; EPIC	Nested case–control; 554, 821; postmenopausal	Radioimmunoassay	Estradiol, ER+ Tertiles, OR = 2.58 (1.69–3.92), P_{trend} < 0.0001 Continuous, OR = 1.63 (1.29–2.107) Estradiol, ER+/PR+ Tertiles, OR = 2.91 (1.62–5.23), P_{trend} = 0.002 Continuous, OR = 1.58 (1.17–2.12) Free estradiol, ER+ Tertiles, OR = 2.05 (1.39–3.02), P_{trend} = 0.003 Continuous, OR = 1.63 (1.31–2.02) Free estradiol, ER+/PR+ Tertiles, OR = 2.09 (1.23–3.54), P_{trend} = 0.01 Continuous, OR = 1.61 (1.21–2.13) Testosterone, ER+ Tertiles, OR = 1.68 (1.16–2.44), P_{trend} = 0.006 Continuous, OR = 1.54 (1.27–1.87) Testosterone, ER+/PR+ Tertiles, OR = 2.27 (1.35–3.81), P_{trend} = 0.002 Continuous, OR = 1.79 (1.36–2.36)

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Tworoger et al. (2011); USA; Nurses' Health Study	Nested case–control; 265, 541; postmenopausal	Radioimmunoassay	Estrone, quintiles All, RR = 2.1 (1.3–3.4) ER+, RR = 2.8 (1.5–5.3) Estradiol, quintiles All, RR = 2.4 (1.4–4.1) ER+, RR = 2.9 (1.4–5.9) Estrone sulfate, quintiles All, RR = 2.4 (1.5–3.9) ER+, RR = 2.2 (1.2–4.0) Testosterone, quintiles All, RR = 1.8 (1.1–2.9) ER+, RR = 2.0 (1.0–3.7) Androstenedione, quintiles All, RR = 2.1 (1.3–3.6) ER+, RR = 2.6 (1.3–5.0) DHEA, quintiles All, RR = 1.5 (0.9–2.4) ER+, RR = 1.6 (0.9–2.9) DHEAS, quintiles All, RR = 2.5 (1.4–4.2) ER+, RR = 2.0 (1.0–3.8)
Fuhrman et al. (2012); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 227, 423; postmenopausal	LC-MS	Unconjugated estradiol, continuous HR = 2.07 (1.19–3.62), P_{trend} = 0.01 2-Hydroxylation pathway, continuous HR = 0.66 (0.51–0.87), P_{trend} = 0.003 2/16-Hydroxylation pathway, continuous HR = 0.62 (0.45–0.86), P_{trend} = 0.05
Sieri et al. (2012); Italy; ORDET Cohort	Nested case–control; 356; 1537	Chemiluminescence immunoassay	SHBG, quartiles, diagnosis > 55 yr RR = 0.60 (0.36–0.99), P_{trend} = 0.059
Würtz et al. (2012); Denmark; Diet, Cancer and Health Cohort	Nested case–control; 348, 348; postmenopausal	Radioimmunoassay	Non-HRT users Estradiol, tertiles RR = 1.56 (0.70–3.51), P_{trend} = 0.55 Estrone, tertiles RR = 2.02 (0.83–4.89), P_{trend} = 0.06 Estrone sulfate, tertiles RR = 4.21 (1.81–9.81), P_{trend} = 0.01

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Fortner et al. (2013); USA; Nurses' Health Study II	Nested case–control; 634, 1264 (514, 1030 with timed samples)	Estrogens and testosterone: organic extraction, celite chromatography, radioimmunoassay SHBG and progesterone: automated immunoassay or chemiluminescence immunometric assay	Follicular phase Estradiol, all Quintiles, OR = 1.0 (0.7–1.5), P_{trend} = 0.76 Doubling, OR = 0.6 (0.4–0.9), P_{trend} < 0.01 Estradiol, invasive Doubling, OR = 0.6 (0.4–0.9), P_{trend} < 0.01 Estradiol, ER+/PR+ Doubling, OR = 0.6 (0.4–0.9), P_{trend} = 0.01 Free estradiol, all Quintiles, OR = 0.8 (0.5–1.3), P_{trend} = 0.48 Doubling, OR = 0.5 (0.4–0.8), P_{trend} < 0.01 Free estradiol, invasive Doubling, OR = 0.5 (0.4–0.7), P_{trend} < 0.01 Free estradiol, ER+/PR+ Doubling, OR = 0.4 (0.4–0.7), P_{trend} < 0.01 Testosterone, all Quintiles, OR = 1.2 (0.9–1.7), P_{trend} = 0.32 SHBG, all Quintiles, OR = 1.2 (0.8–1.6), P_{trend} = 0.23
Key et al. (2013); USA, United Kingdom, several European countries; 7 prospective studies	Pooled analysis; 767, 1699	Radioimmunoassay, competitive immunoassay, LC-MS	Estradiol, quintiles OR = 1.41 (1.02–1.95), P_{trend} = 0.0042 Calculated free estradiol, quintiles OR = 1.19 (0.86–1.64), P_{trend} = 0.014 Estrone, quintiles OR = 1.50 (1.02–2.19), P_{trend} = 0.014 Androstenedione, quintiles OR = 1.68 (1.18–2.39), P_{trend} = 0.0026 DHEAS, quintiles OR = 1.45 (1.07–1.95), P_{trend} = 0.010 Testosterone, quintiles OR = 1.32 (0.98–1.76), P_{trend} = 0.018 Calculated free testosterone, quintiles OR = 1.25 (0.94–1.66), P_{trend} = 0.15
Schernhammer et al. (2013); Italy; ORDET Cohort	Nested case–control; 104, 225; premenopausal	Estradiol: radioimmunoassay Testosterone and free testosterone: radioimmunoassay SHBG: chemiluminescence immunometric assay	Free testosterone, tertiles OR = 2.43 (1.15–5.10), P_{trend} = 0.03 Total testosterone, tertiles OR = 1.27 (0.62–2.61), P_{trend} = 0.51 Progesterone, tertiles OR = 1.16 (0.60–2.27), P_{trend} = 0.75 Estradiol, tertiles OR = 0.69 (0.35–1.35), P_{trend} = 025 SHBG, tertiles OR = 0.93 (0.50–1.72), P_{trend} = 0.78

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Zhang et al. (2013); USA; Nurses' Health Study	Nested case–control; 707; 1414	Radioimmunoassay or LC-MS or solid-phase competitive chemiluminescence enzyme immunoassay	Estradiol, quartiles RR = 2.1 (1.6–2.7), P_{trend} < 0.001 Free estradiol, quartiles RR = 1.9 (1.4–2.4), P_{trend} < 0.001 Testosterone, quartiles RR = 1.5 (1.2–1.9), P_{trend} < 0.001 Free testosterone, quartiles RR = 1.9 (1.5–2.5), P_{trend} < 0.001 DHEAS, quartiles RR = 1.7 (1.3–2.3), P_{trend} = 0.001 SHBG, quartiles RR = 0.68 (0.52–0.88), P_{trend} = 0.004
Dallal et al. (2014); USA; Breast and Bone Follow-up to the Fracture Intervention Trial	Case–cohort; 407, 496; postmenopausal	LC-MS	Estradiol, quintiles HR = 1.86 (1.19–2.90), P_{trend} = 0.04 2-Hydroxylation pathway, quintiles HR = 0.69 (0.46–1.05), P_{trend} = 0.01 4-Hydroxylation pathway, quintiles HR = 0.61 (0.40–0.93), P_{trend} = 0.004 2/16-Hydroxylation pathway, quintiles HR = 0.60 (0.40–0.90), P_{trend} = 0.002
Kaaks et al. (2014b); several European countries; EPIC	Nested case–control; 801, 1132	Estradiol: immunoassay Progesterone and testosterone: radioimmunoassay SHBG: sandwich immunoradiometric assay	Estradiol, quartiles OR = 1.04 (0.93–1.15), P_{trend} = 0.52 Progesterone, quartiles OR = 1.00 (0.89–1.13), P_{trend} = 0.98 SHBG, quartiles OR = 0.98 (0.88–1.08), P_{trend} = 0.64 Testosterone, quartiles OR = 1.56 (1.15–2.13), P_{trend} = 0.02 Free testosterone, quartiles OR = 1.33 (0.99–1.79), P_{trend} = 0.04
Insulin			
Toniolo et al. (2000); USA; New York University Women's Health Study	Nested case–control; premenopausal: 172, 486; postmenopausal: 115, 220	Radioimmunoassay	C-peptide, quartiles Premenopausal, RR = 0.76 (0.44–1.31), P_{trend} = 0.90 Postmenopausal, RR = 1.24 (0.66–2.34), P_{trend} = 0.58
Kaaks et al. (2002); Sweden; Umeå Cohort	Nested case–control; 246, 454	Double-antibody immunoradiometric assay	Insulin, quartiles OR = 0.59 (0.30–1.18), P_{trend} = 0.88
Mink et al. (2002); USA; Atherosclerosis Risk in Communities Study Cohort	Cohort; 189, 7705	Radioimmunoassay	Insulin, quartiles RR = 1.01 (0.55–1.86), P_{trend} = 0.87
Muti et al. (2002); Italy; ORDET Cohort	Nested case–control; premenopausal: 69, 265; postmenopausal: 64, 238	Double-antibody radioimmunoassay	Insulin, quartiles Premenopausal, RR = 1.72 (0.71–4.15), P_{trend} = 0.14 Postmenopausal, RR = 0.85 (0.36–2.00), P_{trend} = 0.76

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Keinan-Boker et al. (2003); The Netherlands; EPIC, PPHV	Nested case–control; EPIC: 71, 163; PPHV: 78, 170; postmenopausal	Competitive radioimmunoassay	C-peptide, quartiles OR = 1.3 (0.7–2.7)
Verheus et al. (2006); several European countries; EPIC	Nested case–control; 1141, 2204	Radioimmunoassay	C-peptide, quintiles Non-fasting ≤ 50 yr, OR = 0.74 (0.30–1.82), P_{trend} = 0.35 50–60 yr, OR = 1.08 (0.56–2.08), P_{trend} = 0.51 > 60 yr, OR = 1.69 (0.97–2.95), P_{trend} = 0.22 Fasting, all ORs: NS
Cust et al. (2009); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 561, 561	Radioimmunoassay	C-peptide, tertiles < 55 yr, OR = 0.75 (0.44–1.29), P_{trend} = 0.34 ≥ 55 yr, OR = 1.32 (0.84–2.05), P_{trend} = 0.20
Gunter et al. (2009); USA; Women's Health Initiative Observational Study	Case–cohort; 835, 816; postmenopausal	ELISA	Insulin, quartiles HR = 1.46 (1.00–2.13), P_{trend} = 0.2 Non-HRT users, HR = 2.48 (1.38–4.47), P_{trend} < 0.001 Adjusted also for estradiol, HR = 2.40 (1.30–4.41), P_{trend} < 0.001
Kabat et al. (2009); USA; Women's Health Initiative	Longitudinal study; 190, 5450; postmenopausal	ELISA	Insulin, tertiles HR = 2.22 (1.39–3.53), P_{trend} = 0.0008
Tworoger et al. (2011); USA; Nurses' Health Study	Nested case–control; 265, 541	ELISA	C-peptide, quintiles All, RR = 1.4 (0.8–2.4)
Sieri et al. (2012); Italy; ORDET Cohort	Nested case–control; 356, 1537	Chemiluminescence immunoassay	Insulin, quartiles Premenopausal, RR = 1.52 (0.92–2.51), P_{trend} = 0.08 Postmenopausal, RR = 1.31 (0.81–2.12), P_{trend} = 0.25
Parekh et al. (2013); USA; Framingham Heart Study-Offspring Cohort	Cohort; 217, 2152	NR	Insulin, tertiles HR = 1.41 (0.88–2.24), P_{trend} = 0.33
IGFs			
Hankinson et al. (1998b); USA; Nurses' Health Study	Nested case–control; 397, 620	ELISA	IGF-1 Premenopausal, tertiles RR = 2.33 (1.06–5.16), P_{trend} = 0.08 Adjusted for IGFBP-3, RR = 2.88 (1.21–6.85), P_{trend} = 0.02 Premenopausal, < 50 yr at blood collection, tertiles RR = 4.58 (1.75–12.0), P_{trend} = 0.02 Adjusted for IGFBP-3, RR = 7.28 (2.40–22.0), P_{trend} = 0.01 Postmenopausal, quintiles RR = 0.85 (0.53–1.39), P_{trend} = 0.63

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Toniolo et al. (2000); USA; New York University Women's Health Study	Nested case–control; premenopausal: 172, 486; postmenopausal: 115, 220	Radioimmunoassay	IGF-1 Premenopausal, quartiles OR = 1.60 (0.91–2.81), P_{trend} = 0.09 Adjusted for IGFBP-3, OR = 1.49 (0.80–2.79) Premenopausal, < 50 yr at blood collection, quartiles OR = 2.30 (1.07–4.94), P_{trend} = 0.03 Adjusted for IGFBP-3, OR = 1.90 (0.82–4.42) Postmenopausal, quintiles OR = 0.95 (0.49–1.86), P_{trend} = 0.87
Kaaks et al. (2002); Sweden; Umeå and Malmö Cohorts	Nested case–control; 513, 987	Double-antibody immunoradiometric assay	IGF-1, quartiles OR = 1.17 (0.84–1.63), P_{trend} = 0.55 < 50 yr at recruitment, OR = 0.63 (0.29–2.39) ≥ 50 yr at recruitment, OR = 1.29 (0.80–2.07)
Muti et al. (2002); Italy; ORDET Cohort	Nested case–control; premenopausal: 69, 265; postmenopausal: 64, 238	Double-antibody immunoradiometric assay	IGF-1, quartiles Premenopausal, RR = 3.12 (1.13–8.60), P_{trend} = 0.01 Postmenopausal, RR = 0.58 (0.24–1.36), P_{trend} = 0.25 All other analytes: NS
Keinan-Boker et al. (2003); The Netherlands; EPIC, PPHV	Nested case–control; 149, 333; postmenopausal	Immunoradiometric assay	IGF-1, quartiles OR = 1.1 (0.6–2.1)
Allen et al. (2005); United Kingdom; Guernsey Cohort	Nested case–control; premenopausal: 70, 209; postmenopausal: 47, 141	Double-antibody ELISA	IGF-1, tertiles Premenopausal, OR = 1.71 (0.74–3.95), P_{trend} = 0.21 Postmenopausal, OR = 0.73 (0.29–1.84), P_{trend} = 0.52
Rinaldi et al. (2005); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study Cohort, ORDET Cohort	Nested case–control; 220, 434; premenopausal	ELISA	IGF-1, quintiles OR = 1.41 (0.75–2.63), P_{trend} = 0.15
Lukanova et al. (2006); Sweden; Northern Sweden Maternity Cohort	Nested case–control; 212, 369	Immunoradiometric assay	IGF-1, tertiles OR = 1.7 (1.1–2.7), P_{trend} = 0.02

