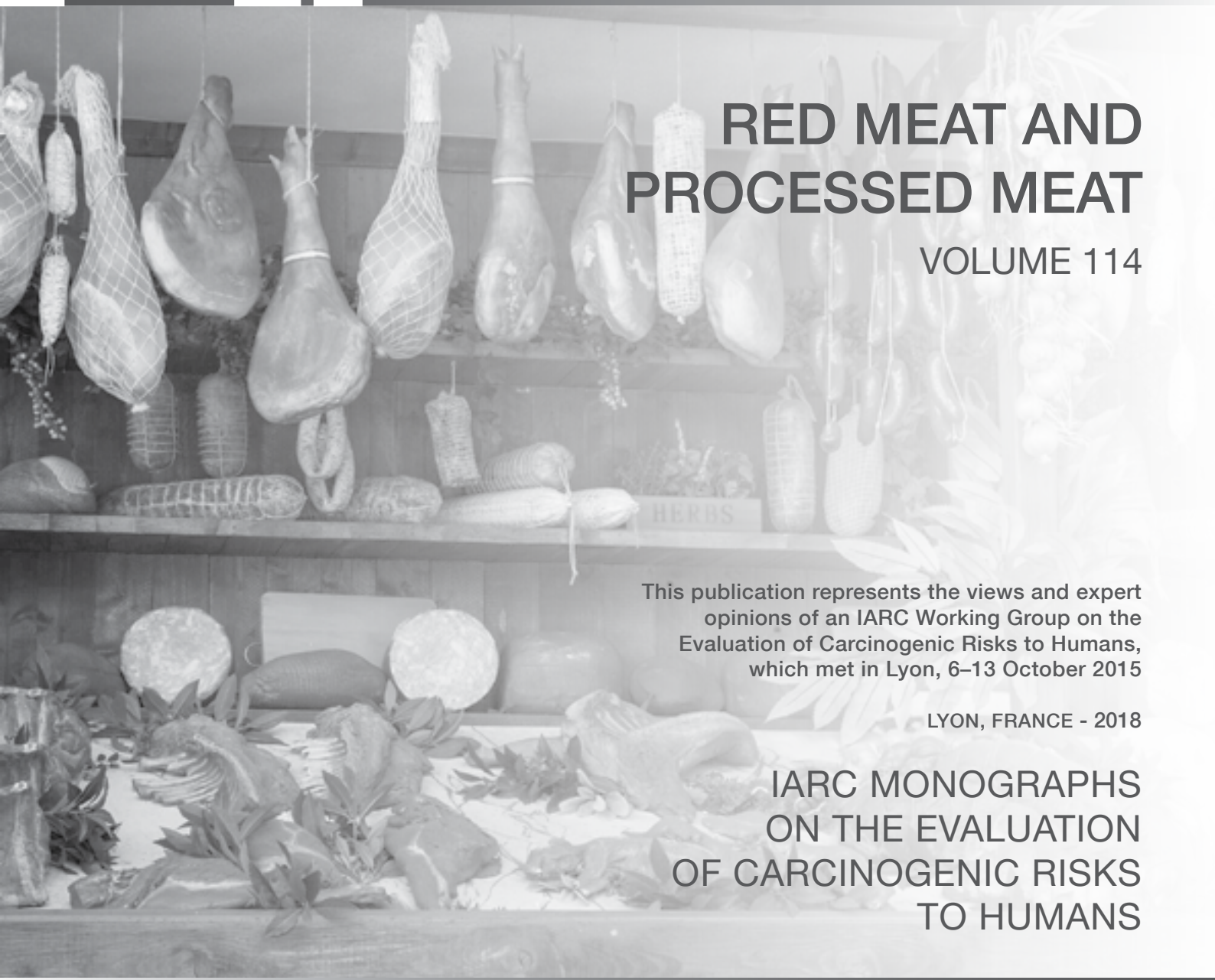
IARC MONOGRAPHS



RED MEAT AND PROCESSED MEAT

VOLUME 114

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 6–13 October 2015

LYON, FRANCE - 2018

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

2. CANCER IN HUMANS

2.1 General issues regarding the epidemiology of cancer and consumption of red meat and processed meat

The association between consumption of red meat or processed meat and cancer risk has been examined in numerous studies. In this section, the Working Group summarized the results of existing studies. For those studies reporting on the same study population and published at different times, the most recent, complete, or informative publication was included when possible.

In reviewing and interpreting the available literature, the Working Group considered the five following criteria: exposure definition; sample size and number of exposed cases; study design; exposure assessment tools; and adjustment for potential confounding factors described below.

2.1.1 Exposure definition

The Working Group placed the greatest emphasis on the studies that reported data separately for unprocessed red meat (i.e. "red meat") or processed meat, and had a clear definition of what questions or types of meats were included in the meat variables. For definitions, please see Section 1 of this *Monograph* and (a) and (b) below. Studies that defined total red meat as including processed meat and studies that reported on "red meat" (unclear whether unprocessed or total red meat) were also included in the Working Group discussion, but were given less weight; the latter studies were given the least weight for many cancers (e.g. cancer of the colorectum).

(a) Red meat

Red meat refers to fresh unprocessed mammalian muscle meat (e.g. beef, veal, pork, lamb, mutton, horse, or goat meat), which may be minced or frozen, and is usually consumed cooked. Studies reporting separate results for individual red meat subtypes (e.g. beef, pork, lamb, etc.) and fresh organ meats (offal) were included as "red meat". Mammalian offal refers to the internal organs and entrails of a butchered animal (scrotum, small intestine, heart, brain, kidney, liver, thymus, pancreas, testicle, tongue, tripe, or stomach) consumed as such. The Working Group considered offal as "red meat".

(b) Processed meat

Processed meat refers to any meat that has been transformed through one or several of the following processes: salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Most processed meats are made from pork or beef, but may also include other meats such as poultry and/or offal, or meat by-products such as blood. It is also important to distinguish between industrial processing and household preparations.

This *Monograph* excluded results on poultry, fish, and seafood; studies of dietary patterns (i.e. clusters of food items grouped by investigators or by statistical analysis); and results of reported ratios of red to white meat. Studies with unspecified meat intake, studies that reported only combined results for red and white meat, or studies of white meat were excluded for most cancers, or were given less weight in the evaluation than others. In addition, studies that only reported on estimated carcinogens derived from meat, but not on "red meat" or "processed meat" variables were excluded.

2.1.2 Sample size and the number of exposed cases

The sample size and the number of exposed cases can have an impact on statistical power. As there was a large number of informative studies, those with a sample size of fewer than 100 cases were excluded.

2.1.3 Study design

For cohort studies, prospective cohort studies and case–control or case–cohort analyses of such studies were considered. For cancer sites with a large number of informative studies and with low case fatality, studies based on mortality data were excluded or given less weight. These decisions are noted, where relevant, in the sections for each specific cancer site. For case–control studies, the selection of hospital-based versus population-based cases and controls was considered. Greater emphasis was given during the evaluation to studies that used population-based controls, as they were more representative of the underlying population. For hospital-based controls, studies that clearly listed the diseases of the controls were given greater emphasis, as the inclusion of controls with conditions related to risk factors for the disease under study may lead to bias. In particular, if the people selected as controls had conditions that could potentially lead to modifications in their diet, they would be less representative of the underlying population, thus leading to biased estimates.

2.1.4 Exposure assessment tools

Greater emphasis was given to studies that used validated dietary instruments and in-person interviews compared with non-validated dietary instruments and mailed, self-administered questionnaires, respectively. The Working Group assessed whether the questionnaires were validated in the population under study, whether the red or processed meat questions captured most subtypes of red or processed meats consumed in that population, and whether there was detailed assessment of portion size (e.g. use of pictures and models, in addition to frequency of consumption).

2.1.5 Adjustment for potential confounding factors

Studies that appropriately adjusted for confounding factors were given greater weight. Studies with insufficient adjustment were either noted and given less weight, or excluded from the review, depending on the number of studies available for a particular cancer site. For each cancer site, potential confounders for associations with meat intake are listed.

In general, total energy/caloric intake, physical activity, and body mass index (BMI) were considered important confounders; however, several other factors were considered for specific cancer sites (e.g. alcohol for cancer of the colorectum and breast, tobacco smoking for cancer of the lung and colorectum, etc.).

Total caloric intake is a putative risk factor for several cancers, and given that red meat and processed meat are significant contributors to total caloric intake, appropriate consideration of this confounder was important. Similarly, given

the established or putative role of other dietary and lifestyle factors that may be correlated with meat intake, the consideration of these factors as possible confounders was important, depending on the cancer site (e.g. dietary fibre, BMI, and physical activity). In particular, it has been shown that individuals who consume high levels of processed meat often tend to eat less fruits and vegetables, to drink more alcoholic beverages, to smoke more tobacco, to consume more calories and more fat, and to be more obese and less active than those who do not consume processed meat (Fung et al., 2003; Dixon et al., 2004; Kesse et al., 2006; Nkondjock & Ghadirian 2005).

References

Dixon LB, Balder HF, Virtanen MJ, Rashidkhani B, Männistö S, Krogh V et al. (2004). Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project. *Am J Clin Nutr*, 80(4):1003–11. PMID:15447912

Fung T, Hu FB, Fuchs C, Giovannucci E, Hunter DJ, Stampfer MJ et al. (2003). Major dietary patterns and the risk of colorectal cancer in women. *Arch Intern Med*, 163(3):309–14. doi:10.1001/archinte.163.3.309 PMID:12578511

Kesse E, Clavel-Chapelon F, Boutron-Ruault MC (2006). Dietary patterns and risk of colorectal tumors: a cohort of French women of the National Education System (E3N). *Am J Epidemiol*, 164(11):1085–93. doi:10.1093/aje/kwj324 PMID:16990408

Nkondjock A, Ghadirian P (2005). Associated nutritional risk of breast and colon cancers: a population-based case-control study in Montreal, Canada. *Cancer Lett*, 223(1):85–91. doi:10.1016/j.canlet.2004.11.034 PMID:15890240

2.2 Cancer of the colorectum

2.2.1 Cohort studies

This section includes prospective cohort studies and case–control studies nested within prospective studies on the association between red or processed meat intake and risk of cancer of the colorectum. The most recent publication of a cohort study, or the publication with the highest number of cases in the analysis, was included in the review. The results of superseded studies were not detailed.

This evaluation excluded prospective studies with colorectal cancer mortality, rather than incidence, as the end-point, and study results on the association between meat intake and colorectal cancer risk when the definition of meat intake included poultry and/or fish. Studies on dietary patterns and studies with fewer than 100 cases in the analyses were also not included.

The results of the included studies are presented according to the type of meat investigated: red meat (i.e. unprocessed red meat), processed meat, and red meat and processed meat combined. When studies reported on two or more of these types of meat, only the data for red meat and processed meat considered separately were treated in detail. A few studies that reported results only for particular aspects of meat consumption, such as doneness or type of meat, are described in this section, but these studies are not included in the tables. Studies on gene–exposure interactions are described in the section of the corresponding meat type, as are studies on the association between cooking methods or meat doneness levels and colorectal cancer.

As studies with greater precision can be considered more informative, particularly when the strength of the association appears to be weak to moderate, the descriptions of the studies are ordered for each section by the number of cases in the analysis, and tables are ordered chronologically. Other study quality criteria are indicated in the text when relevant. The study results most pertinent to the evaluation are included in the tables. Other findings of interest are briefly described in the text.

(a) Red meat

Fourteen cohort studies and two cohort consortia provided informative data on the association between red meat and risk of colorectal cancer (see Table 2.2.1). A few studies investigated specific types of red meat only. The results of these studies are described at the end of this section.

The New York University Women's Health Study (NYUWHS) enrolled women aged 34–65 years at mammographic screening clinics from 1985 to 1991, and followed them up until 1994 through a combination of direct contact and record linkage to cancer registries. A 70–food item, modified Block questionnaire was used to assess diet. Colorectal cancer risk was not significantly associated with red meat intake. The relative risk (RR) for the highest compared with the lowest quartile was 1.23 (95% confidence interval, CI, 0.68–2.22) (Kato et al., 1997). [The Working Group noted that the amount of red meat intake was not reported in the publication, and the study was small (100 cases in the analysis).]

In a nested case–control study using data from the Monitoring Project on Cardiovascular Disease Risk Factors study in the Netherlands (Tiemersma et al., 2002), 102 incident colorectal cancer cases were identified during 8.5 years of follow-up, and a random sample of 537 controls were matched for sex and age. The odds ratio (OR) for consumption of red meat ≥ 5 times/week compared with ≤ 3 times/week was 1.6 (95% CI, 0.9–2.9). In an analysis stratified by sex, a positive association was observed in men (OR, 2.7; 95% CI, 1.1–6.7; P_{trend} = 0.06), but not in women (OR, 1.2; 95% CI, 0.5–2.8; P_{trend} = 0.64). The same comparison was statistically significant

in men and women combined after the exclusion of participants who were younger than age 50 years at the end of the follow-up (RR, 2.0; 95% CI, 1.1–3.8; highest vs lowest intake). The relationship between red meat and colorectal cancer was not modified by *NAT1*, *NAT2*, and *GSTM1* genotypes. [The Working Group noted that a limited number of cancer cases were included in the study, and the assessment of meat intake was not comprehensive. A major source of meat intake – a mix of minced pork and beef – in the Dutch population was missed by the questionnaire. However, the authors indicated that meat consumption was estimated by the questionnaire, with acceptable reproducibility and validity when compared with a dietary history method (data were not given in the paper).]

A cohort study in Takayama, Japan, included 30 221 subjects aged 35 years or older who completed a general questionnaire and a 169–food item, validated food frequency questionnaire (FFQ) at baseline in 1992. Until 2000, 111 cases of colon cancer in men and 102 cases in women were identified through the medical records of two hospitals in Takayama, accounting for about 90% of the colon cancer cases registered in the city cancer registry (Oba et al., 2006). Red meat intake was unrelated to colon cancer risk. Multivariate-adjusted relative risks for the highest compared with the lowest tertile of intake were 1.03 (95% CI, 0.64–1.66; P_{trend} = 0.86) in men and 0.79 (95% CI, 0.49–1.28; P_{trend} = 0.20) in women. Rectal cancer cases were not included in the analysis. [The Working Group noted that a limited number of cancer cases were included in the study, and meat intake was low compared with meat intake in North American and European cohorts.]

In a 6-year follow-up of a cohort of 32 051 non-Hispanic, White members of the Adventist Health Study (AHS) in California, USA (1976–1982), 157 colon cancer cases were identified (Singh & Fraser, 1998). The participants completed at baseline a semiquantitative, 55–food item dietary questionnaire, in which six questions were on meat intake. Participants who consumed beef or pork ≥ 1 time/week were at increased risk of colon cancer compared with those who did not consume beef or pork (RR, 1.90; 95% CI, 1.16–3.11; P_{trend} = 0.02). White meat intake was also positively associated with colon cancer risk. [The Working Group noted that out of the 157 colon cancer cases identified, 42 cases were vegetarians and 40 cases were occasional meat eaters. The association with red meat remained significant in the analysis stratified by intake of white meat, and the analyses were adjusted for tobacco smoking and physical activity. Given the nature of the study population, and that residual confounding could not be ruled out, other lifestyle differences for low meat eaters and vegetarians could at least partially explain the association observed with both red and white meats. The exclusion of current or past smokers, and alcohol consumers did not substantially alter the association with red meat.]

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a randomized, double-blind, placebo-controlled trial on the prevention of incidence of lung cancer in Finnish male smokers, 185 colorectal cancer cases were identified during 8 years of follow-up (Pietinen et al., 1999). Usual diet at baseline was assessed using a self-administered questionnaire with 276 items, and total red meat was defined as beef, lamb, and pork and processed meat. Colorectal cancer was not associated with intake of beef, pork, and lamb (i.e. red meat), specifically; the relative risk for the highest compared with the lowest quartile was 0.8 (95% CI, 0.5–1.2; P_{trend} = 0.74) (Pietinen et al., 1999). Intake of fried meats (determined by adding up the frequency of intake of all dishes where the meat was prepared by frying) was not related to colorectal cancer risk (RR, 0.9; 95% CI, 0.6–1.3; for 204 vs 60 times/year). [The Working Group noted that fried meats may have included fried white meats. No other cooking methods

were reported. A main limitation of this study was the low number of cases.]

In the Iowa Women's Health Study (IWHS), a study in postmenopausal women, 212 incident colon cancer cases were identified during 5 years of follow-up. Diet was assessed using a validated, 127–food item semiquantitative food frequency questionnaire (SQFFQ). Total red meat was defined as beef, lamb, or pork, and processed meat. Consumption of total red meat as defined was not associated with colon cancer, nor was consumption of beef, lamb, or pork as a main dish (RR, 1.21; 95% CI, 0.75–1.96; P_{trend} = 0.16; for > 3 vs < 1 serving/week) (Bostick et al., 1994). This lack of association was observed in women with or without a family history of colon cancer in first-degree relatives (Sellers et al., 1998).

Andersen et al. (2009) conducted a case–cohort study nested in the Danish Diet, Cancer and Health cohort study (372 cases, 765 controls), and reported a null association between intake of red meat and colorectal cancer risk. [Estimates were not adjusted for total energy intake, raising concerns about uncontrolled confounding. In addition,the Working Group noted that the study had a short follow-up (5 years), and cases identified in the first years of follow-up were not excluded from the analyses.]

In a case–cohort study in the Danish Diet, Cancer and Health cohort, including 379 colorectal cancer cases and 769 subcohort members, colorectal cancer was not significantly associated, although it was slightly increased, with intake of red meat (RR, 1.03; 95% CI, 0.97–1.09, per 25 g/day) or fried red meat (RR, 1.09; 95% CI, 0.96–1.23, per 25 g/day). A higher risk was observed in people who reported a preference for brown–dark pan-fried meat (any type of meat) compared with light–light brown meat (RR, 1.36; 95% CI, 1.04–1.77). This risk did not differ significantly between *NAT1* or *NAT2* genotype carriers ($P_{interaction}$ > 0.4) (Sørensen et al., 2008). [The Working Group noted that about 18% of the participants in this cohort were also included in the Danish component of the European Prospective Investigation into Cancer and Nutrition (EPIC).]

In another nested case–control study in the same cohort, a statistically significant increase (RR, 3.70; 95% CI, 1.70–8.04) in colorectal cancer risk per 100 g/day of red meat intake was observed among carriers of the homozygous variant *XPC* Lys939Gln, and no association among carriers of the wildtype allele was observed (Hansen et al., 2007). None of the other polymorphisms investigated (*XPA* A23G, *XPD* Lys751Gln, and *XPD* Asp312Asn) were related to colorectal cancer risk. [The Working Group noted that results regarding the association between *XPC* Lys939Gln and red meat intake on colorectal cancer risk might have been a chance finding, as multiple comparisons were made.]

The Shanghai Women's Health Study (SWHS) included 73 224 women aged 40–70 years at recruitment who completed an FFQ by interview at the baseline assessment beginning in 1997. Follow-up was through active surveys and periodic linkage to the Shanghai Cancer Registry. After a mean follow-up of 7.4 years, 394 incident cases of colorectal cancer (236 colon, 158 rectum) were identified (Lee et al., 2009). The risk of colorectal cancer was not related to the amount of red meat intake. The relative risks for the highest compared with the lowest quintile (> 67 g/day and < 24 g/day, respectively) were 0.8 (95% CI, 0.6–1.1; P_{trend} = 0.53) for colorectal cancer, 0.9 (95% CI, 0.6–1.5; P_{trend} = 0.31) for colon cancer, and 0.6 (95% CI, 0.3–1.1; P_{trend} = 0.79) for rectal cancer. When intakes of 90 g/day and 100 g/day were instead used as cut-points in a further analysis, the relative risk estimates for colorectal cancer were 1.29 (95% CI, 0.88–1.89) and 1.67 (95% CI, 1.11–2.52), respectively. [The Working Group noted that the association may not have been detected in the previous analyses due to an overall low level of meat consumption.] In an analysis of cooking methods, the risk of colon cancer was significantly associated with

preparing food by smoking (RR, 1.4; 95% CI, 1.1–1.9; for ever vs never), but not with other cooking methods. [The Working Group noted that the definition of red meat was not given, but appeared to be unprocessed pork, beef, and lamb. Cooking methods were for all animal foods. The range of meat intake was low in the study.]

In the Melbourne Collaborative Cohort Study, the relative risk of colorectal cancer for consuming red meat more than 6.5 times/week compared with < 3 times/week was 1.4 (95% CI, 1.0–1.9; P_{trend} = 0.2; 451 cases). Red meat was defined as veal, beef, lamb, pork, and rabbit or other game. The association was mainly driven by a positive association with rectal cancer (RR for the same comparison, 2.3; 95% CI, 1.2–4.2; P_{trend} = 0.07; 169 cases). The relative risk for colon cancer was 1.1 (95% CI, 0.7–1.6; P_{trend} = 0.9; 283 cases) (English et al., 2004). In analyses with continuous variables for meat consumption, the relative risks for an increase of 1 time/week were 1.0 (95% CI, 0.94–1.07) for the colon and 1.08 (95% CI, 0.99–1.16) for the rectum.

In the Swedish Mammography Cohort (SMC), 733 incident cases of colorectal cancer were identified after completion of a 67-item, self-administered dietary questionnaire at baseline in 1987–1990. Consumption of unprocessed beef and pork was associated with almost a twofold risk of distal colon cancer for ≥ 4 servings/week, whereas there was no apparent association with risk of proximal colon or rectal cancers (Larsson et al., 2005a). The relative risks for consumption of beef and pork ≥ 4 times/week compared with < 2 times/week were 1.22 (95% CI, 0.98–1.53) for colorectal cancer, 1.10 (95% CI, 0.74–1.64) for proximal colon cancer (234 cases), 1.99 (95% CI, 1.26–3.14; P_{trend} = 0.01) for distal colon cancer (155 cases), and 1.08 (95% CI, 0.72–1.62) for rectal cancer (230 cases), respectively. [The Working Group noted that case ascertainment was virtually complete, and the analyses were controlled for main potential confounders.]

Singaporean Chinese aged 45–74 years who resided in government-built housing estates were enrolled in a prospective study in 1993–1998. At baseline, a 165-item quantitative FFQ, developed for and validated in this population, was administered to assess usual diet over the past year. After an average follow-up duration of nearly 10 years, 941 incident colorectal cancer cases were identified through record linkage to the population-based Singapore Cancer Registry (Butler et al., 2008 b). The adjusted hazard ratio (HR) for the highest compared with the lowest quartile of red meat intake was 1.01 (95% CI, 0.82–1.26; P_{trend} = 0.6). [The Working Group noted that the usual diet was mainly composed of mixed dishes. Red meat appeared to be unprocessed, but the definition was not given in the paper. The cut-off points of the quartiles were not given, and the 95th percentile of red meat intake in non-cases was 76 g/day.]

The EPIC study identified 1329 colorectal cancer cases during a mean follow-up of 4.8 years. Red meat included all fresh, minced, and frozen beef, veal, pork, and lamb. In the EPIC study (Norat et al., 2005), the relative risk for colorectal cancer was 1.17 (95% CI, 0.92–1.49; P_{trend} = 0.08) for an intake of red meat > 80 g/day compared with < 10 g/day. A significant association (RR, 1.21; 95% CI, 1.02–1.43, per 100 g/day; P_{trend} = 0.03) was observed when red meat was expressed as a continuous increment. The association with red meat was strengthened, but not significant, after calibration using 24-hour recall data. The calibrated relative risk for colorectal cancer per 100-g increment was 1.49 (95% CI, 0.91–2.43). The associations were similar for cancers of the colon and rectum, and of the proximal and distal colon. Analysis of specific meat types showed significant positive trends for intake of pork (highest vs lowest intake RR, 1.18; 95% CI, 0.95–0.48; P_{trend} = 0.02) and lamb (HR, 1.22; 95% CI, 0.96–1.55; P_{trend} = 0.03), but not for intake of beef/veal (HR, 1.03; 95% CI, 0.86–1.24; P_{trend} = 0.76). When mutually adjusted,

only the trend for pork remained significant. [The Working Group noted that the strengths of the study were that participants were from 10 European countries with different dietary habits, and detailed validated dietary questionnaires were used. Dietary data were also calibrated using 24-hour recall in a subset of the population to partially correct the relative risk estimates for dietary measurement error. This study investigated red meat, processed meat, and specific meat types in relation to colorectal cancer risk. Follow-up was virtually complete, and the analyses were adjusted for main potential confounders. A potential limitation of the study was that different dietary questionnaires were used in the centres; however, the associations were strengthened after calibration of the dietary data, and no heterogeneity across centres was detected.]

The Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) were among the first American cohorts to investigate the association between red and processed meat and colon cancer risk. The NHS included female, married nurses aged 30–55 years, and diet was assessed by a validated, 61-item SQFFQ. Self-reported cases were validated by medical or pathology records. The HPFS included men aged 40–75 years, and diet was assessed by a self-administered FFQ. Both studies had repeated measures of diet during follow-up (NHS, from 1980 to 2010; HPFS, from 1986 to 2010). Early reports from these cohorts, which included a small number of cases, showed significant positive associations between red and processed meat and colon cancer (age- and energy-adjusted) (Willett et al., 1990; Giovannucci et al., 1994). Several papers on the cohorts have since been published (Wei et al., 2004, 2009; Fung et al., 2010; Zhang et al., 2011; Bernstein et al., 2015), generally showing no association between beef, pork, or lamb as a main dish and colorectal cancer risk (Wei et al., 2004; Fung et al., 2010; Bernstein et al., 2015).

In the most recent analysis of the NHS and the HPFS (Bernstein et al., 2015), which included 2731 colorectal cancer cases (1151 proximal colon, 816 distal colon, and 589 rectum), the cumulative average intake of unprocessed red meat was not associated with colorectal cancer risk (RR per 1 serving/day increase, 0.99; 95% CI, 0.87–1.13; P_{trend} = 0.88). The results were similar when analysed in grams of intake. When analysed by tumour location, red meat consumption was inversely associated with risk of distal colon cancer (RR per 1 serving/day increase, 0.75; 95% CI, 0.68–0.82; $P_{trend} < 0.001$); a weak, non-significant positive association was observed with proximal colon cancer (RR, 1.14; 95% CI, 0.92–1.40; P_{trend} = 0.22)., and no association was observed with rectal cancer (RR, 1.14; 95% CI, 0.86–1.51; P = 0.37). The inverse associations with distal colon cancer were primarily seen after adjustment for specific nutrients, including fibre, folate, and calcium in men and calcium in women. [The Working Group noted that the analyses took into account long-term exposure and several potential risk factors simultaneously. Multiple sensitivity and effect modification analyses were conducted, and the results were robust.]

In a previous nested case–control study of 183 colorectal cancer cases and 443 controls enrolled in the NHS, women with the *NAT2* rapid acetylator genotype who consumed > 0.5 servings/day of beef, pork, or lamb as a main dish had an increased risk of colon cancer compared with women who consumed less red meat (OR, 3.01; 95% CI, 1.10–8.18). No association was observed in slow acetylators (multivariate OR, 0.87; 95% CI, 0.35–2.17; $P_{interaction}$ = 0.07) or in all women (OR, 1.21; 95% CI, 0.85–1.72) (Chan et al., 2005). [The Working Group noted that this study was large. Diet was estimated from repeated questionnaires, and there was a detailed selection of potential confounders.]

The Multiethnic Cohort Study identified 3404 incident cases of colorectal cancer up to 2007 among a sample of African Americans,

Japanese Americans, Latinos, native Hawaiians, and Whites aged 45–75 years living in Hawaii and California, USA (Nöthlings et al., 2009; Ollberding et al., 2012). Red meat intake was not associated with colorectal cancer risk. The relative risk for the highest compared with the lowest quintile (34.86 and 4.59 g/1000 kcal, respectively) was 0.98 (95% CI, 0.87–1.10; P_{trend} = 0.58). For all types of meats considered together, the risk did not vary by doneness preference (cooked until dark brown or well done) or cooking method preference (pan-fried, oven-broiled, or grilled/barbecued); data were not reported by the authors. [The Working Group noted that this was a large study that sampled people from different ethnic groups for better generalizability of results. There was a strong attenuation of the effect estimates after multivariable adjustment.]

In a nested case–control in the United Kingdom Dietary Cohort Consortium, based on seven cohort studies in the United Kingdom (Spencer et al., 2010), diet was assessed using 4-, 5-, or 7-day food diaries. Red meat was defined as including beef, pork, lamb, and meat from burgers, and other non-processed meat items made with these meats. Red meat intake was not related to risk of colorectal cancer (579 cases). The relative risk estimate for an increase in intake of 50 g of red meat was 1.01 (95% CI, 0.84–1.22) for colorectal cancer. Similar relative risks were observed for colon and rectal cancers. [The Working Group noted that meat intake was relatively low in the overall consortium, as many participants were either vegetarians or low meat eaters. The use of food diaries may also have led to overestimation of the number of non-consumers of infrequently consumed food items.]

In a pooled analysis of the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and the Colon Cancer Family Registry (CCFR) (Kantor et al., 2014), which included 9160 cases of colorectal cancer and 9280 controls, the pooled relative risk estimate for colorectal cancer for each serving per day increase in intake of red meat was 1.33 (95% CI, 1.23–1.44) for all studies combined. The purpose of the study was to investigate gene–environment interactions, and the estimates of associations reported were controlled only for age, sex, and study centre. In another paper based on the same pooled study, Figueiredo et al. (2014) reported a relative risk of 1.23 (95% CI, 1.12–1.34) for red meat consumption above versus below the median and a relative risk of 1.15 per quartile of intake. In another publication based on GECCO and the CCFR that included data from case–control studies nested in five cohorts, red meat consumption was related to colorectal cancer risk only from retrospective case–control studies. The pooled odds ratio from four retrospective case–control studies was 1.75 (95% CI, 1.55–1.98). The relationship was not modified by NAT2 enzyme activity (based on polymorphism at rs1495741) (Ananthakrishnan et al., 2015). No interaction involving any gene and red meat was detected in a genome-wide diet–gene interaction analysis in GECCO or in a study on colorectal cancer susceptibility loci (Hutter et al., 2012). [The exact definition of red meat was not given in these studies.]

Five additional cohort studies did not investigate the overall association between colorectal cancer risk and red meat consumption, but did evaluate associations with specific red meat items (data not reported in Table).

In a prospective study conducted by the Norwegian National Health Screening Service (143 cases of colon cancer) among Norwegian men and women aged 20–54 years between 1977 and 1983 (Gaard et al., 1996), consumption of meatballs, meat stews, and fried or roasted meats was unrelated to colon cancer risk. [The Working Group noted that the analyses were only for specific red meat types and adjusted only for age.]

In the Women's Health Study (WHS), a randomized trial in the USA of low-dose aspirin and vitamin E in the primary prevention of cancer and cardiovascular disease, diet was assessed at study baseline using a 131-item FFQ that was

previously validated in the NHS. Two hundred and two incident colorectal cancer cases were identified during 8.7 years of follow-up. The definition of red meat included hot dogs, bacon, and other processed meats. Data for consuming unprocessed red meat were limited to beef or lamb as a main dish and were stratified by cooking method. In comparison with beef or lamb cooked rare or medium–rare, the relative risks were 0.73 (95% CI, 0.47–1.11) for medium doneness, 1.02 (95% CI, 0.68–1.52) for medium well-done meat and 0.94 (95% CI, 0.63–1.41) for well-done meat (P_{trend} = 0.83) (Lin et al., 2004). Meat doneness was available only for beef or lamb as a main dish. This study also reported a positive association between white meats and colorectal cancer.]

In a case–cohort analysis including 448 colon and 160 rectal cancer cases and a subcohort of 2948 participants in the Netherlands Cohort Study (NLCS), intake of beef, pork, minced meat, or liver was not significantly associated with colon or rectal cancer risk, although a positive association was suggested for beef and colon cancer (RR for highest vs lowest category of beef intake, 1.28; 95% CI, 0.96–1.72; P_{trend} = 0.06) (Brink et al., 2005). In another analysis (434 colon cancer cases, 154 rectal cancer cases) (Lüchtenborg et al., 2005), beef consumption was associated with an increased risk of colon tumours without a truncating *APC* somatic mutation. The incidence rate ratio for the highest versus the lowest quartile of intake was 1.58 (95% CI, 1.10–2.25; P_{trend} = 0.01). [The Working Group noted that the follow-up period was short, and cases diagnosed in the first years of follow-up were excluded.]

A recent full cohort analysis of the Netherlands Cohort Study – Meat Investigation Cohort (NLCS-MIC), with all individuals reporting to be vegetarian or to consume meat only 1 day/week, was conducted with 20.3 years of follow-up (Gilsing et al., 2015). For red meat, defined as fresh meat without chicken, no clear association was observed with colon or rectal cancer.

In a cohort study in Japan, 47 605 residents aged 40–64 years from the Miyagi Prefecture completed a self-administered, 40-item FFQ in 1990. Four hundred and seventy-four colorectal cancer cases were identified after an average follow-up of 11 years through linkage to the Miyagi Prefectural Cancer Registry. Relative risk estimates for the highest compared with the lowest intake were 0.93 (95% CI, 0.67–1.30; P_{trend} = 0.63) for beef and 1.13 (95% CI, 0.79–1.74; P_{trend} = 0.31) for pork intake. No associations were observed with risk of cancers of the colon, proximal or distal colon, and rectum (Sato et al., 2006). [The Working Group noted that the number of categories in the questionnaire was low, and there was low variability in meat intake. The median intake in the top category was 7.4 g/week for beef and 26.3 g/week for pork (excluding ham and sausage). Beef and pork combined was not investigated.]

In the Japan Public Health Center-based Prospective Study (JPHC Study), men and women completed a self-administered questionnaire in 1995–1999 at age 45–74 years (Takachi et al., 2011), and 1145 cases of colorectal cancer were identified until the end of 2006. The category of red meat was defined as including processed products and chicken liver. In women, a significant association between beef intake and colon cancer was observed (RR for fifth vs first quintile, 1.62; 95% CI, 1.12–2.34; P_{trend} = 0.04), and a non-significant association was observed for pork (RR for fifth vs first quintile, 1.42; 95% CI, 0.99–2.04; P_{trend} = 0.05) (Takachi et al., 2011). No significant association between beef or pork intake and colon or rectal cancer was observed in men. [The Working Group noted that although red and processed meat consumption was lower in this cohort than in cohorts from Western countries, there was a sevenfold difference in the median intakes of the lowest and highest quintiles. Total consumption of red meat was not investigated.]

(b) Processed meat

Associations between colorectal cancer and consumption of processed meat have been examined in 18 informative cohort studies and two pooled analyses (see Table 2.2.2); some of these studies also reported data for red meat.

Intake of processed meat (ham and sausages) was not related to colorectal cancer risk in the NYUWHS (Kato et al., 1997). The relative risk for the highest compared with the lowest quartile was 1.09 (95% CI, 0.59–2.02; P_{trend} = 0.735; 100 cases). [The Working Group noted that this study had a small sample size. The analyses were adjusted only for energy intake, age, place, and education level.]

Colorectal cancer was not associated with intake of processed meat in the ATBC Study in Finnish male smokers (185 cases) (Pietinen et al., 1999). The relative risk for the highest compared with the lowest quartile (medians, 122 g/day and 26 g/day, respectively) was 1.2 (95% CI, 0.7–1.8; P_{trend} = 0.78). [The Working Group noted that a main limitation of this study was the low number of cases.]

In the WHS, processed meat intake was inversely, although not significantly, associated with colorectal cancer in the analysis including 202 cases (Lin et al., 2004). The relative risk for the highest compared with the lowest quintile was 0.85 (95% CI, 0.53–1.35; P_{trend} = 0.25; medians of the quintiles, 0.5 servings/day and 0 servings/day, respectively). Processed meat was defined as hot dogs, bacon, and other processed meats. [The Working Group noted that this study reported an inverse non-significant association between total red meat and colorectal cancer, and positive associations between white meat and colorectal cancer, in contrast with the results of other cohort studies.]

In the IWHS cohort (Bostick et al., 1994), which included 212 cases, the relative risk of colon cancer for consumption of > 3 servings/week of processed meat compared with none was 1.51 (95% CI, 0.72–3.17; P_{trend} = 0.45). In the same cohort, nitrate-treated meats were not related to colon cancer in women with or without a family history of colon cancer in first-degree relatives (Sellers et al., 1998). [The Working Group noted that this study had a small sample size, follow-up was 5 years, and cases identified in the first years of follow-up were not excluded from the analyses.]

In a community-based prospective study in Takayama, Japan, including 213 cases of colorectal cancer, there was a twofold, significant increased risk of colon cancer only in men who consumed a higher intake of processed meats (Oba et al., 2006). The relative risks for the highest compared with the lowest tertile of intake were 1.98 (95% CI, 1.24–3.16; P_{trend} < 0.01) in men and 0.85 (95% CI, 0.50–1.43; P_{trend} = 0.62) in women. Processed meat was defined as ham, sausage, bacon, and yakibuta (Chinese-style roasted pork). The results did not change after the exclusion of cases diagnosed in the first 3 years of follow-up.