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Baglietto et al. (2007); Australia; Melbourne Collaborative Cohort Study	Case–cohort; 423, 1901	ELISA	IGF-1, quartiles All, HR = 1.20 (0.87–1.65), P_{trend} = 0.38 Premenopausal, HR = 0.83 (0.49–1.38), P_{trend} = 0.29 Postmenopausal, HR = 1.59 (1.03–2.44), P_{trend} = 0.05 ≥ 60 yr at follow-up, HR = 1.61 (1.04–2.51), P_{trend} = 0.06
Vatten et al. (2008); Norway; Janus Biobank	Nested case–control; 325, 647	Double-antibody radioimmunoassay	IGF-1, quintiles, adjusted for IGFBP-3 OR = 1.46 (0.93–2.32), P_{trend} = 0.15 IGFBP-3, quintiles, adjusted for IGF-1 OR = 0.78 (0.49–1.23), P_{trend} = 0.12 T3 for IGF-1 and T1 for IGFBP-3 (tertiles) OR = 2.00 (1.01–3.96)
Gunter et al. (2009); USA; Women's Health Initiative Observational Study	Case–cohort; 835, 816; postmenopausal	ELISA	Total IGF-1, quartiles All, HR = 1.21 (0.85–1.72), P_{trend} = 0.92 Non-HRT users, HR = 0.99 (0.59–1.64), P_{trend} = 0.72
Sakauchi et al. (2009); Japan; Japan Collaborative Cohort Study	Nested case–control; 63, 187	Immunoradiometric assay	IGF-1, tertiles Premenopausal, OR = 1.2 (0.32–4.09), P_{trend} = 0.81 Postmenopausal, OR = 2.8 (0.73–10.6), P_{trend} = 0.17
Key et al. (2010); 12 countries; 17 prospective studies	Pooled analysis; 4790, 9428	NR	IGF-1, quintiles All, OR = 1.28 (1.14–1.44), P_{trend} < 0.0001 Premenopausal, OR = 1.21 (1.00–1.45), P_{trend} = 0.50 Postmenopausal, OR = 1.33 (1.14–1.55), P_{trend} = 0.0002 IGFBP-3, quintiles All, OR = 1.3 (0.99–1.28), P_{trend} < 0.062 IGFBP-3, quintiles Premenopausal, OR = 1.00 (0.82–1.22), P_{trend} = 0.921 Postmenopausal, OR = 1.23 (1.04–1.45), P_{trend} = 0.012
Tworoger et al. (2011); USA; Nurses' Health Study	Nested case–control; 265, 541; postmenopausal	ELISA	IGF-1, quintiles RR = 1.1 (0.6–2.0)

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Kaaks et al. (2014a); several European countries; EPIC	Nested case–control; 938, 1394	ELISA	IGF-1, all Quartiles, OR = 1.34 (1.0–1.78) IGF-1, ER+ Quartiles, OR = 1.41 (1.01–1.98) Continuous, OR = 1.17 (1.04–1.33), P_{trend} = 0.01 IGF-1, ER+, diagnosis ≥ 50 yr Tertiles, OR = 1.38 (1.01–1.89) Continuous, OR = 1.19 (1.04–1.36), P_{trend} = 0.01
Inflammatory factors			
Krajcik et al. (2003); USA; Kaiser Permanente Medical Care Program	Nested case–control; 81, 81; premenopausal	ELISA	TNF-α, quartiles OR = 0.60 (0.15–2.31), P_{trend} = 0.45 sTNFR1, quartiles OR = 0.67 (0.20–2.25), P_{trend} = 0.78 sTNFR2, quartiles OR = 0.46 (0.06–3.50), P_{trend} = 0.63
Stattin et al. (2004a); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 149, 258; postmenopausal	Double-antibody radioimmunoassay	Leptin, quartiles OR = 0.94 (0.53–1.67), P_{trend} = 0.54
Siemes et al. (2006); The Netherlands; Rotterdam Study	Cohort; 184, 3790	Particle immunoassay	CRP Tertiles, HR = 1.59 (1.05–2.41) > 3 vs < 1 mg/L, HR = 1.68 (1.14–2.47) Continuous, HR = 1.28 (1.07–1.54)
Tworoger et al. (2007a); USA; Nurses' Health Study and Nurses' Health Study II Cohorts	Nested case–control; 1477, 296	Radioimmunoassay	Adiponectin, quartiles RR = 0.89 (0.71–1.11), P_{trend} = 0.54 Postmenopausal, RR = 0.73 (0.55–0.98), P_{trend} = 0.08
Allin et al. (2009); Denmark; Copenhagen City Health Study	Cohort; 202, 1624	Turbidimetry/nephelometry	CRP Quintiles, OR = 0.9 (0.5–1.7) > 3 vs < 1 mg/L, HR = 0.7 (0.4–1.4)
Cust et al. (2009); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 561, 561	Double-antibody radioimmunoassay	Leptin, tertiles < 55 yr, OR = 0.80 (0.52–1.22), P_{trend} = 0.29 ≥ 55 yr, OR = 1.15 (0.76–1.74), P_{trend} = 0.53 Stage I, OR = 0.64 (0.41–1.00), P_{trend} = 0.06 Stage II–IV, OR = 1.37 (0.91–1.06), P_{trend} = 0.14 Adiponectin, tertiles < 55 yr, OR = 0.56 (0.28–1.11), P_{trend} = 0.08 ≥ 55 yr, OR = 0.96 (0.55–1.65), P_{trend} = 0.95 Stage I, OR = 0.74 (0.40–1.38), P_{trend} = 0.42 Stage II–IV, OR = 0.83 (0.46–1.51), P_{trend} = 0.53
Harris et al. (2011); USA; Nurses' Health Study II	Nested case–control; 330, 636; premenopausal	Enzyme immunoassay	Leptin, quartiles OR = 0.55 (0.31–0.99), P_{trend} = 0.04

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Gaudet et al. (2013); Cancer Prevention Study-II Nutrition Cohort	Nested case–control; 302, 302; postmenopausal	ELISA	Total adiponectin, tertiles OR = 0.84 (0.54–1.30), P_{trend} = 0.38 CRP, tertiles OR = 1.09 (0.70–1.70), P_{trend} = 0.16
Gross et al. (2013); USA; CLUE II Cohort	Nested case–control; 272, 272; postmenopausal	ELISA	Leptin, tertiles OR = 1.98 (1.20–3.29), P_{trend} = 0.05 Adiponectin, tertiles OR = 1.63 (1.02–2.60), P_{trend} = 0.08 sTNFR2, tertiles OR = 2.44 (1.30–4.58), P_{trend} = 0.008
Liu et al. (2013); 13 studies	Meta-analysis; 3578, 4363	NR	Adiponectin OR = 0.838 (0.744–0.943)
Prizment et al. (2013); USA; Atherosclerosis Risk in Communities Study Cohort	Cohort; 176, 7603	Immunoturbidimetric assay	CRP, continuous HR = 1.27 (1.07–1.51)
Touvier et al. (2013); France; Supplémentation en Vitamines et Minéraux Antioxydants Trial	Nested case–control; 218, 436	ELISA	hsCRP, quartiles OR = 1.25 (0.73–2.14), P_{trend} = 0.7 Leptin, quartiles OR = 0.64 (0.34–1.20), P_{trend} = 0.1 Adiponectin, quartiles OR = 1.13 (0.68–1.87), P_{trend} = 0.4
Dossus et al. (2014); France; Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale	Nested case–control; 549, 1040; postmenopausal	Particle-enhanced immunoturbidimetric assay	CRP, all < 1.5 vs 2.5–10 mg/L, OR = 1.24 (0.92–1.66) Continuous, OR = 1.13 (0.98–1.29), P_{trend} = 0.09 CRP, BMI ≥ 25 kg/m^2 < 1.5 vs 2.5–10 mg/L, OR = 1.92 (1.20–3.08) Continuous, OR = 1.52 (1.16–2.00), P_{trend} = 0.003
Macis et al. (2014); 15 studies	Meta-analysis; 4249	NR	Adiponectin SRR = 0.66 (0.50–87)
Chan et al. (2015); 12 studies	Meta-analysis; 3522, 69 610	NR	CRP, doubling concentration RR = 1.07 (10.2–1.12)

Table 4.2 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Gunter et al. (2015b); USA; Women's Health Initiative	Case–cohort; 875, 839; postmenopausal	CRP: latex-enhanced immunonephelometry Leptin and TNF-α: Milliplex Human Adipokine Panel B Adiponectin, PAI-1, and resistin: Milliplex Human Adipokine Panel A IL-6: ELISA	CRP, quartiles All, HR = 1.24 (0.86–1.80), P_{trend} = 0.12 Non-HRT users, HR = 1.67 (1.04–2.68), P_{trend} = 0.029 Leptin, quartiles All, HR = 1.39 (0.93–2.09), P_{trend} = 0.279 Adiponectin, quartiles All, HR = 0.76 (0.55–1.06), P_{trend} = 0.78 Resistin, quartiles All, HR = 0.93 (0.68–1.27), P_{trend} = 0.664 PAI-1, quartiles All, HR = 1.33 (0.96–1.86), P_{trend} = 0.145 Non-HRT users, HR = 1.71 (1.02–2.89), P_{trend} = 0.077 IL-6, quartiles All, HR = 1.20 (0.85–1.69), P_{trend} = 0.528 TNF-α, quartiles All, HR = 0.82 (0.59–1.14), P_{trend} = 0.292
Wang et al. (2015); China; Kailuan Female Cohort	Cohort; 87, 19 437	Nephelometric assay	hsCRP, < 1 vs > 3 mg/L All, HR = 1.74 (1.01–2.97), P_{trend} = 0.047 Women < 50 yr, HR = 2.76 (1.18–6.48) Excluding CRP > 10 mg/L, HR = 1.89 (1.08–3.32), P_{trend} = 0.029

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; ER+, estrogen receptor-positive; HR, hazard ratio; HRT, hormone replacement therapy; hsCRP, high-sensitivity C-reactive protein; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; LC-MS, liquid chromatography–mass spectrometry; NR, not reported; NS, no significant association; OR, odds ratio; PAI-1, plasminogen activator inhibitor 1; PPHV, Monitoring Project on Cardiovascular Disease Risk Factors; PR+, progesterone receptor-positive; RR, relative risk; SHBG, sex hormone-binding globulin; SRR, summary relative risk; sTNFR, soluble tumour necrosis factor receptor; TNF, tumour necrosis factor; yr, year or years.

Table 4.3 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the endometrium

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Zeleniuch-Jacquotte et al. (2001); USA; New York University Women's Health Study Cohort	Nested case–control; 57, 222; postmenopausal	Estradiol and estrone: organic extraction, celite chromatography, radioimmunoassay SHBG: chemiluminescence immunometric assay Free estradiol: ultrafiltration method Estradiol bound to SHBG: concanavalin A–agarose binding assay	Estradiol, tertiles OR = 1.8 (0.75–4.2), P_{trend} = 0.19 Free estradiol, tertiles OR = 2.8 (1.3–6.4), P_{trend} = 0.004 SHBG-bound estradiol, tertiles OR = 0.60 (0.26–1.4), P_{trend} = 0.22 Estrone, tertiles OR = 3.2 (1.3–7.8), P_{trend} = 0.008 SHBG, tertiles OR = 0.49 (0.22–1.1), P_{trend} = 0.08
Lukanova et al. (2004a); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 124, 236; postmenopausal, non-HRT users	Estrone: radioimmunoassay or double-antibody radioimmunoassay Estradiol: radioimmuno-assay or ultrasensitive double-antibody radio-immunoassay SHBG: immunometric chemiluminescence assay or immunoradiometric assay	Estrone, quartiles OR = 3.67 (1.71–7.88), P_{trend} = 0.0007 Estradiol, quartiles OR = 4.13 (1.76–9.72), P_{trend} = 0.0008 SHBG, quartiles OR = 0.46 (0.20–1.05), P_{trend} = 0.01
Allen et al. (2008); several European countries; EPIC	Nested case–control; 247, 481; premenopausal (55, 107) and postmenopausal (192, 374)	Estrone and estradiol: radioimmunoassay with double-antibody system SHBG: solid-phase sandwich immunoradiometric assay	Postmenopausal women: Estrone, tertiles OR = 2.66 (1.50–4.72), $P_{trend\ (continuous)}$ = 0.002 Estradiol, tertiles OR = 2.07 (1.20–3.60), $P_{trend\ (continuous)}$ = 0.001 Free estradiol, tertiles OR = 1.66 (0.98–2.82), $P_{trend\ (continuous)}$ = 0.001 SHBG, tertiles OR = 0.57 (0.34–0.95), $P_{trend\ (continuous)}$ = 0.004
Gunter et al. (2008a); USA; Women's Health Initiative	Case–cohort; 250, 465; postmenopausal	Vitros ECi immunodiagnostic assay	Estradiol, tertiles HR = 3.16 (1.71–5.81), P_{trend} < 0.001
Brinton et al. (2016); USA; Women's Health Initiative Observational Study	Nested case–control; 313 (271 type I, 42 type II), 354; postmenopausal	Stable-isotope dilution liquid chromatography-tandem mass spectrometry	Estrone, quintiles OR = 3.19 (1.69–6.04), P_{trend} = 0.0001 Estradiol, quintiles OR = 1.41 (0.75–2.67), P_{trend} = 0.4531 Unconjugated estradiol, quintiles OR = 6.19 (2.95–13.03), P_{trend} = 0.0001 Conjugated estradiol, quintiles 0.95 (0.51–1.77), P_{trend} = 0.6747