Processed meat intake was associated with colorectal cancer in the Melbourne Collaborative Cohort Study (451 cases) (English et al., 2004). The relative risks were 1.5 (95% CI, 1.1–2.0; P_{trend} = 0.01) for the highest compared with the lowest intake and 1.07 (95% CI, 1.01–1.13) for an increase of 1 serving/week. Processed meat intake was more strongly associated with risk of rectal cancer than with risk of colon cancer in a categorical analysis. The relative risks for the highest compared with the lowest quartile were 1.3 (95% CI, 0.9–1.9) for the colon and 2.0 (95% CI, 1.1–3.4) for the rectum. The hazard ratios for each additional serving per week were similar; the hazard ratios were 1.07 (95% CI, 1.00–1.14) and 1.08 (95% CI, 0.99–1.18) for the colon and rectum, respectively (P = 0.8, test of homogeneity of trends).

In the Breast Cancer Detection Demonstration Project (BCDDP) in the USA (467 cases), women completed a 62-item National Cancer Institute (NCI)/Block FFQ. The Block FFQ defined processed meat as bacon, ham, lunchmeat,

hot dogs, and sausage (Flood et al., 2003). The relative risk for the highest compared with the lowest quintile of processed meat intake was 0.97 (95% CI, 0.73–1.28; P_{trend} = 0.35; medians of the quintiles, 22.2 and 0.02 g/1000 kcal, respectively) after adjustment for age, energy, and total meat consumption. The inclusion of several other variables, including smoking, alcohol drinking, and BMI, did not materially change the estimates and were not kept in the final models. [The Working Group noted that colorectal cancer diagnosis was self-reported in most cases. Pathology reports were obtained for 79% of these cases, and the diagnosis confirmed in 94% of them, suggesting that case identification was not an issue.]

In the Miyagi Cohort Study in Japan, processed meat consumption was not related to risk of colorectal cancer (colorectum, colon, proximal colon, and distal colon and rectum); the analysis included 474 incident colorectal cancer cases (Sato et al., 2006). The relative risk for the highest compared with the lowest quartile was 0.91 (95% CI, 0.61–1.35; P_{trend} = 0.99). No associations were observed for cancers of the colon, rectum, or proximal and distal colon. [The Working Group noted that the number of categories in the questionnaires was low, and there was low variability in meat intake due to low frequency of consumption of some meat items.]

In the Danish Diet, Cancer and Health study (18% of the cases were included in the Danish component of the EPIC study), the relative risks per 25 g/day increase in intake of processed meats were 1.03 (95% CI, 0.94–1.13; 644 cases) for the colon and 0.93 (95% CI, 0.81–1.07; 345 cases) for the rectum (Egeberg et al., 2013). No significant associations were observed with intakes of sausages, cold cuts, or liver pâté. In addition, associations were not modified by four polymorphisms (*XPA* A23G, *XPC* Lys939Gln, *XPD* Lys751Gln, and *XPD* Asp312Asn) of enzymes involved in the nucleotide excision repair pathway in a case–control study nested in the cohort (405 colorectal cancer cases, 810 controls) (Hansen et al., 2007). Another analysis of 379 colorectal cancer cases and 769 subcohort members showed no association with consumption of processed meat when stratified by *NAT1* or *NAT2* genotypes (Sørensen et al., 2008).

In the SMC (Larsson et al., 2005a), processed meat intake was not related to risk of colorectal cancer or colorectal cancer subsites. The relative risk estimates for the highest compared with the lowest quartile of intake were 1.07 (95% CI, 0.85–1.33; P_{trend} = 0.23) for the colorectum (733 cases), 1.02 (95% CI, 0.69–1.52; P_{trend} = 0.97) for the proximal colon (234 cases), 1.39 (95% CI, 0.86–2.24; P_{trend} = 0.20) for the distal colon (155 cases), and 0.90 (95% CI, 0.60–1.34; P_{trend} = 0.88) for the rectum (230 cases). [The Working Group noted that the dietary questionnaire had 67 food items. Follow-up was long (13.9 years on average), and changes in dietary habits during follow-up were not taken into account. Case ascertainment was virtually complete, and the analyses were controlled for main potential confounders.]

In the Singapore Chinese Health Study (SCHS) (Butler et al., 2008b), the relative risk for the highest compared with the lowest quartile of processed meat intake was 1.16 (95% CI, 0.95–1.41; 941 incident colorectal cancer cases after an average follow-up of 10 years). Types of processed meats were not defined. [The Working Group noted that the cut-points of the quartiles were not given, and processed meat intake was low (the 95th percentile of processed meat intake in non-cases was 10 g/day).]

In the JPHC Study (Takachi et al., 2011) (1145 cases of cancer of the colorectum), processed meat included ham, sausage or wiener sausage, bacon, and luncheon meat. The relative risks of colon cancer for the highest compared with the lowest quintile were 1.27 (95% CI, 0.95–1.71; P_{trend} = 0.10) in men and 1.19 (95% CI, 0.82–1.74; P_{trend} = 0.64) in women. Similar results were observed for proximal and distal colon cancers. The relative risk for rectal cancer was 0.70 (95% CI, 0.45–1.09; P_{trend} = 0.10) in men and 0.98 (95% CI, 0.53–1.79;

P_{trend} = 1.00) in women. [The Working Group noted that the range of processed meat intake was low. The median intake in the top quintile was 16 g/day in men and 15 g/day in women.]

In the European EPIC study (1329 incident colorectal cancer cases), processed meats included mostly pork and beef preserved by methods other than freezing, such as salting (with and without nitrites), smoking, marinating, air-drying, or heating (i.e. ham, bacon, sausages, blood sausages, meat cuts, liver pâté, salami, bologna, tinned meat, luncheon meat, corned beef, and others). The relative risk of colorectal cancer for an intake of > 80 g/day of processed meat compared with < 10 g/day of processed meat was 1.42 (95% CI, 1.09–1.86; P_{trend} = 0.02) (Norat et al., 2005). The relative risk for an increase in intake of 100 g/day of processed meat was 1.32 (95% CI, 1.07–1.63; P_{trend} = 0.009). This was strengthened to 1.70 (95% CI, 1.05–2.76; P_{trend} = 0.03) after calibration using 24-hour recall data from a subset of the study population. The relative risks for the highest versus the lowest quintile were 1.62 (95% CI, 1.04–2.50), 1.48 (95% CI, 0.87–2.53), and 1.19 (95% CI, 0.70–2.01) for rectal, distal, and proximal colon cancer, respectively. No significant differences across cancer sites were observed ($P_{heterogeneity}$ = 0.87). Intake of ham (RR for highest vs lowest intake, 1.12; 95% CI, 0.90–1.37; P_{trend} = 0.44), bacon (HR, 0.96; 95% CI, 0.79–1.17; P_{trend} = 0.34), and other types of processed meats (HR, 1.05; 95% CI, 0.84–1.32; P_{trend} = 0.22) was not significantly related to colorectal cancer risk. [This was a large study in 10 European countries that used extensive dietary questionnaires. Follow-up is virtually complete, and the analyses were adjusted for main potential confounders.] In a substudy of the EPIC-Norfolk study, higher consumption of processed meat was associated with an increased risk of colorectal cancer harbouring a truncating *APC* mutation and, in particular, rectal tumours with GC→AT transitions compared with colorectal cancer without mutations (OR for increment of 19 g/day, 1.68; 95% CI, 1.03–2.75) (Gay et al., 2012).

A case–cohort analysis of the Netherlands Cohort Study (NLCS) included 1535 incident colorectal cancer cases identified after 9.3 years of follow-up through linkage to the Netherlands Cancer Registry (Balder et al., 2006). The relative risks for processed meats (meat items mostly cured, and sometimes smoked or fermented) and colorectal cancer (RR for highest vs lowest quartile) were 1.18 (95% CI, 0.84–1.64; P_{trend} = 0.25) in men and 1.05 (95% CI, 0.74–1.48; P_{trend} = 0.62) in women. No associations were observed for colon or rectal cancer in men or women. In another analysis in the same cohort, consumption of meat products (same definition as for processed meats) was significantly positively associated with risk of colon tumours with a wildtype *K-ras* gene (RR for highest vs lowest quartile of intake, 1.42; 95% CI, 1.00–2.03; P_{trend} = 0.03) (Brink et al., 2005) and *APC*-positive colon cancer (RR for highest vs lowest quartile of intake, 1.61; 95% CI, 0.96–2.71; P_{trend} = 0.04) (Lüchtenborg et al., 2005), but not with other types of colon or rectal tumours. These analyses included more than 430 colon and 150 rectal cancers occurring during 7.3 years of follow-up, excluding the first 2.3 years, and 2948 subcohort members. An analysis of the MIC embedded within the NLCS, which included individuals reporting to be vegetarian or to consume meat only 1 day/week, was conducted with 20.3 years of follow-up (Gilsing et al., 2015). For processed meat, a statistically significant association with rectal cancer was observed (RR, 1.36 for every 25 g/day of intake; 95% CI, 1.01–1.81; P_{trend} = 0.008). No significant association was observed with colon cancer, although a positive association with distal colon cancer was suggested.

The Cancer Prevention Study II (CPS-II) Nutrition Survey enrolled men and women in the USA who completed a mailed FFQ in 1992–1993 (1667 incident colorectal cancer cases) (Chao et al., 2005). The relative risk for the highest quintile compared with the lowest quintile of processed meat intake was

1.13 (95% CI, 0.91–1.41; P_{trend} = 0.02) in women and men combined. A significant trend was observed in men (P_{trend} = 0.03), but not in women (P_{trend} = 0.48). No significant associations were observed with proximal or distal colon cancer, and rectal cancer, although the relative risk estimates were higher for distal and rectal tumours. When long-term consumption of processed meat was considered, based on consumption reported in 1982 and at baseline in 1992–1993, participants in the highest tertile of consumption had an increased risk of distal colon cancer (RR, 1.50; 95% CI, 1.04–2.17). A non-significant 14% and 21% increased risk of cancers of the proximal colon, and rectosigmoid junction and rectum were observed. [The Working Group noted that the 1982 questionnaire did not assess the number of servings per day, and could not differentiate people who ate multiple servings from those who ate processed meat only once per day. It was also not possible to estimate total energy intake from the 1982 dietary questionnaire.]

In the NHS and the HPFS (Bernstein et al., 2015), using cumulative dietary intake data, the relative risk of colorectal cancer per 1 serving/day increment of processed meat was 1.15 (95% CI, 1.01–1.32; P_{trend} = 0.03), and it was 1.08 (95% CI, 0.98–1.18; P_{trend} = 0.13) when diet, as assessed at baseline, was analysed. Using cumulative dietary intake data, the relative risks were 0.99 (95% CI, 0.79–1.24) for proximal colon cancer (1151 cases), 1.36 (95% CI, 1.09–1.69; P_{trend} = 0.006) for distal colon cancer (817 cases), and 1.18 (95% CI, 0.89–1.57) for rectal cancer (589 cases). [The analyses were extensively adjusted for potential risk factors. The use of repeated questionnaires should have reduced dietary measurement error. Several sensitivity and stratified analyses showed the robustness of the results.] In an earlier nested case–control in the NHS including 197 cases identified by the year 2000 (Tranah et al., 2006), colorectal cancer risk was not related to consumption of > 1 slice/week of processed meat (OR, 1.06; 95% CI, 0.73–1.55), > 2 pieces/week of bacon (OR, 0.94; 95% CI, 0.56–1.58), or > 1 hot dog/week (OR, 1.06; 95% CI, 0.68–1.65). Compared with infrequent consumption of these items, no association with all types of processed meats combined was observed. There was no significant interaction on a multiplicative scale between the *MGMT* genotype and intake of processed meat, bacon, and hot dogs in women.

In the Multiethnic Cohort Study, the relative risk of colorectal cancer (n= 3404 cases) for the highest compared with the lowest quintile of processed meat intake was 1.06 (95% CI, 0.94–1.19; P_{trend} = 0.259) (Ollberding et al., 2012). Relative to the significant association that was observed in models adjusted only for age, ethnicity, and sex (HR, 1.25; 95% CI, 1.12–1.40; $P < 0.001$), this relative risk was attenuated after further adjustment for family history of colorectal cancer, history of colorectal polyps, BMI, pack-years of cigarette smoking, nonsteroidal anti-inflammatory drug use, alcohol consumption, vigorous physical activity, history of diabetes, hormone replacement therapy use (women only), total calories, and dietary fibre, calcium, folate, and vitamin D. [The main strengths of this study were its large size, the ethnic diversity of the study population, and the population-based sampling frame that was used, which allowed for better generalizability of the study results. As indicated in the section on red meats, the Working Group noted that there was a strong attenuation of the association estimates after multivariable adjustment.]

The National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study was based on a cohort of over 500 000 men and women from eight states in the USA, aged 50–71 years at baseline (1995–1996), who completed a validated, 124-item FFQ. In an analysis of 5107 colorectal cancer cases, identified on average during 8.2 years of follow-up (Cross et al., 2007), processed meat consumption was significantly related to colorectal cancer risk. The relative risk for the fifth compared with the first quintile of intake was 1.20 (95% CI, 1.09–1.32;

P_{trend} < 0.001). The relative risks were similar for colon cancer and rectal cancer. Similar results were observed in another study in the same cohort that explored the mechanisms relating colorectal cancer and meat intake (Cross et al., 2010). The overall relative risk for the association between colorectal cancer and processed meat intake was 1.16 (95% CI, 1.01–1.32; P_{trend} = 0.017) for the highest compared with the lowest quintile. For colon and rectal cancer separately, the relative risks for the same comparison were 1.11 (95% CI, 0.95–1.29) and 1.30 (95% CI, 1.00–1.68), respectively. Nitrate and nitrite intake from processed meats was estimated using a database containing measured values of nitrate and nitrite from 10 types of processed meats. The relative risk of colorectal cancer for the highest compared with the lowest quintile of intake of nitrate from processed meat was 1.16 (95% CI, 1.02–1.32; P_{trend} = 0.001; medians of the quintiles, 289.2 µg/1000 kcal per day and 23.9 µg/1000 kcal per day, respectively). The association with nitrite from processed meat did not attain statistical significance (RR for highest vs lowest quintile, 1.11; 95% CI, 0.97–1.25; P_{trend} = 0.055; medians of the quintiles, 194.1 µg/1000 kcal per day and 11.9 µg/1000 kcal per day, respectively). In a lag analysis excluding the first 2 years of follow-up (1941 colorectal cancer cases), the association between processed meat intake and colorectal cancer remained significant (HR, 1.19, 95% CI, 1.02–1.39, P_{trend} = 0.013). Participants in the NIH-AARP study also completed a 37-item FFQ about diet 10 years before baseline. Participants in the highest intake category of processed meat 10 years before baseline had a higher risk of cancer of the colon (RR, 1.30; 95% CI, 1.13–1.51; P_{trend} < 0.01) and rectum (RR, 1.40; 95% CI, 1.09–1.81; P_{trend} = 0.02) than participants in the lower intake category (Ruder et al., 2011). [The Working Group noted that the questionnaire to assess diet 10 years before baseline was not validated, and did not allow for estimation of total energy intake.]

In the United Kingdom Dietary Cohort Consortium (Spencer et al., 2010), processed meat was assessed as ham, bacon, the meat component of sausages, and other items made with processed meat. For a 50 g/day increase in consumption of processed meat, the odds ratio for colorectal cancer was 0.88 (95% CI, 0.68–1.15). The odds ratios for colon and rectal cancer separately were also non-significantly different from unity.

In a pooled analysis of the GECCO study (Kantor et al., 2014), the pooled relative risk of colorectal cancer for each serving per day increase in intake of processed meats was 1.48 (95% CI, 1.30–1.70) for all studies combined. [The main strength of the study was the large number of cases included in the analysis.] In genome-wide diet–gene interaction analyses in GECCO, which included five retrospective case–control studies and five case–control studies nested in prospective studies, there was a positive interaction between rs4143094 (10p14/near *GATA3*) and processed meat consumption (OR, 1.17; 95% CI, 1.11–1.23; *P* = 8.7E–09), which was consistently observed across studies ($P_{heterogeneity}$ = 0.78) (Figueiredo et al., 2014). The risk of colorectal cancer associated with processed meat was increased among individuals with the rs4143094–TG (OR, 1.20; 95% CI, 1.13–1.26) and –TT genotypes (OR, 1.39; 95% CI, 1.22–1.59), and null among those with the –GG genotype (OR, 1.03; 95% CI, 0.98–1.07). In another study in GECCO on gene–environment interactions and colorectal cancer susceptibility loci, no interaction with processed meat was detected (all studies combined) (Hutter et al., 2012).

In the prospective study conducted by the Norwegian National Health Screening Service (Gaard et al., 1996), colon cancer risk was higher in women who consumed fried or poached sausages as their main meal ≥ 5 times/month compared with those who reported a consumption of < 1 time/month (RR, 3.50; 95% CI, 1.02–11.9; P_{trend} = 0.03). Among men, a similar, but not significant, association was observed

(RR, 1.98; 95% CI, 0.70–5.58; P_{trend} = 0.35). [The Working Group noted that only specific types of processed meats were investigated. The analyses were only adjusted for age. The 50 535 participants were relatively young (age, 20–54 years) at recruitment in 1977–1983, and only 143 cases of colon cancer were identified through linkage to the Norwegian Cancer Registry after 11.4 years of follow-up.]

(c) Red meat and processed meat combined

Several studies reported on the risk of colorectal cancer associated with measures of meat consumption, which included processed meats and unprocessed red meats, both red and white meats, or meats without a clear definition. The Working Group considered these data to be less informative than associations with red meat and processed meat considered separately. Key findings from this group of studies are summarized in this section and given in Table 2.2.1.

Several other studies reported data for specific red meat items, such as beef or pork, or for unprocessed red meat or processed meat separately, as well as for a broader category including both types of meats (e.g. Bostick et al., 1994; Pietinen et al., 1999; Lin et al., 2004; Larsson et al., 2005a; Norat et al., 2005; Spencer et al., 2010; Takachi et al., 2011; Ollberding et al., 2012; Bernstein et al., 2015). For these studies, the more informative data for red meat and for processed meat are reviewed in the preceding sections, but data for the combined category are not presented.

In the Finnish Mobile Clinic Health Examination Survey (109 colorectal cancer cases), the relative risks for the highest compared with the lowest quartile of red meat intake were 1.50 (95% CI, 0.77–2.94) for colorectal cancer, 1.34 (95% CI, 0.57–3.15) for colon cancer, and 1.82 (95% CI, 0.60–5.52) for rectal cancer (Järvinen et al., 2001). [The Working Group considered that the category of red meat may have included processed items. In contrast with other studies, there was a significant increase of colorectal cancer in participants consuming poultry compared with non-consumers. An important limitation of the study was the small size.]

In the Physicians' Health Study (PHS) (originally designed as a double-blind trial of aspirin and β-carotene as preventive measures for cardiovascular disease and cancer), diet at enrolment was assessed using an abbreviated FFQ, in which red and processed meat intake included beef, pork, lamb, and hot dogs. A case–control study nested in the PHS cohort (212 colorectal cancer cases) (Chen et al., 1998) found that combined red and processed meat intake was not significantly related to colorectal cancer risk (RR, 1.17; 95% CI, 0.68–2.02; for ≥ 1 vs ≤ 0.5 servings/day). There was no significant interaction with *NAT1*/*NAT2* genotypes (all $P_{interaction}$ > 0.16). [The Working Group noted that the definition of red meat included hot dogs, and analyses were not controlled for total energy intake, BMI, and other important confounders.]

A case–cohort study done within the CLUE II cohort (250 genotyped cases) (Berndt et al., 2006) reported a non-statistically significant positive association between red meat [including processed meat] intake and colorectal cancer risk (RR for highest vs lowest tertile, 1.32; 95% CI, 0.86–2.02), when adjusting for age, sex, and total energy. [The main focus of this paper was to explore gene–environment interactions with nucleotide excision repair genes; therefore, analyses of the main effects of meat were limited.]

A nested case–control study, the EPIC-Norfolk component of EPIC, investigated the effect of the variant genotype *MGMT* Ile143Val on colorectal cancer risk among 273 colorectal cancer cases and 2984 matched controls. The odds ratio was 1.43 (95% CI, 0.82–2.48; $P_{interaction}$ = 0.04) for the variant genotype carriers and red and processed meat intake above the median compared with common genotype carriers and red and processed meat intake below the median (Loh et al., 2010). The polymorphism was not related to colorectal cancer risk. [The Working Group noticed that

red and processed meat intakes were assessed according to baseline 7-day food diary data.]

The Breast Cancer Detection Demonstration Project (BCDDP) (487 colorectal cancer cases) (Flood et al., 2003) reported a relative risk of 1.04 (95% CI, 0.77–1.41) for > 52.2 g/1000 kcal compared with < 6.1 g/1000 kcal (quintiles) of combined red and processed meat intake. [The Working Group noted that the associations became stronger after multiple adjustments.]

In a prospective study based on a trial of screening for breast cancer, the Canadian National Breast Screening Study (CNBSS), participants reported their diet in 1982 using an 86–food item SQFFQ (Kabat et al., 2007). Red meat intake, defined as beef, veal, pork, ham, bacon, and pork-based luncheon meats, was related to an increased risk of rectal cancer, but not colon cancer. For the highest compared with the lowest quintile (> 40.3 and < 14.2 g/day, respectively), the relative risks were 1.12 (95% CI, 0.86–1.46) for colorectal cancer (617 cases), 0.88 (95% CI, 0.64–1.21) for colon cancer (428 cases), and 1.95 (95% CI, 1.21–3.16; $P_{trend} = 0.008$) for rectal cancer (195 cases). No associations were observed with cancers of the proximal and distal colon (data were not shown).

In a study based on the Multiethnic Cohort, no clear evidence was found for an interaction with *NAT2* or *NAT1* acetylator genotypes on the association between colorectal cancer risk and red and processed meat intake, or meat doneness preference in 1009 cases and 1522 controls (Nöthlings et al., 2009).

In the CPS-II Nutrition Survey (1667 colorectal cancer cases) (Chao et al., 2005), red meat was defined as including bacon, sausage, liver, hot dogs, ham, bologna, salami, and lunchmeat, as well as unprocessed beef and pork. The relative risk for colon cancer and red meat (as defined above) consumption assessed at baseline was 1.15 (95% CI, 0.90–1.46; $P_{trend} = 0.04$) in men and women combined. Consumption of these meats was related to an increased risk of cancers of the rectosigmoid junction and rectum (RR, 1.71; 95% CI, 1.15–2.52; $P_{trend} = 0.007$; for highest vs lowest quintile), but not to cancers of the rectosigmoid junction only (numerical data were not shown). [The Working Group noted that an earlier questionnaire used to estimate long-term consumption assessed only frequency of intake; thus, estimation of total energy intake from that questionnaire was not possible.]

The NIH-AARP study defined red meat as beef, pork, and lamb, including bacon, cold cuts, ham, hamburger, hot dogs, liver, sausage, and steak. After an average follow-up of 7 years, 2719 colorectal cancer cases were identified. Red meat and processed meat were related to an increased risk of colon and rectal cancer. The relative risks for the highest compared with the lowest quintile of red and processed meat intake (61.6 and 9.5 g/1000 kcal, respectively) were 1.24 (95% CI, 1.09–1.42; $P_{trend} < 0.001$) for colorectal cancer, 1.21 (95% CI, 1.03–1.41; $P_{trend} < 0.001$) for colon cancer, and 1.35 (95% CI, 1.03–1.76; $P_{trend} = 0.024$) for rectal cancer (Cross et al., 2007, 2010). Significant associations were also observed when intake was analysed on a continuous scale. The relative risks were similar for proximal and distal colon cancer. The findings remained the same after exclusion of the first 2 years of follow-up. Study participants also completed a 37-item FFQ on dietary intake 10 years before baseline (Ruder et al., 2011). Participants in the highest intake category of red and processed meat 10 years before baseline (defined as ground beef, roast beef or steak, cold cuts, bacon or sausage, and hot dogs) had a higher risk of colon cancer (RR, 1.46; 95% CI, 1.26–1.69; $P_{trend} = 0.01$) than participants in the lowest intake category. A significant trend was observed for the rectum (RR, 1.24; 95% CI, 0.97–1.59; $P_{trend} = 0.03$). [The Working Group noticed that the FFQ to assess diet 10 years before baseline was not validated, and did not allow for estimation of total energy intake for adjustment of the analyses.]

(d) Haem iron

Data on the association between colorectal cancer risk and haem iron intake were available from five cohort studies reviewed in this section (Lee et al., 2004; Larsson et al., 2005b; Balder et al., 2006; Kabat et al., 2007; Cross et al., 2010). One study reported a statistically significant positive association with proximal, but not distal colon cancer (Lee et al., 2004), and another found a significant positive association with colon cancer after excluding 2 years of follow-up when registry data were believed to be incomplete (Balder et al., 2006). Relative risks were null or non-significantly increased (range, 0.99–1.31) in three other studies that reported data on colon cancer (Larsson et al., 2005b; Kabat et al., 2007; Cross et al., 2010), rectal cancer (Kabat et al., 2007; Cross et al., 2010), and colorectal cancer overall (Kabat et al., 2007; Cross et al., 2010). [The Working Group noted that the overall evidence on haem iron was limited by the possibility of publication bias and the few databases for estimating haem iron intake from dietary questionnaires.]

2.2.2 Case–control studies

Numerous case–control studies have examined the association between red or processed meat intake and risk of colorectal cancers. This section presents studies by how meat was defined in the following order: red meat and processed meat separately, red meat and processed meat combined, and then red meat, unclear whether fresh or processed.

In reviewing and interpreting the available literature, the Working Group considered for each of these categories the criteria summarized in Section 2.1 and the greatest weight was given to studies that met the following criteria:

- Had an unambiguous definition of red and processed meat (studies that reported data for unprocessed red and/or processed meat separately, and/or listed subtypes of meats included in each meat definition) (see criterion 1 in Section 2.1.1);
- Met the definition of a population-based study, or included hospital-based cases using approaches that ensured a representative sample of the underlying population (e.g. community hospitals that serve specific regions in a country) and population-based controls (see criterion 3 in Section 2.1.3);
- Used a previously validated dietary instrument (see criterion 4 in Section 2.1.4); and
- Considered detailed assessment for potential confounders, in particular total energy intake (see criterion 5 in Section 2.1.5).

The Working Group also considered as informative studies that met these criteria but showed limitations in criteria 3, 4, or 5 summarized above. Sample size was considered for informativeness (see criterion 2 in Section 2.1.2). The main limitations identified by the Working Group are noted between brackets in the description of each paper.

The Working Group gave less weight to other studies that showed important limitations in criterion 3, 4, or 5 above, and/or defined "total red meat" without further clarifying whether processed meat was included.

The Working Group excluded the following papers due to the reasons described below. None of the excluded studies are presented in the tables.

Studies with fewer than 100 cases were excluded because of limited statistical power (e.g. Phillips, 1975; Dales et al., 1979; Pickle et al., 1984; Tajima & Tominaga, 1985; Vlajinac et al., 1987; Wohlleb et al., 1990; Nashar & Almurshed, 2008; Guesmi et al., 2010; Ramzi et al., 2014).

Certain dietary patterns (e.g. traditional "Western-type" diet) are often characterized by a higher intake of red and processed meats, but these patterns also capture other foods that tend to be consumed with a diet high in red and processed meats, such as refined grains and a high intake of sugar. Thus, these studies are not

specific enough to address the role of red meat and processed meats. Therefore, the Working Group also excluded from this review studies that reported on dietary patterns or dietary diversity, or only examined red meat in combination with other foods (e.g. McCann et al., 1994; Slattery et al., 1997, 2003; Rouillier et al., 2005; Satia et al., 2009; De Stefani et al., 2012b; Pou et al., 2012, 2014; Chen et al., 2015). In addition, the Working Group also excluded studies that reported on "meat" variables without a clear definition of what types of meats were included, making it impossible to rule out the inclusion of poultry and/or fish (e.g. Zaridze et al., 1992; Roberts-Thomson et al., 1996; Ping et al., 1998; Welfare et al., 1999; Zhang et al., 2002; Kim et al., 2003; Yeh et al., 2003, 2005; Kuriki et al., 2006; Little et al., 2006; Wakai et al., 2006; Skjelbred et al., 2007; Sriamporn et al., 2007; Jedrychowski et al., 2008; Arafa et al., 2011; Mahfouz et al., 2014; Pimenta et al., 2014), and studies that stated clearly that they had included poultry in their meat definition (e.g. Hu et al., 1991; Fernandez et al., 1996; Kuriki et al., 2005; Ganesh et al., 2009).

The Working Group also excluded studies that did not provide sufficient information to abstract risk estimates for red and processed meat intake per se or within strata defined by genotype (e.g. Gerhardsson de Verdier et al., 1990; Ghadirian et al., 1997; Keku et al., 2003; Forones et al., 2008; da Silva et al., 2011; Gialamas et al., 2011; Silva et al., 2012; Zhivotovskiy et al., 2012; Angstadt et al., 2013; Helmus et al., 2013). Studies were not described if they only reported on estimated amounts of carcinogens derived from meat, and not on meat variables. Of note, studies that reported on the same study population, published at different times, were generally summarized together, if applicable. The most recent, complete, or informative publication was included.

A few studies reported on selected red meat types (e.g. beef), groups of red meat types (e.g. beef/pork), or total processed meats, and presented estimates for total red meat variables, including processed meats. For these studies, the Working Group only summarized the estimates for red meat types and/or processed meat, but not the estimates for the combination of both, as the Working Group did not find these as informative.

Studies that unambiguously defined red meat as unprocessed only, or as unprocessed and processed combined, or did not provide an unambiguous definition and referred to "total red meat", are summarized in Table 2.2.3. Studies that unambiguously defined processed meat are summarized in Table 2.2.4.

(a) Red meat

See Table 2.2.3

(i) Studies considered to be informative

The case–control studies that follow reported results for red meat and were considered informative by the Working Group. These studies were given more weight in the evaluation. The studies are presented in order by sample size, from largest to smallest.

Joshi et al. (2015) (3350 cases, 3504 controls) presented results for colorectal cancer, and for colon and rectal cancer, and for subtypes of colorectal cancer defined by mismatch repair (MMR) proficiency from a population-based study done in Canada and the USA. They reported a non-statistically significant positive association with red meat (Q5 vs Q1 OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.085), with no associations for total beef or pork, and a marginal positive association for organ meats (Q5 vs Q1 OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.058). No differences were observed between colon and rectal cancer, and no other differences were observed between MMR-proficient and MMR-deficient tumours. When cooking methods were considered, stronger, statistically significant associations emerged; a positive association was

observed for pan-fried beef steak (Q4 vs Q1 OR, 1.3; 95% CI, 1.1–1.5; $P_{trend} < 0.001$), which was stronger among MMR-deficient cases. A positive association was also observed with pan-fried hamburgers among MMR-deficient colorectal cancer cases (Q4 vs Q1 OR, 1.5; 95% CI, 1.0–2.1; $P_{trend} < 0.01$). Among oven-broiled meats, a statistically significant positive association was reported for short ribs or spare ribs (Q4 vs Q1 OR, 1.2; 95% CI, 1.0–1.5; $P_{trend} = 0.002$), which was restricted and stronger among MMR-deficient colorectal cancer cases (Q4 vs Q1 OR, 1.9; 95% CI, 1.12–3.00; $P_{trend} = 0.003$). No associations were reported for oven-broiled beef steak or hamburgers, grilled beef steak or short ribs or spare ribs; instead, an inverse association was reported for grilled hamburgers (Q4 vs Q1 OR, 0.8; 95% CI, 0.7–0.9; $P_{trend} = 0.002$). When use of marinades was considered ("Asian-style" vs "Western-style"), there was evidence that the use of "Asian-style" marinades (soy-based) was an effect modifier of the association with red meat, suggesting a stronger and statistically significant association among individuals who reported never using a soy-based marinade with their meats (Q5 vs Q1 OR, 1.3; 95% CI, 1.1.–1.6; $P_{trend} = 0.007$; $P_{interaction} = 0.008$). Overall, it was indicated that, given the many estimates obtained, if a Bonferroni correction was applied for multiple testing, the only statistically significant association would be the association between pan-fried beef steak and colorectal cancer risk, particularly for MMR-deficient tumours. The estimates for three different heterocyclic aromatic amines (HAAs), PhIP, DiMeIQx, and MeIQx were presented, and a positive association with increasing levels of DiMeIQx and MMR-deficient colorectal cancer was reported.

As part of a multicancer, population-based case–control study in Canada, which examined 18 cancer sites, Hu et al. (2007) (1723 cases, 3097 controls) reported that beef, pork, or lamb as a main dish and hamburger intake were positively associated with risk of proximal colon cancers in men only, but not in women. In men, the odds ratios for the highest versus the lowest tertile of intake (servings/week) were 1.5 (95% CI, 1.0–2.4; $P_{trend} = 0.05$) for beef, pork, or lamb as a main dish and 2.1 (95% CI, 1.3–3.5; $P_{trend} = 0.006$) for hamburger. A borderline positive association between hamburger intake in men and distal colon cancers was also observed. The odds ratio for the second tertile versus the lowest tertile was 1.4 (95% CI, 1.0–1.9), and the odds ratio for the highest tertile versus the lowest tertile was 1.4 (95% CI, 0.9–2.0; $P_{trend} = 0.11$).

Kampman et al. (1999) (1542 cases, 1860 controls) conducted a population-based case–control study in the USA, and reported that red meat intake was not associated with colon cancer in men (highest vs lowest intake OR, 0.9; 95% CI, 0.7–1.3) or women (OR, 1.0; 95% CI, 0.7–1.5). In both men and women, higher doneness was not significantly associated with risk of colon cancer (well-done vs rare OR, 1.2; 95% CI, 0.9–1.5). Further, no significant interactions between red meat and the examined *NAT2* and *GSTM1* gene variants were found.

In a companion paper, Slattery et al. (1998) examined associations separately by stage of disease. Some non-significant positive associations between red meat and colon cancer by stage were noted. In men, the odds ratios for > 7.9 oz/week versus ≤ 2.6 oz/week were 1.5 (95% CI, 0.9–2.3) for local, 1.2 (95% CI, 0.8–1.9) for regional, and 0.9 (95% CI, 0.4–1.8) for distant metastasis. In women, the odds ratios for > 5.4 oz/week versus ≤ 1.7 oz/week was 1.2 (95% CI, 0.7–2.1) for local, 1.1 (95% CI, 0.7–1.8) for regional, and 0.5 (95% CI, 0.2–1.2) for distant metastasis. Other papers by Slattery et al. (2000, 2002a, b) examined associations by the molecular characteristics of the tumours and borderline positive associations between red meat intake and colon cancers were observed among cancers with *p53* mutations.

In a related publication (Murtaugh et al., 2004) (952 rectal cancer cases, 1205 controls),

no associations were observed between red meat intake and rectal cancers. The odds ratio for men consuming ≥ 6.1 servings/week versus < 2.9 servings/week was 1.08 (95% CI, 0.77–1.51). The odds ratio for women consuming ≥ 4.2 servings/week versus < 1.9 servings/week was 1.05 (95% CI, 0.72–1.53). A higher intake of well-done red meat was associated with a higher risk of rectal cancers in men compared with rare-done meat (OR, 1.33; 95% CI, 0.98–1.79; P_{trend} = 004). *NAT2*-phenotype and *GSTM1* did not consistently modify the rectal cancer risk associated with red meat intake. Follow-up papers combining the two aforementioned study populations reported no evidence for an interaction between red meat intake, cooking temperatures, use of red meat drippings red meat mutagen index or *CYP1A1* genotype and colorectal cancer . Nonetheless in men carrying the CYP1A1*1 allele, a higher intake of well-done red meat compared with rare-done meat intake was associated with a higher risk of colorectal cancer (OR, 1.37; 95% CI, 1.06–1.77; P_{trend} < 005). (Murtaugh et al., 2005). On the other hand, Murtaugh et al. (2006) found a higher risk of rectal cancer among those with a high intake of red meat and the vitamin D receptor gene FF genotype only. For high versus low intake of red meat for the FF genotype, the odds ratio was 1.45 (95% CI, 0.97–2.19), and for the Ff/ff genotypes combined, the odds ratio was 1.08 (95% CI, 0.74–1.58; $P_{interaction}$ = 0.06 additive, 0.09 multiplicative). [The Working Group noted that, in all these studies, the red meat variable included ham, likely baked ham, which is technically a processed meat.]

In a population-based case–control study in the USA (1192 colorectal cases, 1192 controls), Le Marchand et al. (1997) reported a positive association with beef/veal/lamb that was statistically significant among men (highest vs lowest quartile OR, 2.1; 95% CI, 1.4–3.1; P_{trend} < 0.0001), but not among women (highest vs lowest quartile OR, 1.3; 95% CI, 0.9–2.1; P_{trend} = 0.5). There was no association with pork. The odds ratio for the highest versus the lowest quartile in men was 1.2 (95% CI, 0.8–1.9; P_{trend} = 0.90), and the odds ratio in women was 0.7 (95% CI, 0.4–1.2; P_{trend} = 0.3). [The Working Group noted that the researchers also reported on a total red meat variable with more red meat items, but it also included processed meats. A positive statistically significant association was reported for this variable.]