Table 4.3 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Insulin			
Lukanova et al. (2004b); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 166, 315; premenopausal and postmenopausal	Radioimmunoassay	C-peptide, quintiles OR = 4.76 (1.91–11.8), P_{trend} = 0.0002 OR = 4.40 (1.65–11.7), P_{trend} = 0.003, adjusted for BMI, other confounders
Cust et al. (2007a); several European countries; EPIC	Nested case–control; 286, 555; premenopausal and postmenopausal	Immunoradiometric assay	C-peptide, quartiles All, RR = 2.13 (1.33–3.41), P_{trend} = 0.001 Postmenopausal, RR = 1.28 (0.67–2.45), P_{trend} = 0.42, adjusted for free estradiol
Gunter et al. (2008a); USA; Women's Health Initiative	Case–cohort; 250 (205 endometrioid adenocarcinoma), 465; postmenopausal	ELISA	Insulin, quartiles Endometrioid adenocarcinoma, non-HRT users, HR = 2.33 (1.13–4.82), P_{trend} = 0.02, adjusted for age, estradiol BMI ≥ 25 kg/m^2, HR = 4.30 (1.62–11.43), P_{trend} = 0.001
IGFs			
Lukanova et al. (2004b); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 166, 315; premenopausal and postmenopausal	Immunoradiometric assay (IGF-1 after acid–ethanol precipitation of IGFBPs)	IGFBP-1, quintiles OR = 0.30 (0.15–0.62), P_{trend} = 0.002 OR = 0.49 (0.22–1.07), P_{trend} = 0.06, adjusted for BMI, other confounders IGF-1: NS
Cust et al. (2007a); several European countries; EPIC	Nested case–control; 286, 555; premenopausal and postmenopausal	IGFBP-1: immunoradiometric assay IGFBP-2: radioimmunoassay	IGFBP-1, quartiles RR = 0.76 (0.47–1.21), P_{trend} = 0.25 IGFBP-2, quartiles RR = 0.56 (0.35–0.90), P_{trend} = 0.03
Gunter et al. (2008a); USA; Women's Health Initiative	Case–cohort; 250 (205 endometrioid adenocarcinoma), 465; postmenopausal	ELISA	Free IGF, quartiles Endometrioid adenocarcinoma, HR = 0.53 (0.31–0.90), P_{trend} = 0.05, adjusted for age, HRT, estradiol Overweight or obese, HR = 0.43 (0.20–0.97), adjusted for age, HRT, estradiol Total IGF-1: NS
Inflammatory factors			
Cust et al. (2007b); several European countries; EPIC	Nested case–control; 284, 548	ELISA	Adiponectin, quartiles RR = 0.56 (0.36–0.86), P_{trend} = 0.006, adjusted for BMI
Dossus et al. (2010); several European countries; EPIC	Nested case–control; 305, 574	CRP and IL-6: ELISA IL-1Ra: bead-based immunoassay	CRP, quartiles OR = 1.58 (1.03–2.41), P_{trend} = 0.02 IL-6, quartiles OR = 1.66 (1.08–2.54), P_{trend} = 0.008 IL-1Ra, quartiles OR = 1.82 (1.22–2.73), P_{trend} = 0.004 All ORs adjusted for BMI: NS

Table 4.3 (continued)

Reference; country; study	Design; number of cases, controls; menopausal status	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Dossus et al. (2011); several European countries; EPIC	Nested case–control: 270, 518	ELISA	TNF-α, quartiles OR = 1.73 (1.09–2.73), P_{trend} = 0.01
Soliman et al. (2011); USA; Nurses' Health Study	Nested case–control; 146; 377	ELISA	Adiponectin, > 15 µg/mL RR = 0.86 (0.53–1.39), P_{trend} = 0.48, adjusted for BMI
Wang et al. (2011); USA; Women's Health Initiative	Case–cohort; 151, 301; postmenopausal, non-HRT users	CRP: high-sensitivity latex-enhanced immunonephelometry IL-6: ultrasensitive solid-phase ELISA TNF-α: Milliplex Human Adipokine Panel B	CRP, quartiles HR = 2.29 (1.13–4.65), P_{trend} = 0.012, adjusted for age, BMI HR = 1.70 (0.78–3.68), P_{trend} = 0.127, adjusted also for estradiol, insulin IL-6, TNF-α: NS
Dallal et al. (2013); USA; Breast and Bone Follow-up to the Fracture Intervention Trial	Nested case–control; 62, 124	ELISA	Leptin, tertiles OR = 2.96 (1.21–7.25), P_{trend} < 0.01, adjusted for estradiol, C-peptide OR = 2.11 (0.69–6.44), P_{trend} = 0.18, adjusted also for BMI Adiponectin: NS
Luhn et al. (2013); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 167, 327	Radioimmunoassay	Leptin, tertiles All, OR = 2.77 (1.60–4.79), P_{trend} < 0.01 Non-HRT users, OR = 4.72 (1.15–19.38), P_{trend} = 0.02 Adiponectin, tertiles All, OR = 0.48 (0.29–0.80), P_{trend} < 0.01 Non-HRT users, OR = 0.25 (0.08–0.75), P_{trend} = 0.01

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; HRT, hormone replacement therapy; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; NR, not reported; NS, no significant association; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin; TNF-α, tumour necrosis factor alpha.

Table 4.4 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the colorectum

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Gunter et al. (2008b); USA; Women's Health Initiative	Case–cohort; 273, 442; F	Vitros ECi immunodiagnostic assay	Estradiol, tertiles HR = 1.43 (0.95–2.16), P_{trend} = 0.09
Clendenen et al. (2009); USA; New York University Women's Health Study	Nested case–control; 148, 293; F	Estrone and estradiol: radioimmunoassay SHBG: immunometric chemiluminescence assay	Estrone, quartiles OR = 1.6 (0.8–3.0), P_{trend} = 0.09 Estradiol, tertiles OR = 0.8 (0.4–1.7), P_{trend} = 0.43 SHBG, quartiles OR = 0.8 (0.4–1.4), P_{trend} = 0.48
Hyde et al. (2012); Australia; Health in Men Study	Cohort; 104, 3416; M	Chemiluminescence immunoassay	SHBG, 60 vs 40 nmol/L sub-HR = 0.98 (0.62–1.56), P_{trend} = 0.84
Lin et al. (2013); USA; Nurses' Health Study, Women's Health Study, Health Professionals Follow-up Study, Physicians' Health Study II	Nested case–control; M: 439, 719; F: 293, 437	Estrone and estradiol: liquid chromatography-tandem mass spectrometry SHBG: electrochemilumi-nescence immunoassay	Estradiol, quartiles M: RR = 1.15 (0.73–1.81), P_{trend} = 0.67 F: RR = 1.12 (0.62–2.03), P_{trend} = 0.93 Estrone, quartiles M: RR = 1.04 (0.68–1.62), P_{trend} = 0.96 F: RR = 1.30 (0.74–2.26), P_{trend} = 0.55 SHBG, quartiles M: RR = 0.65 (0.42–0.99), P_{trend} = 0.02 F: RR = 1.17 (0.63–2.20), P_{trend} = 0.68
Falk et al. (2015); USA; Breast and Bone Follow-up to the Fracture Intervention Trial	Case–cohort; 187, 501; F	NR	Estradiol, quartiles OR = 0.98 (0.58–1.64), P_{trend} = 1.00 Estrone, quartiles OR = 1.15 (0.69–1.93), P_{trend} = 0.54
Murphy et al. (2015); USA; Women's Health Initiative Clinical Trial	Nested case–control; 401, 802; F	Estrone and estradiol: radioimmunoassay SHBG: immunometric chemiluminescence assay	Estradiol quartiles OR = 0.64 (0.43–0.97), P_{trend} = 0.12 Estrone, quartiles OR = 0.50 (0.33–0.75), P_{trend} = 0.002 SHBG, quartiles OR = 2.30 (1.51–3.51), P_{trend} < 0.0001
Insulin			
Schoen et al. (1999); USA; Cardiovascular Health Study	Cohort; 102, 5747; M&F	Solid-phase radioimmunoassay	Insulin, quartiles RR = 1.2 (0.7–2.1)
Kaaks et al. (2000); USA; New York University Women's Health Study	Nested case–control; 102, 200; F	Radioimmunoassay	C-peptide, quintiles OR = 2.92 (1.26–6.75), P_{trend} = 0.001
Palmqvist et al. (2003); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 168, 376; M&F	Double-antibody immunoradiometric assay	Insulin, quartiles OR = 1.22 (0.64–2.31), P_{trend} = 0.41
Saydah et al. (2003); USA; CLUE II Cohort	Nested case–control; colon: 132, rectum: 41, 346; M&F	Ultrasensitive ELISA	Insulin, quartiles OR = 0.78 (0.45–1.35), P_{trend} = 0.24
Ma et al. (2004); USA; Physicians' Health Study	Nested case–control; 176, 294; M	ELISA	C-peptide, quintiles RR = 2.7 (1.2–6.2), P_{trend} = 0.047

Table 4.4 (continued)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Stattin et al. (2004b); Norway; Janus Biobank	Nested case–control; colon: 235, 235; rectum: 143, 143; M	Radioimmunoassay	C-peptide, quartiles Colon: OR = 1.82 (0.67–4.86), P_{trend} = 0.19 Rectum: OR = 0.44 (0.10–1.99), P_{trend} = 0.21
Wei et al. (2005a); USA; Nurses' Health Study	Nested case–control; 182, 350; F	ELISA	C-peptide, quartiles RR = 1.17 (0.63–2.20), P_{trend} = 0.94
Limburg et al. (2006); Finland; ATBC	Case–cohort; 134, 399; M	Two-site immunoenzymatic assay	Insulin, quartiles, age-adjusted HR = 1.84 (1.03–3.30), P_{trend} = 0.12 Insulin, quartiles, multivariate HR = 1.74 (0.74–4.07), P_{trend} = 0.40
Jenab et al. (2007); several European countries; EPIC	Nested case–control; 1078, 1078; M&F	Radioimmunoassay	C-peptide, quintiles OR = 1.37 (1.00–1.88), P_{trend} = 0.03
Otani et al. (2007); Japan; Japan Public Health Center-based Prospective Study	Nested case–control; M: 196, 392, F: 179, 35	Radioimmunoassay	C-peptide, quartiles M: OR = 3.2 (1.4–7.6), P_{trend} = 0.0072 F: OR = 0.78 (0.38–1.6), P_{trend} = 0.49
Gunter et al. (2008b); USA; Women's Health Initiative	Case–cohort; 429, 800; F	ELISA	Insulin, quartiles HR = 1.89 (1.33–2.69), P_{trend} = 0.0005 Adjusted also for waist circumference, HR = 1.42 (0.91–2.23), P_{trend} = 0.11
Stocks et al. (2008); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 306, 595; M&F	Immunoradiometric assay	C-peptide, quartiles OR = 0.94 (0.62–1.41), P_{trend} = 0.82
Kabat et al. (2012); USA; Women's Health Initiative	Case–cohort; 80, 4669; F	ELISA	Insulin, ≥ 11.85 vs < 7.75 μU/mL HR = 1.11 (0.61–2.01), P_{trend} = 0.75
Ollberding et al. (2012); USA; Multiethnic Cohort Study	Nested case–control; 249, 1571; M&F	ELISA	Insulin, tertiles OR = 1.21 (0.84–1.75), P_{trend} = 0.29
Lin et al. (2013); USA; Nurses' Health Study, Women's Health Study, Health Professionals Follow-up Study, Physicians' Health Study II	Nested case–control; M: 439, 719; F: 293, 437	ELISA or electrochemiluminescence immunoassay	C-peptide, quartiles M: RR = 1.29 (0.80–2.08), P_{trend} = 0.27 F: RR = 1.73 (0.94–3.18), P_{trend} = 0.09
Parekh et al. (2013); USA; Framingham Heart Study-Offspring Cohort	Cohort; 71, 3433; M&F	NR	Insulin, ≥ 10.09 vs < 4.94 pmol/L HR = 2.10 (1.12–3.93), P = 0.0354
Murphy et al. (2015); USA; Women's Health Initiative Clinical Trial	Nested case–control; 401, 802; F	ELISA	Insulin, quartiles OR = 0.76 (0.50–1.14), P_{trend} = 0.21
IGFs			
Ma et al. (1999); USA; Physicians' Health Study	Nested case–control; 193, 318; M	ELISA	IGF-1, quintiles RR = 1.36 (0.72–2.55), P_{trend} = 0.51 Adjusted for IGFBP-3, RR = 2.51 (1.15–5.46), P_{trend} = 0.02 IGFBP-3, quintiles RR = 0.47 (0.23–0.95), P_{trend} = 0.07
Giovannucci et al. (2000); USA; Nurses' Health Study Cohort	Nested case–control; 79, 158; F	ELISA	IGF-1, tertiles RR = 2.18 (0.94–5.08), P_{trend} = 0.10 IGFBP-3, tertiles RR = 0.28 (0.10–0.83), P_{trend} = 0.05

Table 4.4 (continued)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Kaaks et al. (2000); USA; New York University Women's Health Study	Nested case–control; 102, 200; F	Double-antibody immunoradiometric assay	IGF-1, quintiles OR = 1.88 (0.72–4.91), P_{trend} = 0.25 IGFBP-3, quintiles OR = 2.46 (1.09–5.57), P_{trend} = 0.19
Probst-Hensch et al. (2001); China; Shanghai Cohort Study	Nested case–control; 135, 661; M	IGF-1: radioimmunoassay IGFBP-3: immunoradiometric assay	IGF-1, quintiles OR = 1.52 (0.82–2.85), P_{trend} = 0.34 IGFBP-3, quintiles OR = 1.72 (0.91–3.25), P_{trend} = 0.07
Palmqvist et al. (2002); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 168, 336; M&F	Double-antibody immunoradiometric assay	IGF-1, quartiles Colorectum: OR = 1.27 (0.65–2.47), P_{trend} = 0.51 Colon: OR = 2.66 (1.09–6.50), P_{trend} = 0.03 IGFBP-3, quartiles Colorectum: OR = 1.23 (0.68–2.22), P_{trend} = 0.24 Colon: OR = 1.93 (0.92–4.06), P_{trend} = 0.02
Nomura et al. (2003); USA; Honolulu Heart Program	Nested case–control; 282, 282; M	ELISA	IGF-1, quartiles OR = 1.5 (0.8–2.8), P_{trend} = 0.13 IGFBP-3, quartiles OR = 0.8 (0.4–1.6), P_{trend} = 0.45
Wei et al. (2005a); USA; Nurses' Health Study Cohort	Nested case–control; 137, 262; F	ELISA	IGF-1, quartiles, colon RR = 1.95 (0.97–3.91), P_{trend} = 0.09 IGFBP-3, quartiles, colon RR = 1.20 (0.62–2.30), P_{trend} = 0.62
Morris et al. (2006); United Kingdom; British United Provident Association Study	Nested case–control; 147, 440; M	ELISA	IGF-1, quartiles OR = 1.10 (0.56–2.18), P_{trend} = 0.65
Otani et al. (2007); Japan; Japan Public Health Center-based Prospective Study	Nested case–control; M: 196, 392; F: 179, 358	Immunoradiometric assay	IGF-1, quartiles M: OR = 0.83 (0.40–1.7), P_{trend} = 0.91 F: OR = 0.83 (0.38–1.8), P_{trend} = 0.60 IGFBP-3, quartiles M: OR = 1.4 (0.65–2.8), P_{trend} = 0.60 F: OR = 1.1 (0.53–2.3), P_{trend} = 0.73
Gunter et al. (2008b); USA; Women's Health Initiative	Case–cohort; 438, 816; F	ELISA	Total IGF-1, quartiles HR = 1.04 (0.74–1.46), P_{trend} = 0.58 Free IGF-1, quartiles HR = 1.21 (0.86–1.72), P_{trend} = 0.16
Max et al. (2008); Finland; ATBC	Case–cohort; 134, 399; M	ELISA	IGF-1, quartiles RR = 0.92 (0.49–1.70), P_{trend} = 0.90 IGFBP-3, quartiles RR = 0.98 (0.51–1.88), P_{trend} = 0.85
Suzuki et al. (2009); Japan; Japan Collaborative Cohort Study	Nested case–control; 101, 302; M&F	Immunoradiometric assay	IGF-1, tertiles OR = 1.01 (0.49–2.10), P_{trend} = 0.35
Rinaldi et al. (2010); several European countries; EPIC	Nested case–control; 1121, 1121; M&F	ELISA	IGF-1, quintiles OR = 1.07 (0.81–1.40) IGFBP-3, quintiles OR = 1.17 (0.87–1.56)

Table 4.4 (continued)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Ollberding et al. (2012); USA; Multiethnic Cohort Study	Nested case–control; IGF-1: 258, 1701; IGF-2: 255, 1571; M&F	ELISA	IGF-1, tertiles OR = 0.84 (0.60–1.17), P_{trend} = 0.30 IGFBP-3, tertiles OR = 0.63 (0.45–0.88), P_{trend} = 0.48
Murphy et al. (2015); USA; Women's Health Initiative Clinical Trial	Nested case–control; 401, 802; F	ELISA	IGF-1, quartiles OR = 0.70 (0.48–1.03), P_{trend} = 0.15
Inflammatory factors			
Stattin et al. (2003); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 168, 327; M&F	Double-antibody immunoradiometric assay	Leptin, quartiles OR = 2.28 (1.09–4.76)
Stattin et al. (2004b); Norway; Janus Biobank	Nested case–control; colon: 235, 235; rectum: 143, 143; M	Radioimmunoassay	Leptin, quartiles Colon: OR = 2.72 (1.44–5.12), P_{trend} = 0.008 Rectum: OR = 0.91 (0.49–1.70), P_{trend} = 0.68
Tamakoshi et al. (2005); Japan; Japan Collaborative Cohort Study	Nested case–control; 58, 145; F	Immunometric sandwich enzyme immunoassay	Leptin, quintiles OR = 3.94 (1.04–14.9), P_{trend} = 0.02
Wei et al. (2005b); USA; Health Professionals Follow-up Study	Nested case–control; 179, 356; M	Radioimmunoassay	Adiponectin, quintiles RR = 0.42 (0.23–0.78), P_{trend} = 0.01
Stocks et al. (2008); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 306, 595; M&F	Leptin: radioimmunoassay Adiponectin: ELISA	Leptin, quartiles OR = 1.09 (0.74–1.61), P_{trend} = 0.29 Adiponectin, quartiles OR = 0.95 (0.63–1.44), P_{trend} = 0.61
Heikkilä et al. (2009); United Kingdom; British Women's Heart and Health Study, Caerphilly Cohort	Cohort; M: CRP: 41, 897; IL-6: 30, 845; F: 32, 3074	CRP: nephelometric assay IL-6: ELISA	CRP, continuous M: HR = 0.89 (0.66–1.22), P = 0.5 F: HR = 0.97 (0.70–1.34), P = 0.8 IL-6, continuous M: HR = 0.71 (0.41–1.23), P = 0.2 F: HR = 0.92 (0.53–1.60), P = 0.8
Chan et al. (2011); USA; Nurses' Health Study	Nested case–control; 280, 560; F	CRP: immunoturbidimetric assay IL-6 and sTNFR2: ELISA	CRP, quartiles RR = 0.65 (0.40–1.05), P_{trend} = 0.17 IL-6, quartiles RR = 1.18 (0.75–1.85), P_{trend} = 0.55 sTNFR2, quartiles RR = 1.67 (1.05–2.68), P_{trend} = 0.03
Aleksandrova et al. (2012a); several European countries; EPIC	Nested case–control; 1206, 1206; M&F	Multimeric ELISA	Adiponectin, quintiles OR = 0.71 (0.53–0.95), P_{trend} = 0.03
Aleksandrova et al. (2012b); several European countries; EPIC	Nested case–control; 1129, 1129; M&F	ELISA	Leptin, quintiles OR = 1.14 (0.81–1.61), P_{trend} = 0.85

Table 4.4 (continued)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Ho et al. (2012); USA; Women's Health Initiative Observational Study	Nested case–cohort; 457, 841; F	Leptin, adiponectin, PAI-1, resistin, HGF, and TNF-α: multiplex assay IL-6: ultrasensitive solid-phase ELISA	Leptin, quartiles HR = 2.50 (1.70–3.67), $P_{trend} < 0.001$ Adiponectin, quartiles HR = 0.65 (0.45–0.94), $P_{trend} = 0.015$ PAI-1, quartiles HR = 1.87 (1.27–2.76), $P_{trend} = 0.006$ Resistin, quartiles HR = 1.16 (0.81–1.65), $P_{trend} = 0.329$ HGF, quartiles HR = 1.26 (0.87–1.82), $P_{trend} = 0.232$ TNF-α, quartiles HR = 0.97 (0.66–1.42), $P_{trend} = 0.969$ IL-6, quartiles HR = 1.41 (0.97–2.06), $P_{trend} = 0.043$ Adjusted for insulin, HR = 1.04 (0.68–1.58), $P_{trend} = 0.662$
Song et al. (2013); USA; Nurses' Health Study, Health Professionals Follow-up Study	Nested case–control; 616, 1205; M&F	ELISA	Adiponectin, quartiles M: RR = 0.55 (0.35–0.86), $P_{trend} = 0.02$ F: RR = 0.96 (0.67–1.39), $P_{trend} = 0.74$
Ho et al. (2014); USA; Women's Health Initiative Observational Study	Nested case–cohort; 433, 821; F	Milliplex Human Cytokine/ Chemokine Panel	sIL-6R, quartiles RR = 0.56 (0.38–0.83), $P_{trend} = 0.007$ sIL-1R2, quartiles RR = 0.44 (0.29–0.67); $P_{trend} < 0.001$ IL-1Ra, sgp130, sTNFR1, sTNFR2: NS
Zhou et al. (2014); CRP: 18 studies; IL-6: 6 studies	Meta-analysis; CRP: 4706 cases, IL-6: 1068 cases; M&F	NR	CRP, 1 unit change in natural logarithm RR = 1.12 (1.05–1.21) IL-6, 1 unit change in natural logarithm RR = 1.10 (0.88–1.36)
Murphy et al. (2015); USA; Women's Health Initiative Clinical Trial	Nested case–control; 401, 802; F (postmenopausal)	Chemiluminescence immunometric assay	CRP, quartiles OR = 0.89 (0.60–1.34), $P_{trend} = 0.47$

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; HGF, hepatocyte growth factor; HR, hazard ratio; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; M, male; NR, not reported; NS, no significant association; OR, odds ratio; PAI-1, plasminogen activator inhibitor 1; RR, relative risk; SHBG, sex hormone-binding globulin; sTNFR, soluble tumour necrosis factor receptor; TNF-α, tumour necrosis factor alpha.

Table 4.5 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the prostate

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Gann et al. (1996); USA; Physicians' Health Study	Nested case–control; 222, 390	Testosterone, 3α-diolG, DHT, and estradiol: radioimmunoassay SHBG: radioimmunometric assay	Estradiol, quartiles OR = 0.56 (0.32–0.98), P_{trend} = 0.03 Testosterone, quartiles OR = 2.60 (1.34–5.02), P_{trend} = 0.004 DHT, quartiles OR = 0.71 (0.34–1.48), P_{trend} = 0.30 3α-diolG, quartiles OR = 1.60 (0.93–2.76), P_{trend} = 0.09 SHBG, quartiles OR = 0.46 (0.24–0.89), P_{trend} = 0.01
Platz et al. (2005b); USA; Health Professionals Follow-up Study	Nested case–control; 460, 460	Testosterone: chemiluminescence immunoassay SHBG: coated-tube non-competitive immunoradiometric assay	*Total prostate cancer* Testosterone, quartiles OR = 0.79 (0.48–1.31), P_{trend} = 0.79 SHBG, quartiles OR = 1.09 (0.66–1.82), P_{trend} = 0.97 *Gleason score ≥ 7 (n = 148)* Testosterone, quartiles OR = 0.26 (1.0–0.66), P_{trend} = 0.01 SHBG, quartiles OR = 2.72 (1.02–7.24), P_{trend} = 0.05
Severi et al. (2006a); Australia; Melbourne Collaborative Cohort Study	Case–cohort; 524, 1859	Testosterone: electrochemi-luminescence immunoassay SHBG: immunometric assay DHEAS: competitive immunoassay Androstenedione: radioimmunoassay	*Aggressive prostate cancer* Total testosterone, doubling of concentration HR = 0.55 (0.32–0.95) Total testosterone, quartiles HR = 0.53 (0.28–1.03), P_{trend} = 0.03 SHBG, quartiles HR = 0.54 (0.28–1.04), P_{trend} = 0.1 DHEAS, quartiles HR = 0.38 (0.15–0.95), P_{trend} = 0.005 Androstenedione, quartiles HR = 0.46 (0.24–0.88), P_{trend} = 0.007
Wirén et al. (2007); Sweden; Västerbotten Intervention Project	Nested case–control; 392, 392	Testosterone: coated-tube radioimmunoassay SHBG: time-resolved immunofluorometric assay 3α-diolG: direct radioimmunoassay	Total testosterone, quartiles OR = 1.02 (0.62–1.68), P_{trend} = 0.83 Free testosterone, quartiles OR = 1.09 (0.67–1.78), P_{trend} = 0.92 SHBG, quartiles OR = 0.89 (0.55–1.46), P_{trend} = 0.56 3α-diolG, quartiles OR = 0.92 (0.60–1.41), P_{trend} = 1.00
Roddam et al. (2008); 18 prospective studies	Pooled analysis; 3886, 6438	NR	SHBG, quintiles RR = 0.86 (0.75–0.98), P_{trend} = 0.01 Testosterone, calculated free testosterone, DHT, DHEAS, androstenedione, androstanediol glucuronide, estradiol, calculated free estradiol: NS

Table 4.5 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Weiss et al. (2008); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 727, 889	Androstenedione and 3α-diolG: direct double-antibody radioimmunoassay Testosterone: direct radioimmunoassay SHBG: sandwich immunoradiometric assay	Androstenedione, quartiles OR = 0.96 (0.70–1.32), P_{trend} = 0.76 Testosterone, quartiles OR = 1.39 (0.92–2.08), P_{trend} = 0.22 Free testosterone, quartiles OR = 1.20 (0.87–1.65), P_{trend} = 0.36 SHBG, quartiles OR = 0.76 (0.52–1.10), P_{trend} = 0.22 3α-diolG, quartiles OR = 0.87 (0.60–1.18), P_{trend} = 0.31
Sawada et al. (2010); Japan; Japan Public Health Center-based Prospective Study	Nested case–control; 201, 402	Testosterone: electrochemi-luminescence immunoassay SHBG: immunoradiometric assay	Total testosterone, quartiles OR = 0.71 (0.36–1.41), P_{trend} = 0.43 Free testosterone, quartiles OR = 0.70 (0.39–1.27), P_{trend} = 0.08 SHBG, quartiles OR = 1.38 (0.69–2.77), P_{trend} = 0.23
Hyde et al. (2012); Australia; Health in Men Study	Cohort; 297, 3338	Chemiluminescence immunoassay	Total testosterone, continuous HR = 1.10 (0.97–1.25), P = 0.140 Free testosterone, continuous HR = 1.13 (1.03–1.24), P = 0.013 SHBG, continuous HR = 0.97 (0.84–1.11), P = 0.615
Insulin			
Stattin et al. (2000); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 149, 298	Double-antibody radioimmunoassay	Insulin, quartiles OR = 0.98 (0.53–1.81), P_{trend} = 0.23
Hubbard et al. (2004); USA; Baltimore Longitudinal Study of Aging	Longitudinal study; 87, 823	Radioimmunoassay	Fasting insulin, quartiles RR = 0.72 (0.34–1.54), P_{trend} = 0.56 2-Hour insulin, quartiles RR = 0.64 (0.32–1.31), P_{trend} = 0.04
Stocks et al. (2007); Sweden; Västerbotten Intervention Project	Nested case–control; 392, 392	Immunoradiometric assay	C-peptide, continuous OR = 0.96 (0.79–1.16), P = 0.65
Albanes et al. (2009); Finland; ATBC	Case–cohort; 100, 400	Double-antibody immuno-chemiluminometric assay	Insulin, quartiles OR = 2.55 (1.18–5.51), P_{trend} = 0.2
Schenk et al. (2009); USA; Prostate Cancer Prevention Trial	Nested case–control; 698, 709	Multiplex sandwich ELISA	C-peptide, quartiles OR = 0.80 (0.59–1.08), P_{trend} = 0.31
Parekh et al. (2013); USA; Framingham Heart Study-Offspring Cohort	Cohort; 152, 1493	Radioimmunoassay	Insulin, tertiles HR = 1.21 (0.78–1.88), P_{trend} = 0.32
Lai et al. (2014); USA; Health Professionals Follow-up Study	Nested case–control; 1314, 1314	ELISA	C-peptide, continuous OR = 1.00 (0.93–1.08), P_{trend} = 0.99 C-peptide, quartiles OR = 1.05 (0.83–1.33)