Miller et al. (2013) (989 cases, 1033 controls) conducted a population-based study in the USA, and reported no association between red meat intake and colorectal cancer, and no differences between colon and rectal cancer. When considering cooking methods, they reported a positive association with pan-fried red meat (Q5 vs Q1 OR, 1.26; 95% CI, 0.93–1.70; P_{trend} = 0.044), but no associations with grilled/barbecued red meat, microwaved/baked red meat, broiled red meat, or red meat cooked rare/medium or well done/charred. A positive association was reported for estimated total PhIP and rectal cancer (Q5 vs Q1 OR, 1.33; 95% CI, 0.88–2.02; P_{trend} = 0.023). [The Working Group noted the somewhat low participation rate in cases and controls (57% cases, 51% controls), which raised concerns about possible bias introduced by the types of individuals who agreed to participate.]

The North Carolina Colon Cancer Study–Phase II, a population-based case–control study conducted in the USA (945 cases, 959 controls) in Whites and African Americans (Williams et al., 2010), reported that red meat was not significantly associated with risk of distal colorectal cancers. The odds ratios for the highest versus the lowest quartile were 0.66 (95% CI, 0.43–1.00; P_{trend} = 0.90) in Whites and 0.64 (95% CI, 0.27–1.50; P_{trend} = 0.94) in African Americans. [The Working Group noted that distal cancers included cancers of the sigmoid, rectosigmoid, and rectum. Controls had a lower response rate compared with cases (56% vs 74%).]

Chiu et al. (2003) reported on a population-based case–control study in Shanghai, China (931 colon cancer cases, 1552 controls).

Positive associations were observed between red meat and risk of colon cancer for both men and women; however, the associations were only statistically significant among men. The odds ratios for the highest versus the lowest quartile of intake (servings/month) were 1.5 (95% CI, 1.0–2.1; $P_{trend} = 0.03$) among men and 1.5 (95% CI, 1.0–2.2; $P_{trend} = 0.08$) among women. [The Working Group noted that a modified version of the validated Block FFQ was used, but no details regarding whether this modified FFQ was validated were provided. In addition, no reference was provided to confirm whether the modified FFQ captured the foods mostly eaten in that area.]

Using data from the Fukuoka Colorectal Cancer Study, Kimura et al. (2007) (840 hospital-based cases, 833 population-based controls) reported no significant associations between intake of beef/pork and colorectal cancer, regardless of the cancer subsite. There were some significant associations for the quintiles, but not for the highest quintile, and overall P_{trend} was not significant. [The Working Group noted that, even though the authors labelled the study as a population-based case–control study, the cases were recruited in hospitals, and the coverage of cases was not reported. The response rate of the controls (60%) was also considerably lower than that of the cases (80%).]

Tuyns et al. (1988) conducted a population-based study in Belgium (818 colorectal cases, 2851 controls). Higher beef consumption was associated with a higher risk of colon cancer (Q4 vs Q1 OR, 2.09; 95% CI, not reported; $P_{trend} < 0.001$), but not rectal cancer (Q4 vs Q1 OR, 0.71; $P_{trend} = 0.14$). Pork intake was not associated with risk of colon or rectal cancers, and a higher pork intake was associated with a lower risk of colon cancer (Q4 vs Q1 OR, 0.39; $P_{trend} < 0.001$). [The lack of adjustment for energy intake was noted as a limitation. A previous report stated that energy intake was similar between cases and controls, suggesting that it may not have been a confounder of meat in this study; however, data were not provided, and there was unclear validation of the questionnaire. The total pork variable included smoked pork.]

In another population-based case–control study by Le Marchand et al. (2001) (727 colorectal cancer cases, 727 controls), no association was observed between red meat intake and colorectal cancer risk when considering men and women combined. However, among participants with the *NAT2* genotype (rapid acetylators) and *CYP1A2* phenotype, an above the median, higher intake of well-done red meat was significantly associated with a higher risk of colorectal cancer (OR, 3.3; 95% CI, 1.3–8.1). In a subsequent paper (Le Marchand et al., 2002b) on the same study population (Le Marchand et al., 2001), associations with "total" red meat [not defined] intake appeared to be restricted to rectal cancer only (highest vs lowest tertile OR, 1.7; 95% CI, 1.0–3.0; $P_{trend} = 0.16$). No association was observed for colon cancer. Positive associations were reported for total HAAs, in particular DiMeIQx and MeIQx. Interactions were also reported, suggesting that smokers who preferred their red meat well done, and had a rapid metabolic phenotype for both NAT2 and CYP1A2 exhibited a risk that was almost nine times higher compared with those with low NAT2 and CYP1A2 activities and who preferred meat rare or medium done. Well-done red meat was not associated with risk among never-smokers or smokers with the slow or intermediate phenotype. A follow-up study on the same study population (Le Marchand et al., 2002a) reported that participants with a high consumption of red meat and the insert polymorphism in CYP2E1 had approximately a twofold increased risk of rectal cancers compared with those with no insert polymorphism who consumed a low intake of red meat (OR, 2.1; 95% CI, 1.2–3.7).

Gerhardsson de Verdier et al. (1991) conducted a population-based case–control in Stockholm, Sweden (559 colorectal cancer

cases, 505 controls). For colon cancer, significant positive associations were observed with boiled beef/pork (OR, 1.8; 95% CI, 1.2-2.6 $P_{trend} = 0.004$), and for all cases with oven-roasted beef/pork (OR,1.8; 95% CI,, 1.1–2.9 $P_{trend} = 0.02$), and boiled beef/pork (OR, 1.9; 95% CI, 1.2–3.0 $P_{trend} = 0.007$). [The Working Group noted that the researchers did not provide an effect estimate for beef/pork without considering the cooking methods. They only asked about beef and pork, so it was unclear whether this was really representative of the subtypes of red meats consumed in that population. Information on validation of the dietary instrument was not provided.]

A hospital-based study done in the United Kingdom (Turner et al., 2004) (484 cases, 738 controls) reported that higher red meat intake was associated with a higher risk of colorectal cancer (highest vs lowest quartile, servings/month, OR, 2.3; 95% CI, 1.6–3.5; $P_{trend} = 0.0001$). A significant interaction between red meat intake and *GSTP1* ($P_{interaction} = 0.02$, after adjustment for potential confounders) and *NQO1* predicted phenotype ($P_{interaction} = 0.01$) on risk of colorectal cancer was reported. The original study (Barrett et al., 2003) reported no significant interaction between *NAT2* genotype and red meat intake. [The Working Group noted that the associations were reported after adjustment for total energy intake; however, lifestyle factors, such as physical activity, alcohol intake, or smoking, were not adjusted for.]

A hospital-based study done in Córdoba, Argentina (Navarro et al., 2003) (287 colorectal cases, 564 controls), reported that beef intake was inversely associated with colorectal cancer, particularly lean beef. The odds ratios for the highest versus the lowest tertile of intake (g/day) were 0.78 (95% CI, 0.51–1.18) for fatty beef and 0.67 (95% CI, 0.40–0.97) for lean beef. Pork (highest versus the lowest tertile) intake was not associated with risk of colorectal cancer (OR, 0.92; 95% CI, 0.62–1.36) (Navarro et al., 2003). A follow-up report on the same study (Navarro et al., 2004) (296 cases, 597 controls) reported that a higher intake of darkly browned red meat was associated with a higher risk of colorectal cancer, particularly for barbecued, iron pan–cooked, and fried red meat, but not roasted red meat. [Limitations noted by the Working Group included lack of report on the time between diagnosis and interview, lack of clarity whether total red meat included processed meat or not, and lack of adjustment for physical activity.]

Kampman et al. (1995) conducted a population-based study in the Netherlands (232 colon cancer cases, 259 controls), and reported no association between unprocessed red meat intake and colon cancer among men, but a positive association among women. For women consuming > 83 g/day versus < 38 g/day, the odds ratio was 2.35 (95% CI, 0.97–5.66; $P_{trend} = 0.04$), and for men consuming > 102 g/day versus < 60 g/day, the odds ratio was 0.89 (95% CI, 0.43–1.81; $P_{interaction}$ by sex = 0.02). The ratio of red meat to vegetables plus fruit was also positively associated with colon cancer in women. For the highest versus the lowest category, in men, the odds ratio was 1.18 (95% CI, 0.57–2.43; $P_{trend} = 0.89$), and in women, the odds ratio was 3.05 (95% CI, 1.39–6.17; $P_{trend} = 0.0006$; $P_{interaction} = 0.0001$). [The Working Group noted that no information was provided about the validity of the FFQ.]

Steinmetz & Potter (1993) conducted a population-based case–control study in Australia (220 colon cases, 438 controls). Red meat intake was positively, but not significantly, associated with risk of colon cancer in both men and women. The odds ratios for the highest versus the lowest quartile were 1.48 (95% CI, 0.73–3.01) in women and 1.59 (95% CI, 0.81–3.13) in men. [The Working Group concluded that a key limitation was the lack of adjustment for energy intake.]

Juarranz Sanz et al. (2004) conducted a population-based study in Madrid, Spain (196 colorectal cases, 196 controls). They reported positive associations with red meat (g/day) (OR

for red meat as a continuous variable, 1.026; 95% CI, 1.010–1.040; P_{trend} = 0.002) and organ meats (also considered as red meat) (OR, 1.122; 95% CI, 1.027–1.232; P_{trend} = 0.015). [The Working Group concluded that the main weakness was the lack of consideration of important confounders, such as total energy intake or BMI, although it was unclear whether the researchers did or did not find evidence of confounding.]

Boutron-Ruault et al. (1999) (171 colorectal cancer cases, 309 population-based controls) conducted a population-based study in France, and reported a non-statistically significant positive association with beef (OR for highest vs lowest quartile, g/day, 1.4; 95% CI, 0.8–2.4; P_{trend} = 0.31) and lamb (OR for high vs low, g/day, 1.3; 95% CI, 0.9–1.9; P = 0.2), and no association with pork (OR for highest vs lowest quartile, g/day, 1.0; 95% CI, 0.7–2.8). A statistically significant positive association was reported for offal (OR, 1.7; 95% CI, 1.1–2.8; P_{trend} = 0.04), which seemed stronger for rectal than colon cancer. [The Working Group noted that there was no consideration of additional potential confounders, such as BMI, alcohol, or smoking status. A difference in the response rates of cases and controls (80% vs 53%) was noted.]

(ii) Studies considered less informative

The following case–control studies that presented results for red meat were considered less informative by the Working Group. The studies are presented in order by sample size, from largest to smallest.

The hospital-based study by Di Maso et al. (2013) (2390 colorectal cases, 4943 controls) that included previous publications from the same group (i.e. Franceschi et al., 1997 and Levi et al., 1999), reported that a higher red meat intake was associated with a higher risk of colon and rectal cancers in men and women. The odds ratios per 50 g/day increase for colon cancer were 1.17 (95% CI, 1.08–1.26) in men and 1.11 (95% CI, 0.98–1.26) in women, and for rectal cancer, the odds ratios were 1.15 (95% CI, 1.02–1.29) in men and 1.32 (95% CI, 1.54–1.29) in women. Associations did not differ by cooking practice, except for rectal cancers, where the strongest associations were seen with fried/pan-fried red meat intake. The odds ratios per 50 g/day increase were 1.24 (95% CI, 1.07–1.45) for roasting/grilling, 1.32 (95% CI, 1.10–1.58) for boiling/stewing, and 1.90 (95% CI, 1.38–2.61) for frying/pan-frying ($P_{heterogeneity}$ = 0.06). [The Working Group concluded that the limitations included lack of adjustment for total caloric intake and physical activity. The researchers also did not assess the quantiles and differences in standard serving sizes between regions, which may have affected the calculated grams of intake per day.]

The hospital-based study by Tavani et al. (2000) (828 colorectal cases, 7990 controls) in Italy reported a positive association between the highest intake of red meat and both colon (highest vs lowest tertile OR, 1.9; 95% CI, 1.5–2.3; P_{trend} <0.01) and rectal cancer (highest vs lowest tertile OR, 1.7; 95% CI, 1.3–2.2; P_{trend} <0.01). [The Working Group concluded that the main weaknesses were lack of validation of the FFQ, which only included 40 food items, and lack of adjustment for total energy, BMI, and physical activity.]

A hospital-based case–control study was conducted in Harbin, China, by Guo et al. (2015) (600 colorectal cases, 600 controls), and reported a positive association between servings of red meat per week and colorectal cancer risk (> 7 vs < 7 servings/week OR, 1.5; 95% CI, 1.1–2.4; P_{trend} = 0.001). No evidence of interaction was observed for two polymorphisms in the *ADIPOQ* gene. [The Working Group concluded that the main weaknesses were lack of consideration of total energy intake and other dietary factors, and lack of information on whether the FFQ was validated.]

Muscat & Wynder (1994) conducted a hospital-based case–control study (511 colorectal cases, 500 controls) in the USA. No associations were observed between beef doneness and risk

of colorectal cancer in men or women. The odds ratios for well-done versus rare beef were 1.15 (95% CI, 0.6–2.4) in men and 1.0 (95% CI, 0.6–1.5) in women. Estimates were only adjusted for matching variables. Results were only presented for beef doneness as exposure. [The Working Group concluded that the limitations included poor focus on red meat, by reporting only on well-done beef, and lack of validation of exposure survey tools.]

Kotake et al. (1995) conducted a hospital-based case–control study in Japan (363 colorectal cases, 363 controls). No significant associations between beef or pork intake and colon and rectal cancer were found. For an intake of > 3–4 times/week versus 1–2/week, the odds ratios for colon cancer were 1.7 (95% CI, 0.85–3.28) for beef and 0.8 (95% CI, 0.50–1.33) for pork, and the odds ratios for rectal cancer were 0.8 (95% CI, 0.38–1.52) for beef and 1.6 (95% CI, 0.95–2.73) for pork. [The Working Group concluded that the limitations were lack of use of quantiles for exposure variables, unclear validation status of the FFQ, lack of adjustment for energy intake, and inclusion of hospital controls with other tumours, including 49 cases with upper gastrointestinal tract cancers.]

A hospital-based study was done in Thailand (Lohsoonthorn & Danvivat, 1995) (279 colorectal cases, 279 controls), and reported null associations with either beef or pork intake. [The Working Group noted that the main weakness of this study was lack of consideration of any potential confounders.]

Freedman et al. (1996) reported on a hospital-based study in New York, USA (163 cases, 326 controls). They reported a positive association with beef (highest vs lowest tertile OR, 2.01; 95% CI, 0.96–4.20; P_{trend} = 0.03). They also subtyped tumours based on p53 expression and reported that the association with beef intake (highest vs lowest) was stronger among tumours that lacked overexpression of p53 (OR, 3.17; 95% CI, 1.83–11.28; P_{trend} = 0.006). The association was very modest and not statistically significant among p53+ tumours. [The Working Group concluded that the limitations of this study were lack of consideration of total energy adjustment, and lack of consideration of other dietary and lifestyle covariates.]

A population-based study in China (Chen et al., 2006) (140 colorectal cases, 343 controls) reported no association between red meat and colon cancer, but a non-significant association with rectal cancer (OR, 1.4; 95% CI, 0.7–2.82). Interactions with *SULT1A1* were also reported, without conclusive results. [The Working Group concluded that the limitations included lack of adjustment for total energy intake and other potential confounders, and unclear definition of red meat.]

A population-based case–control study in southern Italy (Centonze et al., 1994) (119 cases, 119 controls) reported a lack of association between beef intake and colorectal cancer risk; odds ratio for medium (>22 g/day) vs low (~21 g/day) intake of beef was, 0.95; 95% CI, 0.50–1.80. [The Working Group concluded that the use of a validated questionnaire was among the major strengths. The limitations were a small sample size, the fact that the researchers presented results for beef only, and the lack of total caloric intake adjustment.]

The study by Iscovich et al. (1992) (110 colon cancers, 220 controls) in Argentina reported a positive association with red meat intake, which was observed only in the second quartile (Q1 vs Q2 OR, 2.29; 95% CI, 1.03–5.08; Q1 vs Q3 OR, 0.82; 95% CI, 0.39–1.70; Q1 vs Q4, no estimates presented). [The Working Group concluded that the limitations of this study included lack of information about FFQ validation, lack of adjustment for energy intake, and limited distribution of red meat, given the very high consumption of red meat in Argentina, which limited the variability of red meat intake.]

Manousos et al. (1983) conducted a hospital-based case–control study of colorectal cancer

(100 cases, 100 controls) in Greece, and reported positive associations with beef (OR, 1.77) and lamb (OR, 2.61). [The Working Group concluded that the major limitations were lack of consideration of important confounders, such as total energy intake, among others, and small samples size.]

(b) Processed meat

(i) Studies considered informative

The following case–control studies reported results for processed meat separately and were considered informative by the Working Group (see Table 2.2.4). These studies were given more weight in the evaluation. The studies are presented in order by sample size, from largest to smallest. Many of these studies were described in the previous section.

Joshi et al. (2015) (3350 cases, 3504 controls), which was described as an informative study in Section 2.2.2(b), reported a positive association for processed meat (5th Quintile vs 1st quintile OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.054).; a similar positive association was reported for sausage and lunchmeats (Q5 vs Q1 OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.187). Analyses that considered subtypes of colorectal cancer defined by MMR status showed a statistically significant association with sausages and lunchmeats among MMR-proficient cases (Q5 vs Q1 OR, 1.3; 95% CI, 1.0–1.7; P_{trend} = 0.029). When cooking methods were considered, positive associations were noted for pan-fried sausage (4th quartile vs 1st quartile OR, 1.2; 95% CI, 1.0–1.3; P_{trend} = 0.041) and pan-fried spam or ham (Q4 vs Q1 OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.048). The latter seemed restricted and stronger among MMR-proficient cases. No associations were noted for pan-fried bacon and for grilled/barbecued sausages. No differences were noted for colon versus rectal cancers for any of these variables. [The limitations were the same as those described in Section 2.2.2(b).]

Hu et al. (2007) (1723 cases, 3097 controls), described as an informative study in Section 2.2.2(b),reported that processed meat intake was significantly positively associated with both proximal and distal colon cancers in both sexes, with risk estimates ranging between 1.5 and 1.6 for the highest compared with the lowest quartile of intake. Positive associations appeared to be stronger for bacon than for sausage intake, which was not significantly associated with proximal or distal cancers in men or women. For the highest tertile compared with the lowest tertile of bacon intake, the odds ratios for proximal cancer were 1.5 (95% CI, 1.0–2.2; P_{trend} = 0.04) in men and 2.2 (95% CI, 1.4–3.3; P_{trend} = 0.001) in women; andthe odds ratios for distal cancer were 1.4 (95% CI, 1.0–1.9; P_{trend} = 0.05) in men and 1.8 (95% CI, 1.2–2.8; P_{trend} = 0.01) in women. [It was unclear why associations were presented for bacon and sausage, but not for other types of processed meats.] A later published companion paper by the same group using the same study population confirmed their previous findings for processed meat and colon cancer (≥ 5.42 vs ≤ 0.94 servings/week OR, 1.5; 95% CI, 1.2–1.8; P_{trend} < 0.0001) (Hu et al., 2011). This publication also reported results for rectal cancer separately (≥ 5.42 vs ≤ 0.94 servings/week OR, 1.5; 95% CI, 1.2–2.0; P_{trend} = 0.001). [The limitations were the same as those noted for Hu et al. (2007).]

Kampman et al. (1999) (1542 cases, 1860 controls), an informative study described in Section 2.2.2(b), also reported on processed meats. They reported a statistically significant positive association with risk of colon cancers in men who consumed > 3.1 servings/week versus men who consumed ≤ 0.5 servings/week of processed meats (OR, 1.4; 95% CI, 1.0–1.9), but no significant associations were found in women. Moreover, stronger positive associations between processed meats and colon cancer were observed among those with the intermediate or rapid *NAT2* acetylator phenotype (albeit not a statistically significant interaction), while associations

did not appear to differ by *GSTM1* genotype. A follow-up paper by this group (Slattery et al., 2000) reported that, among cases, higher processed meat intake was less likely to be associated with tumours with G→A transitions in the *KRAS* gene (OR, 0.4; 95% CI, 0.2–0.8; P_{trend} = 0.14). In a later publication by the same group focusing on rectal cancer (Murtaugh et al., 2004), processed meat intake was not significantly associated with risk of rectal cancer. For the highest versus the lowest intake, the odds ratios were 1.18 (95% CI, 0.87–1.61) in men and 1.23 (95% CI, 0.84–1.81) in women. [For the limitations, refer to Section 2.2.2(b).]

Le Marchand et al. (1997) (1192 cases, 1192 controls), an informative study described in Section 2.2.2(b),reported positive associations between processed meat intake and colorectal cancer; however, the associations appeared to be restricted to men only (highest vs lowest quartile of intake among men, OR, 2.3; 95% CI, 1.5–3.4; P_{trend} = 0.001; among women, OR, 1.2; 95% CI, 0.8–2.0; P_{trend} = 0.20; $P_{interaction}$ = 0.05). When considering processed meat subtypes, positive associations were reported for beef or pork luncheon meats, salami, sausage, and beef wieners among men only. In contrast, among women, a positive association was observed with spam (highest vs lowest quartile of intake among women OR, 1.8; 95% CI, 1.1–2.9; P_{trend} = 0.02). [The limitations were the same as those described in Section 2.2.2(b).]

Miller et al. (2013) (989 cases, 1033 controls), an informative study described in Section 2.2.2(b),reported a slight positive association between processed red meat and colorectal cancer; however, neither the estimates by intake category nor trend of association werestatistically significant. No differences were observed between colon and rectal cancer or between proximal and distal colon cancer. A statistically significant positive association between estimated levels of total nitrites and proximal cancer (Q5 vs Q1, OR, 1.57; 95% CI, 1.06–2.34; P_{trend} = 0.023) was reported. [For the limitations, refer to Section 2.2.2(b); additionally, processed red meat and processed poultry meat were considered separately and so total processed meat was not reported.]

In the study by Williams et al. (2010) (945 cases, 959 controls), described in Section 2.2.2(b), a positive association between processed meat intake and colon cancer was reported for the third quartile among Whites, but there was no evidence of a linear trend. No significant associations were observed among African Americans. [For the limitations, refer to Section 2.2.2(b).]

Kimura et al. (2007) (840 cases, 833 controls), described in Section 2.2.2(b), reported that processed meat was not associated with colorectal cancer, regardless of the cancer subsite. For Q5 versus Q1, the odds ratios were 1.15 (95% CI, 0.83–1.60) for colorectal cancer, 1.2 (95% CI, 0.72–2.03) for proximal colon cancer, 1.32 (95% CI, 0.82–2.11) for distal colon cancer, and 1.14 (95% CI, 0.73–1.77) for rectal cancer (all $P_{trend} \geq 0.27$). [The Working Group concluded that a limitation was the lack of information on how processed meat was defined.]

A study by Tuyns et al. (1988) (818 cases, 2851 controls), described in Section 2.2.2(b), also reported data on "charcuterie", and reported no association with risk of colon or rectal cancers. [For the limitations, refer to Section 2.2.2(b).]

A study by Gerhardsson de Verdier et al. (1991) (559 cases, 505 controls), described in Section 2.2.2(b), also reported on individual processed meats and considered cooking methods. Significant positive associations were observed between intake of boiled sausage (P_{trend} = 0.04) and risk of colon cancer. Furthermore, positive associations were also found between bacon/smoked ham (P_{trend} = 0.025), oven-roasted sausage (P_{trend} = 0.038), and boiled sausage (P_{trend} < 0.001) and risk of rectal cancer. Associations did not appear to differ consistently by sex or colon subsites. [The Working Group noted that a limitation was the reduced number of processed meat

items, as it was unclear whether the items were representative of the subtypes of processed meats consumed in this population. For other limitations, refer to Section 2.2.2(b).]

The study by Le Marchand et al. (2002a) (521 cases, 639 controls), described in Section 2.2.2(b), also reported that, among participants with a high intake of processed red meat and the *CYP2E1* insert polymorphism, a threefold risk was observed compared with those with low consumption and no insert polymorphism (OR, 3.1; 95% CI, 1.8–5.6; $P_{interaction} = 0.22$).

Squires et al. (2010) (518 cases, 688 controls) conducted a population-based case–control study in Canada. They reported that a higher consumption of pickled meat (food commonly eaten in Newfoundland) was significantly associated with an increased risk of colorectal cancer in both men and women (OR for men, 2.07; 95% CI, 1.37–3.15; OR for women, 2.51; 95% CI, 1.45–4.32).

Rosato et al. (2013) (329 cases, 1361 controls) conducted a hospital-based case–control study of young-onset colorectal cancer (diagnosis ≤ 45 years of age) in Italy. The study included individuals from three previously reported case–control studies on colorectal cancers – Levi et al. (1999), La Vecchia et al. (1991), and Negri et al. (1999). [Participants in these previous studies may have overlapped.] A statistically significant positive association was observed between processed meat intake and colorectal cancer (highest vs lowest tertile OR for processed meat, 1.56; 95% CI, 1.11–2.20; $P_{trend} = 0.008$). [The limitations of this study were lack of definition of meat types included in the processed meat variable, lack of clarity on the overlap with previous studies, and no consideration of alcohol and smoking as potential confounders.]

A study by Navarro et al. (2003) (287 cases, 564 controls), described in Section 2.2.2(b),reported that processed meat was positively associated with risk of colorectal cancer (highest vs lowest tertile OR, 1.47; 95% CI, 1.02–2.15). [For the limitations, refer to Section 2.2.2(b).]

Steinmetz & Potter (1993) (220 cases, 438 controls), described in Section 2.2.2(b), reported that processed meat intake was not associated with risk of colon cancer in either sex. For the highest compared with the lowest quartile, the odds ratios were 0.77 (95% CI, 0.35–1.68) in women and 1.03 (95% CI, 0.55–1.95) in men. [For the limitations, refer to Section 2.2.2(b).]

Juarranz Sanz et al. (2004) (196 cases, 196 controls), described in Section 2.2.2(b), reported positive associations between processed meat intake (12.9 ± 11.4 g/day vs 5.62 ± 7.6 g/day) and colorectal cancer (OR, 1.070; 95% CI, 1.035–1.107; $P_{trend} = 0.001$). [The Working Group noted that processed meat was not clearly defined. For other limitations, refer to Section 2.2.2(b).]

Boutron-Ruault et al. (1999) (171 cases, 309 controls), summarized in Section 2.2.2(b), reported that a higher intake of delicatessen (processed) meat was associated with a higher risk of colorectal cancer (highest vs lowest quartile, g/day, OR, 2.4; 95% CI, 1.3–4.5). [For the limitations, refer to Section 2.2.2(b).]

(ii) Studies considered less informative

The following case–control studies reported results for processed meat separately and were considered less informative by the Working Group. The studies are presented in order by sample size, from largest to smallest.

A hospital-based study was done by Franceschi et al. (1997) (1953 colorectal cancer cases, 4154 controls) in Italy. The study reported no statistically significant associations between processed meat and risk of colorectal cancer. Similarly, no associations were observed for colon or rectal cancer separately. [Processed meat was not defined.]

Macquart-Moulin et al. (1986) (399 colorectal cases, 399 controls) reported no statistically significant associations between a high intake of processed meats and colorectal cancer. [The

Working Group concluded that the main weaknesses of this study were lack of consideration of dietary fibre or total vegetables, and lack of details on the analytical models, such as confidence intervals.]

A hospital-based case–control study was done in Montevideo, Uruguay. De Stefani et al. (2012a) (361 colorectal cases, 2532 controls) reported that a higher intake of processed meat was associated with a higher risk of colon and rectal cancers in both sexes. For the highest tertile compared with the lowest tertile of intake (g/day), the odds ratios for colon cancer were 2.01 (95% CI, 1.07–3.76; P_{trend} = 0.03) in men and 3.53 (95% CI, 1.93–6.46; P_{trend} = 0.0001) in women, and the odds ratios for rectal cancer were 1.76 (95% CI, 1.03–3.01; P_{trend} = 0.03) in men and 3.18 (95% CI, 1.54–6.57; P_{trend} = 0.01) in women. A previous hospital-based study by the same group (De Stefani et al., 1997) (250 colorectal cases, 500 controls) had reported no statistically significant associations between processed meat and colorectal cancer, and no differences by cancer subsite (colon vs rectum) or by sex. [A major limitation of this study was that the control group may have included patients with diseases related to diet, increasing the likelihood of biased results. In addition, in the 1997 study, the researchers did not consider adjusting for energy intake.]

A hospital-based case–control study was done in the canton of Vaud, Switzerland, by Levi et al. (2004) (323 colorectal cases, 611 controls) and later included in the study by Di Maso et al. (2013), although the latter did not report on processed meat. A higher intake of processed meat was associated with a higher risk of colorectal cancer (OR for highest vs lowest category of intake, 2.35; 95% CI, 1.50-4.27; P_{trend} < 0.001).

A population-based case–control study in Majorca, Spain (Benito et al., 1990) (286 cases; 498 controls, which included some hospital-based), reported no significant associations with processed meat intake. [Lack of energy adjustment, lack of detailed analysis, use of a non-validated FFQ, and limited sample size were among the limitations of this study.]

Lohsoonthorn & Danvivat (1995) (279 colorectal cases, 279 controls), described in Section 2.2.2(b), reported positive associations with bacon (>10 vs ≤ 5 times/month OR, 12.49; 95% CI, 1.68–269) and with sausage (>10 vs ≤ 5 times/month OR, 1.26; 95% CI, 0.71–2.25), and a null association with salted beef. [The main weakness of this study was lack of consideration of any potential confounders.]

In a population-based study in France (Faivre et al., 1997) (171 colorectal cases, 309 controls) a positive association was reported between a high intake of processed meat and delicatessen and colorectal cancer risk (OR, 3.0; 95% CI, 2.1–4.8; P_{trend} < 0.001). [The key weaknesses included lack of information regarding how the processed meat estimate was obtained, and lack of consideration of smoking, BMI, dietary fibre, and alcohol.]

A population-based case–control study in Italy (Centonze et al., 1994) (119 cases, 119 controls), previously described in Section 2.2.2(b), reported that processed meat was not associated with colorectal cancer risk (OR for ≥ 3g/day vs < 2g/day processed meat, 1.01; 95% CI, 0.57–1.69). [For the limitations, refer to Section 2.2.2(b).]

Fernandez et al. (1997) (112 cases and 108 controls), based on data from a case–control study in northern Italy, focused on subjects with a family history of cancer and reported that some processed meats were positively associated with colorectal cancer. For the highest versus the lowest tertile, the odds ratios were 2.1 (95% CI, 0.9–4.9; P_{trend} > 0.05) for raw ham, 2.6 (95% CI, 1.0–6.8; P_{trend} > 0.05) for ham, and 1.9 (95% CI, 1.0–3.3; P_{trend} < 0.05) for canned meat. [The limitations of this study were the unclear definition of processed meats, the modest sample size, and the lack of adjustment for energy intake and other potential confounders.]

Iscovich et al. (1992) (110 cases, 220 controls), described in Section 2.2.2(b), reported that processed meat was inversely associated with risk

of colon cancers, regardless of fat content (OR for highest vs lowest, 0.45; 95% CI, 0.23–0.90; P_{trend} = 0.017; for fat with skin; OR, 0.38; 95% CI, 0.19–0.75; for lean processed meat; P_{trend} = 0.002). [For the limitations, refer to Section 2.2.2(b).]

(c) Red meat and processed meat combined

In this subsection, the term "total red meat" as used in many studies refers to "unprocessed and processed red meats combined".

(i) Studies considered informative

The following case–control studies that reported results for red meat and processed meat combined were considered informative by the Working Group. The studies are presented in order by sample size, from largest to smallest.

A population-based colorectal case–control study conducted in Canada (Cotterchio et al., 2008) (1095 cases, 1890 controls) reported a positive association with total red meat (OR for highest vs lowest intake of total red meat, servings/week, 1.67; 95% CI, 1.36–2.05) and well-done total red meat (OR for > 2 servings/week of total well-done red meat vs ≤2 servings/week of rare total red meat, 1.57; 95% CI, 1.27–1.93). Polymorphisms in 15 xenobiotic-metabolizing enzymes (XMEs) were considered, and no statistically significant gene-environment interactions were observed, with two exceptions. In analyses stratified by genotypes, the relative risk of colorectal cancer for > 2 servings/week of "well-done" compared with ≤ 2 servings/week of "rare/regular" red meat was higher in *CYP1B1* wildtype variants compared with other genotypes with increased activity ($P_{interaction}$ = 0.04), and higher in the *SULT1A1* GG genotype compared with AA/GA genotypes ($P_{interaction}$ = 0.03). A follow-up study with a subset of the individuals (Mrkonjic et al., 2009) investigated gene-environment interactions, focusing on two single-nucleotide polymorphisms on the apolipoprotein E (*APOE)* gene and considering tumour subtypes with microsatellite instability (MSI). They reported that *APOE* isoforms might modulate the risk of MSI-high and MSI-low/normal colorectal cancers among high total red meat consumers. [The Working Group concluded that the major limitations of these studies were use of a dietary instrument that was not validated for red meat and lack of energy adjustment.]

Kune et al. (1987) reported on a population-based case–control study conducted in Melbourne, Australia (715 colorectal cases, 727 controls). They reported a positive association between high intake of beef, unprocessed and processed (> 360 g/week), and colorectal cancer risk for men and women combined (OR, 1.75; 95% CI, 1.26–2.44), and a positive association of similar magnitude for the colon and rectum. Results for men showed similar estimates. Estimates for women were not presented. In contrast, for pork, inverse associations were reported with colorectal cancer for men and women combined (OR, 0.55; 95% CI, 0.42–0.73) and similarly by sex and by cancer location (i.e. colon and rectum). [The lack of total energy adjustment and consideration of lifestyle risk factors were noted. The data analysis strategy and presentation were not sufficiently clear, and did not allow for proper interpretation of the findings.]

The North Carolina Colon Cancer Study (Butler et al., 2003), a population-based case–control study in the USA (620 colon cancer cases, 1038 controls), reported a twofold risk of colon cancer for total red meat intake (highest vs lowest intake OR, 2.0; 95% CI, 1.3–3.2). In addition, statistically significant associations between colon cancer risk and pan-fried red meat (OR, 2.0; 95% CI, 1.4–3.0) and well-done red meat (OR, 1.7; 95% CI, 1.2–2.5) were reported. In another paper (Satia-Abouta et al., 2004), differences by ethnic group were examined ("Caucasians" vs African Americans), and it was reported that the positive associations previously reported by Butler et al. (2003) for all individuals combined were no longer observed with ethnic stratification e (e.g. Q4 vs Q1 total red meat among Whites OR, 1.1;

95% CI, 0.7–1.8; P_{trend} = 0.61). Follow-up studies (Butler et al., 2005, 2008a) considered *UGT1A7* and *NAT1* polymorphisms in a subset of cases, and reported no significant gene–environment interactions. In a subset of cases (486 cases), Satia et al. (2005) observed that the positive association between total red meat intake and colon cancers seemed restricted to MSI-high cases (49 cases only), but was not statistically significant, and was null among MSI-low/MSI-stable tumours (total red meat intake T3 vs T1 OR for MSI-high cancers: 1.3; 95% CI, 0.6–3.0; P_{trend} = 0.42; and OR for MSI-low or MSI-stable cancers, 0.9; 95% CI, 0.7–1.3; P_{trend} = 0.90). A subsequent study conducted by Steck et al. (2014) considered gene-environment interactions between total red meat, pan-fried total red meat, and well-done or very well-done total red meat and seven single-nucleotide polymorphisms in five nucleotide excision repair genes (*XPD, XPF, XPG, XPC, RAD23B*). No significant interactions were reported. [Slightly lower response rates were noted for controls compared with cases, although this is not unusual for studies that include minority populations, and the response rates were still within an acceptable range.]