Table 4.5 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
IGFs			
Chan et al. (1998); USA; Physicians' Health Study	Nested case–control; 152, 152	ELISA	IGF-1, quartiles RR = 2.41 (1.23–4.74), P_{trend} = 0.006
Stattin et al. (2000); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 149, 298	Double-antibody immunoradiometric assay	IGF-1, quartiles OR = 1.72 (0.93–3.19), P_{trend} = 0.006 < 59 yr, IGF-1, tertiles OR = 4.30 (1.19–15.50), P_{trend} = 0.01
Woodson et al. (2003); Finland; ATBC	Case–cohort; 100, 400	ELISA	IGF-1, quartiles OR = 1.00 (0.54–1.87), P_{trend} = 0.76
Stattin et al. (2004c); Sweden; Northern Sweden Health and Disease Study Cohort	Nested case–control; 281, 560	Immunoradiometric assay	IGF-1, quartiles OR = 1.67 (1.02–2.71), P_{trend} = 0.05
Meyer et al. (2005); France; Supplémentation en Vitamines et Minéraux Antioxydants Trial	Nested case–control; 100, 400	Chemiluminescence immunoassay on an Immulite analyser	IGF-1, quartiles OR = 1.80 (0.76–4.27), P_{trend} = 0.13
Platz et al. (2005b); USA; Health Professionals Follow-up Study	Nested case–control; 462, 462	ELISA	IGF-1, quartiles OR = 1.37 (0.92–2.03), P_{trend} = 0.05
Severi et al. (2006b); Australia; Melbourne Collaborative Cohort Study	Case–cohort; 524, 1826	ELISA	IGF-1, quartiles HR = 1.07 (0.79–1.46), P_{trend} = 0.5
Allen et al. (2007); several European countries; EPIC	Nested case–control; 630, 630	ELISA plus acid–ethanol precipitation	IGF-1, tertiles OR = 1.35 (0.99–1.82), P_{trend} = 0.08 Adjusted for IGFBP-3, OR = 1.39 (1.02–1.89), P_{trend} = 0.12
Weiss et al. (2007); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 727, 887	ELISA	IGF-1, quartiles OR = 1.14 (0.86–1.51), P_{trend} = 0.18
Mucci et al. (2010); USA; Physicians' Health Study	Nested case–control; 545, 545	ELISA	Free IGF-1, quartiles RR = 0.9 (0.6–1.3), P_{trend} = 0.78
Price et al. (2012); several European countries; EPIC	Nested case–control; 1542, 1542	DSL-10-5600 ACTIVE ELISA or IDS-iSYS immunoassay system	IGF-1, quartiles OR = 1.69 (1.35–2.13), P_{trend} = 0.0002 IGF-1, doubling OR = 1.38 (1.17–1.64), P_{trend} = 0.0002

Table 4.5 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Travis et al. (2016); 17 prospective and 2 cross-sectional studies	Pooled analysis; 10 554, 13 618	NR	*Prospective studies* IGF-1, quintiles OR = 1.29 (1.16–1.43), $P_{trend} < 0.001$ IGF-2, quintiles OR = 1.20 (1.00–1.43), $P_{trend} = 0.038$ IGFBP-1, quintiles OR = 0.81 (0.68–0.96), $P_{trend} = 0.053$ IGFBP-2, quintiles OR = 1.26 (1.03–1.54), $P_{trend} < 0.001$ IGFBP-3, quintiles OR = 1.25 (1.12–1.40), $P_{trend} < 0.001$
Inflammatory factors			
Stocks et al. (2007); Sweden; Västerbotten Intervention Project	Nested case–control; 392, 392	Double-antibody radioimmunoassay	Leptin, continuous OR = 0.93 (0.89–0.97), $P = 0.002$
Heikkilä et al. (2009); United Kingdom; Caerphilly Cohort	Cohort; CRP: 36, 897; IL-6: 40, 845	CRP: nephelometric assay IL-6: ELISA	CRP, continuous HR = 1.12 (0.81–1.56), $P = 0.5$ IL-6, continuous HR = 0.61 (0.40–0.96), $P = 0.031$
Schenk et al. (2009); USA; Prostate Cancer Prevention Trial	Nested case–control; 698, 709	Multiplex sandwich ELISA	Leptin, quartiles OR = 1.05 (0.73–1.50), $P_{trend} = 0.48$ Adiponectin, quartiles OR = 0.65 (0.47–0.87), $P_{trend} = 0.004$
Li et al. (2010); USA; Physicians' Health Study	Nested case–control; 654, 644	Competitive radioimmunoassay	Leptin, quartiles RR = 1.06 (0.65–1.72), $P_{trend} = 0.8$ Adiponectin, quartiles RR = 0.73 (0.46–1.14), $P_{trend} = 0.38$
Touvier et al. (2013); France; Supplémentation en Vitamines et Minéraux Antioxydants Trial	Nested case–control; 156, 312	ELISA	Leptin, quartiles OR = 0.69 (0.27–1.75), $P_{trend} = 0.9$ Adiponectin, quartiles OR = 1.34 (0.69–2.61), $P_{trend} = 0.3$ hsCRP, quartiles OR = 2.52 (1.18–5.39), $P_{trend} = 0.03$
Lai et al. (2014); USA; Health Professionals Follow-up Study	Nested case–control; 1314, 1314	ELISA	Leptin, continuous OR = 0.94 (0.86–1.02), $P_{trend} = 0.14$

3α-diolG, 5α-androstane-3α,17β-diol glucuronide; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; CRP, C-reactive protein; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; NR, not reported; NS, no significant association; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin; yr, year or years.

Table 4.6 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the ovary

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Helzlsouer et al. (1995); USA; population-based serum bank	Nested case–control; 31, 62	Estrone and estradiol: solvent extraction, celite chromatography, radioimmunoassay Progesterone: radioimmunoassay	Estrone, estradiol, progesterone: NS
Lukanova et al. (2003a); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 132, 258; postmenopausal women	Estrone: double-antibody radioimmunoassay SHBG: immunoradiometric assay	Estrone, quartiles OR = 1.15 (0.47–2.82), P_{trend} = 0.47 SHBG, quartiles OR = 1.66 (0.67–4.09), P_{trend} < 0.19
Rinaldi et al. (2007); several European countries; EPIC	Nested case–control; 192, 346	Sandwich immunoradiometric assay	SHBG, continuous $\log_2$ scale All cases: NS BMI < 26.8, OR = 0.31 (0.14–0.68) BMI ≥ 26.8, OR = 2.48 (1.31–4.71) $P_{heterogeneity}$ = 0.0001
Trabert et al. (2016); USA; Women's Health Initiative	Nested case–control; 169, 412	Stable-isotope dilution liquid chromatography-tandem mass spectrometry	Estrone, quintiles OR = 1.54 (0.82–2.90), P_{trend} = 0.05 2-Methoxyestrone metabolites, quintiles OR = 2.03 (1.06–3.88), P_{trend} = 0.02 4-Methoxyestrone metabolites, quintiles OR = 1.86 (0.98–3.56), P_{trend} = 0.01
Insulin			
Lukanova et al. (2003b); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 132, 263	Radioimmunoassay	C-peptide, quartiles OR = 0.89 (0.44–1.81), P_{trend} = 0.92
IGFs			
Lukanova et al. (2002); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 132, 263	Peptides: double-antibody immunoradiometric assay IGF-1: acid–ethanol precipitation of IGFBPs	IGF-1, tertiles All cases: NS < 55 yr, OR = 4.97 (1.22–20.2) IGFBP-3, tertiles All cases: NS
Lukanova et al. (2003b); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 132, 263	IGFBP-1: immunoradiometric assay IGFBP-2: radioimmunoassay	IGFBP-1, quartiles OR = 0.79 (0.38–1.62) IGFBP-2, quartiles OR = 0.87 (0.45–1.68)

Table 4.6 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Peeters et al. (2007); several European countries; EPIC	Nested case–control; 214, 388	Peptides: ELISA IGF-1: acid–ethanol precipitation of IGFBPs	IGF-1, tertiles All, OR = 1.1 (0.7–1.7), P_{trend} = 0.94 Diagnosis ≤ 55 yr, OR = 2.4 (0.9–6.4), P_{trend} = 0.08 Diagnosis > 55 yr, OR = 0.9 (0.5–1.6), P_{trend} = 0.74 IGFBP-3, tertiles All, OR = 1.1 (0.7–1.8), P_{trend} = 0.65 Diagnosis ≤ 55 yr, OR = 2.1 (0.8–5.4), P_{trend} = 0.12 Diagnosis > 55 yr, OR = 1.0 (0.6–1.7), P_{trend} = 0.91
Tworoger et al. (2007b); USA; Nurses' Health Study, Nurses' Health Study II, Women's Health Study	Nested case–control; 222, 599	ELISA after acid extraction	IGF-1, quartiles RR = 0.56 (0.32–0.97), P_{trend} = 0.14 IGFBP-2, IGFBP-3, IGF-1 ratio to IGFBPs: NS
Inflammatory factors			
Lundin et al. (2009); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 237, 427	High-sensitivity immunoturbidimetric assay	CRP, > 10 vs ≤ 1 mg/L All, OR = 4.4 (1.8–10.9) Diagnosis > 2 yr after blood donation, OR = 3.0 (1.2–8.0) Diagnosis > 5 yr after blood donation, OR = 3.6 (1.0–13.2)
Clendenen et al. (2011); USA, Sweden, Italy; New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Cohort	Nested case–control; 230, 432	Luminex xMAP technology	IL-2, quartiles OR = 1.57 (0.98–2.52), P_{trend} = 0.07 IL-4, quartiles OR = 1.50 (0.95–2.38), P_{trend} = 0.06 IL-6, quartiles OR = 1.63 (1.03–2.58), P_{trend} = 0.03 IL-12p40, quartiles OR = 1.60 (1.02–2.51), P_{trend} = 0.06 IL-13, quartiles OR = 1.42 (0.90–2.26), P_{trend} = 0.11
Poole et al. (2013); USA; Nurses' Health Study, Nurses' Health Study II, Women's Health Study	Nested case–control; Nurses' Health Studies: 217, 434; Women's Health Study: 159, NR	CRP: validated immunoturbidimetric method IL-6: quantitative sandwich enzyme immunoassay TNF-α-R2: ELISA	CRP Quartiles, RR = 0.53 (1.05–2.23), P_{trend} = 0.01 > 10 vs ≤ 1 mg/L, RR = 2.16 (1.23–3.78) IL-6, TNF-α-R2, Nurses' Health Studies: NS

Table 4.6 (continued)

Reference; country; study	Design; number of cases, controls	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Trabert et al. (2014); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 149, 149	Luminex bead-based assay	CRP, tertiles OR = 2.04 (1.06–3.93), P_{trend} = 0.03 IL-1α, detectable vs undetectable OR = 2.23 (1.14–4.34) TNF-α, tertiles OR = 2.21 (1.06–4.63), P_{trend} = 0.04 IL-8, tertiles OR = 1.86 (0.96–3.61), P_{trend} = 0.05 *Serous ovarian cancer* (n = 83) CRP, tertiles OR = 3.96 (1.14–11.14), P_{trend} = 0.008 IL-8, tertiles OR = 3.05 (1.09–8.51), P_{trend} = 0.03
Ose et al. (2015); several European countries; EPIC	Nested case–control; 754, 1497	CRP: high-sensitivity immunoassay IL-6: high-sensitivity quantitative sandwich enzyme immunoassay	CRP All cases: NS > 10 vs ≤ 1 mg/L, OR = 1.67 (1.03–2.70) IL-6 All cases: NS Waist circumference ≤ 80 cm, OR_{log2} = 0.97 (0.81–1.16) Waist circumference 80–88 cm, OR_{log2} = 0.85 (0.66–1.11) Waist circumference > 88 cm, OR_{log2} = 1.78 (1.28–2.48) $P_{heterogeneity}$ ≤ 0.01

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; IGF, insulin growth factor; IGFBP, IGF binding protein; IL, interleukin; NR, not reported; NS, no significant association; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin; TNF-α, tumour necrosis factor alpha; TNF-α-R, tumour necrosis factor alpha receptor; yr, year or years.

Table 4.7 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the liver (including the biliary tract)

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Sex hormones			
Lukanova et al. (2014); several European countries; EPIC	Nested case–control; 125, 247; M&F	Radioimmunoassay	SHBG, tertiles HCC: OR = 6.64 (2.58–17.1), P_{trend} < 0.001
Insulin			
Chao et al. (2011); Taiwan, China; Hepatitis B virus-positive Cohort	Case–cohort; 124, 1084; M	Radioimmunoassay	Insulin, > 6.10 vs 2.75–4.10 µU/mL HCC: HR = 2.36 (1.43–3.90), P_{trend} = 0.014
Aleksandrova et al. (2014); several European countries; EPIC	Nested case–control; HCC: 125, 250; IBDC: 34, 68; GBTC: 137, 274; M&F	Immulite 2000	C-peptide, tertiles HCC: RR = 3.13 (1.20–8.12), P_{trend} = 0.009 IBDC: RR = 9.89 (1.21–80.45), P_{trend} = 0.03 GBTC: RR = 0.77 (0.39–1.52), P_{trend} = 0.58
IGFs			
Mazziotti et al. (2002); Italy; Hepatitis C virus-related cirrhosis Cohort	Cohort; 20, 84; M&F	Immunoradiometric assay	IGF-1 HCC: significantly lower levels, P < 0.001
Lukanova et al. (2014); several European countries; EPIC	Nested case–control; 125, 247; M&F	ELISA	IGF-1, tertiles HCC: OR = 0.21 (0.09–0.50), P_{trend} < 0.001
Inflammatory factors			
Aleksandrova et al. (2014); several European countries; EPIC	Nested case–control; HCC: 125, 250; IBDC: 34, 68; GBTC: 137, 274; M&F	CRP: Turbidimetric Modular system Leptin and adiponectin: ELISA IL-6: ECLIA Modular system	CRP, tertiles HCC: RR = 1.41 (0.67–2.96), P_{trend} = 0.05 IBDC: RR = 3.92 (0.78–19.68), P_{trend} = 0.05 GBTC: RR = 2.26 (1.26–4.07), P_{trend} = 0.009 Leptin, tertiles HCC: RR = 1.18 (0.43–3.26), P_{trend} = 0.94 IBDC: RR = 3.73 (0.36–38.47), P_{trend} = 0.14 GBTC: RR = 0.52 (0.24–1.13), P_{trend} = 0.05 Adiponectin, tertiles HCC: RR = 1.50 (0.69–3.28), P_{trend} = 0.29 IBDC: RR = 0.42 (0.11–1.29), P_{trend} = 0.23 GBTC: RR = 1.82 (0.93–3.53), P_{trend} = 0.04 IL-6, tertiles HCC: RR = 3.85 (1.31–11.38), P_{trend} = 0.004 IBDC: RR = 1.87 (0.43–8.12), P_{trend} = 0.22 GBTC: RR = 1.19 (0.54–2.62), P_{trend} = 0.68
Ohishi et al. (2014); Japan; Adult Health Study Cohort	Nested case–control; 188, 605; M&F	CRP: autoanalyser and high-sensitivity assay kit IL-6: multiplex bead array assay	CRP, tertiles HCC: RR = 1.94 (0.72–5.51) IL-6, tertiles HCC: RR = 5.12 (1.54–20.1)

CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; GBTC, gall bladder and biliary tract cancers outside of the liver; HCC, hepatocellular carcinoma; HR, hazard ratio; IBDC, intrahepatic bile duct cancer; IGF, insulin growth factor; IL, interleukin; M, male; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin.

Table 4.8 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the pancreas

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Insulin			
Stolzenberg-Solomon et al. (2005); Finland; ATBC	Case–cohort; 169, 400; M	2-site immunoenzymatic assay	Insulin, quartiles HR = 2.01 (1.03–3.93), P_{trend} = 0.03
Grote et al. (2011); several European countries; EPIC	Nested case–control; 466, 466; M&F	Double-antibody radioimmunoassay	C-peptide, quartiles OR = 1.15 (0.70–1.91), P_{trend} = 0.886
Wolpin et al. (2013); USA; 5 prospective studies	Nested case–control; 449, 982; M&F	NR	Insulin, quintiles OR = 1.57 (1.08–2.30), P_{trend} = 0.002 Proinsulin, quintiles OR = 2.22 (1.50–3.29), P_{trend} < 0.001
IGFs			
Stolzenberg-Solomon et al. (2004); Finland; ATBC	Case–cohort; 93, 400; M	ELISA	IGF-1, tertiles OR = 0.67 (0.37–1.21), P_{trend} = 0.17
Wolpin et al. (2007); USA; 4 prospective studies	Nested case–control; 212, 635; M&F	ELISA	IGF-1, quartiles OR = 0.94 (0.60–1.48), P_{trend} = 0.97 IGF-2, quartiles OR = 0.96 (0.61–1.52), P_{trend} = 0.93
Douglas et al. (2010); USA; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Nested case–control; 187, 374; M&F	ELISA	IGF-1, quartiles OR = 1.58 (0.91–2.76), P_{trend} = 0.25 IGF-2, quartiles OR = 0.86 (0.49–1.50), P_{trend} = 0.31
Rohrmann et al. (2012); several European countries; EPIC	Nested case–control; 422, 422; M&F	ELISA	IGF-1, quartiles OR = 1.21 (0.75–1.93), P_{trend} = 0.30
Inflammatory factors			
Stolzenberg-Solomon et al. (2008); Finland; ATBC	Case–cohort; 311, 510; M	ELISA	Adiponectin, quintiles OR = 0.65 (0.39–1.07), P_{trend} = 0.04
Grote et al. (2012a); several European countries; EPIC	Nested case–control; 455, 455; M&F	CRP: multiplex immunoassay IL-6: ELISA	CRP, quartiles OR = 1.02 (0.66–1.57), P_{trend} = 0.6 IL-6, quartiles OR = 1.01 (0.64–1.61), P_{trend} = 0.7
Grote et al. (2012b); several European countries; EPIC	Nested case–control; 452, 452; M&F	Multiplex immunoassay	Adiponectin, quartiles OR = 1.10 (0.69–1.75), P_{trend} = 0.71
Bao et al. (2013a); USA; 5 prospective studies	Nested case–control; 470, 1094; M&F	NR	CRP, quintiles OR = 1.10 (0.74–1.63), P_{trend} = 0.81 IL-6, quintiles OR = 1.19 (0.81–1.76), P_{trend} = 0.08
Bao et al. (2013b); USA; 5 prospective studies	Nested case–control; 468, 1080; M&F	ELISA	Adiponectin, quintiles OR = 0.63 (0.43–0.92), P_{trend} = 0.01
Stolzenberg-Solomon et al. (2015); USA, Finland; 3 prospective studies	Nested case–control; 731, 909; M&F	ELISA	Leptin, quintiles OR = 1.13 (0.75–1.71), P_{trend} = 0.38

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; HR, hazard ratio; IGF, insulin growth factor; IL, interleukin; M, male; NR, not reported; OR, odds ratio; RR, relative risk.

Table 4.9 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the stomach

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Insulin			
Hidaka et al. (2015); Japan; Japan Public Health Center-based Prospective Study	Nested case–control; 77, 477; M&F	Human Endocrine Milliplex kit	Insulin, tertiles OR = 1.91 (1.15–3.18), P_{trend} = 0.01 C-peptide, tertiles OR = 1.31 (0.82–2.11), P_{trend} = 0.26
IGFs			
Yatsuya et al. (2005); Japan; Japan Collaborative Cohort Study	Nested case–control; 210, 410; M&F	Immunoradiometric assay	IGF-1, mean cases/controls ± SD M: 127 ± 52 vs 131 ± 54 ng/mL, P = 0.70 F: 121 ± 53 vs 117 ± 53 ng/mL, P = 0.41 IGF-2, mean cases/controls ± SD M: 548 ± 127.4 vs 571 ± 139.2 ng/mL, P = 0.13 F: 618 ± 122 vs 607 ± 118 ng/mL, P = 0.40
Inflammatory factors			
Wong et al. (2011); China; Shanghai Women's Health Study	Nested case–control; 141, 282; F	LINCOplex kit	IL-6, > 4.06 vs < 1.76 pg/mL OR = 1.73 (1.00–3.00), P_{trend} = 0.04 TNF-α, > 7.17 vs < 4.86 pg/mL OR = 0.74 (0.42–1.30), P_{trend} = 0.27
Epplein et al. (2013); China; Shanghai Men's Health Study	Nested case–control; 180, 358; M	Milliplex MAP high-sensitivity Human Cytokine Magnetic Bead Panel assay kit	IL-8, quartiles OR = 2.30 (1.26–4.19), P_{trend} = 0.008 TNF-α, quartiles OR = 1.37 (0.77–2.44), P_{trend} = 0.22

CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; F, female; IGF, insulin growth factor; IL, interleukin; M, male; OR, odds ratio; RR, relative risk; SD. standard deviation; TNF-α, tumour necrosis factor alpha.

Table 4.10 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the kidney

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
IGFs			
Major et al. (2010); Finland; ATBC	Nested case–control; 100, 400; M	ELISA	IGF-1, quartiles OR = 0.40 (0.18–0.90), P_{trend} = 0.03
Inflammatory factors			
Liao et al. (2013); Finland; ATBC	Nested case–control; 273, 273; M	ELISA	Leptin, continuous OR = 0.93 (0.84–1.03) Adiponectin, continuous OR = 0.87 (0.78–0.97) Resistin, continuous OR = 1.04 (0.94–1.16)

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; IGF, insulin growth factor; M, male; OR, odds ratio; RR, relative risk.

Table 4.11 Molecular epidemiological studies of obesity–cancer related mechanisms for cancer of the oesophagus

Reference; country; study	Design; number of cases, controls; sex	Assays	Biomarker, categories; RR, highest vs lowest (95% CI), P_{trend}
Inflammatory factors			
Hardikar et al. (2014); USA; Seattle Barrett's Esophagus Study	Case–cohort; CRP: 43, 386; IL-6: 45, 394; M&F	CRP: immunonephelometric assay IL-6: ELISA	CRP, quartiles HR = 1.55 (0.56–4.24), P_{trend} = 0.04 IL-6, quartiles HR = 1.17 (0.42–3.26), P_{trend} = 0.87
Keeley et al. (2014); Islamic Republic of Iran; Golestan Cohort Study	Nested case–control; 36, 81; M&F	Luminex xMAP multiplex assay	Interferon-γ, quartiles OR = 5 (1.87–13.36) TNF-α, quartiles OR = 8.2 (2.66–25.31)

CI, confidence interval; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; F, female; HR, hazard ratio; IL, interleukin; M, male; OR, odds ratio; RR, relative risk; TNF-α, tumour necrosis factor alpha.

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5. SUMMARY OF DATA

5.1 Exposure data

Obesity is the accumulation of excess body fat. Body mass index (BMI) is commonly used as a proxy measure of body fatness, because it correlates strongly with both absolute body fat and body fat percentage. BMI is calculated by dividing the body weight (in kilograms) by the square of the height (in metres). In adults, overweight is defined as BMI ≥ 25 kg/m^2 and obesity as BMI ≥ 30 kg/m^2. Obesity can be further classified by severity into class I (30–34.9 kg/m^2), class II (35–39.9 kg/m^2), and class III (≥ 40 kg/m^2). In children younger than 5 years, overweight and obesity are defined as a weight-for-height more than 2 standard deviations (SD) and more than 3 SD, respectively, above the WHO Child Growth Standards median. In children and adolescents from age 5 years to younger than 19 years, overweight and obesity are defined as a BMI-for-age more than 1 SD and more than 2 SD, respectively, above the WHO Growth Reference median.

In 2014, an estimated 640 million adults were obese, 6 times the number in 1975. In 2013, 110 million children and adolescents aged 2–19 years were obese, twice the number in 1980. The estimated prevalence of obesity in 2014 was 10.8% in men, 14.9% in women, and 5.0% in children. Obesity in adults and children is prevalent in countries with high, middle, or low income, and globally more people are overweight or obese than are underweight. Inequalities between and within countries play a major role in the burden of obesity. In addition, recent estimates have highlighted the double burden of malnutrition (the coexistence of undernutrition and overnutrition) in some low-income countries. Perceptions about the magnitude of body weight and about body weight change may vary according to personal beliefs, contextual factors, and cultural norms.

Body weight appears to have a very modest genetic component; it is estimated that about 3% of the population variation in BMI can be explained by known genetic variants, highlighting the important role of modifiable risk factors in the development of overweight and obesity. Current evidence indicates that excess energy intake (food and drinks) and, to a lesser extent, physical inactivity are the major risk factors for excess body fatness and body weight gain throughout life. Global economic development has an impact on the built environment and on sociocultural factors, with major effects on food availability, patterns of food intake, and levels of physical activity. The most notable stimuli for excess energy intake are the availability, the frequency of consumption, and the portion sizes of energy-dense foods and drinks. Enhanced urbanization, more labour-saving devices, and increased concerns about outdoor safety have led to decreases in physical activity and increases in time spent sedentary, in the household, in transportation, and in the employment (or unemployment) and leisure domains, thereby decreasing overall energy expenditure.

Studies investigating dietary patterns in relation to body weight control and obesity have found that diets characterized by increased intake of energy-dense and highly processed foods that are high in added sugars, fat, and salt and low in fibre are positively related to weight gain, whereas diets that consist largely of nutrient-dense foods, such as the traditional Mediterranean diet, are inversely related to weight gain and obesity. Meal patterns and sleep duration may also affect the risk of excess body fatness. Other factors that have the potential to influence energy balance, apparently to a lesser extent, are internal regulatory control of hunger, satiety, and metabolic homeostasis, the fermentation activity of the microbiome and its impact on the metabolism, production, and storage of fatty acids, and endocrine disruptors.

Throughout the life-course, there are a range of critical time points and transition events that affect body weight and body weight change. Perinatal factors, including maternal body weight and weight gain during pregnancy, birth weight, infant feeding practices, and early growth trajectories, have been consistently shown to affect body fatness in infancy, childhood, and later life. Body weight changes have also been observed during the transition from school to higher education or to employment, the transition from single status to marriage or cohabitation, the postpartum period, and changes in employment or unemployment status. Body weight gain is also associated with smoking cessation, a range of comorbidities, and use of certain medications.

There are a large number of anthropometric measurement techniques for body fatness. BMI is the most widely used measure to assess overall body fatness, because weight and height are easy and inexpensive to measure and can be assessed accurately (even by self-report), and because BMI is strongly correlated with overall body fatness and enables comparisons across studies. However, BMI does not differentiate between lean mass and fat mass, the relative proportions of which vary between individuals and with age, sex, and race/ethnicity. Waist circumference is widely used as an indirect measure of abdominal obesity, because it is strongly correlated with total abdominal fat mass and with abdominal visceral fat, which is highly metabolically active and is more difficult to assess.

More sophisticated assessment methods (e.g. bioelectrical impedance, dual-energy X-ray absorptiometry, and magnetic resonance imaging) can provide more accurate estimates of body composition and body fat distribution, but their use in epidemiological studies is limited because of associated costs and concerns about radiation exposure, and they are therefore not typically used in population-based assessments. In children and adolescents, BMI (referenced to appropriate growth standards and recommended cut-offs) is the preferred measure.

5.2 Cancer-preventive effects in humans

The evidence from studies addressing body fatness and cancer risk has rapidly expanded. With continued follow-up of cohorts around the world, there are now data for many cancer sites from hundreds of prospective studies and case–control studies. Pooled analyses and meta-analyses have also been carried out, facilitating the evaluation of associations with less common cancers. Most studies have measured body fatness using BMI. A smaller number have used other measures, most importantly waist circumference, and fewer still have assessed changes in weight over time.

5.2.1 Cancer of the colorectum

For cancers of the colon and rectum, evidence from more than 30 prospective studies and about 10 case–control studies published after 2000 confirmed a positive dose–response relationship between BMI and risk. This association

was observed consistently across studies and geographical regions. The association was weaker in women than in men, and was weaker for cancer of the rectum than for cancer of the colon. For cancer of the colon, there was a statistically significant increase in risk of about 10% per 5 kg/m^2 increase in BMI in women and of 25% per 5 kg/m^2 increase in men. Waist circumference was also positively associated with risk of cancer of the colon (and was less consistently associated with cancer of the rectum). Results from two studies using Mendelian randomization were consistent with these findings.

5.2.2 Cancer of the oesophagus

(a) Adenocarcinoma of the oesophagus

For adenocarcinoma of the oesophagus, evidence from 10 prospective studies and 10 case–control studies published after 2000 confirmed a statistically significant positive dose–response relationship between BMI and risk. This association was observed in almost all studies, in men and women, and across geographical regions. Compared with BMI < 25 kg/m^2, the relative risk was about 1.5 for overweight, 2.4 for obesity class I, 2.8 for obesity class II, and 4.8 for obesity class III, estimated from a pooled analysis of 10 case–control studies and 2 cohort studies. Results from a study using Mendelian randomization were consistent with these findings.

(b) Squamous cell carcinoma of the oesophagus

Squamous cell carcinoma of the oesophagus was examined in nine individual prospective studies, several case–control studies, and one meta-analysis published after 2000. In all studies, BMI was inversely associated with risk of cancer. Residual confounding by tobacco smoking is likely to account for the inverse associations.

5.2.3 Cancer of the stomach

(a) Cancer of the gastric cardia

For cancer of the gastric cardia, evidence from 10 prospective studies and several case–control studies indicated a statistically significant positive dose–response relationship between BMI and risk. This association was observed in men and women and across geographical regions. Compared with normal body weight, the relative risk was about 1.2 for overweight and about 1.8 for obesity, estimated from a meta-analysis of seven prospective studies.