A population-based study of colorectal cancer was done by Joshi et al. (2009) (577 cases, 361 controls) and reported a positive association with total red meat (OR for > 3 vs ≤ 3 servings/week, 1.8; 95% CI, 1.3–2.5; P_{trend} = 0.001), which was restricted to colon cancer cases, and not rectal cases, and a similar association with total red meat cooked using high-temperature methods (pan-frying, broiling, grilling OR, 1.6; 95% CI, 1.1–2.2). No associations were reported for total red meat doneness (on the outside or inside of the meat) and colorectal cancer. Polymorphisms in five genes in the nucleotide excision repair pathway (*ERCC1, XPA, XPC, XPD, XPF, XPG*) and two genes in the MMR pathway (*MLH1, MSH2*) were considered. Overall, results suggested that a high intake of total red meat browned on the outside may increase the risk of colorectal cancer (especially rectal cancer) among carriers of the *XPD* codon 751 Lys/Lys genotype (OR, 3.8; 95% CI, 1.1–13; $P_{interaction}$ = 0.037). Two subsequent studies investigated additional interactions between these meat variables and polymorphisms in the base excision repair pathway (*APEX1, OGG1, PARP, XRCC1*) (Brevik et al., 2010) and carcinogen metabolism enzymes (*CYP1A2, CYP1B1, GSTP1, PTGS2, EPHX, NAT2*) (Wang et al., 2012). They reported a stronger association between a higher intake of total red meat cooked at high temperatures and colorectal cancer among carriers of one or two copies of the *PARP* codon 762 Ala allele (OR, 2.64; 95% CI, 1.54–4.51; $P \leq 0.0001$) than among carriers of two copies of the Val allele (OR, 1.17; 95% CI, 0.76–1.77; $P = 0.484$; $P_{interaction} = 0.012$) (Brevik et al., 2010). They also reported that the *CYP1A2* –154 A > C single-nucleotide polymorphism may modify the association between intake of total red meat cooked using high-temperature methods ($P_{interaction} < 0.001$) and colorectal cancer risk, and the association between total red meat heavily browned on the outside and rectal cancer risk ($P_{interaction} < 0.001$) (Wang et al., 2012). [The Working Group concluded that a limitation of these studies was the use of sibling controls, which may have reduced power to detect associations with red meat variables; however, the use of a case-only design improved power for gene–environment interaction testing. Total energy intake was considered, but was obtained from a separate questionnaire than the ones used for meat assessment; therefore, residual confounding could not be excluded.]

A population-based case–control study of colorectal cancer was conducted in western Australia (Tabatabaei et al., 2011) (567 cases, 713 controls). The study reported that intake of total red meat cooked with different cooking methods (pan-fried, barbecued, stewed) was not significantly associated with risk of colorectal cancer, although a statistically significant inverse association with baked total red meat was observed.

For the highest versus the lowest intake, the odds ratios were 0.8 (95% CI, 0.57–1.13; $P_{trend} = 0.27$) for pan-fried, 0.89 (95% CI, 0.63–1.24; $P_{trend} = 0.17$) for barbecued, 0.73 (95% CI, 0.53–1.01; $P_{trend} = 0.04$) for baked, and 0.95 (95% CI, 0.67–1.33; $P_{trend} = 0.53$) for stewed. Results were not provided for red meat per se, only by cooking method. [The Working Group concluded that the main limitations were the lack of information regarding whether the FFQ was validated and the fact that the researchers inquired about meat intake 10 years before inclusion into the study, which may have increased the likelihood of misclassification of exposures.]

Squires et al. (2010) (518 cases, 686 controls) conducted a study in Newfoundland, Canada, summarized in Section 2.2.2(c), and reported a positive, but non-statistically significant, association between total red meat intake and colorectal cancer among women, but not among men. For the highest compared with the lowest category of intake (servings/day), the odds ratio among men was 0.75 (95% CI, 0.43–1.29), and among women, it was 1.81 (95% CI, 0.94–3.51; no $P_{interaction}$ by sex reported). In addition, a higher intake of well-done red meat was associated with a higher risk of colorectal cancer in women (> 2 servings well done vs < 2 servings rare/regular, OR, 3.1; 95% CI, 1.11–8.69).

Shannon et al. (1996) conducted a population-based study in Seattle, USA (424 colon cases, 414 controls), and reported no statistically significant associations between total red meat intake and colon cancer among women, but did report a statistically non-significant positive association among men (Q4 vs Q1 OR, 1.48; 95% CI, 0.82–2.66; $P_{trend} = 0.53$).

Nowell et al. (2002) conducted a hospital-based case–control study (155 cases, 380 population-based controls) in Arkansas and Tennessee, USA, and reported a positive association with total red meat cooked well/very well done (Q4 vs Q1 OR, 4.36; 95% CI, 2.08–9.60). They also reported a positive association with estimated levels of MeIQx (Q4 vs Q1 OR, 4.09; 95% CI, 1.94–9.08). Estimates for total red meat, without considering the cooking methods, were not provided. [A limitation was the lack of consideration of total energy adjustment, BMI, smoking, alcohol, and dietary fibre. Results reported on only one HAA, even though more exposure estimates were available.]

(ii) Studies considered less informative

The following case–control studies that reported results for red meat and processed meat combined were considered less informative by the Working Group. The studies are presented in order by sample size, from largest to smallest.

A case–control study was done in Scotland by Theodoratou et al. (2008) (1656 hospital-based cases, 2292 population-based controls). A validated FFQ was used to investigate gene–environment interactions between total red meat intake (minced meat, sausages, burgers, beef, pork, lamb, bacon, liver, gammon, liver sausage, liver pâté, haggis, black pudding) and two polymorphisms in the *APC* gene (Asp1822Val and Glu1317Gln). Overall, their findings suggested that, among carriers of the *APC* 1822 variant, diets high in total red meat may increase the risk of colorectal cancer. [No main effects were presented for total red meat.]

Bidoli et al. (1992) conducted a colorectal case–control study in Italy (248 cases, 699 controls), and reported that a higher intake of total red meat was associated with a higher risk of both colon and rectal cancers (highest vs lowest intake, colon cancer OR, 1.6; $P_{trend} = 0.07$; rectal cancer OR, 2.0; $P_{trend} = 0.01$). [Several limitations were noted, including lack of adjustment for caloric intake, use of a non-validated dietary instrument, and recruitment of cases and controls from different hospitals, which introduces potential selection bias.] A companion study (Fernandez et al., 1997), previously described in Section 2.2.2(c), focusing on subjects with a family history of cancer reported

that, among participants with a positive family history, total red meat intake was positively associated with colorectal cancer (highest vs lowest tertile OR, 2.9; 95% CI, 1.4–6.0; $P_{trend} < 0.05$). [For the limitations, refer to Section 2.2.2(c).]

(d) Red meat – unclear if processed meat was included

The following studies were given little weight in the evaluation. The studies are presented in order by sample size, from largest to smallest.

A hospital-based case–control study by La Vecchia et al. (1996) in Italy (1326 colorectal cases, 2024 controls) reported a positive association with both colon and rectal cancer using a dichotomous variable for red meat (high vs low OR for colon cancer, 1.6; 95% CI, 1.3–1.9; OR for rectal cancer, 1.6; 95% CI, 1.3–2.0). [The limitations were the lack of clear definition of red meat, the use of a dichotomous variable, and the potential for partial overlap with studies that followed from this group; specifically, this study recruited from 1985 to 1992, and the follow-up study by Di Maso et al. (2013) was from 1991 to 2009.]

A hospital-based study in France (Pays de la Loire region) (1023 colorectal cancer cases with a family history and young onset, 1121 controls) (Küry et al., 2007) reported that an intake of red meat > 5 times/week was associated with a higher risk of colorectal cancers (OR, 2.81; 95% CI, 1.52–5.21; $P = 0.001$) compared with an intake of red meat < 5 times/week. They also examined gene–environment interactions between red meat intake and polymorphisms in cytochrome P450 genes (*CYP1A2, CYP2E1, CYP1B1, CYP2C9*) and colorectal cancer risk, with evidence of interaction for multiple combinations of polymorphisms; however, confidence intervals among high–red meat eaters were very wide, and no formal test of interaction was provided. [The Working Group concluded that the crude assessment of meat intake based on one question on a questionnaire and lack of detail on which covariates were added to the final model, including total energy intake, were among the limitations of this study.]

Morita et al. (2009) conducted a hospital-based study in Fukuoka, Japan (685 cases, 833 population-based controls), and reported a positive association between red meat and colon cancer, but only among carriers of one or two alleles for the 96-bp insertion for *CYP2E1* ($P_{interaction} = 0.03$). They did not report on the main effects of red meat, only on gene- interaction analyses between meat and these polymorphisms. [The Working Group concluded that the main weakness was the lack of presentation of the main effects of red meat.]

A study conducted in the Liverpool postcode area in the United Kingdom (Evans et al., 2002) (512 cases, 512 population-based controls) reported a positive association between red meat and colorectal cancer (highest vs lowest quartile OR, 1.51; 95% CI, 1.06–2.15). Associations appeared to be stronger for proximal cancers (OR for proximal cancer, 3.32; 95% CI, 1.42–7.73; OR for distal and rectal cancer, 1.38; 95% CI, 0.89–2.12). [The Working Group concluded that the key limitations of this study were lack of consideration of potential confounders, presentation of univariate analyses only, and unclear definition of red meat.]

Three papers on a matched, hospital-based case–control study from China (400 cases, 400 controls) (Hu et al., 2013, 2014, 2015) examined gene–environment interactions between red meat intake and different gene polymorphisms associated with insulin resistance pathways, focusing on adiponectin (*ADIPOQ)* rs2241766, uncoupling protein 2 (*UCP2*) rs659366, and fatty acid binding protein 2 (*FABP2*) rs1799883 (Hu et al., 2013); *ADIPOQ* rs2241766, *ADIPOQ* rs1501299, and calpain 10 (*CAPN-10)* rs3792267 (Hu et al., 2015); and *CAPN-10* SNP43 and SNP19 polymorphisms (Hu et al., 2014). A statistically significant positive association between red meat intake and colorectal cancer risk was observed (high vs low, > 7 vs ≤ 7 times/week, OR, 1.87; 95%

CI, 1.39–2.51) (Hu et al., 2013). [The Working Group concluded that lack of a validated dietary instrument, crude assessment of meat intake, lack of a clear definition of red meat, potential for residual confounding, and especially, lack of adjustment for total energy intake were among the main limitations of the study.]

The study by Rosato et al. (2013) (329 cases, 1361 controls), described in Section 2.2.2(c), also reported on red meat intake. They reported no association between red meat and risk of colorectal cancer (highest vs lowest tertile OR for red meat, 1.07; 95% CI, 0.79–1.64; P_{trend} = 0.63). [No definition was provided for red meat. For additional limitations, refer to Section 2.2.2(c).]

A hospital-based study conducted in Uruguay (De Stefani et al., 1997) (250 colorectal cases, 500 controls) reported positive associations between red meat and colorectal cancer (OR, 2.60; 95% CI, 1.64–4.13), with similar estimates for men and women. Similarly, a positive association was reported for beef (OR, 3.88; 95% CI, 2.34–6.45), but not for lamb. Estimates of HAAs were also provided, showing statistically significant associations with PhIP, MeIQx, and DiMeIQx. [The Working Group concluded that the limitations included concerns about hospital-based controls and lack of adjustment for energy intake.]

A hospital-based case–control study was done in Singapore (Lee et al., 1989) (203 colorectal cancer cases, 425 controls), and reported no statistically significant associations between red meat intake and risk of colorectal, colon, or rectal cancers. For the highest compared with the lowest tertile, the odds ratios were 1.29 (95% CI, 0.84–1.97) for colorectal cancer, 1.41 (95% CI, 0.87–2.31) for colon cancer, and 0.97 (95% CI, 0.48–1.92) for rectal cancer (all $P_{trend} > 0.05$). [The Working Group concluded that no adjustment for total energy intake and other potential confounders were among the limitations.]

A population-based study of colorectal cancer was done by Saebø et al. (2008) (198 cases, 222 controls), and reported a non-significant positive association between red meat and colorectal cancer (T3 vs T1 OR, 1.58; 95% CI, 0.71–3.47). No association was found when the doneness level was considered. Interactions with *CYP1A2* polymorphism were also examined, without conclusive results. [The Working Group concluded that the limitations included unclear details of the questionnaire used; lack of consideration of appropriate confounders, such as total energy intake; and unclear definition of red meat.]

A hospital-based study conducted in Jordan (Abu Mweis et al., 2015) (167 cases, 240 controls) reported a non-statistically significant inverse association between red meat and colorectal cancer risk (OR for ≥ 1 vs < 1 serving/week, 0.64; 95% CI, 0.37–1.11). [The Working Group concluded that the choice of the control population, limited sample size, lack of definition of the red meat variable, and crude categorization of exposure were among the limitations of this study.]

Seow et al. (2002) reported results from a hospital-based colorectal case–control study done in Singapore (121 cases, 222 population-based controls), and reported a positive association between red meat portions per year and colorectal cancer (highest vs first tertile OR, 2.2; 95% CI, 1.1–4.2). They also reported results stratified by total vegetable intake and reported that results for red meat were stronger among individuals with a low intake of vegetables; however, no test of heterogeneity was provided. [The Working Group concluded that the main weaknesses of this study were the limited dietary assessment and lack of proper consideration of total energy intake.]

(e) Cooking practices

Most meat products require cooking for consumption. In spite of this, only a subset of studies distinguished meat types by cooking method and/or doneness level, limiting the evaluation of more specific categories of meat.

When considering red meat, among the studies previously reviewed, there were four studies that reported on cooking practices in relation to colorectal cancer risk (Barrett et al., 2003; Navarro et al., 2004; Miller et al., 2013; Joshi et al., 2015), four studies on colon cancer risk (Gerhardsson de Verdier et al., 1991; Kampman et al., 1999; Miller et al., 2013; Joshi et al., 2015), and four studies on rectal cancer risk (Gerhardsson de Verdier et al., 1991; Murtaugh et al., 2004; Miller et al., 2013; Joshi et al., 2015). For colorectal cancer risk, data were available from two of the largest population-based case–control studies (Joshi et al., 2015; Miller et al., 2013), which reported on a combined total of 4312 cases ascertained from the USA and Canada. These two studies considered separate cooking methods (pan-frying, broiling, grilling/barbecuing), and both reported positive associations with pan-frying; pan-fried beef steak (Q4 vs Q1 OR, 1.3; 95% CI, 1.1–1.5) was reported by Joshi et al. (2015), and pan-fried red meat (Q5 vs Q1 OR, 1.26; 95% CI, 0.93–1.70) was reported by Miller et al. (2013). Overall, of the seven studies that reported on red meat cooking practices and colorectal, colon, or rectal cancer, six reported positive associations with red meat when high-temperature methods and/or doneness levels were considered.

There were additional studies that considered red meat and processed meats combined in relation to colorectal cancer risk (Le Marchand et al., 2002b; Nowell et al., 2002; Cotterchio et al., 2008; Joshi et al., 2009; Squires et al., 2010; Tabatabaei et al., 2011), colon cancer risk (Le Marchand et al., 2002b; Butler et al., 2003; Joshi et al., 2009), and rectal cancer risk (Joshi et al., 2009). Overall, of the seven studies that reported on cooking practices and colorectal cancer, colon cancer, or rectal cancer, five reported associations with high-temperature cooking methods and/or doneness levels. Of these studies, the only one that looked at cooking methods in detail was Butler et al. (2003), which was in agreement with the studies by Joshi et al. (2015) and Miller et al. (2013) previously described for red meat (only), and reported a positive association with pan-fried red meat (OR, 2.0; 95% CI, 1.4–3.0) in addition to well-done red meat (OR, 1.7; 95% CI, 1.2–2.5).

2.2.3 Meta-analyses

High intakes of red meat and processed meats were associated with a moderate, but significant, increase in colorectal cancer risk in several meta-analyses conducted before 2010 (Sandhu et al., 2001; Norat et al., 2002; Larsson et al., 2006; Huxley et al., 2009). The results of more recent meta-analyses of the associations between colorectal cancer and consumption of unprocessed red meat and processed meat, as well as specific meat types, haem iron, and genetic interactions with red and processed meat intake are described here.

In all meta-analyses, similar methods were used to derive summary estimates of dose–response and relative risks for the highest compared with the lowest intake categories. In most analyses, significant associations were observed for all prospective studies combined. However, because the magnitudes of the summary associations were moderate to small, the statistical significance was often lost in subgroup analyses with fewer studies. In addition, some inconsistencies in the results remained unexplained, as the relatively low number of studies in each subgroup did not allow for extensive exploration of all potential sources of heterogeneity.

Chan et al. (2011) summarized the results of prospective studies on red and processed meat and colorectal cancer risk for the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) Continuous Update Project. For red meat, the relative risks for the highest compared with the lowest intake were 1.10 (95% CI, 1.00–1.21; I^2 = 22%; 12 studies) for colorectal cancer, 1.18 (95% CI, 1.04–1.35; I^2 = 0%; 10 studies) for colon cancer, and 1.14 (95% CI,

0.83–1.56; I^2 = 38%; 7 studies) for rectal cancer. Within the colon, the summary risk for increase of cancer was 13% for proximal colon cancer and 57% for distal colon cancer, but the associations were not significant. The relative risk for an increase of 100 g/day of red meat was 1.17 (95% CI, 1.05–1.31; 8 studies) for colorectal cancer, 1.17 (95% CI, 1.02–1.33; 10 studies) for colon cancer, and 1.18 (95% CI, 0.98–1.42; 7 studies) for rectal cancer. For processed meats, the relative risk for the highest compared with the lowest intake was 1.17 (95% CI, 1.09–1.25; I^2 = 6%; 13 studies) for colorectal cancer, 1.19 (95% CI, 1.11–1.29; I^2 = 0%; 11 studies) for colon cancer, and 1.19 (95% CI, 1.02–1.39; I^2 = 20%; 9 studies) for rectal cancer. Within the colon, the summary risk for increase of cancer was 4% for proximal colon cancer and 20% for distal colon cancer, but the associations were not significant (five studies in the analyses). The relative risks for an increase of 50 g/day were 1.18 (95% CI, 1.10–1.28; I^2 = 12%; 9 studies) for colorectal cancer, 1.24 (95% CI, 1.13–1.35; I^2 = 0%; 10 studies) for colon cancer, and 1.12 (95% CI, 0.99–1.28; I^2 = 0%; 8 studies) for rectal cancer.

The most recent, comprehensive meta-analysis of colorectal cancer and meat consumption included data from 27 prospective cohort studies, published in the English language and identified through 2013 (Alexander et al., 2015). Statistical analyses were based on comparisons of the highest intake category with the lowest intake category. Intake levels in these categories varied across studies. Linear dose–response slopes were derived from categorical meta-analyses of two subgroups, based on the units of red meat intake reported by the studies (grams or servings). Random effect models were used. The summary relative risk of colorectal cancer for the highest compared with the lowest intake of red meat and processed meat was 1.11 (95% CI, 1.03–1.19; I^2 = 33.6%; P = 0.014). Heterogeneity was reduced when the analysis was restricted to studies on (unprocessed) red meat. The summary relative risk for those 17 studies was 1.05 (95% CI, 0.98–1.12; I^2 = 8.4%; P = 0.328).

In analyses by cancer site, the association was significant with no heterogeneity for the colon (RR, 1.11; 95% CI, 1.04–1.18; 16 studies), and not significant with high heterogeneity for the rectum (RR, 1.17; 95% CI, 0.99–1.39; I^2 = 51.97%; 13 studies). When the analyses were restricted to studies of (unprocessed) red meat, there was no evidence of heterogeneity across studies (RR, 1.06; 95% CI, 0.97–1.16; 11 studies) for colon cancer and 1.03 (95% CI, 0.88–1.21; 10 studies) for rectal cancer.

Stronger but more heterogeneous associations were observed in studies conducted in North America compared with studies published in other countries. The weakest associations were observed in Asian studies, where meat intake is lower than in North America and Europe.

In the dose–response analysis, the relative risks were 1.02 (95% CI, 1.00–1.14; 10 studies) for 1 serving/day increase, and heterogeneity was moderate to low (I^2 = 26.5%), and 1.05 (95% CI, 0.97–1.13; 13 studies) for each 70 g/day increase.

Alexander et al. (2015) did not investigate processed meats. However, in an earlier meta-analysis, Alexander et al. (2010) reported the relative risks for the highest compared with the lowest intake of processed meat as 1.16 (95% CI, 1.10–1.23; $P_{heterogeneity}$ = 0.556; 20 studies) for any colorectal cancer, 1.19 (95% CI, 1.10–1.28; 12 studies) for colon cancer, and 1.18 (95% CI, 1.03–1.36; 8 studies) for rectal cancer. The relative risk of any colorectal cancer was 1.10 (95% CI, 1.05–1.15; 9 studies) for an increase of 30 g of processed meat intake and 1.03 (95% CI, 1.01–1.05; 6 studies) for each serving per week intake.

[The Working Group noted that there was no significant evidence of publication bias. The pooled analyses of the GECCO study, which included some cohorts included in the meta-analysis, did not find an association between red and processed meats and colorectal cancer. The Danish Diet, Cancer and Health study (Egeberg

et al., 2013), in which red and processed meats were not related to colorectal cancer risk, was published after the preparation of the meta-analysis, and therefore was not included. The Japanese study by Takachi et al. (2011) was included in Alexander et al. (2015), but was published after the end of the search for the meta-analysis by Chan et al. (2011).]

The statistical methods used by Alexander et al. (2015) and Chan et al. (2011) were similar. However, Chan et al. (2011) rescaled times consumed or servings to grams of intake using values reported in the studies, or standard portion sizes of 120 g for red meat and 50 g for processed meat, following the methodology of the WCRF/AICR second expert report. [The Working Group noted that the rescaling may have increased the measurement error of the diet in the rescaled studies, but allowed for the inclusion of all studies in the analyses. Chan et al. (2011) reported that the summary risk estimate in the studies using serving as the intake unit was lower than that in the studies using grams (same finding in Alexander et al. (2010) for processed meats). It is possible that the rescaling of the intake may have attenuated the observed association. Another difference between the meta-analyses is that Chan et al. (2011) grouped the studies according to exposure: red and processed meats, red meats (unprocessed), and processed meats.]

A meta-analysis of six Japanese cohort studies reported no significant associations between total and specific meat types and colorectal cancer risk (Pham et al., 2014). For red meat consumption, the summary relative risk estimates for the highest compared with the lowest intake in the studies were 1.20 (95% CI, 1.00–1.44; 4 cohort studies) for colon cancer and 0.95 (95% CI, 0.71–1.28; 3 studies) for rectal cancer. For processed meats, the summary relative risks for the same comparison were 1.18 (95% CI, 0.92–1.53; 4 studies) for colon cancer and 0.94 (95% CI, 0.72–1.21; 3 studies) for rectal cancer. When the authors combined the results of the cohort studies with those of 13 case–control studies, the summary relative risks for red meat were 1.16 (95% CI, 1.001–1.34) and 1.21 (95% CI, 1.03–1.43) for colorectal and colon cancer, respectively, and those for processed meat consumption were 1.17 (95% CI, 1.02–1.35) and 1.23 (95% CI, 1.03–1.47) for colorectal and colon cancer, respectively.

Another meta-analysis of prospective studies summarized the associations between types of red meats and risk of colorectal cancer (Carr et al., 2016). The meta-analysis included one study from the Netherlands, one from Denmark, two from Japan, and the 10 European cohorts participating in the EPIC study. For the highest compared with the lowest intake of beef, the summary relative risks were 1.11 (95% CI, 1.01–1.22), 1.24 (95% CI, 1.07–1.44), and 0.95 (95% CI, 0.78–1.16) for colorectal, colon, and rectal cancer, respectively. Higher consumption of lamb was also associated with an increased risk of colorectal cancer (RR, 1.24; 95% CI, 1.08–1.44). No association was observed for pork (RR, 1.07; 95% CI, 0.90–1.27).

Qiao & Feng (2013) summarized the results of eight prospective studies on haem iron intake. The summary relative risk of colorectal cancer for the highest versus the lowest intake was 1.14 (95% CI, 1.04–1.24). The observed associations were not significantly modified by cancer site or sex. In the dose–response analyses, the summary relative risk was 1.11 (95% CI, 1.03–1.18) for an increment of haem iron intake of 1 mg/day.

In another meta-analysis, people with the *NAT2* fast acetylator phenotype who consumed a high intake of total meat had a statistically non-significant increased risk of colorectal cancer compared with slow acetylators who consumed a low intake of total meat (4 cohorts; $P_{interaction} = 0.07$) (Andersen et al., 2013). No interaction with the *NAT1* phenotype was observed (cohort studies) on the multiplicative scale.

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kato et al. (1997) USA 1985–1994 Cohort study	14 727; New York University Women's Health Study (NYUWHS) Exposure assessment method: questionnaire	Colon and rectum	Red meat intake (quartiles) Q1 (lowest quartile) Q2 Q3 Q4 (highest quartile) Trend-test *P* value: 0.545	 NR NR NR NR	 1.00 1.28 (0.72–2.28) 1.27 (0.71–2.28) 1.23 (0.68–2.22)	Total caloric intake, age, a place at enrolment and level of education
Chen et al. (1998) USA 1982–1995 Nested case–control study	Cases: 212; Physicians' Health Study (PHS); self-report, medical records, and death certificates Controls: 221; cohort, matched by age and smoking Exposure assessment method: questionnaire; abbreviated FFQ red meat included: beef, pork, or lamb as main dish, in sandwiches or hot dogs	Colon and rectum	Red meat/processed meat (servings/day) ≤ 0.5 > 0.5–1.0 > 1.0 Trend-test *P* value: 0.59	 62 103 43	 1.00 0.98 (0.64–1.52) 1.17 (0.68–2.02)	Age, smoking status, BMI, physical activity, alcohol intake
Singh and Fraser (1998) California, USA Enrolment, 1976–1982; follow-up, 1977–1982 Cohort study	32 051; non-Hispanic, White members of the Adventist Health Study (AHS), California, USA Exposure assessment method: questionnaire; mailed, 55-item SQFFQ; six questions on current consumption of specific meats; red meat included beef and pork	Colon and rectum	Red meat (times/wk) Never > 0 to < 1 ≥ 1 Trend-test *P* value: 0.02	 42 40 45	 1.00 1.40 (0.87–2.25) 1.90 (1.16 – 3.11)	Age, sex, BMI, physical activity, parental history of colorectal cancer, current smoking, past smoking, alcohol consumption, aspirin use
Pietinen et al. (1999) Finland Enrolment, 1985 and 1988; follow-up to 1995 Cohort study	27 111; male smokers in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study Exposure assessment method: questionnaire; self-administered, modified dietary history of usual diet 12 mo prior to baseline (276 food items)	Colon and rectum	Beef, pork, and lamb, quartile median (g/day) 35 52 69 99 Trend-test *P* value: 0.74	 55 35 50 45	 1.0 0.6 (0.4–1.1) 0.9 (0.6–1.3) 0.8 (0.5–1.2)	Age, supplement group, years of smoking, BMI, alcohol, education, physical activity, calcium intake

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Järvinen et al. (2001) Finland Enrolment, 1967–1972; follow-up until late 1999 Cohort study	9959; men and women participating in the population-based Finnish Mobile Clinic Health Examination Survey Exposure assessment method: questionnaire; structured questionnaires including more than 100 foods and mixed dishes; food models and real foods used in portion size estimation [red meat may have included processed meat]	Colon and rectum	Red meat/processed meat Quartiles of intake (g/day)			Age; sex; BMI; occupation; smoking; geographical area; total energy intake; consumption of vegetables, fruits, cereals
			< 94 in men and < 61 in women	NR	1.00	
			94–141 in men, 61–92 in women	NR	1.06 (0.67–2.01)	
			142–206 in men, 93–134 in women	NR	1.55 (0.88–2.73)	
			> 206 in men, > 134 in women	NR	1.50 (0.77–2.94)	
		Colon	Quartiles of intake (g/day)			
			< 94 in men, < 61 in women	NR	1.00	
			94–141 in men, 61–92 in women	NR	0.71 (0.33–1.51)	
			142–206 in men, 93–134 in women	NR	1.29 (0.63–2.66)	
			> 206 in men, > 134 in women	NR	1.34 (0.57–3.15)	
		Rectum	Quartiles of intake (g/day)			
			< 94 in men, < 61 in women	NR	1.00	
			94–141 in men, 61–92 in women	NR	2.18 (0.93–5.10)	
			142–206 in men, 93–134 in women	NR	2.11 (0.84–5.28)	
			> 206 in men, > 134 in women	NR	1.82 (0.60–5.52)	

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Tiemersma et al. (2002) The Netherlands 1987–1998 Nested case–control study	Cases: 102; national and regional cancer registries Controls: 537; cohort, frequency-matched by sex, age, and centre Exposure assessment method: questionnaire; short SQFFQ method, validated by a dietary history method; fresh red meat was beef and pork	Colon and rectum	0–3.0 times/wk	22	1.0	Age, sex, centre, total energy intake, alcohol consumption, body height
			3.1–4.5 times/wk	35	1.3 (0.7–2.3)	
			≥ 5.0 times/wk	45	1.6 (0.9–2.9)	
			Trend-test *P* value: 0.1			
			Women:			
			0–3.0 times/wk	15	1.0	
			3.1–4.5 times/wk	18	0.8 (0.4–1.8)	
			≥ 5.0 times/wk	15	1.2 (0.5–2.8)	
			Trend-test *P* value: 0.64			
			Men:			
			0–3.0 times/wk	7	1.0	
			3.1–4.5 times/wk	17	2.7 (1.1–6.9)	
			≥ 5.0 times/wk	30	2.7 (1.1–6.7)	
			Trend-test *P* value: 0.06			
			Slow and normal *NAT1*:			
			0–3.0 times/wk	NR	1.0	
			3.1–4.5 times/wk	NR	1.2 (0.6–2.4)	
			≥ 5.0 times/wk	NR	1.4 (0.7–2.9)	
			Fast *NAT1*: 0–3.0 times/wk	NR	0.7 (0.3–1.9)	
			3.1–4.5 times/wk	NR	0.9 (0.4–2.0)	
			≥ 5.0 times/wk	NR	1.4 (0.6–3.0)	
			Slow and normal *NAT2*:			
			0–3.0 times/wk	NR	1.0	
			3.1–4.5 times/wk	NR	1.0 (0.5–2.2)	
			≥ 5.0 times/wk	NR	1.4 (0.7–2.9)	
			Fast and intermediate *NAT2*:			
			0–3.0 times/wk	NR	0.7 (0.3–1.9)	
			3.1–4.5 times/wk	NR	1.1 (0.5–2.4)	
			≥ 5.0 times/wk	NR	1.4 (0.6–3.1)	

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Tiemersma et al. (2002) The Netherlands 1987–1998 Nested case–control study (cont.)			*GSTM1* genotype present:			
			0–3.0 times/wk	NR	1.0	
			3.1–4.5 times/wk	NR	1.5 (0.6–3.7)	
			≥ 5.0 times/wk	NR	2.0 (0.8–5.0)	
			GSTM1 genotype null:			
			0–3.0 times/wk	NR	1.7 (0.7–4.4)	
			3.1–4.5 times/wk	NR	1.7 (0.7–4.1)	
			≥ 5.0 times/wk	NR	2.2 (0.9–5.2)	
Flood et al. (2003) USA 1987–1998 Cohort study	61 431; Breast Cancer Detection Demonstration Project (BCDDP) Exposure assessment method: questionnaire; 62-item NCI Block FFQ; red meat was pork, beef, hamburger, processed meats, and liver in previous year	Colon and rectum	Red meat/processed meat (quintile median, g/1000 kcal)			Age, total energy intake by multivariate nutrient density method, total meat intake
			6.1	NR	1.00	
			14.6	NR	1.04 (0.79–1.36)	
			22.6	NR	0.95 (0.72–1.26)	
			32.7	NR	0.95 (0.71–1.27)	
			52.2	NR	1.04 (0.77–1.41)	
			Trend-test *P* value: 0.73			
English et al. (2004) Melbourne, Australia 1990–2002 Cohort study	41 528; residents of Melbourne aged 40–69 yr Exposure assessment method: FFQ; red meat was veal, beef, lamb, pork, rabbit, or other game; diet assessed through 121-item FFQ	Colon and rectum	< 3.0 times/wk	66	1.00	Age; sex; country of birth; intake of energy, fat, cereal products
			3.0–4.4 times/wk	123	1.40 (1.10–1.90)	
			4.5–6.4 times/wk	142	1.50 (1.10–2.10)	
			≥ 6.5 times/wk	120	1.40 (1.00–1.90)	
			Trend-test *P* value: 0.2			
			For increase of 1 time/wk	451	1.03 (0.98–1.08)	
			Trend-test *P* value: 0.9			
		Colon	< 3.0 times/wk	NR	1.00	
			3.0–4.4 times/wk	NR	1.20 (0.80–1.70)	
			4.5–6.4 times/wk	NR	1.30 (0.90–1.90)	
			≥ 6.5 times/wk	NR	1.10 (0.70–1.60)	
			Trend-test *P* value: 0.9			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
English et al. (2004) Melbourne, Australia 1990–2002 Cohort study (cont.)		Colon	For an increase of 1 time/wk	283	1.00 (0.94–1.07)	
		Rectum	< 3.0 times/wk	NR	1.00	
			3.0–4.4 times/wk	NR	2.20 (1.30–4.00)	
			4.5–6.4 times/wk	NR	2.20 (1.20–3.90)	
			≥ 6.5 times/wk	NR	2.30 (1.20–4.20)	
			Trend-test *P* value: 0.07			
			For an increase of 1 time/wk	169	1.08 (0.99–1.16)	
			Trend-test *P* value: 0.07			
Chao et al. (2005) USA 1992–2001 Cohort study	148 610; Cancer Prevention Study II (CPS-II) Nutrition Survey cohort Exposure assessment method: questionnaire; diet assessed through 68-item, modified Block FFQ; red meat included beef, pork, processed meats, and liver	Colon	Red meat/processed meat, quintile median (g/day)			Age; education; BMI; cigarette smoking; recreational physical activity; multivitamin use; aspirin use; intake of beer, wine, liquor, fruits, vegetables, high-fibre grain foods
			Men:			
			100	88	1.00	
			253	121	1.14 (0.86–1.50)	
			398	141	1.16 (0.88–1.53)	
			612	191	1.22 (0.92–1.61)	
			999	125	1.30 (0.93–1.81)	
			Trend-test *P* value: 0.08			
			Red meat/processed meat, quintile median (g/day)			
			Women:			
			43	76	1.00	
			168	154	0.98 (0.74–1.30)	
			278	72	0.94 (0.68–1.31)	
			416	144	0.98 (0.73–1.32)	
			712	86	0.98 (0.68–1.40)	
			Trend-test *P* value: 0.45			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Chao et al. (2005) USA 1992–2001 Cohort study (cont.)		Colon	Red meat/processed meat			
			Men and women (sex-specific quintiles):			
			Q1	164	1.00	
			Q2	275	1.07 (0.88–1.31)	
			Q3	213	1.07 (0.86–1.31)	
			Q4	335	1.11 (0.91–1.36)	
			Q5	210	1.15 (0.90–1.46)	
			Trend-test *P* value: 0.4			
		Proximal colon	Red meat/processed meat (sex-specific quintiles)			
			Q1	88	1.00	
			Q2	169	1.21 (0.93–1.58)	
			Q3	113	1.08 (0.81–1.44)	
			Q4	182	1.17 (0.89–1.53)	
			Q5	116	1.27 (0.91–1.76)	
			Trend-test *P* value: 0.05			
		Distal colon	Red meat/processed meat (sex-specific quintiles)			
			Q1	69	1.00	
			Q2	76	0.72 (0.52–1.00)	
			Q3	79	0.89 (0.64–1.24)	
			Q4	120	0.87 (0.63–1.21)	
			Q5	64	0.71 (0.47–1.07)	
			Trend-test *P* value: 0.92			
		Rectosigmoid junction and rectum	Red meat/processed meat (sex-specific quintiles)			
			Q1	57	1.00	
			Q2	118	1.43 (1.03–1.96)	
			Q3	85	1.26 (0.89–1.78)	
			Q4	114	1.18 (0.84–1.67)	
			Q5	96	1.71 (1.15–2.52)	
			Trend-test *P* value: 0.007			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Larsson et al. (2005a) Sweden 1987–2003 Cohort study	61 433; Swedish women aged 40–76 yr Exposure assessment method: questionnaire; 67-item, 6-mo FFQ; red meat included bacon, ham, hot dogs, and lunchmeat; beef and pork as a main dish reported separately	Colon and rectum	Beef and pork (servings/wk), quartiles (quartile median)			Age; BMI; education level; intake of total energy, alcohol, saturated fat, calcium, folate, fruits, vegetables, whole-grain foods
			< 2.0 (1.5)	NR	1.00	
			2.0 to < 3.0 (2.5)	NR	1.13 (0.95–1.36)	
			3.0 to < 4.0 (4.0)	NR	0.90 (0.70–1.17)	
			≥ 4.0 (5.5)	NR	1.22 (0.98–1.53)	
			Trend-test *P* value: 0.32			
		Colon: proximal colon	Beef and pork (servings/wk), quartiles (quartile median)			
			< 2.0 (1.5)	NR	1.00	
			2.0 to < 3.0 (2.5)	NR	0.90 (0.65–1.24)	
			3.0 to < 4.0 (4.0)	NR	0.78 (0.45–1.17)	
			≥ 4.0 (5.5)	NR	1.10 (0.74–1.64)	
			Trend-test *P* value: 0.9			
		Colon: distal colon	Beef and pork (servings/wk), quartiles (quartile median)			
			< 2.0 (1.5)	NR	1.00	
			2.0 to < 3.0 (2.5)	NR	1.26 (0.84–1.90)	
			3.0 to < 4.0 (4.0)	NR	0.98 (0.55–1.75)	
			≥ 4.0 (5.5)	NR	1.99 (1.26–3.14)	
			Trend-test *P* value: 0.01			
		Rectum	Beef and pork (servings/wk), quartiles (quartile median)			
			< 2.0 (1.5)	NR	1.00	
			2.0 to < 3.0 (2.5)	NR	1.18 (0.86–1.62)	
			3.0 to < 4.0 (4.0)	NR	0.87 (0.55–1.37)	
			≥ 4.0 (5.5)	NR	1.08 (0.72–1.62)	
			Trend-test *P* value: 0.98			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study	478 040; European Prospective Investigation into Cancer and Nutrition (EPIC) study Exposure assessment method: questionnaire; country-specific, validated dietary questionnaires (88–266 items), self-administered in most countries; second 24-h recall measurement from an 8% random sample to calibrate measurements across countries and correct for systematic error	Colon and rectum	Red meat (g/day)			Age, sex, energy from non-fat sources, energy from fat sources, height, weight, occupational physical activity, smoking status, dietary fibre, alcohol intake, stratified by centre
			< 10	132	1.00	
			10–20	138	1.00 (0.78–1.28)	
			20–40	323	1.03 (0.83–1.28)	
			40–80	486	1.16 (0.94–1.43)	
			> 80	250	1.17 (0.92–1.49)	
			Trend-test *P* value: 0.08			
		Colon	Red meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.04 (0.77–1.41)	
			20–40	NR	1.02 (0.78–1.32)	
			40–80	NR	1.16 (0.90–1.51)	
			> 80	NR	1.20 (0.88–1.61)	
			Trend-test *P* value: 0.14			
		Colon: right colon	Red meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.13 (0.70–1.84)	
			20–40	NR	1.00 (0.65–1.54)	
			40–80	NR	1.36 (0.90–2.07)	
			> 80	NR	1.18 (0.73–1.91)	
			Trend-test *P* value: 0.22			
		Colon: left colon	Red meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.07 (0.68–1.68)	
			20–40	NR	1.10 (0.65–1.63)	
			40–80	NR	1.11 (0.75–1.64)	
			> 80	NR	1.24 (0.80–1.94)	
			Trend-test *P* value: 0.38			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study (cont.)		Rectum	Red meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	0.93 (0.60–1.44)	
			20–40	NR	1.07 (0.74–1.55)	
			40–80	NR	1.16 (0.80–1.66)	
			> 80	NR	1.13 (0.74–1.71)	
			Trend-test *P* value: 0.32			
		Colon and rectum	For an increase of 100 g/day (observed intake)	1329	1.21 (1.02–1.43)	
			Trend-test *P* value: 0.03			
		Colon and rectum	For an increase of 100 g/day (calibrated intake)	1329	1.49 (0.91–2.43)	
			Trend-test *P* value: 0.11			
		Colon	For an increase of 100 g/day (observed intake)	855	1.20 (0.96–1.48)	
			Trend-test *P* value: 0.1			
		Colon	For an increase of 100 g/day (calibrated intake)	855	1.36 (0.74–2.50)	
			Trend-test *P* value: 0.32			
		Rectum	For an increase of 100 g/day (observed intake)	474	1.23 (0.94–1.62)	
			Trend-test *P* value: 0.14			
		Rectum	For an increase of 100 g/day (calibrated intake)	474	1.75 (0.93–3.30)	
			Trend-test *P* value: 0.08			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Berndt et al. (2006) Maryland, USA 1989–2003 Nested case–control study	Cases: 272; identified via population-based registry from participants in the CLUE II cohort Controls: 2224; 10% age-stratified sample of CLUE II cohort participants without cancer Exposure assessment method: FFQ; validated, administered by mail, and considered frequency and serving size; red meat was hamburgers, cheeseburgers, meatloaf, beef, beef stew, pork, hot dogs, bacon, sausage, ham, bologna, salami, and lunchmeats	Colon and rectum	Red meat/processed meat (g/day) < 44 44 to < 86.3 ≥ 86.3	 NR NR NR	 1.00 1.16 (0.80–1.70) 1.32 (0.86–2.02)	Age, ethnicity, total energy intake
Oba et al. (2006) Takayama, Japan 1992–2000 Cohort study	30 221; community-based cohort of men and women aged ≥ 35 yr in Takayama, Japan Exposure assessment method: questionnaire; self-administered, 169-item, validated SQFFQ; red meat defined as beef and pork	Colon	Men (tertile median, g/day): 18.7 34.4 56.6 Trend-test *P* value: 0.86 Women (tertile median, g/day): 10.7 25.2 42.3 Trend-test *P* value: 0.2	 40 39 32 50 25 27	 1.00 1.14 (0.73–1.77) 1.03 (0.64–1.66) 1.00 0.64 (0.39–1.03) 0.79 (0.49–1.28)	Age, height, BMI, total pack-years of cigarette smoking, alcohol intake, physical activity