(b) Non-cardia gastric cancer

Findings from more than 10 prospective studies and several case–control studies showed a weak relationship, or no relationship, between BMI and risk of non-cardia gastric cancer.

5.2.4 Cancer of the liver (hepatocellular carcinoma)

There was evidence from more than 20 prospective studies and several case–control studies that BMI is positively associated with risk of either hepatocellular carcinoma or cancer of the liver overall. This association was reported in studies from Asia, Europe, and the USA. Compared with normal body weight, the relative risk was about 1.5 for overweight and about 1.8 for obesity, estimated from a meta-analysis of 26 prospective studies of cohorts of the general population.

5.2.5 Cancer of the gall bladder

For cancer of the gall bladder, evidence from more than 10 individual prospective studies and a comprehensive meta-analysis of 12 prospective and 8 case–control studies indicated a statistically significant positive dose–response relationship between BMI and risk. Compared with normal body weight, the relative risk was about 1.2 for

overweight and about 1.6 for obesity, estimated from the meta-analysis.

5.2.6 Cancers of the biliary tract

For cancers of the biliary tract, the evidence was inconsistent.

5.2.7 Cancer of the pancreas

For cancer of the pancreas, evidence from more than 20 prospective studies, more than 10 case–control studies, and several large pooled analyses of cohorts indicated a statistically significant positive dose–response relationship between BMI and risk. This association was observed in the large majority of studies and was found in both men and women. Compared with normal body weight, the relative risk was about 1.2 for overweight and about 1.5 for obesity, estimated from a pooled analysis of 14 cohorts.

5.2.8 Cancer of the lung

For cancer of the lung, the results of about 20 prospective studies and about 10 case–control studies consistently suggested an inverse association between BMI and risk, but studies in non-smokers generally showed no association. Because tobacco smoking is strongly related to both cancer of the lung and reduced body weight, residual confounding by tobacco smoking is likely to account for the inverse associations. Results from two studies using Mendelian randomization were inconsistent with these findings in that they showed a positive association between BMI and risk of cancer of the lung; however, these results are difficult to interpret because of concerns about failure to account for smoking status.

5.2.9 Cancer of the breast in women

More than 30 prospective studies and about 400 case–control studies published after 2000 provided data on the association between BMI and risk of cancer of the breast in women. In postmenopausal women, very consistent positive associations were observed with BMI measured in adulthood. This association was most pronounced in women not using hormone replacement therapy (HRT) and for estrogen receptor-positive tumours. This association was not consistently observed in Hispanic women. A large meta-analysis in postmenopausal women estimated a statistically significant relative risk of about 1.12 per 5 kg/m^2 in women not using HRT, but no association was found in women using HRT. Waist circumference and adult body weight gain, both from age 18 years and from age 50 years, were also positively associated with risk of cancer of the breast in postmenopausal women.

In premenopausal women, consistent inverse associations were observed between BMI and risk; however, positive associations between waist circumference and body weight gain and risk have been reported. Results from a study using Mendelian randomization were not consistent with a positive association between adult BMI and risk of cancer of the breast in postmenopausal women.

5.2.10 Cancer of the breast in men

For cancer of the breast in men, results from a pooled analysis of 11 case–control studies indicated an association between BMI and risk, whereas pooled risk estimates based on 10 cohort studies did not.

5.2.11 Cancer of the endometrium

For cancer of the endometrium, evidence from more than 20 prospective studies and 30 case–control studies published after 2000

confirmed a statistically significant positive, exponential dose–response relationship between BMI and risk. This association was observed in all cohort and case–control studies and was consistent across geographical regions. The association was particularly pronounced for type 1 cancer of the endometrium: compared with normal body weight, the relative risk for type 1 endometrial cancer was about 1.5 for overweight, about 2.5 for obesity class I, about 4.5 for obesity class II, and about 7.1 for obesity class III, estimated from the most recent pooled analysis of 10 cohorts and 14 case–control studies. Meta-analyses showed a stronger association between BMI and risk of cancer of the endometrium in never-users of HRT than in ever-users (relative risk per 5 kg/m^2, 1.18 in ever-users vs 1.90 in never-users). Results from a study using Mendelian randomization were consistent with these findings.

5.2.12 Cancer of the cervix

For cancer of the cervix, the evidence was inconsistent.

5.2.13 Cancer of the ovary

Evidence from more than 15 prospective studies and more than 30 case–control studies indicated a positive dose–response relationship between BMI and risk of epithelial cancer of the ovary. Based on a pooled analysis of 47 studies, the relative risk in never-users of HRT was about 1.1 for overweight and about 1.2 for obesity, compared with normal body weight. There was no association in users of HRT. Results from a study using Mendelian randomization were consistent with these findings.

5.2.14 Cancer of the prostate

For cancer of the prostate, evidence from about 50 prospective studies and more than 40 case–control studies suggested a positive association between BMI and risk of fatal cancer of the prostate. There was no consistent association between BMI and incidence of total, non-aggressive (non-advanced), or aggressive (advanced) cancer of the prostate. Results from three studies using Mendelian randomization were also inconsistent.

5.2.15 Cancer of the testis

One cohort study and more than 10 case–control studies have addressed the relationship between BMI and risk of cancer of the testis. The association between BMI and risk of cancer of the testis was inconsistent, and a meta-analysis did not identify sources of heterogeneity.

5.2.16 Cancer of the kidney (renal cell carcinoma)

For cancer of the kidney (renal cell carcinoma), evidence from about 20 prospective studies and 10 case–control studies published after 2000 confirmed a positive dose–response relationship between BMI and risk. This association was observed in almost all studies and was consistent in men and women and across geographical regions. Compared with normal body weight, there was a statistically significant relative risk of about 1.3 for overweight and about 1.8 for obesity, estimated from the most recent meta-analysis of 21 cohort studies. Results from a study using Mendelian randomization were consistent with an association between BMI and risk of cancer of the kidney.

5.2.17 Cancer of the urinary bladder

Findings from more than 20 prospective cohorts and 4 case–control studies indicated inconsistent relationships between BMI and risk of cancer of the urinary bladder. Residual confounding by tobacco smoking could not be excluded.

5.2.18 Primary tumours of the brain and central nervous system

For meningioma, five prospective studies and two case–control studies showed a consistent positive association between BMI and risk.

For glioma, five cohort studies and two case–control studies, with only moderate sample sizes, reported inconsistent associations between BMI and risk.

5.2.19 Cancer of the thyroid

For cancer of the thyroid, evidence from more than 10 prospective studies and 10 case–control studies indicated a positive dose–response relationship between BMI and risk. The relative risk per 5 kg/m^2 was 1.17 in men and 1.04 in women, both statistically significant, estimated from a pooled analysis of 22 prospective studies.

5.2.20 Tumours of the haematopoietic system

(a) Lymphoid tumours

For multiple myeloma, there was substantial evidence from at least 20 prospective studies and several case–control studies and meta-analyses or pooled analyses showing positive associations between BMI at baseline and risk. The association appeared to be dose-related and was observed for overweight and obesity. From a pooled analysis of 20 cohorts, the relative risk of multiple myeloma mortality was 1.15–1.24 for overweight, about 1.23 for obesity class I, and about 1.52 for obesity class II or higher, compared with normal body weight.

For diffuse large B-cell lymphoma, findings from nine individual prospective studies and two case–control studies, as well as meta-analyses or pooled analyses, suggested a positive association between BMI and risk, but the results were not fully consistent. Compared with normal body weight, the relative risk was about 1.1 for overweight and about 1.3 for obesity, estimated from a meta-analysis of 10 cohort studies.

For Hodgkin lymphoma, cohort studies generally found non-significant positive associations with obesity compared with normal BMI; the relative risk was about 1.4, estimated from a meta-analysis of five prospective studies. Findings from case–control studies were largely null.

For non-Hodgkin lymphoma and B-cell lymphoma as a group, findings for an association between BMI and risk from individual studies and meta-analyses were inconsistent. The inconsistency within the broader category of B-cell lymphoma may be due to heterogeneity among subtypes. There were too few studies on T-cell lymphoma to enable conclusions to be drawn.

(b) Other haematopoietic malignancies

For total leukaemia and myeloid leukaemia, findings for an association between BMI and risk from individual studies were inconsistent.

5.2.21 Cancers of the head and neck

Epidemiological studies on this heterogeneous group of cancers have examined associations between BMI and risk of cancers of the oral cavity, pharynx (i.e. nasopharynx, oropharynx, and hypopharynx), larynx, and salivary glands. Evidence from five prospective studies, two case–control studies, and four meta-analyses or pooled analyses that examined BMI in relation to cancers of the head and neck overall was inconsistent. Several studies examined associations between BMI and risk of cancer of the oral cavity, pharynx, or larynx specifically, and the findings from these studies were also inconsistent. Some of the inconsistencies for these cancers might be explained by residual confounding by tobacco use and/or alcohol consumption.

5.2.22 Malignant melanoma

For cutaneous malignant melanoma, eight prospective studies showed no clear relationship between BMI and risk. A weak positive relationship was suggested by the results of nine case–control studies and one pooled analysis of eight case–control studies.

5.2.23 Excess body fatness in early life and subsequent cancer risk

Studies that have evaluated relationships between excess body fatness in childhood, adolescence, and early adulthood (age ≤ 25 years) and subsequent cancer risk include studies that directly measured weight and height in childhood, studies that determined body shape in early adulthood by recall, and studies that determined trajectories of body shape from childhood to late adulthood. Collectively, these studies indicated positive associations with several cancer types known to be associated with excess body fatness in middle and later adulthood, except for cancer of the breast in postmenopausal women (see Section 5.2.9); there was some evidence for an inverse association between excess body fatness in early life and subsequent risk of cancer of the breast in postmenopausal women.

5.2.24 Excess body fatness in cancer survivors

A large number of studies have evaluated the relationship between BMI at the time of diagnosis of cancer and cancer-related mortality. The data were most consistent for cancer of the breast, for which high BMI has been associated with an increased risk of cancer-related mortality in individual reports and meta-analyses. Data were fewer and/or less consistent for other malignancies. The effect of intentional body weight loss after cancer diagnosis on cancer mortality has been tested in one intervention trial.

5.2.25 Sustained weight loss and cancer risk

The few observational studies that have evaluated body weight loss, and in particular sustained body weight loss, in relation to subsequent cancer risk are limited to observational studies on weight loss in relation to incidence of cancer of the breast and on the impact of intentional weight loss after bariatric surgery on cancer risk in morbidly obese patients. Findings from cohort studies of weight loss and cancer of the breast were inconsistent, in part reflecting the problem of distinguishing between intentional and unintentional weight loss.

In studies of large series of morbidly obese patients who underwent bariatric surgery and with sufficient follow-up, sustained substantial body weight loss is associated with reduced risk of subsequent cancer, especially for cancer of the endometrium.

5.3 Cancer-preventive effects in experimental animals

5.3.1 Excess body weight

Numerous models in experimental animals have been developed to study the association between obesity and cancer of the mammary gland, colon, liver, prostate, skin, pancreas, endometrium of the uterus, and haematopoietic system. Most such animal models are genetically manipulated (transgenic) animals: animals are either genetically modified to induce carcinogenicity and fed a modified diet to induce obesity, or genetically modified to induce obesity and administered chemicals to induce cancer.

For cancer of the mammary gland, the association between obesity and cancer was tested in five studies in genetically obese mice, five studies of diet-induced obesity in mice, two studies of chemically induced obesity in mice, four studies in genetically obese rats, and one study in obesity-prone rats. In all studies except one, obesity

increased the incidence of hyperplastic alveolar nodules and/or of tumours of the mammary gland, shortened tumour latency, and/or increased tumour volume and growth rate.

For cancer of the colon, the association between obesity and cancer was tested in six studies in genetically obese mice, including one study using a transgenic model of carcinogenicity, one study of diet-induced obesity in mice, and three studies in transgenic obese rats. In all studies, obesity increased the incidence of pre-neoplastic aberrant crypt foci and/or of tumours of the colon (primarily adenocarcinoma), and/or increased tumour size and multiplicity.

For cancer of the liver, the association between obesity and cancer was tested in five studies in genetically obese mice, four studies of diet-induced obesity in mice, and one study in diabetic obese rats. In all studies except one, obesity increased the incidence of hepatocellular tumours (adenoma and carcinoma), shortened tumour latency, and/or increased tumour volume and growth rate.

For cancer of the prostate, the association between obesity and cancer was tested in five studies of diet-induced obesity in mice, including three studies using a transgenic model of carcinogenicity, two studies in genetically obese mice, and one study of chemically induced obesity in mice. In most studies, obesity enhanced the development of pre-neoplastic prostatic intraepithelial neoplasia and of adenocarcinoma, leading to more advanced disease, and/or increased tumour volume.

For cancer of the skin, the association between obesity and cancer was tested in four studies in genetically obese mice and two studies of diet-induced obesity in mice. In all studies, obesity shortened latency, increased multiplicity, and/or accelerated the progression of subcutaneously injected melanoma cells or of tumours of the skin induced by ultraviolet light.

For cancer of the pancreas, the association between obesity and cancer was tested in four studies of diet-induced obesity in mice and one study in two models of genetically obese mice. In the three studies of genetically induced tumours of the pancreas in the diet-induced obesity model, obesity increased the incidence of pancreatic intraepithelial neoplasia and of pancreatic ductal adenocarcinoma. In the other two studies (one in transgenic mice and one of diet-induced obesity), subcutaneous injection of syngeneic pancreatic tumour cells led to the development of significantly larger tumours and higher metastatic rates in obese mice than in lean mice.

For cancer of the endometrium of the uterus, the association between obesity and cancer was tested in one study of diet-induced obesity in mice. In that study, obesity increased the incidence of pre-neoplastic glandular epithelial hyperplasia and adenocarcinoma.

For cancers of the haematopoietic system, the association between obesity and cancer was tested in two studies of diet-induced obesity in mice. In both studies, obesity shortened latency for the development of acute lymphoblastic leukaemia.

Overall, the data showed that obesity in rodents promotes tumorigenesis and increases the age-specific incidence of cancers of the mammary gland, colon, liver, pancreas, prostate (advanced stage cancer), and skin.

5.3.2 Dietary/calorie restriction

(a) Cancer of the mammary gland

More than 40 studies in several different mouse and rat models have evaluated the effect of dietary restriction on the development or progression of tumours of the mammary gland. Overall, most studies showed that dietary restriction decreased the incidence of mammary tumours, extended latency, and/or decreased tumour burden.