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kabat et al. (2007) Canada 1980–2000 Cohort study	49 654; Canadian National Breast Screening Study (CNBSS) Exposure assessment method: questionnaire; self-administered, 86-item FFQ with 22 meat items and two mixed dishes containing meat; red meat included ham, bacon, and pork-based luncheon meats	Colon and rectum	Red meat, processed meat (g/day)			Age; BMI; menopausal status; oral contraceptive use; hormone replacement use; pack-years of smoking; alcohol intake; education; physical activity; dietary intake of fat, fibre, folic acid, total calories
			< 14.25	NR	1.00	
			14.25 to < 21.02	NR	1.10 (0.85–1.42)	
			21.02 to < 28.74	NR	1.17 (0.90–1.50)	
			28.74–40.30	NR	0.97 (0.74–1.27)	
			≥ 40.30	NR	1.12 (0.86–1.46)	
			Trend-test *P* value: 0.66			
		Colon	Red meat/processed meat (g/day)			
			< 14.25	NR	1.00	
			14.25 to < 21.02	NR	1.06 (0.79–1.42)	
			21.02 to < 28.74	NR	0.97 (0.72–1.32)	
			28.74–40.30	NR	0.84 (0.61–1.15)	
			≥ 40.30	NR	0.88 (0.64–1.21)	
			Trend-test *P* value: 0.16			
		Rectum	Red meat/processed meat (g/day)			
			< 14.25	NR	1.00	
			14.25 to < 21.02	NR	1.25 (0.75–2.08)	
			21.02 to < 28.74	NR	1.79 (1.11–2.88)	
			28.74–40.30	NR	1.42 (0.85–2.35)	
			≥ 40.30	NR	1.95 (1.21–3.16)	
			Trend-test *P* value: 0.008			
Butler et al. (2008b) Singapore, China 1993–2005 Cohort study	61 321; Singaporean Chinese aged 45–74 yr Exposure assessment method: FFQ; validated, 165-item, 12-mo quantitative FFQ	Colon and rectum	Quartile 4 vs quartile 1	NR	1.01 (0.82–1.26)	Age, sex, total energy intake, dialect group, interview year, alcohol intake, BMI, diabetes, education, physical activity, smoking history, first-degree history of colorectal cancer
			Trend-test *P* value: 0.6			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Sørensen et al. (2008) Denmark Enrolment, 1993–1997; follow-up to 2003 Cohort study	Case–cohort: 379 cases with colorectal cancer and 769 subcohort members; Danish men and women aged 50–64 yr free of cancer Exposure assessment method: questionnaire; FFQ with 192 foods and recipes, 63 meat items and meat dishes, and standard portion sizes; red meat was beef, veal, pork, lamb, and offal	Colon and rectum	Red meat, all (per 25 g/day increase)	105	1.03 (0.97–1.09)	Age; sex; intake of poultry, fish, alcohol, dietary fibre; BMI; HRT; smoking status
			Red meat for different polymorphisms (per 25 g/day increase)			
			NAT1 fast	NR	1.06 (0.97–1.17)	
			NAT1 slow	NR	1.02 (0.95–1.09)	
			NAT2 slow	NR	1.06 (0.97–1.14)	
			NAT2 fast	NR	1.01 (0.93–1.09)	
Andersen et al. (2009) Denmark 1994–1997 Nested case–control study	Cases: 372; case–cohort study within the Danish Diet, Cancer and Health cohort Controls: 765; subcohort members with DNA and questionnaire data available; frequency-matched to cases by sex Exposure assessment method: FFQ; mailed in, validated, 192-item FFQ; red meat was beef, veal, pork, lamb, and offal	Colon and rectum	Red meat (g/day)			Sex, age, tumour localization (proximal or distal colon, rectum, NOS), BMI, alcohol, processed meat, dietary fibre, smoking status, NSAID use, HRT use
			Per 25 g/day	NR	1.02 (0.94–1.12)	
Lee et al. (2009) Shanghai, China Enrolment, 1997–2000; follow-up to December, 2005 Cohort study	73 224; Shanghai Women's Health Study (SWHS), a population-based prospective cohort study of women aged 40–70 yr living in Shanghai, China Exposure assessment method: questionnaire; validated quantitative FFQ (including 19 food items/groups of animal origin)	Colon and rectum	Red meat (g/day), quintiles			Age, education, income, survey season, tea consumption, NSAID use, energy intake, fibre intake
			< 24	108	1.0	
			24–< 36	80	0.9	
			36–< 49	65	0.7	
			49–< 67	79	1.0	
			≥ 67	62	0.8 (0.6–1.1)	
			Trend-test *P* value: 0.53			
		Colon	Red meat (g/day), quintiles			
			< 24	63	1.0	
			24–< 36	49	0.9	
			36–< 49	40	0.8	
			49–< 67	43	0.9	
			≥ 67	41	0.9 (0.6–1.5)	
			Trend-test *P* value: 0.31			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
		Rectum	Red meat (g/day), quintiles			
			< 24	45	1.0	
			24–< 36	31	0.8	
			36–< 49	25	0.7	
			49–< 67	36	1.0	
			≥ 67	21	0.6 (0.3–1.1)	
			Trend-test *P* value: 0.79			
Cross et al. (2010) USA 1995–2003 Cohort study	300 948; National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study in men and women aged 50–71 yr from six USA states and two metropolitan areas Exposure assessment method: FFQ; 124-item FFQ calibrated against two 24-h dietary recalls; red meat included beef, pork, lamb, bacon, cold cuts, ham, hamburger, hot dogs, liver, and sausage	Colon and rectum	Red meat/processed meat (median, g/1000 kcal)			Sex, BMI, dietary fibre intake, education level, smoking habits, dietary calcium intake, total energy intake, white meat intake
			9.5	451	1.00	
			20.9	484	1.00 (0.87–1.14)	
			30.7	502	0.99 (0.87–1.13)	
			42.1	614	1.18 (1.03–1.34)	
			61.6	668	1.24 (1.09–1.42)	
			Trend-test *P* value: 0.001			
		Colon and rectum	For an increase of 100 g/day	2719	1.23 (1.10–1.36)	
			Trend-test *P* value: 0.001			
		Colon	Red meat/processed meat (median, g/1000 kcal)			
			9.5	340	1.00	
			20.9	345	0.94 (0.81–1.09)	
			30.7	367	0.96 (0.82–1.12)	
			42.1	457	1.16 (1.00–1.36)	
			61.6	486	1.21 (1.03–1.41)	
			Trend-test *P* value: 0.001			
		Colon	For 100 g/day increase	1995	1.20 (1.05–1.36)	
			Trend-test *P* value: 0.024			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2010) USA 1995–2003 Cohort study (cont.)		Rectum	Red and processed meat (median, g/1000 kcal)			
			9.5	111	1.00	
			20.9	139	1.18 (0.91–1.52)	
			30.7	135	1.09 (0.84–1.42)	
			42.1	157	1.21 (0.93–1.58)	
			61.6	182	1.35 (1.03–1.76)	
			Trend-test *P* value: 0.024			
		Rectum	For 100 g/day increase	724	1.31 (1.07–1.61)	
			Trend-test *P* value: 0.024			
		Proximal colon	Red and processed meat intake, quintiles			
			Q5 vs Q1	1150	1.15 (0.94–1.41)	
			Trend-test *P* value: 0.024			
		Distal colon	Red and processed meat intake, quintiles			
			Q5 vs Q1	787	1.29 (1.00–1.66)	
			Trend-test *P* value: 0.018			
Ollberding et al. (2012) California or Hawaii, USA 1993–2007 Cohort study	131 763; multiethnic sample of African Americans, Japanese Americans, Latinos, native Hawaiians, and Whites aged 45–75 yr Exposure assessment method: questionnaire; validated quantitative FFQ that captured 85% of the intake of key nutrients	Colon and rectum	Red meat, excluding processed (quintile median, g/1000 kcal per day)			Age, ethnicity, family history of colorectal cancer, history of colorectal polyps, BMI, smoking, NSAID use, alcohol, physical activity, history of diabetes, HRT use (females), total calories, intake of dietary fibre, calcium, folate, vitamin D
			4.59	654	1.00	
			11.13	702	0.99 (0.89–1.11)	
			16.86	712	1.00 (0.90–1.12)	
			23.40	677	0.97 (0.87–1.09)	
			34.86	659	0.98 (0.87–1.10)	
			Trend-test *P* value: 0.58			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Figueiredo et al. (2014) International – USA, Canada, and Europe NR Pooled case–control study and nested-case-control studies	Cases: 9287; identified from five case–control and five nested case–control studies within prospective cohorts from the Colon Cancer Family Registry (CCFR) and the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) Controls: 9117; controls from the same population as cases Exposure assessment method: questionnaire; unclear harmonized red meat variable (in some studies, it included processed meats; in others, it did not)	Colon and rectum	Red meat intake Per quartile of increasing intake (P = 1.63e–18)	NR	1.15	Age at the reference time, sex (when appropriate), centre (when appropriate), total energy consumption (if available), first three principal components from EIGENSTRAT to account for potential population substructure
Ananthakrishnan et al. (2015) USA, Canada, and Australia NR Pooled case–control study and nested case-control studies	Cases: 8290; cases were incident colorectal cancer patients enrolled in the Colon Cancer Family Registry (CCFR) and 10 different studies that were part of the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) Controls: 9115; controls were enrolled as part of CCFR and as part of the 10 studies that were part of GECCO Exposure assessment method: questionnaire; red meat and other covariates were harmonized across all the 11 studies; therefore, the definition of red meat was heterogeneous, with some studies including processed meat and others not	Colon and rectum	Red meat/processed meat (servings/day) Q1 Q2 Q3 Q4	 NR NR NR NR	 1.00 1.15 (1.03–1.28) 1.17 (1.05–1.29) 1.29 (1.15–1.44)	Age, sex, study site, smoking status, aspirin use, NSAID use, BMI, dietary calcium, folate, servings of fruits and vegetables

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bernstein et al. (2015) USA Nurses' Health Study, 1980–2010; Health Professionals Follow-Up Study, 1986– 2010 Cohort study	87 108 women and 47 389 men; Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS) Exposure assessment method: FFQ; diet from FFQs collected about every 4 yr during follow-up (see Wei et al., 2004)	Colon and rectum	Red meat (1 serving/day) Baseline intake Trend-test *P* value: 0.61 Red meat (1 serving/day) Cumulative average Trend-test *P* value: 0.88	2731 2731 	1.02 (0.94–1.12) 0.99 (0.87–1.13) 	Age, follow-up, family history, endoscopy, smoking, alcohol drinking, BMI, physical activity, medications and supplements, menopausal status, hormone use, total caloric intake, folate, calcium, vitamin D, fibre intake
		Proximal colon	Red meat (1 serving/day) Baseline intake Trend-test *P* value: 0.07 Red meat (1 serving/day) Cumulative intake Trend-test *P* value: 0.22	 1151 1151 	 1.13 (0.99–1.29) 1.14 (0.92–1.40) 	
		Distal colon	Red meat (1 serving/day) Baseline intake Trend-test *P* value: 0.16 Red meat (1 serving/day) Cumulative intake Trend-test *P* value: < 0.01	 817 817 	 0.88 (0.75–1.05) 0.75 (0.68–0.82) 	
		Rectum	Processed red meat (1 serving/day) Baseline intake Trend-test *P* value: 0.64 Processed red meat (1 serving/day) Cumulative intake Trend-test *P* value: 0.25	 589 589 	 1.05 (0.84–1.32) 1.14 (0.86–1.51 	

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; GWAS, genome-wide association study; h, hour; HRT, hormone replacement therapy; mo, month; NOS, not otherwise specified; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SQFFQ, semiquantitative food frequency questionnaire; wk, week; yr, year

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bostick et al. (1994) USA Enrolment,1985; follow-up, 1986–1990 Cohort study	35 216; women aged 55–69 yr, mostly White, in the Iowa Women's Health Study (IWHS) Exposure assessment method: FFQ; 127-item, validated SQFFQ; processed meat was bacon, hot dogs, and other processed meats	Colon	Processed meats (servings/wk)			Age, total energy intake, height, parity, total vitamin E intake, interaction term vitamin E–age, vitamin A supplement
			0	91	1.00	
			0.5	67	1.00 (0.73–1.38)	
			1.0	32	1.07 (0.71–1.61)	
			2.0–3.0	14	0.81 (0.46–1.44)	
			> 3.0	8	1.51 (0.72–3.17)	
			Trend-test *P* value: 0.45			
Kato et al. (1997) USA Enrolment, 1985–1991; follow-up to 1994 Cohort study	14 727; women aged 34–65 yr in the New York University Women's Health Study (NYUWHS) enrolled at mammographic screening clinics in New York and Florida Exposure assessment method: FFQ; 70-item FFQ; processed meats were ham and sausages	Colon and rectum	Ham and sausage intake, quartiles			Total caloric intake, age, place at enrolment and level of education
			Q1 (lowest quartile)	NR	1.00	
			Q2	NR	1.39 (0.81–2.38)	
			Q3	NR	1.38 (0.79–2.42)	
			Q4 (highest quartile)	NR	1.09 (0.59–2.02)	
			Trend-test *P* value: 0.735			
Pietinen et al. (1999) Finland Enrolment, 1985 and 1988; follow-up, 30 April 1995 (average, 8 yr) Cohort study	27 111; male smokers aged 50 and 69 yr in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study Exposure assessment method: FFQ; self-administered, modified, 12-mo dietary history method (276 food items); processed meat was mostly sausages	Colon and rectum	Processed meat (g/day)			Age, supplement group, smoking, BMI, alcohol, education, physical activity at work, calcium intake
			26	41	1.00	
			50	58	1.5 (1–2.2)	
			73	44	1.1 (0.7–1.8)	
			122	42	1.2 (0.7–1.8)	
			Trend-test *P* value: 0.78			
Flood et al. (2003) USA 1987–1998 Cohort study	45 496; follow-up of a subset of the women in the Breast Cancer Detection Demonstration Project (BCDDP) Exposure assessment method: FFQ; 62-item Block FFQ with 17 meat items; processed meats were bacon, ham, or other lunchmeats, hot dogs, and sausage	Colon and rectum	Processed meat (quintile median, g/1000 kcal)			Age, total energy intake by multivariate nutrient density method
			Q1 (0.02)	NR	1.00	
			Q2 (2.40)	NR	0.90 (0.68–1.18)	
			Q3 (5.90)	NR	0.83 (0.63–1.11)	
			Q4 (11.00)	NR	1.09 (0.84–1.43)	
			Q5 (22.20)	NR	0.97 (0.73–1.28)	
			Trend-test *P* value: 0.35			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
English et al. (2004) Melbourne, Australia 1990–2002 Cohort study	41 528; residents of Melbourne aged 40–69 yr Exposure assessment method: questionnaire; 121-item FFQ; processed meat was salami, sausages, bacon, ham, corned beef, and luncheon meats	Colon and rectum	Processed meat intake (times/wk)			Age; sex; country of birth; intake of energy, fat, cereal products
			< 1.0	80	1.00	
			1.5–1.9	105	1.30 (1.00–1.70)	
			2.0–3.9	129	1.00 (0.80–1.40)	
			≥ 4.0	137	1.50 (1.10–2.00)	
			Trend-test *P* value: 0.01			
			For an increase of 1 time/wk	451	1.07 (1.02–1.13)	
			Trend-test *P* value: 0.9			
		Colon	Processed meat intake (times/wk)			
			< 1.0	NR	1.00	
			1.5–1.9	NR	1.10 (0.80–1.60)	
			2.0–3.9	NR	0.80 (0.60–1.10)	
			≥ 4.0	NR	1.30 (0.90–1.90)	
			Trend-test *P* value: 0.06			
			For an increase of 1 time/wk	283	1.07 (1.00–1.14)	
		Rectum	Processed meat intake (times/wk)			
			< 1.0	NR	1.00	
			1.5–1.9	NR	1.90 (1.10–3.20)	
			2.0–3.9	NR	1.70 (1.00–2.90)	
			≥ 4.0	NR	2.00 (1.10–3.40)	
			Trend-test *P* value: 0.09			
			For an increase of 1 time/wk	169	1.08 (0.99–1.18)	

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lin et al. (2004) USA 1993–2003 Cohort study	36 976; Women's Health Study (WHS) Exposure assessment method: FFQ; validated, 131-item SQFFQ; correlation ≥ 0.5 for most items	Colon and rectum	Processed meat (median, servings/day)			Age, random treatment assignment, BMI, family history of colorectal cancer, history of colorectal polyps, physical activity, cigarette smoking, alcohol consumption, postmenopausal hormone therapy, total energy intake
			0	51	1.00	
			0.07	45	1.18 (0.79–1.77)	
			0.13	42	1.27 (0.84–1.91)	
			0.21	32	0.95 (0.60–1.49)	
			0.50	32	0.85 (0.53–1.35)	
			Trend-test *P* value: 0.25			
Chao et al. (2005) USA Enrolment, 1992–1993; follow-up to 2001 Cohort study	148 610; adults in the Cancer Prevention Study II (CPS-II) aged 50–74 yr in 21 states Exposure assessment method: FFQ; 68-item, modified Block FFQ; processed meats were bacon, sausage, hot dogs, and ham, bologna, salami, or lunchmeat	Colon	Processed meat (g/wk)			Age; total energy intake; education; BMI; cigarette smoking; recreational physical activity; multivitamin use; aspirin use; intake of beer, wine, liquor, fruits, vegetables, high-fibre grain foods
			Men:			
			0	64	1.00	
			< 60	125	0.75 (0.55–1.02)	
			61–160	225	1.02 (0.76–1.36)	
			161–240	108	1.11 (0.80–1.54)	
			> 240	143	1.11 (0.80–1.54)	
			Trend-test *P* value: 0.03			
			Processed meat (g/wk)			
			Women:			
			0	89	1.00	
			< 30	125	1.11 (0.84–1.46)	
			31–60	96	0.95 (0.71–1.27)	
			61–120	104	0.94 (0.70–1.26)	
			> 120	118	1.16 (0.85–1.57)	
			Trend-test *P* value: 0.48			
			Processed meat, quintiles			
			Men and women:			
			Q1	153	1.00	
			Q2	250	0.90 (0.74–1.11)	
			Q3	321	1.01 (0.83–1.23)	
			Q4	212	1.02 (0.82–1.27)	
			Q5	261	1.13 (0.91–1.41)	
			Trend-test *P* value: 0.02			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Chao et al. (2005) USA Enrolment, 1992–1993; follow-up to 2001 Cohort study (cont.)		Proximal colon	Processed meat, quintiles			
			Men and women:			
			Q1	96	1.00	
			Q2	133	0.79 (0.61–1.03)	
			Q3	174	0.92 (0.71–1.19)	
			Q4	131	1.03 (0.78–1.35)	
			Q5	133	0.97 (0.72–1.29)	
			Trend-test *P* value: 0.17			
		Distal colon	Processed meat, quintiles			
			Men and women:			
			Q1	44	1.00	
			Q2	98	1.19 (0.83–1.70)	
			Q3	111	1.15 (0.80–1.65)	
			Q4	58	0.95 (0.63–1.43)	
			Q5	97	1.39 (0.94–2.05)	
			Trend-test *P* value: 0.11			
		Rectosigmoid and rectum	Processed meat, quintiles			
			Men and women:			
			Q1	50	1.00	
			Q2	106	1.14 (0.81–1.60)	
			Q3	134	1.24 (0.88–1.74)	
			Q4	86	1.31 (0.91–1.88)	
			Q5	94	1.26 (0.86–1.83)	
			Trend-test *P* value: 0.18			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Larsson et al. (2005a) Sweden 1987–2003 Cohort study	61 433; Swedish women aged 40–76 yr Exposure assessment method: FFQ; 67-item, 6-mo FFQ (nine items on red and processed meats); processed meats were bacon, hot dogs, ham, or other lunchmeats and blood pudding	Colon and rectum	Processed meats (g/day), quartiles (quartile median)			Age; BMI; education level; intake of total energy, alcohol, saturated fat, calcium, folate, fruits, vegetables, wholegrain foods
			< 12 (6)	NR	1.00	
			12–21 (16)	NR	0.89 (0.72–1.90)	
			22–31 (26)	NR	1.01 (0.82–1.24)	
			≥ 32 (41)	NR	1.07 (0.85–1.33)	
			Trend-test *P* value: 0.23			
		Proximal colon	Processed meats (g/day), quartiles (quartile median)			
			< 12 (6)	NR	1.00	
			12–21 (16)	NR	0.92 (0.66–1.32)	
			22–31 (26)	NR	0.85 (0.58–1.24)	
			≥ 32 (41)	NR	1.02 (0.69–1.52)	
			Trend-test *P* value: 0.97			
		Distal colon	Processed meats (g/day), quartiles (quartile median)			
			< 12 (6)	NR	1.00	
			12–21 (16)	NR	1.05 (0.67–1.64)	
			22–31 (26)	NR	0.98 (0.61–1.58)	
			≥ 32 (41)	NR	1.39 (0.86–2.24)	
			Trend-test *P* value: 0.2			
		Rectum	Processed meats (g/day), quartiles (quartile median)			
			< 12 (6)	NR	1.00	
			12–21 (16)	NR	0.78 (0.52–1.12)	
			22–31 (26)	NR	1.02 (0.75–1.55)	
			≥ 31 (41)	NR	0.90 (0.60–1.34)	
			Trend-test *P* value: 0.88			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lüchtenborg et al. (2005) The Netherlands 1989–1994 Nested case–control study	Cases: 588; cases were identified from the subcohort of the Netherlands Cancer Study (NLCS); this was the same population described by Brink et al. (2005); incident cases with colorectal cancer, with available tumour tissue and FFQ data, were included in this study Controls: 2948; subcohort without colorectal cancer at the last follow-up Exposure assessment method: FFQ; self-administered; see description for Goldbohm et al. (1994); meat products were preserved meat, "sandwich fillings"	Colon	Meat products (g/day); *APC*– genotype			Age, sex, family history of colorectal cancer, smoking, BMI, energy intake
			Q1	71	1.00	
			Q2	62	0.90 (0.62–1.30)	
			Q3	71	0.97 (0.68–1.39)	
			Q4	70	1.07 (0.73–1.56)	
			Trend-test *P* value: 0.66			
			Meat products (g/day); *APC*+ genotype			
			Q1	26	1.00	
			Q2	23	0.87 (0.49–1.56)	
			Q3	33	1.15 (0.67–1.97)	
			Q4	45	1.61 (0.96–2.71)	
			Trend-test *P* value: 0.04			
		Rectum	Meat products (g/day); *APC*– genotype			
			Q1	20	1.00	
			Q2	12	0.57 (0.27–1.19)	
			Q3	19	0.85 (0.44–1.65)	
			Q4	22	1.02 (0.52–1.99)	
			Trend-test *P* value: 0.73			
			Meat products (g/day); *APC*+ genotype-			
			Q1	15	1.00	
			Q2	12	0.79 (0.36–1.74)	
			Q3	14	0.89 (0.41–1.92)	
			Q4	16	1.03 (0.47–2.27)	
			Trend-test *P* value: 0.88			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study	478 040; European Prospective Investigation into Cancer and Nutrition (EPIC) study Exposure assessment method: questionnaire; country-specific, validated dietary questionnaires (88–266 items), self-administered in most countries; second 24-h recall measurement from an 8% random sample to calibrate measurements across countries and correct for systematic error	Colon and rectum	Processed meat (g/day)			Age, sex, energy from non-fat sources, energy from fat sources, height, weight, occupational physical activity, smoking status, dietary fibre, alcohol intake, stratified by centre
			<10	232	1.00	
			10–20	256	1.10 (0.91–1.32)	
			20–40	402	1.12 (0.94–1.35)	
			40–80	318	1.14 (0.94–1.40)	
			> 80	121	1.42 (1.09–1.86)	
			Trend-test *P* value: 0.02			
		Colon and rectum	For an increase of 100 g/day (observed intake)	1329	1.32 (1.07–1.63)	
			Trend-test *P* value: 0.009			
		Colon and rectum	For an increase of 100 g/day (calibrated intake)	1329	1.70 (1.05–2.76)	
			Trend-test *P* value: 0.03			
		Colon	Processed meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.04 (0.77–1.41)	
			20–40	NR	1.02 (0.78–1.32)	
			40–80	NR	1.16 (0.90–1.51)	
			> 80	NR	1.20 (0.88–1.61)	
			Trend-test *P* value: 0.14			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study (cont.)		Colon	For an increase of 100 g/day (observed intake)	855	1.39 (1.06–1.82)	
			Trend-test *P* value: 0.01			
		Colon	For an increase of 100 g/day (calibrated intake)	855	1.68 (0.87–3.27)	
			Trend-test *P* value: 0.12			
		Proximal colon	Processed meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.04 (0.73–1.49)	
			20–40	NR	0.95 (0.67–1.34)	
			40–80	NR	1.17 (0.80–1.70)	
			> 80	NR	1.19 (0.70–2.01)	
			Trend-test *P* value: 0.22			
		Distal colon	Processed meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.30 (0.92–1.83)	
			20–40	NR	1.32 (0.94–1.85)	
			40–80	NR	1.45 (1.00–2.11)	
			> 80	NR	1.48 (0.87–2.53)	
			Trend-test *P* value: 0.38			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study (cont.)		Rectum	Processed meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.13 (0.81–1.58)	
			20–40	NR	1.27 (0.93–1.74)	
			40–80 g/day	NR	1.05 (0.74–1.50)	
			> 80 g/day	NR	1.62 (1.04–2.50)	
			Trend-test *P* value: 0.2			
		Rectum	For an increase of 100 g/day (observed intake)	474	1.22 (0.87–1.71)	
			Trend-test *P* value: 0.25			
		Rectum	For an increase of 100 g/day (calibrated intake)	474	1.70 (0.83–3.47)	
			Trend-test *P* value: 0.14			
Balder et al. (2006) The Netherlands 1986–1996 Cohort study	152 852 men and women; case–cohort analysis of the Netherlands Cohort Study (NLCS) Exposure assessment method: FFQ; 150-item FFQ for 12 mo before enrolment	Colon and rectum	Processed meat (g/day) Men:			Age, BMI, family history, smoking, alcohol intake, physical activity, vegetable consumption, total energy intake
			0	78	1.00	
			0.1–9.9	277	1.02 (0.74–1.41)	
			10.0–19.9	239	0.98 (0.71–1.36)	
			≥ 20.0	275	1.18 (0.84–1.64)	
			Trend-test *P* value: 0.25			
			Processed meat (g/day) Women:			
			0	87	1.00	
			0.1–9.9	295	1.04 (0.78–1.39)	
			10.0–19.9	169	1.13 (0.82–1.55)	
			≥ 20.0	115	1.05 (0.74–1.48)	
			Trend-test *P* value: 0.62			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Oba et al. (2006) Takayama, Japan 1992–2000 Cohort study	30221; community-based cohort with 13 894 men and 16 327 women in Takayama, Japan, aged 35 yr or older Exposure assessment method: FFQ; validated, self-administered, 169-item SQFFQ; processed meats were ham, sausage, bacon, and yakibuta (Chinese-style roasted pork)	Colon	Processed meat (tertile mean, g/day)			Age, height, BMI, total pack-years of cigarette smoking, alcohol intake, physical activity
			Men:			
			3.9	33	1.00	
			9.3	34	1.25 (0.75–1.95)	
			20.3	44	1.98 (1.24–3.16)	
			Trend-test *P* value: < 0.01			
			Processed meat (tertile mean, g/day)			
			Women:			
			3.0	42	1.00	
			7.3	37	1.13 (0.72–1.75)	
			16.3	23	0.85 (0.50–1.43)	
			Trend-test *P* value: 0.62			
Sato et al. (2006) Japan Enrolment, 1990; 11-yr follow-up to 2001 Cohort study	47 605; men and women aged 40–64 yr who were residents in Miyagi Prefecture Exposure assessment method: questionnaire; 40-item FFQ with five meat items; processed meat was ham or sausages	Colon and rectum	Median (g/day)			Sex; age; smoking status; alcohol consumption; BMI; education; family history of cancer; time spent walking; consumption of fat, calcium, dietary fibre; total energy intake
			0	75	1.00	
			1.1	118	0.98 (0.74–1.31)	
			4.5	128	1.02 (0.77–1.36)	
			15.8	37	0.91 (0.61–1.35)	
			Trend-test *P* value: 0.99			
		Colon	Median (g/day)			
			0	49	1.00	
			1.1	78	1.00 (0.70–1.42)	
			4.5	70	0.86 (0.60–1.25)	
			15.8	20	0.75 (0.45–1.27)	
			Trend-test *P* value: 0.25			
		Proximal colon	Median (g/day)			
			0	23	1.00	
			1.1	47	1.28 (0.78–2.11)	
			4.5	34	0.86 (0.50–1.46)	
			15.8	9	0.69 (0.32–1.51)	
			Trend-test *P* value: 0.2			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Sato et al. (2006) Japan Enrolment, 1990; 11-yr follow-up to 2001 Cohort study (cont.)		Distal colon	Median (g/day)			
			0	21	1.00	
			1.1	22	0.86 (0.36–1.20)	
			4.5	26	0.79 (0.44–1.41)	
			15.8	7	0.65 (0.28–1.55)	
			Trend-test *P* value: 0.5			
		Rectum	Median (g/day)			
			0	22	1.00	
			1.1	57	0.87 (0.53–1.42)	
			4.5	62	0.90 (0.55–1.47)	
			15.8	16	0.97 (0.51–1.86)	
			Trend-test *P* value: 0.92			
Butler et al. (2008b) Singapore 1993–2005 Cohort study	61 321; Singaporean Chinese aged 45–74 yr Exposure assessment method: questionnaire; validated, 165-item, 12-mo quantitative FFQ	Colon and rectum	Quartile 4 vs quartile 1	NR	1.16 (0.95–1.41)	Age, sex, total energy intake, dialect group, interview year, alcohol intake, BMI, diabetes, education, physical activity, smoking history, first-degree history of colorectal cancer
			Trend-test *P* value: 0.1			
			Per 25 g/day	NR	1.00 (0.85–1.19)	
Cross et al. (2010) USA Enrolment, 1995–1996; follow-up until end of 2003 Cohort study	300 948; prospective cohort of men and women aged 50–71 yr in the National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study Exposure assessment method: questionnaire; 124-item FFQ calibrated within the study population against two non-consecutive 24-h dietary recalls; processed meats were red and white meats	Colon and rectum	Processed meat (quintile median, g/1000 kcal)			Sex, education, BMI, smoking, total energy intake, dietary calcium, non-processed meat intake
			1.6	440	1.00	
			4.3	496	1.04 (0.91–1.18)	
			7.4	538	1.07 (0.94–1.23)	
			12.1	612	1.16 (1.02–1.32)	
			22.3	633	1.16 (1.01–1.32)	
			Trend-test *P* value: 0.017			
		Colon and rectum	For an increase of 100 g/day	2719	1.19 (0.96–1.48)	
			Trend-test *P* value: 0.001			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2010) USA Enrolment, 1995–1996; follow-up until end of 2003 Cohort study (cont.)		Colon	Processed meat (quintile median, g/1000 kcal)			
			1.6	334	1.00	
			4.3	357	0.98 (0.84–1.14)	
			7.4	393	1.03 (0.89–1.20)	
			12.1	453	1.14 (0.98–1.32)	
			22.3	458	1.11 (0.95–1.29)	
			Trend-test *P* value: 0.057			
			For an increase of 100 g/day	1995	1.13 (0.88–1.45)	
			Trend-test *P* value: 0.001			
		Rectum	Processed meat (quintile median, g/1000 kcal)			
			1.6	106	1.00	
			4.3	139	1.22 (0.94–1.58)	
			7.4	145	1.20 (0.93–1.56)	
			12.1	159	1.24 (0.95–1.61)	
			22.3	175	1.30 (1.00–1.68)	
			Trend-test *P* value: 0.145			
			For an increase of 100 g/day	724	1.38 (0.93–2.05)	
			Trend-test *P* value: 0.001			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Takachi et al. (2011) Japan Follow-up, from 1995–1999 to December 2006 Cohort study	80 658; Japanese in the Japan Public Health Center-based Prospective Study (JPHC Study) Cohorts I and II, registered in 11 public health centre areas, who responded to a self-administered, 5-yr follow-up questionnaire at ages 45–74 yr Exposure assessment method: questionnaire; validated, self-administered, 138-item FFQ including 16 meat items Processed meat included ham, sausages, bacon, and luncheon meat	Colon	Processed meat (quintile median, g/day); in men			Age; area; BMI; smoking status; alcohol consumption; physical activity; medication use for diabetes; history of diabetes; screening examinations; intake of energy, calcium, vitamin D, vitamin B6, folate, dietary fibre, dried and salted fish
			0.2	106	1.00	
			1.9	106	1.11 (0.85–1.46)	
			3.9	81	0.91 (0.68–1.22)	
			7.3	89	1.05 (0.79–1.41)	
			16.0	99	1.27 (0.95–1.71)	
			Trend-test *P* value: 0.1			
		Proximal colon	Processed meat (quintile median, g/day); in men			
			0.2	36	1.00	
			1.9	51	1.60 (1.04–2.46)	
			3.9	37	1.20 (0.75–1.91)	
			7.3	39	1.31 (0.82–2.08)	
			16.0	37	1.38 (0.85–2.25)	
			Trend-test *P* value: 0.54			
		Distal colon	Processed meat (quintile median, g/day); in men			
			0.2	64	1.00	
			1.9	53	0.92 (0.64–1.33)	
			3.9	39	0.73 (0.49–1.10)	
			7.3	46	0.93 (0.63–1.38)	
			16.0	55	1.19 (0.80–1.77)	
			Trend-test *P* value: 0.19			
		Rectum	Processed meat (quintile median, g/day); in men			
			0.2	66	1.00	
			1.9	49	0.84 (0.58–1.21)	
			3.9	35	0.64 (0.42–0.97)	
			7.3	48	0.91 (0.62–1.33)	
			16.0	35	0.70 (0.45–1.09)	
			Trend-test *P* value: 0.25			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Takachi et al. (2011) Japan Follow-up, from 1995–1999 to December 2006 Cohort study (cont.)		Colon	Processed meat (quintile median, g/day); in women			
			0.4	61	1.00	
			2.2	69	1.26 (0.89–1.79)	
			4.3	60	1.10 (0.76–1.58)	
			7.6	58	1.12 (0.77–1.62)	
			15.0	59	1.19 (0.82–1.74)	
			Trend-test *P* value: 0.64			
		Proximal colon	Processed meat (quintile median, g/day); in women			
			0.4	31	1.00	
			2.2	42	1.51 (0.95–2.42)	
			4.3	37	1.33 (0.82–2.16)	
			7.6	38	1.42 (0.87–2.31)	
			15.0	31	1.23 (0.73–2.07)	
			Trend-test *P* value: 0.87			
		Distal colon	Processed meat (quintile median, g/day); in women			
			0.4	26	1.00	
			2.2	23	0.98 (0.55–1.73)	
			4.3	19	0.79 (0.43–1.44)	
			7.6	18	0.77 (0.42–1.44)	
			15.0	24	1.03 (0.57–1.87)	
			Trend-test *P* value: 0.88			
		Rectum	Processed meat (quintile median, g/day); in women			
			0.4	27	1.00	
			2.2	27	1.09 (0.64–1.87)	
			4.3	21	0.85 (0.47–1.52)	
			7.6	27	1.19 (0.68–2.08)	
			15.0	22	0.98 (0.53–1.79)	
			Trend-test *P* value: 1.00			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Ollberding et al. (2012) California and Hawaii, USA 1993–2007 Cohort study	15 717; multiethnic sample of African Americans, Japanese Americans, Latinos, native Hawaiians, and Whites aged 45–75 yr Exposure assessment method: FFQ; validated quantitative FFQ	Colon and rectum	Processed meat (quintile median, g/1000kcal per day)			Age, ethnicity, family history of colorectal cancer, history of colorectal polyps, BMI, smoking, NSAID use, alcohol, physical activity, history of diabetes, HRT use (females), total calories, intake of dietary fibre, calcium, folate, vitamin D
			1.70	599	1.00	
			4.48	626	0.98 (0.87–1.09)	
			7.28	706	1.04 (0.93–1.16)	
			10.86	704	1.00 (0.90–1.13)	
			17.98	769	1.06 (0.94–1.19)	
			Trend-test *P* value: 0.259			
Egeberg et al. (2013) Denmark 1993–2009 Cohort study	53 988; Danish men and women aged 50–64 yr free of cancer Exposure assessment method: FFQ; 192-item FFQ with 63 meat items and meat dishes, including specific processed meat products, mainly from pork; standard portion sizes	Colon	Processed meat (g/day)			Age, sex, waist circumference, schooling, smoking status, HRT use, sports activities, alcohol abstainer, alcohol intake, NSAID use, dietary fibre intake, total energy intake
			≤ 16	172	1.00	
			> 16 to ≤ 27	160	0.96 (0.77–1.20)	
			> 27 to ≤ 42	145	0.96 (0.75–1.22)	
			> 42	167	1.02 (0.78–1.34)	
			Continuous per 25 g/day	644	1.03 (0.94–1.13)	
			Trend-test *P* value: 0.53			
		Rectum	Processed meat (g/day)			
			< 16	75	1.00	
			> 16 to ≤ 27	96	1.21 (0.89–1.65)	
			> 27 to ≤ 42	93	1.18 (0.84–1.64)	
			> 42	81	0.88 (0.60–1.30)	
			Continuous, per 100 g/day	345	0.93 (0.81–1.07)	
			Trend-test *P* value: 0.32			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bernstein et al. (2015) USA Nurses' Health Study, 1980–2010; Health Professionals Follow-Up Study, 1986–2010 Cohort study	87 108 women and 47 389 men; Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS) Exposure assessment method: FFQ; diet from FFQs collected about every 4 yr during follow-up (see Wei et al, 2004)	Colon and rectum	Processed red meat (1 serving/day)			Age, follow-up, family history, endoscopy, smoking, alcohol drinking, BMI, physical activity, medications and supplements, menopausal status, hormone use, total caloric intake, folate, calcium, vitamin D, fibre
			Baseline intake	2731	1.08 (0.98–1.18)	
			Trend-test *P* value: 0.13			
			Processed red meat (1 serving/day)			
			Cumulative average	2731	1.15 (1.01–1.32)	
			Trend-test *P* value: 0.03			
		Proximal colon	Processed red meat (1 serving/day)			
			Baseline intake	1151	0.98 (0.84–1.15)	
			Trend-test *P* value: 0.82			
			Processed red meat (1 serving/day)			
			Cumulative intake	1151	0.99 (0.79–1.24)	
			Trend-test *P* value: 0.93			
		Distal colon	Processed red meat (1 serving/day)			
			Baseline intake	817	1.23 (1.05–1.44)	
			Trend-test *P* value: 0.009			
			Processed red meat (1 serving/day)			
			Cumulative intake	817	1.36 (1.09–1.69)	
			Trend-test *P* value: 0.006			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bernstein et al. (2015) USA Nurses' Health Study, 1980–2010; Health Professionals Follow-Up Study, 1986–2010 Cohort study (cont.)		Rectum	Processed red meat (1 serving/day)			
			Baseline intake	589	1.05 (0.86–1.3)	
			Trend-test *P* value: 0.64			
			Processed red meat (1 serving/day)			
			Cumulative intake	589	1.18 (0.89–1.57)	
			Trend-test *P* value: 0.25			

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; h, hour; HRT, hormone replacement therapy; mo, month; NOS, not otherwise specified; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SQFFQ, semiquantitative food frequency questionnaire; wk, week; yr, year

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Manousos et al. (1983) Athens, Greece 1974–1980	Cases: 100; hospital-based incident colorectal cancer cases Controls: 100; hospital-based patients seen at an orthopaedic clinic, matched to cases by age and sex Exposure assessment method: questionnaire; frequency questionnaire with 80 items, administered in person; individual red meats only were beef and lamb	Colon and rectum	Increase from 1 to 2 times/wk			Age, sex, vegetables
			Beef meat	NR	1.77	
			Lamb meat	NR	2.61	
Kune et al. (1987) Melbourne, Australia 1980–1981	Cases: 715; population-based cases Controls: 727; population-based controls matched to cases by age and sex Exposure assessment method: questionnaire; validated questionnaire with 300 items, administered in person; individual red meats were beef (steak, roast beef, ground beef, beef casserole, corned beef, beef sausages, canned beef meals) and pork (pork chops, roast pork, ham, bacon, pork sausages)	Colon and rectum	Beef (g/wk), men and women:			Age, sex, fibre, cruciferous vegetables, dietary vitamin C, pork, fish, other meat, fat, milk, supplements
			< 360	130	1.00	
			> 360	258	1.75 (1.26-2.44)	
		Colon	Beef (g/wk), men:			
			< 360	NR	1.00	
			> 360	NR	1.58	
		Rectum	Beef (g/wk), men:			
			< 360	NR	1.00	
			> 360	NR	1.88	
		Colon and rectum	Pork (g/wk), men and women:			
			≤ 58	370	1.00	
			> 58	332	0.55 (0.42–0.73)	
			Pork (g/wk), women:			
			≤ 58	212	1.00	
			> 58	115	0.52	
			Pork (g/wk), men:			
			≤ 58	159	1.00	
			> 58	217	0.59	
		Colon	Pork (g/wk), men:			
			≤ 58	NR	1.00	
			> 58	NR	0.73	
			Pork (g/wk), women:			
			≤ 58	159	1.00	
			> 58	217	0.62	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kune et al. (1987) Melbourne, Australia 1980–1981 (cont.)		Rectum	Pork (g/wk), men:			
			≤ 58	159	1.00	
			> 58	217	0.47	
			Pork (g/wk), women:			
			≤ 58	159	1.00	
			> 58	217	0.39	
		Colon and rectum	Beef (g/wk), men:			
			Q1 (≤ 250)	74	1.00	
			Q2 (> 250–360)	56	0.80	
			Q3: (> 260–500)	84	1.54	
			Q4 (> 500–720)	75	1.24	
			Q5: (> 720)	99	2.14	
		Colon and rectum	Pork (g/wk), men:			
			Q1 (≤ 15)	95	1.00	
			Q2 (> 15–58)	63	0.55	
			Q3 (> 58–106)	79	0.64	
			Q4 (> 106–174)	63	0.65	
			Q5 (> 174)	75	0.59	
		Colon and rectum	Pork (g/wk), women:			
			Q1 (≤ 0)	73	1.00	
			Q2 (> 0–27)	77	1.16	
			Q3 (> 27–58)	62	0.68	
			Q4 (> 58–114)	65	0.64	
			Q5 (> 114)	50	0.38	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Tuyns et al. (1988) Belgium 1978–1982	Cases: 818; population-based cases, identified through treatment centres Controls: 2851; population-based Exposure assessment method: questionnaire; validated, administered in person, and captured frequency and serving size; individual red meat was beef (veal, lean beef, half-fat beef, and fat beef) or pork (lean and half-fat pork, fat pork, and smoked pork)	Colon	Beef consumption (g/wk)			Age (10-yr age groups), sex, province
			0	NR	1.00	
			>0– 226	NR	1.76	
			> 227 to ≤ 360	NR	1.60	
			> 361 to ≤ 538	NR	2.09	
			Trend-test *P* value: < 0.0001			
		Colon	Pork consumption (g/wk), quartiles			
			Level 1	NR	1.00	
			≤ 200	NR	0.85	
			> 200 to ≤ 330	NR	0.58	
			> 330 to ≤ 509	NR	0.39	
			Trend-test *P* value: < 0.0001			
		Rectum	Beef consumption (g/wk), quartiles			
			Level 1	NR	1.00	
			≤ 226	NR	1.20	
			> 227 to ≤ 360	NR	1.21	
			> 361 to ≤ 538	NR	0.71	
			Trend-test *P* value: 0.14			
		Rectum	Pork consumption (g/wk), quartiles			
			Level 1	NR	1.00	
			≤ 200	NR	0.89	
			> 200 to ≤ 330	NR	0.75	
			> 330 to ≤ 509	NR	0.70	
			Trend-test *P* value: 0.016			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lee et al. (1989) Singapore 1985–1987	Cases: 203; hospital-based colorectal cases, identified at Singapore General Hospital Controls: 425; hospital-based, identified from eye and orthopaedic wards in the same hospital as cases; frequency-matched by age and sex; GI disease excluded Exposure assessment method: questionnaire; validated, administered in person, and included 116 items; red meat was pork, beef, and mutton; unclear if red meat included processed meat	Colon and rectum	Total red meat intake (g/day), tertiles			Age, sex, dialect group, occupational group
			T1	NR	1.00	
			T2	NR	1.18 (0.77–1.81)	
			T3	NR	1.29 (0.84–1.97)	
			Trend-test: *P* value: NS			
		Rectum	Total red meat intake (g/day), tertiles			
			T1	NR	1.00	
			T2	NR	1.43 (0.75–2.74)	
			T3	NR	0.97 (0.48–1.92)	
			Trend-test *P* value: NS			
		Colon	Total red meat intake (g/day), tertiles			
			T1	NR	1.00	
			T2	NR	1.01 (0.60–1.70)	
			T3	NR	1.41 (0.87–2.31)	
			Trend-test *P* value: NS			
Gerhardsson de Verdier et al. (1991) Stockholm, Sweden 1986–1988	Cases: 559; population-based colorectal cases, identified through local hospitals and regional cancer registry Controls: 505; population-based, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation, self-administered, and included 55 items; red meat was beef and pork; assessed cooking methods	Colon	Red meat intake (Tertile 3 vs T1, i.e. > 1 time/wk vs more seldom)			Year of birth,sex, fat intake
			Beef/pork, fried	193	1.1 (0.7–1.8)	
			Trend-test *P* value: 0.353			
			Beef/pork, oven-roasted	57	1.2 (0.8–1.8)	
			Trend-test *P* value: 0.428			
			Beef/pork, boiled	104	1.8 (1.2–2.6)	
			Trend-test *P* value: 0.004			
		Rectum	Red meat intake (> 1 time/wk vs more seldom)			
			Beef/pork, fried	124	1.6 (0.9–3.0)	
			Trend-test *P* value: 0.073			
			Beef/pork, oven-roasted	47	1.8 (1.1–2.9)	
			Trend-test *P* value: 0.019			
			Beef/pork, boiled	69	1.9 (1.2–3.0)	
			Trend-test *P* value: 0.007			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bidoli et al. (1992) Province of Pordenone, Italy 1986–NR (possibly 1992)	Cases: 248; hospital-based Controls: 699; hospital-based, excluded patients with cancer, digestive-tract disorders, or any condition related to alcohol or tobacco consumption Exposure assessment method: questionnaire; not validated and administered in person; total red meat was beef and pork from all sources; assessed frequency	Colon	Total red meat consumption (frequency)			Age, sex, social status
			T1	35	1.0	
			T2	48	1.5	
			T3	40	1.6	
			Trend-test *P* value: 0.07			
		Rectum	Total red meat consumption (frequency)			
			T1	35	1.0	
			T2	50	1.5	
			T3	40	2.0	
			Trend-test *P* value: 0.01			
Iscovich et al. (1992) La Plata, Argentina 1985–1986	Cases: 110; hospital-based, identified through local hospitals Controls: 220; population-based, identified from neighbourhoods of cases and matched to cases by sex; controls with conditions that may have affected diet were excluded Exposure assessment method: questionnaire; unclear validation, administered in person, and included 140 items; red meat was beef, veal, pork, horse, red wild meat, goat, and hare	Colon	Red meat intake, quartiles			Matching variables
			Q1	NR	1.00	
			Q2	NR	2.29 (1.03–5.08)	
			Q3	NR	0.82 (0.39–1.70)	
			Q4	NR	NR	
			Trend-test *P* value: 0.076			
Steinmetz and Potter (1993) Adelaide, Australia 1979–1980	Cases: 220; population-based colon cases, identified via the South Australian Cancer Registry Controls: 438; population-based; two controls per case selected via the electoral roll; individually matched to cases by age and sex Exposure assessment method: questionnaire; validated, included 141 items, and self-administered; red meat was hamburger (with bread roll), grilled steak, fried steak, grilled pork chop, fried pork chop, grilled lamb chop, fried lamb chop, roast pork, roast beef, veal, crumbed veal (schnitzel), mince, and roast lamb	Colon	Red meat intake (servings/wk), quartiles			Age at first live birth, Quetelet index, alcohol intake, the matching variable age
			Women:			
			Q1 (≤ 3.4)	NR	1.00	
			Q2 (3.5–5.0)	NR	1.44 (0.70–2.93)	
			Q3 (5.1–7.1)	NR	1.15 (0.57–2.32)	
			Q4 (≥ 7.2)	NR	1.48 (0.73–3.01)	
			Red meat intake (servings/wk), quartiles			Occupation, Quetelet index, alcohol intake, the matching variable age
			Men:			
			Q1 (≤ 3.9)	NR	1.00	
			Q2 (4.0–5.5)	NR	1.80 (0.92–3.52)	
			Q3 (5.6–8.2	NR	1.64 (0.82–3.27)	
			Q4 (≥ 8.3)	NR	1.59 (0.81–3.13)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Centonze et al. (1994) Southern Italy 1987–1989	Cases: 119; population-based colorectal cases, identified from a population-based cancer registry Controls: 119; population-based, matched to cases by age, sex, and general practitioner Exposure assessment method: questionnaire; unclear validation, administered by in-person interview, and included 70 food items; red meat was beef, reported on individually	Colon and rectum	Beef intake (g/day) Low: 21 Medium (≥ 22)	 92 27	 1.00 0.95 (0.50–1.80)	Age , sex, level of education, smoking status, modifications of diet over the past 10 yr
Muscat and Wynder (1994) USA 1989–1992	Cases: 511; hospital-based cases Controls: 500; hospital-based patients with disease unrelated to dietary fat or fibre intake; frequency-matched to cases by sex, race, hospital, and age Exposure assessment method: questionnaire; administered in person; red meat was beef, steaks, roasts, or hamburgers; assessed doneness level	Colon and rectum	Beef doneness, men: Rare Medium Well done Beef doneness, women: Rare Medium Well done	 82 133 54 83 89 35	 1.00 1.00 1.15 (0.6–2.4) 1.00 0.95 (0.6–1.5) 1.00	Matching factors of sex, race, hospital, age, time of the case interview