Six recent studies in various transgenic mouse models indicated that the pattern of restriction is also important in the protective

effect of dietary restriction. Periods of intermittent restriction had a stronger effect in the prevention of mammary tumours than did the same overall degree of restriction implemented in a prolonged fashion. One study using a model of chemically induced mammary tumours in rats showed similar results.

In general, dietary restriction interventions were implemented in young animals (shortly after weaning, or up to age 9–10 weeks), and then maintained throughout the course of the study. This approach usually led to a lower rate of body weight gain than in animals fed ad libitum. Only two studies have addressed the issue of body weight loss induced by dietary restriction in obese animals and its impact on the development of tumours of the mammary gland. In both studies, body weight loss reduced the development or progression of tumours.

Recently, several studies in mice and rats have used chemical mimetics of calorie restriction (metformin, buformin, phenformin, and 2-deoxyglucose) to assess prevention of tumours of the mammary gland. Protective effects were observed in two of three studies in the HER2/neu mouse model with metformin, as well as in three of five studies in the rapidly emerging tumour model in rats (one study each using 2-deoxyglucose, buformin, or phenformin); metformin had no effect in the remaining two studies.

In addition, several studies were conducted in strains that have different responses to high-fat diets with regard to the rate of body weight gain, thus providing the opportunity to evaluate the effect of body weight independent of diet. In these studies, lower body weight was accompanied by longer tumour latency.

(b) Cancer of the colon

Several models in rats and mice using either chemical carcinogens or allografts to induce tumours of the colon have been developed. Nine studies have assessed the effect of dietary restriction on the development or progression of such tumours. In all three studies using allografts, dietary restriction significantly reduced tumour growth. In three of four studies using a model of chemically induced tumours, dietary restriction reduced the incidence of adenoma and carcinoma of the colon. In one study in the genetically obese Zucker rat, dietary restriction did not have an impact on body weight, and had no protective effect on the development of chemically induced aberrant crypt foci. Similarly, no effect was observed in one study using a transgenic mouse model.

(c) Cancer of the liver

In three lifespan studies in different strains of male and female mice, 40% dietary restriction reduced the incidence of spontaneous liver tumours, mostly hepatocellular adenoma or carcinoma. The reduction did not always reach statistical significance in all analyses (adenomas, carcinomas, or adenomas and carcinomas combined), because of the small numbers of animals and the low incidence of tumours in animals fed ad libitum. In two studies of chemically induced liver tumours in mice, 30% or 40% dietary restriction significantly reduced the incidence of hepatocellular tumours, mostly carcinomas.

(d) Cancer of the pancreas

In all three studies using transgenic mouse models to induce tumours of the pancreatic duct, 25–30% dietary restriction decreased the incidence and severity of pre-neoplastic pancreatic lesions or carcinoma and/or increased survival. In one study using a model of chemically induced carcinogenesis in rats, in which animals were "meal-fed" (i.e. fed ad libitum for 5–6 hours per day, resulting in 10–15% dietary restriction), similar results were observed. In one of three lifespan study in rats, dietary restriction reduced the incidence of spontaneously occurring islet cell tumours. In one study using a model of chemically induced carcinogenesis

in Syrian golden hamsters, 20% or 40% dietary restriction had no effect. In one study in mice injected with pancreatic tumour cells, dietary restriction inhibited tumour growth.

(e) Cancer of the skin

Lifespan studies in mice and rats that have assessed the effect of dietary restriction on tumours of the skin gave inconclusive results because of the low incidence of spontaneously occurring tumours. Nine studies using carcinogen-induced models have assessed the effect of a range of levels (15–50%) of dietary restriction at the initiation, promotion, or progression phase. In all studies, all levels of dietary restriction inhibited the development of skin papilloma, the progression of papilloma to carcinoma, or the multiplicity of these tumours when dietary restriction was imposed at the promotion phase and/or thereafter.

In one study using a B16 melanoma cell line injected subcutaneously into mice, dietary restriction inhibited tumour growth.

(f) Cancer of the pituitary gland

Tumours of the anterior pituitary gland are prevalent in old female mice and in old male and female rats. In all five lifespan studies in mice or rats, 35% and 40% dietary restriction reduced the incidence of spontaneous tumours of the pituitary gland.

In two studies using the estrogen-induced prolactinoma models in female and male F344 rats, 40% dietary restriction inhibited the increase in the weight of the pituitary gland, which is used as an index of tumour growth in this model. Dietary restriction had no effect in three studies using this model in either male Holtzman rats or female ACI ovariectomized rats.

(g) Cancer of the prostate

The transgenic animal models used to study cancer of the prostate are characterized by the development of highly aggressive disease. Eight studies examined the impact of dietary restriction on development of cancer of the prostate: five in transgenic animals, two in models of hormonally induced tumours, and one of spontaneous tumours. In three studies in transgenic animals, dietary restriction reduced the incidence of adenocarcinoma or high-grade lesions. In one study using a model of hormonally induced cancer, dietary restriction reduced the incidence of adenocarcinoma. The one study of spontaneous tumours showed a reduction in incidence of adenocarcinoma with dietary restriction. All studies initiated dietary restriction in young animals (aged 3–9 weeks) and reported attenuated weight gain compared with control animals.

(h) Cancers of the haematopoietic system

Malignant lymphoma and histiocytic sarcoma commonly occur in old mice. In three of five lifespan studies in male or female mice, dietary restriction reduced the incidence of lymphoma and/or histiocytic sarcoma. In one study using knockout $p53^{-/-}$ mice (prone to cancer in many organs), dietary restriction resulted in a moderate reduction in the incidence of lymphoma, and a significant delay of death due to lymphoma. In one lifespan study in $B10C3F_1$ mice, dietary restriction also increased the mean lifespan of mice with lymphoma.

Mononuclear (large granular) cell leukaemia is prevalent in old F344/N rats, and the incidence and severity of disease increase with increased longevity. One 2-year study in F344/N rats showed a significant reduction in the incidence of large granular cell leukaemia with 7–20% dietary restriction. In another lifespan study, 40% dietary restriction had no significant effect. To address the issue of increased lifetime incidence of leukaemia, one study assessed the onset rate of leukaemia, and reported a significant 20% reduction with 40% dietary restriction, although the lifetime incidence did not differ from that in the group fed ad libitum.

5.4 Mechanistic and other relevant data

A short summary of the data is presented at the end of each chapter of Section 4.

The Working Group assessed which cellular and molecular mechanisms known to be dysregulated during the carcinogenesis process are causally linked with obesity, and assessed the relevance of each mechanism for cancer overall, as well as – when sufficient data were available – for individual organ sites. The findings and levels of evidence are summarized below, by the strength of the evidence of the mechanism.

The currently available data in humans and experimental models are consistent with the effects of intentional weight loss on cancer risk being mediated, at least in part, by regulation of the balance between cell proliferation and apoptosis in carcinogenic progression. The cellular machinery that accounts for such regulation includes proteins involved in the G1/S cell cycle transition and apoptotic induction, whether via the intrinsic (mitochondrial) or extrinsic pathways.

5.4.1 Sex hormone metabolism

Estrogen levels correlate with amount of body fat in postmenopausal women. Estrogens play a significant role in cancers of the breast and endometrium, and there are consistent data in humans to demonstrate that women with higher levels of estrogen have an increased risk of these malignancies. For other tumours, the role of sex hormones is less clear. For cancer of the colorectum, estrogen may be anti-tumorigenic and therefore would not represent a mechanism linking adiposity with this cancer. Data linking sex hormones with cancers of the prostate and ovary are inconsistent and may be dependent on tumour subtype. There was little evidence that sex hormones play a role in the development of other obesity-related cancers, such as those of the kidney, pancreas, oesophagus, or liver.

Overall, there is *strong* evidence that the sex hormone-mediated pathway is a major mechanism underlying the link between obesity and certain cancers.

5.4.2 Inflammation

Obesity leads to subclinical inflammation. Several clinical and experimental studies indicate that intentional weight loss by behavioural interventions, bariatric surgery, or pharmacological approaches can reverse obesity-associated inflammatory changes. The most established marker of inflammation in these studies, and the most consistently responsive to intentional weight loss, is C-reactive protein, but it is unclear whether C-reactive protein is a true biological mediator of inflammation and cancer or a marker of other aspects of inflammation. Other markers related to inflammation – including interleukin-6, tumour necrosis factor alpha (TNF-α), prostaglandins, cyclooxygenase-2 (COX-2), leptin, and adiponectin – either have inconsistent associations or have not yet been adequately studied. The obesity-associated pro-inflammatory state appears to be triggered by adipose tissue dysregulation resulting from excess triglyceride accumulation in adipocytes, leading to the recruitment and reprogramming of macrophages and other immune cells that interact with the lipid-engorged adipocytes to increase secretion of multiple cytokines and other inflammatory mediators. The chronic reinforcement of this pro-inflammatory state leads to remodelling of adipose tissue, including infiltration of lipids into the liver, pancreas, and other tissues to create a pro-tumorigenic environment. In addition, several emerging contributors to the obesity-associated pro-inflammatory state, including activation of the COX-2/prostaglandin pathway as a result of increased cytokine levels, and the obesity-induced increase in

inflammation-related molecules from the microbiome, also probably play an important role.

The findings support a role for the inflammatory process in the development of cancers of the breast and colorectum, and to a lesser extent of cancer of the ovary. Data for other sites are sparse. Overall, there is *strong* evidence that inflammation is a major mechanism underlying the link between obesity and certain cancers.

5.4.3 Insulin and insulin-like growth factor

Insulin and insulin-like growth factor 1 (IGF-1) are growth factors that activate the mammalian target of rapamycin (mTOR)/phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, which have mitogenic and anti-apoptotic effects. Hyperinsulinaemia and insulin resistance are common in obese individuals and can raise levels of bioavailable IGF-1 through suppression of IGF-binding proteins.

From epidemiological studies, there is *strong* evidence for a role for insulin in the development of cancer of the endometrium. There is *moderate* evidence linking insulin to cancer of the breast, whereas recent pooled analyses and meta-analytical approaches indicate a role for IGF-1 in the development of cancer of the breast. There is *moderate* to *strong* evidence that both insulin and IGF-1 play a role in cancer of the colorectum. For prostate cancer, there is *moderate* evidence that higher levels of IGF-1 increase the risk of this malignancy, whereas the evidence for insulin is heterogeneous. For other tumour sites, the data are much more limited and inconsistent. Overall, there is *moderate* evidence that insulin and IGF-1 play a role in obesity-induced cancer.

5.4.4 Epigenetic alterations

Structural modifications of DNA, including epigenetic alterations, play an important role in tumorigenesis. However, few studies have investigated the role of epigenetics in mediating the effects of obesity on cancer. Currently, there is *weak* evidence.

5.4.5 Oxidative stress

Oxidative stress can affect DNA integrity and has been linked to obesity, metabolic syndrome, and cancer. However, evidence of the involvement of oxidative stress in obesity-induced cancer is limited by methodological issues. Currently, there is *weak* evidence.

5.4.6 DNA repair

The role of DNA repair function in cancer risk is well established for cancers of the colorectum, breast, endometrium, and skin. Several studies point towards a link between increased BMI and DNA mismatch repair deficiencies. In spite of this, a causal link with obesity and weight control is lacking, because of methodological challenges. Currently, there is *weak* evidence.

5.4.7 Telomeres

Telomere maintenance is directly linked to immortalization. Likewise, inherited disruptions in telomere maintenance have emerged as predictors of cancer predisposition at numerous cancer sites. Evidence from several studies indicates that obesity is inversely associated with telomere length. Overall, telomere shortening may be a relevant emerging mechanism linking obesity to risk of cancer. Currently, there is *weak* evidence.

5.4.8 Other mechanisms

For several mechanisms or mechanistically linked conditions that are potentially related to obesity and cancer, i.e. vitamin D status, the gut microbiome, gut hormones, non-alcoholic fatty liver disease, immune function, and cancer stem cell enrichment, currently, there is *weak* evidence.

6. EVALUATION

6.1 Cancer-preventive effects in humans

There is *sufficient evidence* in humans for a cancer-preventive effect of absence of excess body fatness. Absence of excess body fatness prevents cancers of the colon and rectum, oesophagus (adenocarcinoma), stomach (gastric cardia), liver (hepatocellular carcinoma), gall bladder, pancreas, breast in postmenopausal women, endometrium, ovary, kidney (renal cell carcinoma), and thyroid, as well as meningioma and multiple myeloma. In addition, inverse associations have been observed between absence of excess body fatness and fatal prostate cancer, diffuse large B-cell lymphoma, and cancer of the breast in men.

6.2 Cancer-preventive effects in experimental animals

There is *sufficient evidence* in experimental animals for a cancer-preventive effect of limitation of body weight gain by dietary restriction. Limitation of body weight gain by dietary restriction prevents cancer of the mammary gland, colon, liver, pancreas, skin, and pituitary gland. In addition, inverse associations have been observed for cancer of the prostate, and for lymphoma and leukaemia.

6.3 Mechanistic and other relevant data

There is *strong* evidence that sex hormone metabolism and inflammation are major mechanisms underlying the link between excess body fatness and certain cancers, whereas there is *moderate* evidence for the role of insulin and insulin-like growth factor. The effects were not uniform across the organ sites considered.

There was generally convincing evidence that a reduction in excess body fatness through intentional weight loss positively affects these biomarkers and mechanisms.

6.4 Overall evaluation

Absence of excess body fatness prevents cancer in humans (Group A). Absence of excess body fatness prevents cancers of the colon and rectum, oesophagus (adenocarcinoma), stomach (gastric cardia), liver (hepatocellular carcinoma), gall bladder, pancreas, breast in postmenopausal women, endometrium, ovary, kidney (renal cell carcinoma), and thyroid, as well as meningioma and multiple myeloma.

IARC HANDBOOKS

A Working Group of 21 independent experts from 8 countries, convened by the International Agency for Research on Cancer (IARC) in April 2016, reviewed the scientific evidence and assessed the cancer-preventive effects of the absence of excess body fatness.

The mean body mass index (BMI) in the adult population has increased dramatically worldwide over the past 40 years, and IARC recently estimated that close to 4% of all new cancer cases in adults were attributable to a high BMI; the number of cases is highest in high-income countries and is expected to rise in low- and middle-income countries.

This publication provides an important update of the 2002 IARC Handbook on Weight Control and Physical Activity, with evidence-based evaluation of the association between excess body fatness and cancer at more than 20 sites. In addition, the Working Group reviewed the evidence on childhood obesity and cancer in later life, the impact of excess body fatness in cancer patients on cancer survival and recurrence, and the few intervention studies of weight control on cancer outcome.