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kampman et al. (1995) The Netherlands 1989–1993	Cases: 232; population-based colon cases, identified from hospitals using a cancer registry Controls: 259; population-based, identified through rosters of general practitioners of participating cases; frequency-matched to cases by age, sex, and degree of urbanization Exposure assessment method: questionnaire; unclear validation, administered in person, included 289 items, and considered frequency and serving size; red meat was unprocessed red meat; no further details provided	Colon	Red meat intake (g/day), women:			Age, urbanization level, total energy intake, alcohol intake, family history of colon cancer, cholecystectomy
			< 38	12	1.00	
			38–59	25	1.82 (0.75–4.46)	
			60–83	36	2.71 (1.15–6.38)	
			> 83	29	2.35 (0.97–5.66)	
			Trend-test *P* value: 0.04			
			Red meat intake (g/day), men:			
			< 60	33	1.00	
			60–83	35	0.80 (0.39–1.61)	
			84–102	24	0.57 (0.27–1.30)	
			> 102	38	0.89 (0.43–1.81)	
			Trend-test *P* value: 0.62			
			Ratio of red meat: vegetables + fruit, men:			
			< 0.14	32	1.00	
			0.14–0.22	33	1.04 (0.51–2.13)	
			0.22–0.33	24	0.79 (0.38–1.64)	
			> 0.33	40	1.18 (0.57–2.43)	
			Trend-test *P* value: 0.69			
			Ratio of red meat: vegetables + fruit, women:			
			< 0.09	16	1.00	
			0.09–0.13	11	0.81 (0.30–2.17)	
			0.13–0.20	26	1.53 (0.67–3.51)	
			> 0.20	48	3.05 (1.39–6.17)	
			Trend-test *P* value: 0.0006			
Kotake et al. (1995) Japan 1992–1994	Cases: 363; hospital-based colorectal cases Controls: 363; hospital-based, individually matched to cases by sex and age group Exposure assessment method: questionnaire; unknown validation and administration; exposure definition for red meat was beef and pork, examined separately	Colon	Beef or pork intake (> 3–4 times/wk vs 1–2 times/wk)			Matching variables (other variables not reported)
			Beef	NR	1.70 (0.85–3.28)	
			Pork	NR	0.80 (0.50–1.33)	
		Rectum	Beef or pork intake (> 3–4 times/wk vs 1–2 times/wk)			
			Beef	NR	0.80 (0.38–1.52)	
			Pork	NR	1.60 (0.95–2.73)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lohsoonthorn and Danvivat (1995) Bangkok, Thailand NR	Cases: 279; hospital-based colorectal cases Controls: 279; hospital-based, individually matched to cases by sex, age, admission period, hospital; included cancer patients with cancer in other organs Exposure assessment method: questionnaire; unclear validation and number of items asked; assessed frequency only; red meat (individual types only) was beef and pork	Colon and rectum	Beef consumption (times/mo)			None
			< 5	180	1.00	
			6– ≥ 10	99	1.00 (0.70–1.44)	
			Trend-test *P* value: 0.95			
			Pork consumption (times/mo)			
			< 5	29	1.00	
			6– ≥ 10	250	1.00 (0.56–1.78)	
			Trend-test *P* value: 0.95			
Freedman et al. (1996) New York, USA 1982–1992	Cases: 163; hospital-based Controls: 326; hospital-based, frequency-matched to cases by age and sex (2:1 ratio); 21.5% had non-malignant GI diseases Exposure assessment method: questionnaire; unclear validation, self-administered, and included 66 items; beef was hamburger, steak, roast, and stew; assessed frequency	Colon and rectum	Beef intake (times/mo)			Age, sex
			≤ 1	37	1.00	
			1–4	109	1.61 (1.03–2.52)	
			5–7	17	2.01 (0.96–4.20)	
			Trend-test *P* value: 0.03			
			Beef intake (times/mo); *p53*+ genotype			
			≤ 1	22	1.00	
			1–4	45	1.12 (0.63–1.98)	
			5–7	6	1.25 (0.45–3.49)	
			Trend-test *P* value: 0.63			
			Beef intake (times/mo)); *p53*– genotype			
			≤ 1	15	1.00	
			1–4	64	2.35 (1.26–4.39)	
			5–7	11	3.17 (1.83–11.28)	
			Trend-test *P* value: 0.006			
La Vecchia et al. (1996) Northern Italy 1985–1992	Cases: 1326; hospital-based colorectal cases Controls: 2024; hospital-based, identified from same hospitals as cases for non-cancer, non-GI conditions Exposure assessment method: questionnaire; unclear validation, administered by in-person interview, and assessed frequency only; red meat was not defined	Colon	Red meat intake (portions/wk)			Age, sex, total caloric intake, β-carotene, vitamin C intake, meal frequency/day, major seasoning fat score, family history of colorectal cancer
			≥4 vs <4	NR	1.6 (1.3–1.9)	
		Rectum	Red meat intake (portions/wk)			
			≥4 vs <4	NR	1.6 (1.3–2)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Shannon et al. (1996) Seattle, USA 1985–1989	Cases: 424; population-based colon cancer cases, identified through the SEER Seattle–Puget Sound Registry Controls: 414; population-based controls, identified through random digit dialling; matched to cases by age, sex, and county of residence Exposure assessment method: questionnaire; validated, included 71 items, administered in person, and assessed frequency and portion sizes; total red meat was casserole dishes, beef, ham, lamb, veal, pork and beef roasts, hamburger, ribs, pot roast, bacon, liver, organ meats, wieners, sausages, and luncheon meats	Colon	Total red meat (servings/day), women:			Age, total energy intake
			Q1 (0–0.49)	46	1.00	
			Q2 (> 0.49–0.79)	44	0.90 (0.50–1.64)	
			Q3 (> 0.79–1.20)	49	1.03 (0.55–1.90)	
			Q4 (> 1.20)	47	0.72 (0.37–1.38)	
			Trend-test *P* value: 0.41			
			Total red meat (servings/day), men:			
			Q1 (0–0.78)	49	1.00	
			Q2 (> 0.78–1.20)	51	1.00 (0.58–1.74)	
			Q3 (> 1.20–1.70)	60	1.05 (0.61–1.83)	
			Q4 (> 1.70)	78	1.48 (0.82–2.66)	
			Trend-test *P* value: 0.53			
De Stefani et al. (1997) Montevideo, Uruguay 1993–1995	Cases: 250; hospital-based colorectal cases Controls: 500; hospital-based, identified at same hospitals as the cases and afflicted with a variety of disorders unrelated to tobacco smoking, alcohol, or diet Exposure assessment method: questionnaire; unclear validation, administered in person, and included 60 items; unclear what was included in red meat; assessed cooking methods and HAAS estimates	Colon and rectum	Red meat, quartiles			Age, residence, education, family history of colon cancer in a first-degree relative, BMI, vegetable and dessert intake
			Q1	NR	1.00	
			Q2	NR	1.22 (0.76 –1.94)	
			Q3	NR	1.44 (0.90–2.29)	
			Q4	NR	2.60 (1.64–4.13)	
			Trend-test *P* value: <0.001			
			Beef, tertiles			
			T1	NR	1.00	
			T2	NR	1.66 (1.16–2.38)	
			T3	NR	3.88 (2.34–6.45)	
			Trend-test *P* value: <0.001			
			Lamb, tertiles			
			T1	NR	1.00	
			T2	NR	1.15 (0.78–1.68)	
			T3	NR	1.46 (0.97–2.19)	
			Trend-test *P* value: 0.07			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (1997) Montevideo, Uruguay 1993–1995 (cont.)			IQ intake estimates, quartiles			
			Q1	NR	1.00	
			Q2	NR	1.63 (1.02–2.62)	
			Q3	NR	2.30 (1.43 –3.72)	
			Q4	NR	3.08 (1.87 –5.07)	
			Trend-test *P* value: <0.001			
			MeIQx intake estimates, quartiles			
			Q1	NR	1.00	
			Q2	NR	1.21 (0.74–1.98)	
			Q3	NR	2.30 (1.44 –3.68)	
			Q4	NR	3.23 (2.02 –5.16)	
			Trend-test *P* value: <0.001			
			PhiP intake estimates, quartiles			
			Q1	NR	1.00	
			Q2	NR	1.43 (0.89 –2.29)	
			Q3	NR	2.12 (1.32 –3.41)	
			Q4	NR	3.01 (1.87 –4.83)	
			Trend-test *P* value: <0.001			
Fernandez et al. (1997) Province of Pordenone, Italy 1985–1992	Cases: 112; cases with a family history of colorectal cancer; see Bidoli et al. (1992) Controls: 108; controls with a family history of colorectal cancer; see Bidoli et al. (1992) Exposure assessment method: questionnaire; see Bidoli et al. (1992)	Colon and rectum	Total red meat intake, tertiles			Sex, age, area of residence
			T1	NR	1.0	
			T2	NR	0.9 (0.5–1.7)	
			T3	NR	2.9 (1.4–6.0)	
			Trend-test *P* value: <0.05			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Le Marchand et al. (1997) Hawaii, USA 1987–1991	Cases: 1192; population-based cases, identified through the Hawaii Tumor Registry; cases included Japanese, Caucasian (White), Filipino, Hawaiian, and Chinese patients Controls: 1192; population-based, identified through the Hawaii State Department of Health; individually matched to each case by sex, race, and age Exposure assessment method: questionnaire; validated, administered in person, and included 280 items; red meat was beef, pork, and lamb	Colon and rectum	Total beef, veal, and lamb; quartiles			Age; family history of colorectal cancer; alcoholic drinks per wk; pack-years; lifetime recreational activity; BMI 5 yr ago; caloric, dietary fibre, calcium intakes
			Men:			
			Q1	NR	1.0	
			Q2	NR	1.3	
			Q3	NR	1.3	
			Q4	NR	2.1 (1.4–3.1)	
			Trend-test *P* value <0.0001			
			Total beef, veal, and lamb; quartiles			
			Women:			
			Q1	NR	1.0	
			Q2	NR	1.4	
			Q3	NR	0.8	
			Q4	NR	1.3 (0.9–2.1)	
			Trend-test *P* value: 0.5			
Boutron-Ruault et al. (1999) Burgundy, France 1985–1990	Cases: 171; population-based, identified from GI and surgery departments, in conjunction with the registry of digestive cancers Controls: 309; population-based, identified through a census list; frequency-matched to cases by age and sex Exposure assessment method: questionnaire; validated and administered in person; red meat was beef, pork, and lamb, reported individually	Colon and rectum	Beef intake (g/day), quartiles			Age, sex, caloric intake, sex-specific cut-offs for quartiless
			Q1	NR	1.0	
			Q2	NR	1.5 (0.9–2.6)	
			Q3	NR	1.7 (0.9–2.9)	
			Q4	NR	1.4 (0.8–2.4)	
			Trend-test *P* value: 0.31			
			Pork intake (g/day), quartiles			
			Q1	NR	1.0	
			Q2	NR	1.0 (0.6–1.7)	
			Q3	NR	1.5 (0.9–2.5)	
			Q4	NR	1.0 (0.6–2.8)	
			Trend-test *P* value: 0.61			
			Lamb intake			
			None	NR	1.0	
			Any	NR	1.3 (0.9–1.9)	
			Trend-test *P* value: 0.20			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kampman et al. (1999) California, Utah, and Minnesota, USA 1991–1994	Cases: 1542; cases identified through the Kaiser Permanente Medical Care Program of Northern California, Utah, and metropolitan twin cities area in Minnesota Controls: 1860; population-based, frequency-matched to cases by sex and age; identified using membership lists of the Kaiser Permanente Medical Care Program, random digit dialling, drivers' licence and identification lists, and Health Care Financing Administration forms Exposure assessment method: questionnaire; validated, administered by in-person interview, and included > 800 items; red meat was ground beef, hamburger, ground beef casseroles, hamburger helper, pot roast, steak, and ham; assessed cooking methods and mutagen index	Colon	Red meat, including ham (servings/wk), men			Age at diagnosis (cases) or selection (controls), BMI, lifetime physical activity, total energy intake, usual number of cigarettes smoked per day, intake of dietary fibre
			≤ 2.2	NR	1.0	
			2.3–3.7	NR	0.8 (0.6–1.0)	
			3.8–5.6	NR	1.1 (0.8–1.0)	
			5.7–8.8	NR	1.0 (0.7–1.4)	
			> 8.8	NR	0.9 (0.7–1.3)	
			Red meat, including ham (servings/wk), women			
			≤ 1.5	NR	1.0	
			1.6–2.5	NR	1.1 (0.8–1.5)	
			2.6–4.0	NR	1.3 (0.9–1.8)	
			4.1–6.2	NR	1.3 (0.9–1.8)	
			> 6.2	NR	1.0 (0.7–1.5)	
Tavani et al. (2000) Milan, Italy 1983–1991	Cases: 828; hospital-based colorectal cases Controls: 7990; hospital-based, admitted to the same network of hospitals as the cancer cases for acute non-neoplastic conditions, but excluded conditions that may have affected diet Exposure assessment method: questionnaire; non-validated but reproducible, 40 items, administered in person; red meat was beef, veal, and pork	Colon	Red meat (servings/wk)			Age, year of recruitment, sex, education, tobacco smoking, alcohol, fats in seasoning, fruits, vegetables
			≤ 3	206	1.0	
			>3 – ≤6	228	1.1 (0.9–1.3)	
			> 6	394	1.9 (1.5–2.3)	
			Per increment of 1 serving/day	828	1.5 (1.1–2.0)	
			Trend-test *P* value ≤ 0.01			
		Rectum	Red meat (servings/wk)			
			≤ 3	123	1.0	
			>3 – ≤6	150	1.1 (0.9–1.5)	
			> 6	225	1.7 (1.3–2.2)	
			Per increment of 1 serving/day	498	1.7 (1.2–2.4)	
			Trend-test *P* value ≤0.01			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Le Marchand et al. (2001) Hawaii, USA 1994–1998	Cases: 727; population-based colorectal cases, identified through the Hawaii Tumor Registry; cases included Japanese, Caucasians, and native Hawaiians Controls: 727; population-based, selected through the Hawaii State Department of Health and the Health Care Financing Administration; individually matched to cases by sex, ethnicity, and age Exposure assessment method: questionnaire; validated, administered in person, and included 280 items; red meat was beef and pork; considered cooking methods, and interactions with *NAT2* and *CYP1A2* phenotypes, and *NAT* genotype	Colon and rectum	Red meat intake (g/day) in all interviewed participants (768 cases, 768 controls)			Pack-years of cigarette smoking; lifetime recreational physical activity; lifetime aspirin use; BMI 5 yr ago; years of schooling; intakes of non-starch polysaccharides from vegetables and calcium from foods and supplements; the matching variables age, sex, ethnicity
			≤ 18.9	162	1.0	
			19.0–37.4	170	1.0 (0.7–1.4)	
			37.5–68.5	209	1.1 (0.8–1.5)	
			> 68.6	186	1.0 (0.7–1.4)	
			Trend-test *P* value: 0.98			
			Red meat intake (g/day) in all phenotyped participants (349 cases, 467 controls)			
			≤ 18.9	68	1.0	
			19.0–37.4	74	1.0 (0.7–1.6)	
			37.5–68.5	108	1.2 (0.8–1.9)	
			> 68.6	99	1.0 (0.6–1.5)	
			Trend-test *P* value: 0.86			
			Red meat preference in all interviewed participants			
			Did not eat/rare/ medium–rare	328	1.0	
			Medium	188	1.0 (0.7–0.9)	
			Well done/very well done	211	1.2 (0.9–1.5)	
			Trend-test *P* value: 0.29			
			Red meat preference in all phenotyped participants			
			Did not eat/rare/ medium–rare	158	1.0	
			Medium	92	0.8 (0.6–1.1)	
			Well done/very well done	99	1.1 (0.8–1.6)	
			Trend-test *P* value: 0.73			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Le Marchand et al. (2001) Hawaii, USA 1994–1998 (cont.)		Colon and rectum	Three-way interaction for *NAT2* genotype, *CYP1A2* phenotype, and red meat preference (well-done vs medium-rare red meat)			Age; sex; ethnicity; pack-years of cigarette smoking; number of cigarettes, cigars, pipes smoked during the 2 wk preceding the caffeine test; lifetime recreational physical activity; lifetime aspirin use; BMI 5 yr ago; yrs of schooling; intakes of non-starch polysaccharides from vegetables and calcium from foods and supplements
			NAT2 genotype (slow/intermediate); *CYP1A2* (≤ median)	31	1.2 (0.7–2.3)	
			NAT2 genotype (rapid); *CYP1A2* (≤ median)	19	1.0 (0.5–1.9)	
			NAT2 genotype (slow/intermediate); *CYP1A2* (> median)	28	1.0 (0.6–1.9)	
			NAT2 genotype (rapid); *CYP1A2* (> median)	21	3.3 (1.3–8.1)	
			P value for interaction = 0.12			
Evans et al. (2002) Liverpool, United Kingdom NR	Cases: 512; population-based colorectal cases, identified from the Merseyside and Cheshire Cancer Registry Controls: 512; population-based, identified from general primary care practice lists; matched by age, sex, postal code, and primary care practitioner Exposure assessment method: questionnaire; validated, administered by telephone interview, and included160 items; red meat was not defined; frequency and portion size were assessed	Colon and rectum	Red meat (servings/day)			Only presented univariate odds ratios in tables
			Q1: 0–3	NR	1.00	
			Q2: > 3–5	NR	0.96 (0.65–1.42)	
			Q3: > 5–6	NR	1.03 (0.64–1.66)	
			Q4: > 6–22	NR	1.51 (1.06–2.15)	
		Proximal colon	Red meat (servings/day)			
			Q1: 0–3	NR	1.00	
			Q2: > 3–5	NR	0.91 (0.39–2.09)	
			Q3: > 5–6	NR	1.30 (0.47–3.62)	
			Q4: > 6–22	NR	3.32 (1.42–7.73	
		Distal colon + rectum	Red meat (servings/day)			
			Q1: 0–3	NR	1.00	
			Q2: > 3–5	NR	1.02 (0.65–1.59)	
			Q3: > 5–6	NR	0.97 (0.62–1.52)	
			Q4: > 6–22	NR	1.38 (0.89–2.12)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Le Marchand et al. (2002b) Hawaii, USA 1994–1998	Cases: 727; see Le Marchand et al. (2001) Controls: 727; see Le Marchand et al. (2001) Exposure assessment method: other; see Le Marchand et al. (2001)	Colon	Red meat intake, tertiles			Pack-years of cigarette smoking, physical activity, aspirin use, BMI, education, non-starch polysaccharides from vegetables, total calcium, and the matching variables age and sex
			T1	NR	1.0	
			T2	NR	0.9 (0.6–1.3)	
			T3	NR	1.0 (0.7–1.5)	
			Trend-test *P* value: 0.8			
		Rectum	Red meat intake, tertiles			
			T1	NR	1.0	
			T2	NR	1.9 (1.1–3.3)	
			T3	NR	1.7 (1.0–3.0)	
			Trend-test *P* value: 0.16			
		Colon	Red meat preference			
			Rare	NR	1.0	
			Medium	NR	0.8 (0.6–1.1)	
			Well done	NR	1.0 (0.7–1.3)	
			Trend-test *P* value: 0.62			
		Rectum	Red meat preference			
			Rare	NR	1.0	
			Medium	NR	1.1 (0.7–1.7)	
			Well done	NR	1.5 (0.9–2.4)	
			Trend-test *P* value: 0.11			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
		Colon	Highest vs lowest tertile of HAAs from red meat			Pack-years of cigarette smoking; physical activity; aspirin use; BMI; education; non-starch polysaccharides from vegetables and total calcium; PhIP, MeIQx, and DiMeIQx models for rectal cancer were further adjusted for intake of other HAAs; the matching variables age, sex, ethnicity
			PhIP	NR	1.0 (0.6–1.6)	
			MeIQx	NR	1.0 (0.6–1.1)	
			DiMeIQx	NR	1.1 (0.7–1.7)	
			Total HAAs	NR	1.0 (0.6–1.6)	
		Rectum	Highest vs lowest tertile of HAAs from red meat			
			PhIP	NR	1.7 (0.3–3.8)	
			MeIQx	NR	3.1 (1.3–7.7)	
			Trend-test *P* value:0.01			
			DiMeIQx	NR	2.7 (1.1–6.3)	
			Total HAAs	NR	2.2 (1.0–4.7)	
Nowell et al. (2002) Arkansas and Tennessee, USA 1993–1999	Cases: 157; hospital-based Controls: 380; population-based, identified from Arkansas drivers' licence records; matched to cases by ethnicity, age, and county of residence Exposure assessment method: questionnaire; validated and administered in person; total red meat was burgers, steak, pork chops, bacon, and sausage; cooking methods were assessed using the CHARRED database to estimate HAAs	Colon and rectum	Total red meat cooked well/very well done (g/day)			Age, ethnicity, sex
			Q1	25	1.00	
			Q2	34	1.91 (0.85–4.41)	
			Q3	42	2.42 (1.11–5.47)	
			Q4	54	4.36 (2.08–9.60)	
			MeIQx (ng/day)			
			Q1	29	1.00	
			Q2	32	1.75 (0.78–4.05)	
			Q3	40	2.87 (1.32–6.52)	
			Q4	53	4.09 (1.94–9.08)	
Seow et al. (2002) Singapore 1999–2000	Cases: 121; hospital-based colorectal cases Controls: 222; population-based controls, identified using random sampling from electoral records Exposure assessment method: questionnaire; red meat was pork, beef, lamb, and mutton; unclear if red meat included processed meat	Colon and rectum	Red meat (portions/yr)			Age, family history of colorectal cancer, sex, smoking, education, physical exercise
			< 39	20	1.0	
			39 to < 117	34	1.1 (0.5–2.2)	
			≥ 117	66	2.2 (1.1–4.2)	
			Trend-test Pvalue <0.05			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Butler et al. (2003) North Carolina, USA 1996–2000	Cases: 620; population-based colon cancer cases, identified through the North Carolina Central Cancer Registry; included White and African American cases Controls: 1038; population-based, identified through the Division of Motor Vehicles; frequency-matched to cases by race, age, and sex Exposure assessment method: questionnaire; unclear validation, administered in person, and included 150 items; red meat was hamburger, steak, pork chop, sausage, and bacon; cooking methods were assessed and HAAs estimated using the CHARRED database	Colon	Total red meat (g/day)			Age, race, sex, energy-adjusted fat intake, energy intake, fibre intake, total meat intake, offsets
			≤ 11.8	97	1.0	
			11.9–22.4	90	0.9 (0.6–1.3)	
			22.5–33.6	99	1.0 (0.7–1.5)	
			33.7–51.8	138	1.5 (1.0–2.2)	
			≥ 51.8	196	2.0 (1.3–3.2)	
			Total red meat intake by doneness (g/day), highest vs lowest intake category (number of cases)			
			Rare/medium done (> 22.7 vs 0)	93	1.2 (0.9–1.7)	
			Well/very well done (> 42.7 vs ≤ 5.9)	192	1.7 (1.2–2.5)	
			Baked (> 7.7 vs 0)	44	1.1 (0.7–1.7)	
			Pan-fried (> 25.2 vs 0)	199	2.0 (1.4–3.0)	
			Broiled (> 16.5 vs 0)	68	1.3 (0.9–1.9)	
			Grilled/barbecued (22.7 vs 0)	97	0.9 (0.6–1.3)	
Chiu et al. (2003) Shanghai, China 1990–1993	Cases: 931; population-based, identified through the Shanghai Cancer Registry Controls: 1552; population-based, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; administered in person, included 86 items, and asked frequency and servings; red meat was pork, organ meats, beef, and mutton	Colon	Red meat (servings/mo of food group)			Age, total energy, education, BMI, income, occupational physical activity
			Men:			
			Q1	NR	1.0	
			Q2	NR	1.2 (0.8–1.6)	
			Q3	NR	1.3 (0.9–1.8)	
			Q4	NR	1.5 (1.0–2.1)	
			Trend-test *P* value: 0.03			
			Red meat (servings/mo of food group)			
			Women:			
			Q1	NR	1.0	
			Q2	NR	1.3 (0.9–1.8)	
			Q3	NR	1.0 (0.7–1.4)	
			Q4	NR	1.5 (1.0–2.2)	
			Trend-test *P* value: 0.08			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Navarro et al. (2003) Córdoba, Argentina 1993–1998	Cases: 287; hospital-based colorectal cases, identified at hospitals in Córdoba Controls: 564; hospital-based control residents, identified at the same hospitals for acute non-neoplastic conditions unrelated to digestive tract diseases or long-term modifications Exposure assessment method: questionnaire; validated, administered in person, and evaluated frequency and portion size; individual red meats included fatty and lean beef, pork, and bovine viscera; unclear if total red meat included processed meats	Colon and rectum	Fatty beef intake (median, g/day)			Sex, age, BMI, social status, total energy intake, total lipids, proteins, glucids, and soluble and insoluble fibres
			T1	NR	1.00	
			T2 (37.3)	NR	0.80 (0.55–1.18)	
			T3 (76.71)	NR	0.78 (0.51–1.18)	
			Lean beef intake (median, g/day)			
			T1	NR	1.00	
			T2 (53.13)	NR	0.64 (0.43–0.94)	
			T3 (95.94)	NR	0.67 (0.40–0.97)	
			Pork intake (median, g/day)			
			T1	NR	1.00	
			T2 (0.05)	NR	0.98 (0.67–1.43)	
			T3 (2.02)	NR	0.92 (0.62–1.36)	
Juarranz Sanz et al. (2004) Madrid, Spain 1997–1998	Cases: 196; population-based colorectal cases, identified through a cancer registry Controls: 196; population-based, identified through health care rosters from the same districts of the identified cases; individually matched to cases by age, sex, and geographical region Exposure assessment method: questionnaire; validated, included 72 items, administered by phone, and asked about frequency and portion size; red meat was beef, pork, and lamb	Colon and rectum	Continuous variables (g/day)			Olives, processed meat, organ meat, cherries/strawberries, oranges, raw tomatoes, yogurt, fresh juice
			Red meat	NR	1.026 (1.010–1.040)	
			Trend-test *P* value: 0.002			
			Continuous variables (g/day)			
			Organ meat	NR	1.122 (1.027–1.232)	
			Trend-test *P* value: 0.015			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2004) California and Utah, USA 1997–2001	Cases: 952; population-based rectal cancer cases, identified through a cancer registry and online pathology reports from the Kaiser Permanente Northern California Cancer Registry Controls: 1205; controls were randomly selected from membership lists, social security lists, drivers' licence lists; frequency-matched to cases by sex and 5-y age groups Exposure assessment method: questionnaire; validated, administered in person, and included > 800 items; red meat included ground beef, hamburger, ground beef casseroles, hamburger helper, pot roast, steak, and ham; cooking methods were assessed, and interactions with *NAT2* phenotype and *GSTM1* genotypes were assessed	Rectum	Red meat (servings/wk)			
			Men:			
			< 2.9	156	1.00	
			≥ 2.9 to < 6.1	188	1.10 (0.82–1.48)	
			≥ 6.1	212	1.08 (0.77–1.51)	
			Red meat (servings/wk)			
			Women:			
			< 1.9	112	1.00	
			≥ 1.9 to < 4.2	114	0.93 (0.65–1.31)	
			≥ 4.2	163	1.05 (0.72–1.53)	
			Red meat (servings/wk) by *NAT2* phenotype			
			Men: slow acetylator			
			< 2.9	NR	1.00	
			3.0–6.1r	NR	1.20 (0.77–1.87)	
			> 6.1	NR	0.92 (0.58–0.92)	
			Men: rapid or intermediate acetylator			
			< 2.9	NR	1.16 (0.73–1.84)	
			3.0–6.1	NR	0.86 (0.55–1.34)	
			> 6.1	NR	0.96 (0.57–1.60)	
			Red meat (servings/wk by *NAT2* phenotype)			
			Women: slow acetylator			
			< 1.9	NR	1.00	
			2.0–4.2	NR	0.55 (0.32–0.96)	
			> 4.2	NR	0.70 (0.40–1.23)	
			Women: rapid or intermediate acetylator			
			< 1.9	NR	0.53 (0.30–0.93)	
			2.0–4.2	NR	0.66 (0.38–1.16)	
			> 4.2	NR	0.76 (0.42–1.36)	
			P value for interaction on additive scale = significant			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2004) California and Utah, USA 1997–2001 (cont.)			Highest vs lowest category			
			Men:			
			Red meat (≥ 6.1 vs < 2.9 servings/wk)	212	1.08 (0.77–1.51)	
			Use of red meat drippings (> 52 vs never frequency/yr)	135	1.03 (0.76–1.39)	
			Doneness of red meat (well done vs rare)	187	1.33 (0.98–1.79)	
			Red meat mutagen index (> 468 vs ≤ 104;	175	1.39 (1.00–1.94)	
			Trend-test *P* value for mutagen index: <0.05			
			Highest vs lowest category			Age, BMI, energy intake, dietary fibre, calcium, lifetime physical activity, usual number of cigarettes smoked
			Women:			
			Red meat (≥ 4.2 vs < 1.9 servings/wk)	163	1.05 (0.72–1.53)	
			Use of red meat drippings (> 52 vs never frequency/yr;	97	0.72 (0.51–1.01)	
			Trend-test *P* value: <0.05			
			Doneness of red meat (well done vs rare)	165	1.05 (0.74–1.50)	
			Red meat mutagen index (≥ 624 vs ≤ 104)	72	0.88 (0.57–1.35)	
			Use of red meat drippings (frequency/yr) by *NAT2* phenotype			
			Men: slow acetylator			
			Never	NR	1.00	
			1–52	NR	0.70 (0.47–1.05)	
			> 52	NR	1.12 (0.72–1.75)	
			Men: rapid or intermediate acetylator			
			Never	NR	1.00 (0.68–1.47)	
			1–52	NR	0.70 (0.46–1.07)	
			> 52	NR	0.93 (0.58–1.47)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2004) California and Utah, USA 1997–2001 (cont.)			Use of red meat drippings (frequency/yr) by *NAT2* phenotype			
			Women: slow acetylator			
			Never,	NR	1.00	
			1–52	NR	0.50 (0.30–0.84)	
			> 52	NR	0.40 (0.23–0.68)	
			Women: rapid or intermediate acetylator			
			Never	NR	0.60 (0.37–0.95)	
			1–52	NR	0.52 (0.31–0.85)	
			> 52	NR	0.62 (0.36–1.05)	
			P value for interaction on multiplicative scale < 0.05			
Navarro et al. (2004) Córdoba, Argentina 1994–2000	Cases: 296; hospital-based colorectal cases, identified at hospitals in Córdoba Controls: 597; hospital-based control residents, identified at the same hospitals for acute non-neoplastic conditions unrelated to digestive tract diseases or long-term modifications Exposure assessment method: questionnaire; validated, administered in person, and evaluated frequency and portion size; individual red meats included fatty and lean beef, pork, and bovine viscera; unclear if total red meat included processed meats	Colon and rectum	Red meat intake (g/day), darkly browned vs no preference			Sex, age, BMI, smoking habit, socioeconomic status
			Barbecued red meat	176	2.85 (1.97–4.10)	
			Trend-test *P* value: <0.05			
			Roasted red meat	110	1.08 (0.76–1.54)	
			Pan–cooked red meat	167	2.44 (1.71–3.47)	
			Trend-test *P* value: <0.05			
			Fried red meat	145	1.74 (1.23–2.45)	
			Trend-test *P* value: <0.05			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Satia-Abouta et al. (2004) North Carolina, USA 1996–2000	Cases: 613; Controls: 996 see Butler et al. (2003); Exposure assessment method: questionnaire; see Butler et al. (2003); red meat was hamburger, cheeseburger, beef (roast, steak, sandwiches), beef stew, pot pie, liver (including chicken liver), pork, beef, veal, lamb, roast beef, meatloaf, pork roast, tacos or burritos, spaghetti meat sauce, hot dogs, bacon, ham, sausage, bologna, and lunchmeats	Colon	Total red meat intake (frequency/wk), quartiles; Caucasians			Potential confounders examined included age, sex, education, BMI, smoking history, physical activity, family history of colon cancer, NSAID use, fat, carbohydrates, dietary fibre, vitamin C, vitamin E, β-carotene, calcium, folate, fruits, vegetables; covariables ≥ 10% change in parameter coefficient included in model
			Q1	60	1.0	
			Q2	68	1.0 (0.7–1.6)	
			Q3	89	1.2 (0.8–1.9)	
			Q4	120	1.1 (0.7–1.8)	
			Trend-test *P* value: 0.61			
			Total red meat intake (frequency/wk), quartiles; African Americans			
			Q1	60	1.0	
			Q2	68	0.7 (0.4–1.1)	
			Q3	89	0.8 (0.5–1.4)	
			Q4	120	0.7 (0.4–1.3)	
			Trend-test *P* value: 0.61			
Barrett et al. (2003) Dundee, Perth, Leeds, and York, United Kingdom 1997–2001	Cases: 484; hospital-based, identified from hospitals in Dundee, Perth, Leeds, and York, United Kingdom Controls: 738; hospital-based, identified from the practice lists of the cases' general practitioners; matched to cases by age and sex Exposure assessment method: questionnaire; validated, administered in person, and included 132 items; red meat was beef (roast, steak, mince, stew or casserole), beef burgers, pork (roast, chops, stew, or slices), and lamb (roast, chops, or stew)	Colon and rectum	Red meat (servings/mo, quartiles) by *NAT2* genotype			Smoking status; BMI at age 40 yr; the main effects of fruits, vegetables, red meat, and the polymorphism of interest, plus the fruit–vegetable interaction, and the interaction between the polymorphism and the dietary factor of interest
			Men:			
			Slow acetylators			
			Q1	NR	1.00	
			Q2	NR	0.85 (0.42–1.74)	
			Q3	NR	1.22 (0.63–2.37)	
			Q4	NR	1.49 (0.77–2.90)	
			Fast acetylators			
			Q1	NR	1.00	
			Q2	NR	1.57 (0.71–3.44)	
			Q3	NR	1.73 (0.83–3.63)	
			Q4	NR	1.65 (0.77–3.55)	
			P value for interaction: 0.46			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Barrett et al. (2003) Dundee, Perth, Leeds, and York, United Kingdom 1997–2001 (cont.)			Red meat (servings/mo, quartiles) by *NAT2* genotype			
			Women:			
			Slow acetylators			
			Q1	NR	1.00	
			Q2	NR	1.16 (0.55–2.42)	
			Q3	NR	1.02 (0.46–2.27)	
			Q4	NR	2.14 (0.99–4.66)	
			Fast acetylators			
			Q1	NR	1.00	
			Q2	NR	0.93 (0.30–2.87)	
			Q3	NR	2.22 (0.73–6.78)	
			Q4	NR	2.81 (1.00–7.89)	
			P value for interaction: 0.35			
Turner et al. (2004) Dundee, Perth, Leeds, and York, United Kingdom 1997–2001	Cases: 484; hospital-based, identified from hospitals in Dundee, Perth, Leeds, and York, United Kingdom Controls: 738; hospital-based, identified from the practice lists of the cases' general practitioners; matched to cases by age and sex Exposure assessment method: questionnaire; validated, administered in person, and included 132 items; red meat was beef (roast, steak, mince, stew, or casserole), beef burgers, pork (roast, chops, stew, or slices), and lamb (roast, chops, or stew)	Colon and rectum	Red meat (servings/mo), quartiles			The matching variables age, sex, energy intake
			Q1 (≤ 6)	88	1.0	
			Q2 (> 6 to ≤ 14)	87	1.0 (0.7–1.7)	
			Q3 (> 14 to ≤ 19)	146	1.7 (1.2–2.6)	
			Q4 (> 19)	153	2.3 (1.6–3.5)	
			Trend-test *P* value: 0.0001			
			Red meat (highest vs lowest intake by *GSTP1* Ile105Val			Smoking status; BMI at age 40 yr; the main effects of fruits, vegetables, red meat, and the polymorphism of interest, plus the fruit–vegetable interaction, and the interaction between the polymorphism and the dietary factor of interest
			Homozygous rare variant	103	1.0 (0.4–2.1)	
			Heterozygous	401	1.9 (1.3–2.8)	
			Homozygous common variant	367	2.3 (1.5–3.5)	
			Trend-test *P* value: 0.02			
			Red meat (highest vs lowest intake) by *NQO1*			
			Deficient	48	0.3 (0.1–1.0)	
			Intermediate	307	2.7 (1.7–4.3)	
			Fast	516	1.8 (1.2–2.5)	
			Trend-test *P* value: 0.04			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2005) California and Utah, USA Colon, 1991–1994; rectum, 1997–2002	Cases: 2298; Controls: 2749; Exposure assessment method: questionnaire; see Murtaugh et al. (2004) and Kampman et al. (1999); interactions with *CYP1A1* and *GSTM1* genotypes were assessed	Colon and rectum	Highest vs lowest category for *CYP1A1*1* allele			Age, BMI, energy intake, dietary fibre, calcium, lifetime physical activity, usual number of cigarettes smoked
			Men:			
			Red meat (> 6.1 vs ≤ 3.1 servings/wk)	NR	0.95 (0.73–1.25)	
			Use of red meat drippings, (> 36 vs never frequency/yr)	NR	0.90 (0.72–1.12)	
			Doneness of red meat (well done vs rare)	NR	1.37 (1.06–1.77)	
			Red meat mutagen index (> 468 vs ≤ 104)	NR	1.05 (0.79–1.39)	
			Highest vs lowest category for *CYP1A1*1* allele			
			Women:			
			Red meat (> 4.2 vs < 1.9 servings/wk)	NR	1.05 (0.77–1.43)	
			Use of red meat drippings (> 36 vs never frequency/yr)	NR	0.72 (0.55–0.93)	
			Doneness of red meat (well done vs rare)	NR	0.90 (0.67–1.19)	
			Red meat mutagen index (> 624 vs ≤ 104)	NR	0.68 (0.47–0.99)	
			Highest vs lowest category for *CYP1A1* any *2 variant			
			Men:			
			Red meat (> 6.1 vs ≤ 3.1 servings/wk)	NR	0.87 (0.61–1.25)	
			Use of red meat drippings (> 36 vs never frequency/yr)	NR	0.84 (0.61–1.16)	
			Doneness of red meat (well done vs rare)	NR	1.22 (0.87–1.70)	
			Red meat mutagen index (> 468 vs ≤ 104)	NR	0.86 (0.58–1.27)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2005) California and Utah, USA Colon, 1991–1994; rectum, 1997–2002 (cont.)			Highest vs lowest category for *CYP1A1* any *2 variant			
			Women:			
			Red meat (> 4.2 vs < 1.9 servings/wk)	NR	1.24 (0.82–1.88)	
			Use of red meat drippings (> 36 vs never frequency/yr)	NR	0.79 (0.53–1.17)	
			Doneness of red meat (well done vs rare)	NR	1.05 (0.72–1.53)	
			Red meat mutagen index (> 624 vs ≤ 104)	NR	0.77 (0.44–1.33)	
Chen et al. (2006) China 1990–2002	Cases: 140; population-based colorectal cases Controls: 343; population-based Exposure assessment method: questionnaire; unclear validation, administered in person, and assessed portion size and frequency; red meat was pork, beef, and lamb; assessed genotypes in *SULT1A1*	Rectum	Red meat (kg/yr)			Age, sex, smoking, colorectal cancer history
			≤ 5	17	1.00	
			> 5	40	0.85 (0.40–1.80)	
		Colon	Red meat (kg/yr)			
			≤ 5	13	1.00	
			> 5	70	1.40 (0.70–2.82)	
Hu et al. (2007) Canada 1994–1997	Cases: 1723; cases identified via the National Enhanced Cancer Surveillance System (NECSS), including the provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Prince Edward Island, Nova Scotia, and Newfoundland Controls: 3097; population-based controls from each province, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; validated FFQ with 70 items, administered by mail; red meat was beef, pork, or lamb; also reported on hamburger	Proximal colon	Beef, pork, and lamb intake as main dish (servings/wk), tertiles			10-yr age group, province, BMI (< 25.0, 25.0–29.9, ≥ 30.0), strenuous activity (h/mo), total energy intake.
			Men:			
			T1	141	1.0	
			T2	175	1.2 (0.9–1.6)	
			T3	58	1.5 (1.0–2.4)	
			Trend-test *P* value: 0.05			
			Hamburger intake (servings/wk), tertiles			
			Men:			
			T1	50	1.0	
			T2	257	2.3 (1.5–3.4)	
			T3	71	2.1 (1.3–3.5)	
			Trend-test *P* value: 0.006			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2007) Canada 1994–1997 (cont.)		Proximal colon	Beef, pork, and lamb intake as main dish (servings/wk), tertiles			
			Women:			
			T1	180	1.0	
			T2	130	1.1 (0.8–1.5)	
			T3	36	1.1 (0.7–1.8)	
			Trend-test *P* value: 0.45			
			Hamburger intake (servings/wk), tertiles			
			Women:			
			T1	61	1.0	
			T2	236	1.2 (0.8–1.6)	
			T3	44	1.2 (0.7–1.9)	
			Trend-test *P* value: 0.47			
		Distal colon	Beef, pork, and lamb intake as main dish (servings/wk), tertiles			
			Men:			
			T1	235	1.0	
			T2	241	0.9 (0.7–1.2)	
			T3	86	1.1 (0.8–1.6)	
			Trend-test *P* value: 0.94			
		Distal colon	Hamburger intake (servings/wk), tertiles			
			Men:			
			T1	91	1.0	
			T2	362	1.4 (1.0–1.9)	
			T3	110	1.4 (0.9–2.0)	
			Trend-test *P* value: 0.11			
		Distal colon	Beef, pork, and lamb intake as main dish (servings/wk), tertiles			
			Women:			
			T1	191	1.0	
			T2	163	1.3 (1.0–1.7)	
			T3	52	1.2 (0.8–1.9)	
			Trend-test *P* value: 0.16			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2007) Canada 1994–1997 (cont.)		Distal colon	Hamburger intake (servings/wk), tertiles			
			Women:			
			T1	76	1.0	
			T2	273	1.2 (0.8–1.7)	
			T3	57	1.2 (0.7–2.0)	
			Trend-test *P* value: 0.42			
Kimura et al. (2007) Fukuoka, Japan 2000–2003	Cases: 840; hospital-based cases admitted to hospitals in Fukuoka and three adjacent areas Controls: 833; population-based controls from 15 different areas, sampled based on frequency of age and sex of cases Exposure assessment method: questionnaire; validated, administered in person, and included 148 items; reported on beef and pork combined	Colon and rectum	Beef/pork, likely fresh meat (quintile median, g/day)			Age, sex, residential area, BMI 10 yr before, parental colorectal cancer, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium, dietary fibre
			Q1 (14.2)	142	1.00	
			Q2 (27.3)	188	1.35 (0.98–1.85)	
			Q3 (37.4)	161	1.28 (0.92–1.79)	
			Q4 (48.6)	140	0.03 (0.73–1.44)	
			Q5 (70.1)	151	1.13 (0.80–1.61)	
			Trend-test *P* value: 0.94			
		Proximal colon	Beef/pork (g/day), quintiles			
			Q1	23	1.00	
			Q2	48	2.21 (1.26–3.88)	
			Q3	41	2.00 (1.12–3.58)	
			Q4	35	1.67 (0.91–3.06)	
			Q5	30	1.44 (0.76–2.71)	
			Trend-test *P* value: 0.64			
		Distal colon	Beef/pork (g/day), quintiles			
			Q1	54	1.00	
			Q2	65	1.24 (0.80–1.94)	
			Q3	46	0.94 (0.58–1.52)	
			Q4	41	0.80 (0.49–1.31)	
			Q5	56	1.23 (0.75–2.00)	
			Trend-test *P* value: 0.97			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kimura et al. (2007) Fukuoka, Japan 2000–2003 (cont.)		Rectum	Beef/pork (g/day), quintiles			
			Q1	63	1.00	
			Q2	73	1.18 (0.78–1.79)	
			Q3	70	1.18 (0.77–1.81)	
			Q4	57	0.88 (0.56–1.38)	
			Q5	64	1.01 (0.64–1.60)	
			Trend-test *P* value: 0.64			
Küry et al. (2007) Pays de la Loire region, France 2002–2006	Cases: 1023; hospital-based colorectal cases with a family history of colorectal cancer, diagnosed at an age < 40 yr Controls: 1121; hospital-based, identified from health examination centres or the University Hospital of Nantes; matched to cases by sex, age, and geography Exposure assessment method: questionnaire; unclear validation and administered in person; red meat was beef and lamb; assessed genotypes in *CYP1A2*, *CYP2E1*, *CYP1B1*, and *CYP2C9*	Colon and rectum	Red meat intake (times/wk)			The matching variables age, sex, residence
			1– 4	NR	1.00	
			≥ 5	NR	2.81 (1.52–5.21)	
			Trend-test *P* value: 0.001			
Cotterchio et al. (2008) Ontario, Canada 1997–2000	Cases: 1095; population-based colorectal cases, identified through the Ontario Cancer Registry; familial cases were included Controls: 1890; population-based, identified through random digit dialling Exposure assessment method: questionnaire; not validated and self-administered; total red meat was beef, steak, hamburger, prime rib, ribs, beef hot dogs, beef-based processed meat, veal, pork, bacon, pork sausage, ham, lamb, and venison; assessed frequency only, cooking methods, and polymorphisms in 15 xenobiotic-metabolizing enzymes (CYPs, GSTs, UGTs, SULT, NATs, mEH, AHR), *CYP2C9*, and *NAT2*	Colon and rectum	Total red meat (servings/wk)			Age
			0–2.0	307	1.00	
			2.1–3.0	224	1.37 (1.10–1.70)	
			3.1–5.0	265	1.45 (1.18–1.78)	
			> 5.0	276	1.67 (1.36–2.05)	
			Total red meat doneness (servings/wk)			
			≤ 2 "rare/regular"	234	1.00	
			≤ 2 "well done"	278	1.23 (0.99–1.53)	
			> 2 "rare/regular"	211	1.24 (0.98–1.56)	
			> 2 "well done"	321	1.57 (1.27–1.93)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cotterchio et al. (2008) Ontario, Canada 1997–2000 (cont.)			Total red meat doneness (servings/wk) *CYP1B1* combined variance (derived)			
			Wildtype (> 2 "well done" vs ≤ 2 "rare/ regular")	NR	4.09 (2.17–7.71)	
			Increased activity (> 2 "well done" vs ≤ 2 "rare/regular")	NR	1.52 (1.15–2.01)	
			P value for interaction = 0.04			
			Total red meat doneness (servings/wk) *SULT1A1*–638			
			GG (> 2 "well done" vs ≤ 2 "rare/regular")	NR	2.43 (1.66–3.57)	
			AA/GA (> 2 "well done" vs ≤ 2 "rare/ regular")	NR	1.39 (0.99–1.95)	
			P value for interaction = 0.03			
Saebø et al. (2008) Norway NR	Cases: 198; population-based colorectal cases, identified through a screening study Controls: 222; population-based, identified through a screening study and determined to be polyp-free by flexible sigmoidoscopy Exposure assessment method: questionnaire; unclear validation; red meat was not defined; assessed polymorphism in *CYP1A2*	Colon and rectum	Total red meat (g/day)			Age, sex, ever-smoking
			≤ 22.5	74	1.00	
			> 22.5 to ≤ 45.0	48	1.07 (0.54–2.14)	
			> 45.0	23	1.58 (0.71–3.47)	
			Doneness level			
			Rare/medium	45	1.00	
			Well done	73	0.69 (0.36–1.32)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2009) USA 1997–2002	Cases: 577; population-based colorectal cases, identified through cancer registries from California, North Carolina, Arizona, Minnesota, New Hampshire, and Colorado Controls: 361; unaffected siblings of cases who were older than cases Exposure assessment method: questionnaire; not validated and assessed frequency and cooking methods; total red meat was beef, steak, hamburger, prime rib, ribs, veal, lamb, bacon, pork, pork in sausages, or venison	Colon and rectum	Total red meat (servings/wk)			None
			≤ 3	131	1.00	
			> 3	177	1.8 (1.3–2.5)	
			Trend-test *P* value: 0.001			
		Colon	Total red meat (servings/wk)			
			≤ 3	79	1.00	
			> 3	106	1.8 (1.1–2.8)	
			Trend-test *P* value: 0.019			
		Rectum	Total red meat (servings/wk)			
			≤ 3	40	1.00	
			> 3	44	1.3 (0.6–2.5)	
			Trend-test *P* value: 0.517			
		Colon and rectum	Doneness of total red meat (estimated from outside colour).)			
			Light or medium browned	214	1.00	
			Heavily browned	94	1.1 (0.8–1.6)	
			Trend-test *P* value: 0.559			
			Test of heterogeneity, colon vs rectum (*P* = 0.613)			
		Colon and rectum	Doneness of red meat (estimated from insidecolour)			
			Red or pink	153	1.00	
			Brown	155	1.2 (0.8–1.6)	
			Trend-test *P* value: 0.362			
			Test of heterogeneity, colon vs rectum (*P* = 0.351)			
		Rectum	Doneness of red meat (estimated from outside colour); among carriers of XPD Lys751Lys			
			Light or medium browned	22	1.00	
			Heavily browned	13	3.8 (1.1–13.)	
			Trend-test *P* value = 0.037			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Morita et al. (2009) Fukuoka, Japan 2000–2003	Cases: 685; hospital-based colorectal cases Controls: 833; population-based Exposure assessment method: questionnaire; validated, administered by in-person interview, and included 148 items; red meat was beef and pork	Colon	Red meat intake (median, g/2000 kcal per day); among carriers of 0 alleles for *CYP2E1* 96-bp insertion			Sex, age, area, cigarette smoking, BMI, type of job, physical activity, parental colorectal cancer
			21	88	1.00	
			38	73	0.79 (0.52–1.18)	
			63	63	0.75 (0.48–1.16)	
			Trend-test *P* value: 0.18			
			Red meat intake (median, g/2000 kcal per day); among carriers of 1 or 2 alleles for *CYP2E1* 96-bp insertion			
			21	46	1.00	
			38	56	1.44 (0.85–2.42)	
			63	55	1.42 (0.82–2.43)	
			Trend-test *P* value: 0.21			
			P value for interaction = 0.03			
Squires et al. (2010) Newfoundland and Labrador, Canada 1999–2003	Cases: 518; population-based colorectal cases, identified through a cancer registry Controls: 686; population-based, identified through random digit dialling; frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation of local foods, administered by mail, and included 169 items. Total red meat was beef, steak, hamburger, prime rib, ribs, beef hot dogs, beef-based processed meat, veal, pork, bacon, pork sausage, ham, lamb, and venison; assessed cooking methods	Colon and rectum	Total red meat intake (servings/day)			Age; BMI; smoking status; level of education; intake of vegetables, fruits, folic acid, cholesterol, dietary fibre, saturated fat, alcohol; caloric intake; level of physical activity; NSAID use; presence of inflammatory bowel disease
			Men:			
			≤ 2	125	1.00	
			> 2 to ≤ 3	74	0.96 (0.59–1.57)	
			> 3 to ≤ 5	49	0.95 (0.56–1.59)	
			> 5	53	0.75 (0.43–1.29)	
			Total red meat intake (servings/day)			
			Women:			
			≤ 2	81	1.00	
			> 2 to ≤ 3	41	1.14 (0.61–2.11)	
			> 3 to ≤ 5	40	1.46 (0.73–2.93)	
			> 5	39	1.81 (0.94–3.51)	
			Red meat doneness (servings/day)			
			Women:			
			≤ 2 “rare/regular”	17	1.00	
			≤ 2 “well-done”	106	1.94 (0.81–4.62)	
			> 2 “rare/regular”	10	3.95 (1.02–15.25)	
			> 2 “well-done”	32	3.1 (1.11–8.69)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Squires et al. (2010) Newfoundland and Labrador, Canada 1999–2003 (cont.)			Red meat doneness (servings/day)			
			Men:			
			≤ 2 "rare/regular"	71	1.00	
			≤ 2 "well-done"	132	1.23 (0.76–2.00)	
			> 2 "rare/regular"	18	1.42 (0.61-3.33)	
			> 2 "well-done"	42	1.44 (0.76-2.72)	
Williams et al. (2010) North Carolina, USA 2001–2006	Cases: 945; population-based distal colorectal cancer cases, identified through the North Carolina Central Cancer Registry; African Americans were oversampled Controls: 959; population-based, selected from the North Carolina Department of Motor Vehicles or Centers for Medicare and Medicaid Services Exposure assessment method: questionnaire; validated, administered in person, and included portion size and frequency; red meat was veal, lamb, beef steaks, beef roast, beef mixtures, burgers, ham (not luncheon meat), pork, and ribs	Distal colorectum	Red meat (quartile median, g/day) in Whites			Age, sex, education, BMI, family history, NSAID use, physical activity, calcium, fibre, total energy intake
			Q1 (16.2)	149	1.00	
			Q2 (32.9)	186	1.09 (0.78–1.52)	
			Q3 (53.6)	199	1.05 (0.74–1.49)	
			Q4 (94.8)	186	0.66 (0.43–1.00)	
			Trend-test *P* value: 0.90			
			Red meat (quartile median, g/day) in African Americans			
			Q1 (12.7)	58	1.00	
			Q2 (27.8)	39	0.54 (0.27–1.09)	
			Q3 (45.5)	65	0.83 (0.42–1.63)	
			Q4 (108.6)	63	0.64 (0.27–1.50)	
			Trend-test *P* value: 0.94			
Tabatabaei et al. (2011) Australia 2005–2007	Cases: 567; population-based colorectal cases, identified through the Western Australian Cancer Registry Controls: 713; population-based, identified from electoral rolls; frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation, administered by mail, and included 74 items; total red meat included hamburger/cheeseburger, beef/veal, lamb/mutton, pork chops/ham steaks, bacon, and sausages; assessed cooking methods	Colon and rectum	Total red meat intake (highest vs lowest quartile, servings/wk) by cooking method			BMI, physical activity at ages 35–50 yr, smoking habits, alcohol consumption, fruit and vegetable consumption, supplemental vitamin intake, total energy, fat and fibre consumption, the matching variables age and sex
			Pan-fried	NR	0.80 (0.57–1.13)	
			Trend-test *P* value: 0.27			
			Barbecued	NR	0.89 (0.63–1.24)	
			Trend-test *P* value: 0.17			
			Baked	NR	0.73 (0.53–1.01)	
			Trend-test *P* value: 0.04			
			Stewed	NR	0.95 (0.67–1.33)	
			Trend-test *P* value: 0.53			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Di Maso et al. (2013) Italy and Switzerland 1991–2009	Cases: 2390; hospital-based colorectal cases, identified from hospitals as part of a network of case–control studies Controls: 4943; hospital-based, identified through the same network of hospitals as cases; frequency-matched to cases for variables not specified Exposure assessment method: questionnaire; validated, administered in person, included 77 items, and assessed frequency and serving size; red meat was beef, veal, pork, horse meat, and half of the first course, including meat sauce (e.g. lasagne, pasta/rice with bologna sauce); assessed cooking methods	Colon	Red meat intake (g/day) in men			Age, sex, education, BMI, tobacco use, alcohol drinking, vegetable consumption, fruit consumption, study centre
			< 60	446	1.00	
			60–89	443	1.19 (1.02–1.38)	
			≥ 90	554	1.22 (1.05–1.41)	
			Per 50 g/day increase	NR	1.17 (1.08–1.26)	
			Trend-test *P* value: 0.02			
		Rectum	< 60	268	1.00	
			60–89	279	1.25 (1.04–1.51)	
			≥ 90	380	1.35 (1.12–1.62)	
			Per 50 g/day increase	NR	1.22 (1.11–1.33)	
			Trend-test *P* value< 0.01			
		Rectum	For every 50 g/day increase in red meat by cooking practice			
			Roasting/ grilling	NR	1.24 (1.07–1.45)	
			Boiling/stewing	NR	1.32 (1.10–1.58)	
			Frying/ pan-frying	NR	1.90 (1.38–2.61)	
Hu et al. (2013) Sichuan, China 2010–2012	Cases: 400; hospital-based cases from the Sichuan Cancer Hospital Controls: 400; hospital-based, identified among individuals who underwent routine medical examinations at a health centre; individually matched by sex and age Exposure assessment method: questionnaire; unclear validation; red meat was beef, pork, and lamb; assessed frequency; genotypes for *ADIPOQ*, *UCP2*, and *FABP2* were assessed	Colon and rectum	Red meat (times/wk)			Family per capita annual income, family history of colorectal cancer, sitting (h/day), BMI, smoking habit, alcohol-drinking habit, tea-drinking habit
			≤ 7	144	1.00	
			> 7	256	1.87 (1.39–2.51)	
			Trend-test *P* value< 0.001			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Miller et al. (2013) Pennsylvania, USA 2007–2011	Cases: 989; incident cases, identified through the Pennsylvania State Cancer Registry Controls: 1033; identified through random digit dialling; frequency-matched to cases by age, sex, and race Exposure assessment method: questionnaire; validated, in-person FFQ with 137 items; meat-cooking module was used with the CHARRED database to estimate carcinogens; red meat was beef and pork (hamburger, roast beef, pot roast, roast pork, steak, pork chops, pork or beef spare ribs, liver, meat added to mixed dishes)	Colon and rectum	Red meat intake (g/1000 kcal)			Age, sex, BMI, past NSAID use, total energy, total fruits and vegetables, total poultry
			Q1 (< 8.7)	184	1.00	
			Q2 (8.7–14.5)	217	1.24 (0.92–1.67)	
			Q3 (14.6–22.6)	184	1.05 (0.78–1.43)	
			Q4 (22.7–35.6)	231	1.38 (1.03–1.86)	
			Q5 (> 35.6)	173	1.02 (0.75–1.40)	
			Trend-test *P* value: 0.975			
		Colon	Red meat intake (g/1000 kcal)			
			Q1 (< 8.7)	139	1.00	
			Q2 (8.7–14.5)	146	1.12 (0.81–1.55)	
			Q3 (14.6–22.6)	127	1.00 (0.72–1.40)	
			Q4 (22.7–35.6)	162	1.34 (0.97–1.86)	
			Q5 (> 35.6)	119	1.00 (0.71–1.40)	
			Trend-test *P* value: 0.865			
		Rectum	Red meat intake (g/1000 kcal)			
			Q1 (< 8.7)	42	1.00	
			Q2 (8.7–14.5)	71	1.72 (1.10–2.68)	
			Q3 (14.6–22.6)	55	1.28 (0.81–2.03)	
			Q4 (22.7–35.6)	67	1.61 (1.02–2.52)	
			Q5 (> 35.6)	54	1.21 (0.76–1.94)	
			Trend-test *P* value: 0.997			
		Colon and rectum	Total DiMeIQx (ng/1000 kcal)			Age, sex, BMI, past NSAID use, total energy, total fruits and vegetables
			Q1 (< 0.23)	181	1.00	
			Q2 (0.23–0.67)	185	1.04 (0.77–1.40)	
			Q3 (0.68–1.23)	203	1.09 (0.81–1.47)	
			Q4 (1.24–2.20)	183	1.03 (0.77–1.39)	
			Q5 (> 2.20)	237	1.36 (1.02–1.82)	
			Trend-test *P* value: 0.027			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Miller et al. (2013) Pennsylvania, USA 2007–2011 (cont.)		Colon and rectum	Total MeIQx (ng/1000 kcal)			
			Q1 (< 4.2)	194	1.00	
			Q2 (4.2–8.3)	170	0.90 (0.67–1.22)	
			Q3 (8.4–14.2)	185	0.96 (0.71–1.29)	
			Q4 (14.3–23.8)	197	1.05 (0.78–1.41)	
			Q5 (> 23.8)	243	1.22 (0.91–1.64)	
			Trend-test *P* value: 0.047			
			Total PhIP (ng/1000 kcal)			
			Q1 (< 7.2)	223	1.00	
			Q2 (7.2–17.4)	207	0.97 (0.73–1.29)	
			Q3 (17.4–33.7)	186	0.87 (0.65–1.16)	
			Q4 (33.8–68.3)	190	0.98 (0.73–1.31)	
			Q5 (> 68.3)	183	1.06 (0.79–1.43)	
			Trend-test *P* value: 0.439			
			Total BaP (ng/1000 kcal)			
			Q1 (< 0.32)	264	1.00	
			Q2 (0.32–2.20)	219	0.95 (0.72–1.25)	
			Q3 (2.30–6.60)	152	0.69 (0.52–0.93)	
			Q4 (6.70–19.00)	184	0.92 (0.69–1.23)	
			Q5 (> 19.00)	170	0.90 (0.67–1.21)	
			Trend-test *P* value: 0.906			
			Grilled/barbecued red meat (g/1000 kcal)			Age, sex, BMI, past NSAID use, total energy, total fruits and vegetables, total poultry
			T1 (0)	285	1.00	
			T2 (0.01–4.35)	352	0.84 (0.66–1.06)	
			T3 (> 4.36)	352	0.94 (0.74–1.20)	
			Trend-test *P* value: 0.808			
			Pan-fried red meat (g/1000 kcal)			
			Q1 (< 0.36)	178	1.00	
			Q2 (0.36–1.39)	181	0.97 (0.71–1.31)	
			Q3 (1.40–3.33)	183	0.99 (0.73–1.34)	
			Q4 (3.34–6.79)	188	0.93 (0.69–1.26)	
			Q5 (> 6.79)	259	1.26 (0.93–1.70)	
			Trend-test *P* value: 0.044			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Miller et al. (2013) Pennsylvania, USA 2007–2011 (cont.)		Colon and rectum	Microwaved/baked red meat (g/1000 kcal)			
			Q1 (< 4.65)	213	1.00	
			Q2 (4.65–7.56)	194	0.89 (0.67–1.20)	
			Q3 (7.57–11.40)	196	0.93 (0.69–1.24)	
			Q4 (11.50–18.60)	204	0.97 (0.72–1.30)	
			Q5 (> 18.60)	182	0.87 (0.65–1.17)	
			Trend-test *P* value: 0.533			
			Broiled red meat (g/1000 kcal)			
			No consumption	727	1.00	
			Ever	262	0.99 (0.8–1.22)	
			Trend-test *P* value: 0.891			
			Red meat, rare/medium (g/1000 kcal)			
			T1 (0)	279	1.00	
			T2 (0.01–4.08)	362	0.94 (0.75–1.90)	
			T3 (> 4.08)	348	0.99 (0.79–1.26)	
			Trend-test *P* value: 0.844			
			Well-done/charred red meat (g/1000 kcal)			
			Q1 (< 0.89)	210	1.00	
			Q2 (0.89–2.41)	176	0.77 (0.57–1.03)	
			Q3 (2.42–4.70)	197	0.92 (0.69–1.24)	
			Q4 (4.71–8.96)	204	1.01 (0.75–1.35)	
			Q5 (> 8.96)	202	0.87 (0.64–1.16)	
			Trend-test *P* value: 0.857			
Rosato et al. (2013) Italy and Switzerland 1985–2009	Cases: 329; hospital-based cases with young-onset colorectal cancer (< 45 yr) Controls: 1361; hospital-based, identified from the same hospitals as cases; conditions unrelated to colorectal cancer risk factors or dietary modifications Exposure assessment method: questionnaire; validated and administered in person; red meat was not defined, and unclear if it included processed meat	Colon and rectum	Red meat intake			Age, sex, centre, study, year of interview, education, family history, alcohol, energy intake
			Low	101	1.00	
			Medium	88	0.93 (0.67–1.29)	
			High	140	1.07 (0.79–1.47)	
			Trend-test *P* value: 0.57			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Abu Mweis et al. (2015) Jordan 2010–2012	Cases: 167; hospital-based colorectal cases recruited from five major Jordanian hospitals Controls: 240; hospital-based, identified from hospital personnel, outpatients, visitors, and accompanying individuals; matched by age, sex, occupation, and marital status Exposure assessment method: questionnaire; validated, administered in person, and included 109 items; red meat was not defined	Colon and rectum	Red meat intake (serving/wk) < 1 ≥ 1	 103 51	 1.00 0.64 (0.37–1.11)	Age, sex, total energy, metabolic equivalent, smoking, education level, marital status, work, income, family history of colorectal cancer
Guo et al. (2015) Harbin, China 2008–2013	Cases: 600; hospital-based colorectal cases Controls: 600; hospital-based, identified at the community health centre and individually matched to cases by age and sex Exposure assessment method: questionnaire; non-validated and administered in person; red meat was pork, beef, and lamb; unclear if processed meat was included	Colon and rectum	Red meat (times/wk) ≤ 7 > 7 Trend-test *P* value: 0.001	 NR NR	 1.00 1.54 (1.114–2.424)	BMI, family income, drinking, smoking, regular tea drinking, daily sedentary time, family history of cancer

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002	Cases: 3350; population-based, identified through cancer registries in Ontario, Canada; Hawaii, California, Arizona, North Carolina, New Hampshire, Colorado, Minnesota, USA; cases with familial cases included Controls: 3504; cancer-free siblings of the cases (n = 1759), unaffected spouses of the cases (n = 138), and population-based controls (n = 1607) Exposure assessment method: questionnaire; validated, administered by mail, included 200 items, included portion size and frequency of intake, and used the CHARRED database to estimate carcinogens; red meat was beef, pork, veal, lamb, and game; cooking methods were considered	Colon and rectum	Red meat (g/1000 kcal per day)			Age, BMI, sex, race, saturated fat, dietary fibre, centre, vegetables, physical activity, total caloric intake
			Q1 (0–10.81)	633	1.0	
			Q2 (10.81–16.04)	644	1.0 (0.9–1.2)	
			Q3 (16.04–21.11)	707	1.2 (1.0–1.4)	
			Q4: 21.12–28.19	680	1.2 (1.0–1.4)	
			Q5 (28.19–102.43)	686	1.2 (1.0–1.4)	
			Trend-test P value: 0.085			
		Colon	Red meat (g/1000 kcal per day)			
			Q1 (0–10.81)	396	1.0	
			Q2 (10.81–16.04)	380	1.1 (0.9–1.3)	
			Q3 (16.04–21.11)	429	1.2 (1.0–1.5)	
			Q4 (21.12–28.19)	396	1.2 (1.0–1.4)	
			Q5 (28.19–102.43)	391	1.2 (0.9–1.4)	
			Trend-test P value: 0.152			
		Rectum	Red meat (g/1000 kcal per day)			
			Q1 (0–10.81)	171	1.0	
			Q2 (10.81–16.04)	152	0.8 (0.6–1.0)	
			Q3 (16.04–21.11)	201	1.0 (0.8–1.3)	
			Q4 (21.12–28.19)	179	0.8 (0.7–1.1)	
			Q5 (28.19–102.43)	173	0.8 (0.6–1.0)	
			Trend-test P value: 0.104			
		Colon and rectum	Beef (g/1000 kcal per day)			
			Q1 (0–7.69)	687	1.0	
			Q2 (7.70–11.49)	652	1.0 (0.9–1.2)	
			Q3 (11.49–15.08)	654	1.0 (0.9–1.2)	
			Q4 (12.09–20.06)	672	1.1 (0.9–1.3)	
			Q5 (20.08–83.77)	685	1.1 (0.9–1.3)	
			Trend-test P value: 0.289			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon	Beef (g/1000 kcal per day)			
			Q1 (0–7.69)	426	1.0	
			Q2 (7.70–11.49)	377	9.0 (0.8–1.1)	
			Q3 (11.49–15.08)	396	1.0 (0.8–1.2)	
			Q4 (12.09–20.06)	400	1.1 (0.9–1.3)	
			Q5 (20.08–83.77)	383	1.0 (0.8–1.2)	
			Trend-test *P* value: 0.593			
		Rectum	Beef (g/1000 kcal per day)			
			Q1 (0–7.69)	155	1.0	
			Q2 (7.70–11.49)	185	1.2 (0.9–1.5)	
			Q3 (11.49–15.08)	174	1.1 (0.8–1.4)	
			Q4 (12.09–20.06)	184	1.1 (0.9–1.6)	
			Q5 (20.08–83.77)	209	1.2 (0.9–1.6)	
			Trend-test *P* value: 0.252			
			Test of heterogeneity, colon vs rectum ($P = 0.292$)			
		Colon and rectum	Pork (g/1000 kcal per day)			
			Q1 (0–1.32)	617	1.0	
			Q2 (1.32–3.01)	641	1.0 (0.9–1.2)	
			Q3 (3.01–4.84)	660	1.1 (0.9–1.2)	
			Q4 (4.85–7.44)	743	1.2 (1.0–1.4)	
			Q5 (7.44–49.62)	689	1.1 (1.0–1.3)	
			Trend-test *P* value: 0.069			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon	Pork (g/1000 kcal per day)			
			Q1 (0–1.32)	383	1.0	
			Q2 (1.32–3.01)	388	1.0 (0.8–1.2)	
			Q3 (3.01–4.84)	383	1.0 (0.9–1.2)	
			Q4 (4.85–7.44)	440	1.2 (1.0–1.4)	
			Q5 (7.44–49.62)	398	1.1 (0.9–1.3)	
			Trend-test *P* value: 0.224			
		Rectum	Pork (g/1000 kcal per day)			
			Q1 (0–1.32)	154	1.0	
			Q2 (1.32–3.01)	163	1.0 (0.8–1.3)	
			Q3 (3.01–4.84)	178	1.1 (0.8–1.3)	
			Q4 (4.85–7.44)	207	1.2 (0.9–1.5)	
			Q5 (7.44–49.62)	205	1.1 (0.9–1.5)	
			Trend-test *P* value: 0.133			
		Colon and rectum	Organ meats (g/1000 kcal per day)			
			Q1 (0–0)	884	1.0	
			Q2 0–0)	282	1.2 (1.0–1.4)	
			Q3 (0–0)	650	1.1 (1–1.3)	
			Q4 (0–0.02)	755	1.0 (0.9–1.2)	
			Q5 (0.02–0.64)	779	1.2 (1.0–1.4)	
			Trend-test *P* value: 0.058			
		Colon and rectum	Pan-fried beef steak (g/1000 kcal per day)			
			Q1 (0–0)	1692	1.0	
			Q2 (0.01–0.02)	506	1.0 (0.8–1.1)	
			Q3 (0.02–0.04)	511	1.0 (0.9–1.2)	
			Q4 (0.04–0.99)	619	1.3 (1.1–1.5)	
			Trend-test *P* value: <0.001			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Pan-fried beef steak(g/1000 kcal per day); MMR proficient			
			Q1	469	1.0	
			Q2	129	0.9 (0.7–1.1)	
			Q3	119	0.9 (0.7–1.1)	
			Q4	155	1.0 (1.0–1.5)	
			Trend-test *P* value:0.098			
			Pan-fried beef steak(g/1000 kcal per day); MMR deficient			
			Q1	121	1.0	
			Q2	33	1.0 (0.7–1.5)	
			Q3	35	1.1 (0.8–1.7)	
			Q4	54	1.7 (1.2–2.4)	
			Trend-test *P* value:0.002			
			Test of heterogenicity MMR-deficient vs MMR-proficient (*P*=0.059)			
			Pan-fried hamburger (g/1000 kcal per day)			
			Q1 (0–0)	1297	1.0	
			Q2 (0.01–0.02)	627	0.9 (0.8–1.1)	
			Q3 (0.02–0.05)	707	1.0 (0.9–1.2)	
			Q4 (0.05–0.99)	697	1.1 (0.9–1.2)	
			Trend-test *P* value: 0.209			
			Pan-fried hamburger (g/1000 kcal per day); MMR-proficient			
			Q1 (0–0)	381	1.0	
			Q2 (0.01–0.02)	164	0.8 (0.7–1.0)	
			Q3 (0.02–0.05)	178	1.0 (0.8–1.2)	
			Q4 (0.05–1.37)	150	0.9 (0.7–1.1)	
			Trend-test *P* value: 0.516			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Pan-fried hamburger (g/1000 kcal per day); MMR-deficient			
			Q1 (0–0)	89	1.0	
			Q2 (0.01–0.02)	34	0.8 (0.5–1.2)	
			Q3 (0.02–0.05)	56	1.3 (0.9–1.9)	
			Q4 (0.05–0.99)	63	1.5 (1.0–2.1)	
			Trend-test *P* value: 0.01			
			Test of heterogeneity, MMR-deficient vs MMR-proficient ($P = 0.026$)			
			Oven-broiled beef steak (g/1000 kcal per day)			
			Q1 (0–0)	2145	1.0	
			Q2 (0.01–0.02)	399	1.0 (0.8–1.2)	
			Q3 (0.02–0.04)	397	1.1 (0.9–1.3)	
			Q4 (0.04–1.37)	346	0.9 (0.8–1.1)	
			Trend-test *P* value: 0.742			
			Oven-broiled hamburger (g/1000 kcal per day)			
			Q1 (0–0)	2506	1.0	
			Q2 (0.01–0.02)	241	0.8 (0.7–1.0)	
			Q3 (0.02–0.04)	279	1.0 (0.8–1.2)	
			Q4 (0.04–0.99)	283	1.0 (0.9–1.2)	
			Trend-test *P* value: 0.989			
			Oven-broiled short ribs or spare ribs (g/1000 kcal per day)			
			Q1 (0–0)	2389	1.0	
			Q2 (0.01–0.02)	319	1.2 (1.0–1.5)	
			Q3 (0.02–0.03)	299	1.3 (1.1–1.6)	
			Q4 (0.03–0.99)	306	1.2 (1.0–1.5)	
			Trend-test *P* value: 0.002			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Oven-broiled short ribs or spare ribs (g/1000 kcal per day); MMR-proficient			
			Q1 (0–0)	656	1.0	
			Q2 (0.01–0.02)	91	1.3 (1.0–1.7)	
			Q3 (0.02–0.04)	64	1.1 (0.8–1.5)	
			Q4 (0.04–0.99)	58	1.0 (0.8–1.4)	
			Trend-test *P* value: 0.415			
			Oven-broiled short ribs or spare ribs (g/1000 kcal per day); MMR-deficient			
			Q1 (0–0)	178	1.0	
			Q2 (0.01–0.02)	15	0.9 (0.5–1.5)	
			Q3 (0.02–0.04)	21	1.5 (0.9–2.4)	
			Q4 (0.04–0.99)	26	1.9 (1.2–3.0)	
			Trend-test *P* value: 0.003			
			Test of heterogeneity, MMR-proficient vs MMR-deficient ($P = 0.052$)			
			Grilled beef steak (g/1000 kcal per day)			
			Q1 (0–0)	1314	1.0	
			Q2 (0.01–0.02)	726	0.9 (0.8–1.1)	
			Q3 (0.02–0.04)	677	1.0 (0.8–1.1)	
			Q4 (0.04–0.99)	582	0.9 (0.8–1.0)	
			Trend-test *P* value: 0.212			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Grilled hamburger (g/1000 kcal per day)			
			Q1 (0–0)	1401	1.0	
			Q2 (0.01–0.02)	690	0.9 (0.7–1.0)	
			Q3 (0.02–0.05)	686	0.9 (0.8–1.1)	
			Q4 (0.05–0.99)	542	0.8 (0.7–0.9)	
			Trend-test *P* value: 0.002			
			Grilled short ribs or spare ribs (g/1000 kcal per day)			
			Q1 (0–0)	2239	1.0	
			Q2 (0.01–0.02)	360	0.9 (0.8–1.1)	
			Q3 (0.02–0.03)	344	1.1 (0.9–1.3)	
			Q4 (0.03–0.99)	361	1.1 (0.9–1.3)	
			Trend-test *P* value: 0.166			

AHR, aryl hydrocarbon receptor; BaP, benzo[*a*]pyrene; BMI, body mass index; CHARRED, Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease; CI, confidence interval; CYP, cytochrome P450; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline; FFQ, food frequency questionnaire; GI, gastrointestinal; GST, glutathione S-transferase; h, hour; HAA, heterocyclic aromatic amine; HRT, hormone replacement therapy; kg, kilogram; mEH, microsomal epoxide hydrolase; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; min, minute; MMR, mismatch repair; mo, month; NAT, *N*-acetyltransferase; NOS, not otherwise specified; NR, not reported; NS, not significant; NSAID, nonsteroidal anti-inflammatory drug; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; SEER, Surveillance, Epidemiology, and End Results; SULT, sulfotransferase; UGT, UDP glucuronosyltransferase; wk, week; yr, year

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Macquart-Moulin et al. (1986) Marseille, France 1979–1984	Cases: 399; hospital-based colorectal cases Controls: 399; hospital-based, identified from centres treating injuries or trauma; no GI disease, no alcohol-related diseases, and matched to cases by sex and age Exposure assessment method: questionnaire; unknown validation, administered in person, included 158 items, and considered frequency and portion size; processed meat was ham, salami, sausages, and pâté	Colon and rectum	Processed meats (percentiles)			Age, sex, weight, total calories
			Q1	112	1.00	
			Q2 (25th)	109	1.31	
			Q3 (50th)	90	0.88	
			Q4 (75th)	88	0.89	
			Trend-test *P* value: 0.22			
Tuyns et al. (1988) Belgium 1978–1982	Cases: 818; population-based cases, identified through treatment centres Controls: 2851; population-based Exposure assessment method: questionnaire; validated, administered in person, and captured frequency and serving size; processed meat was "charcuterie"	Colon	"Charcuterie" (g/wk)			Age, sex, province
			0	NR	1.00	
			>0–50	NR	1.16	
			>50–125	NR	0.83	
			>125	NR	0.90	
			Trend-test *P* value: 0.26			
		Rectum	"Charcuterie" (g/wk)			
			0	NR	1.00	
			>0–50	NR	1.38	
			>50–125	NR	0.94	
			>125	NR	0.98	
			Trend-test *P* value: 0.63			
Benito et al. (1990) Majorca, Spain 1984–1988	Cases: 286; population-based colorectal cases in a case–control study Controls: 498; population-based, identified from the electoral census and frequency-matched to cases by age and sex; hospital-based, selected from ophthalmology and orthopaedic clinics from hospitals where the majority of cases were identified; Exposure assessment method: questionnaire; not validated, included 99 items, and administered in person; exposure definition was processed meat including all types of cured meat and meats processed with other animal products, such as blood and fats	Colon and rectum	Processed meat (intake per mo), quartiles			Age, sex, weight 10 yr before interview
			Q1	22	1.00	
			Q2	89	1.35	
			Q3	94	1.42	
			Q4	81	1.36	
			Trend-test *P* value: 0.4			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Gerhardsson de Verdier et al. (1991) Stockholm, Sweden 1986–1988	Cases: 559; population-based colorectal cases, identified through local hospitals and a regional cancer registry Controls: 505; population-based, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation, self-administered, and included 55 items; processed meat was bacon/smoked ham and sausage assessed separately; assessed cooking methods	Colon	Processed meat intake (Tertile 3 vs T1, i.e. > 1 time/wk vs more seldom)			Year of birth, sex, fat intake
			Bacon/smoked ham	84	1.3 (0.8–1.9)	
			Trend-test *P* value = 0.34			
			Sausage, fried	90	1.0 (0.6–1.4)	
			Trend-test *P* value = 0.91:			
			Sausage, oven-roasted	12	1.2 (0.5–2.8)	
			Trend-test *P* value = 0.36			
			Sausage, boiled	57	1.4 (0.9–2.2)	
			Trend-test *P* value = 0.04			
		Rectum	Processed meat intake (> 1 time/wk vs more seldom)			
			Bacon/smoked ham	53	1.7 (1.1–2.8)	
			Trend-test *P* value = 0.025			
			Sausage, fried	71	1.5 (0.9–2.4)	
			Trend-test *P* value = 0.093			
			Sausage, oven-roasted	13	2.1 (0.9–4.9)	
			Trend-test *P* value = 0.038			
			Sausage, boiled	53	3.0 (1.8–4.9)	
			Trend-test *P* value: <0.001			
Iscovich et al. (1992) La Plata, Argentina 1985–1986	Cases: 110; hospital-based, identified through local hospitals Controls: 220; population-based, identified from neighbourhoods of cases and matched to cases by sex; controls with conditions that may have affected diet were excluded Exposure assessment method: questionnaire; unclear validation, administered in person, and included 140 items; processed meat was sausage, mortadella, salami (with skin), ham, and cooked skinless meat	Colon	Processed meat intake (fat with skin), quartiles			Matching variables
			Q1	NR	1.00	
			Q2	NR	0.76 (0.38–1.52)	
			Q3	NR	0.63 (0.28–1.41)	
			Q4	NR	0.45 (0.23–0.90)	
			Trend-test *P* value: 0.017			
			Processed meat intake (lean), quartiles			
			Q1	NR	1.00	
			Q2	NR	0.73 (0.36–1.49)	
			Q3	NR	0.50 (0.20–1.24)	
			Q4	NR	0.38 (0.19–0.75)	
			Trend-test *P* value: 0.002			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Steinmetz and Potter (1993) Adelaide, Australia 1979–1980	Cases: 220; population-based colon cases, identified via the South Australian Cancer Registry Controls: 438; population-based; two controls per case selected via the electoral roll and individually matched to cases by age and sex Exposure assessment method: questionnaire; validated, self-administered, and included 141 items; processed meat was grilled bacon, fried bacon, grilled pork sausage, fried pork sausage, grilled beef sausage, fried beef sausage, sausage roll, cold meat (e.g. ham, "fritz"), and spicy meat (e.g. salami)	Colon	Processed meat intake (servings/wk), quartiles Women: Q1 (≥ 1.4) Q2 (1.5–2.8) Q3 (2.9–4.3) Q4 (≥ 4.3) Processed meat intake (servings/wk), quartiles Men: Q1 (≤ 2.2) Q2 (2.3–4.3) Q3 (4.4–7.6) Q4 (≥ 7.7)	 NR NR NR NR NR NR NR NR	 1.00 0.54 (0.25–1.23) 0.81 (0.37–1.77) 0.77 (0.35–1.68) 1.00 0.69 (0.35–1.37) 0.68 (0.35–1.34) 1.03 (0.55–1.95)	Age at first live birth, Quetelet index, alcohol intake, the matching variable age Occupation, Quetelet index, alcohol intake for males, the matching variable age
Centonze et al. (1994) Southern Italy 1987–1989	Cases: 119; population-based colorectal cases, identified from a population-based cancer registry Controls: 119; population-based, matched to cases by age, sex, and general practitioner Exposure assessment method: questionnaire; unclear validation, administered by in-person interview, and included 70 food items; processed meat was sausage, ham, and tinned meat	Colon and rectum	Processed meat (g/day) <2 ≥3	 66 53	 1.00 1.01 (0.57–1.69)	Age, sex, level of education, smoking status, modifications of diet in the past 10 yr
Lohsoonthorn and Danvivat (1995) Bangkok, Thailand NR	Cases: 279; hospital-based colorectal cases Controls: 279; hospital-based, individually matched to cases by sex, age, admission period, and hospital; included cancer patients with cancer in other organs Exposure assessment method: questionnaire; unclear validation and number of items asked; assessed frequency only; processed meat (individual types only) was bacon, salted beef, and sausage	Colon and rectum	Bacon consumption (times/mo) < 5 6– ≥ 10 Trend-test *P* value: 0.82 Salted beef consumption (times/mo) < 5 6– ≥ 10 Trend-test *P* value: 0.93 Sausage consumption (times/mo) < 5 6– ≥ 10 Trend-test *P* value: 0.79	 267 12 184 95 247 32 	 1.00 12.49 (1.68–269) 1.00 0.97 (0.67–1.39) 1.00 1.26 (0.71–2.25) 	Not specified

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (1997) Montevideo, Uruguay 1993–1995	Cases: 250; hospital-based colorectal cases Controls: 500; hospital-based, identified at the same hospitals as the cases and had a variety of disorders unrelated to tobacco smoking, alcohol, or diet Exposure assessment method: questionnaire; unclear validation, administered in person, and included 60 items; unclear what was included in processed meat; assessed cooking methods	Colon and rectum	Processed meat, quartiles			Age, residence, education, family history of colon cancer in a first-degree relative, BMI, vegetable and dessert intake
			Men:			
			Q1	NR	1.00	
			Q2	NR	1.19 (0.65–2.15)	
			Q3	NR	0.70 (0.39–1.25)	
			Q4	NR	0.75 (0.40–1.37)	
			Trend-test *P* value: 0.17			
			Processed meat, quartiles			
			Women:			
			Q1	NR	1.00	
			Q2	NR	0.81 (0.39–1.65)	
			Q3	NR	0.93 (0.44–1.95)	
			Q4	NR	1.35 (0.65–2.82)	
			Trend-test *P* value: 0.37			
		Colon	Processed meat, quartiles			
			Men:			
			Q1	NR	1.00	
			Q2	NR	1.68 (0.77–3.66)	
			Q3	NR	1.09 (0.50–2.39)	
			Q4	NR	1.21 (0.55–2.66)	
			Trend-test *P* value: 0.99			
			Processed meat, quartiles			
			Women:			
			Q1	NR	1.00	
			Q2	NR	0.64 (0.27–1.49)	
			Q3	NR	0.87 (0.37–2.03)	
			Q4	NR	1.37 (0.59–3.19)	
			Trend-test *P* value: 0.36			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (1997) Montevideo, Uruguay 1993–1995 (cont.)		Rectum	Processed meat, quartiles			
			Men:			
			Q1	NR	1.00	
			Q2	NR	0.98 (0.47–2.04)	
			Q3	NR	0.51 (0.24–1.09)	
			Q4	NR	0.54 (0.25–1.17)	
			Trend-test *P* value: 0.04			
			Processed meat, quartiles			
			Women:			
			Q1	NR	1.00	
			Q2	NR	1.10 (0.36–3.33)	
			Q3	NR	0.90 (0.26–3.09)	
			Q4	NR	1.19 (0.36–3.92)	
			Trend-test *P* value: 0.85			
Faivre et al. (1997) Burgundy, France 1985–1990	Cases: 171; population-based colorectal cases, identified through a registry Controls: 309; population-based; no more information was provided Exposure assessment method: questionnaire; validated, administered in person, included 39 items, and queried frequency and portion sizes; no details were provided for processed meat and delicatessen; pâtés and meat spreads were included	Colon and rectum	Processed meat and delicatessen			Age, sex, caloric intake
			NR	NR	3.0 (2.1–4.8)	
			Trend-test *P* value: <0.001			
Fernandez et al. (1997) Province of Pordenone, Italy 1985–1992	Cases: 112; cases with a family history of colorectal cancer; Controls: 108 controls; controls with a family history of colorectal cancer; Exposure assessment method: questionnaire; data on salami/sausage, raw ham and ham intake	Colon and rectum	Processed meat intake (highest vs lowest tertile, times/wk)			Age, sex, area of residence
			Raw ham	NR	2.1 (0.9–4.9)	
			Trend-test *P* value: < 0.05			
			Ham	NR	2.6 (1.0–6.8)	
			Trend-test *P* value: < 0.05			
			Canned meat	NR	1.9 (1.0–3.3)	
			Trend-test *P* value: <0.05			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Franceschi et al. (1997) Italy 1992–1996	Cases: 1953; hospital-based colorectal cases, identified at multiple sites Controls: 4154; hospital-based, identified in the same catchment areas of cases; included acute non-neoplastic, non-gynaecological conditions unrelated to hormonal or digestive tract diseases or to long-term modifications of diet Exposure assessment method: questionnaire; validated, administered in person, and included 79 items; processed meat was not defined	Colon and rectum	Processed intake (servings/wk), quintiles			Age, sex, centre, education, physical activity, total energy intake
			Q1	NR	1.00	
			Q2	NR	1.21 (1.03–1.42)	
			Q3	NR	1.06 (0.89–1.26)	
			Q4	NR	1.24 (1.02–1.49)	
			Q5	NR	1.02 (0.84–1.24)	
			Trend-test *P* value: 0.13			
		Colon	Processed meat intake			
			Increase of 1 serving/day	NR	1.08 (0.87–1.36)	
		Rectum	Processed meat intake			
			Increase of 1 serving/day	NR	0.78 (0.57–1.06)	
		Colon and rectum	Processed meat intake			
			Increase of 1 serving/day	NR	0.97 (0.79–1.18)	
Norat et alt al. (1997) Hawaii, USA 1987–1991	Cases: 1192; population-based cases, identified through the Hawaii Tumor Registry; cases included Japanese, Caucasian (White), Filipino, Hawaiian, and Chinese patients Controls: 1192; population-based, identified through the Hawaii State Department of Health and individually matched to each case by sex, ethnicity, and age Exposure assessment method: questionnaire; validated, administered in person, and included 280 items; processed meat was luncheon meat, salami, wieners, sausage, spam, and bacon	Colon and rectum	Processed meat intake, quartiles			Age; family history of colorectal cancer; alcoholic drinks per wk; pack-years; lifetime recreational activity; BMI 5 yr ago; caloric, dietary fibre, calcium intakes
			Men:			
			Q1	NR	1.0	
			Q2	NR	1.7	
			Q3	NR	2.2	
			Q4	NR	2.3 (1.5–3.4)	
			Trend-test *P* value: 0.001			
			Processed meat intake, quartiles			
			Women: Q1	NR	1.0	
			Q2	NR	0.8	
			Q3	NR	1.1	
			Q4	NR	1.2 (0.8–2.0)	
			Trend-test *P* value: 0.2			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Boutron-Ruault et al. (1999) Burgundy, France 1985–1990	Cases: 171; population-based, identified from GI and surgery departments in conjunction with a registry of digestive cancers Controls: 309; population-based, identified from a census list and frequency-matched to cases by age and sex Exposure assessment method: questionnaire; validated and administered in person; processed meat was "delicatessen"	Colon and rectum	Intake of delicatessen (g/day), quartiles Q1 Q2 Q3 Q4 Trend-test *P* value: 0.01	 NR NR NR NR	 1.0 1.6 (0.9–2.9) 1.2 (0.6–2.2) 2.4 (1.3–4.5)	Age, sex, caloric intake
Kampman et al. (1999) California, Utah, and Minnesota, USA 1991–1994	Cases: 1542; cases identified through the Kaiser Permanente Medical Care Program of Northern California, Utah, and metropolitan twin cities area in Minnesota Controls: 1860; population-based, frequency-matched to cases by sex and age; identified using membership lists of the Kaiser Permanente Medical Care Program, random digit dialling, drivers' licence and identification lists, and Health Care Financing Administration forms Exposure assessment method: questionnaire; exposure definition, validated, in-person interview, and > 800 items; processed meat was bacon, sausages, and cold cuts; assessed cooking methods and mutagen index	Colon	Processed meat (servings/wk) Men: ≤ 0.5 0.6–1.0 1.1–1.8 1.9–3.1 > 3.1 Processed meat (servings/wk) Women: ≤ 0.2 0.3–0.5 0.6–0.9 1.0–1.7 > 1.7	 NR NR NR NR NR NR NR NR NR	 1.0 1.1 (0.8–1.6) 1.2 (0.9–1.8) 1.3 (1.0–1.8) 1.4 (1.0–1.9) 1.0 1.3 (1.0–1.9) 1.2 (0.9–1.7) 1.3 (0.9–1.8) 1.1 (0.8–1.6)	Age at diagnosis (cases) or selection (controls), BMI, lifetime physical activity, total energy intake, usual number of cigarettes smoked per day, intake of dietary fibre
Navarro et al. (2003) Córdoba, Argentina 1993–1998	Cases: 287 colorectal cancer cases (163 men, 124 women); hospital-based colorectal cases identified at hospitals in Córdoba Controls: 564 (309 men, 255 women); hospital-based control residents identified at the same hospitals for acute non-neoplastic conditions unrelated to digestive tract diseases or long-term modifications Exposure assessment method: questionnaire; validated, administered in person, and evaluated frequency and portion size; processed meats were cold cuts (ham, bologna, salami, cured meat of pork, etc.) and sausages	Colon and rectum	Processed meat ("cold cuts/sausages", g/day) T1 T2 (median intake, 7.39 g/day) T3 (median intake, 16.52 g/day)	 NR NR	 1.00 1.07 (0.72–1.59) 1.47 (1.02–2.15)	Sex, age, BMI, social status, energy, total lipids, proteins, carbohydrates, soluble and insoluble fibre intake

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Juarranz-Sanz et al. (2004) Madrid, Spain 1997–1998	Cases: 196; population-based colorectal cases, identified through a cancer registry Controls: 196; population-based, identified through a health care roster from the same districts of the identified cases; individually matched to cases by age, sex, and geographical region Exposure assessment method: questionnaire; validated, included 72 items, administered by phone, and asked about frequency and portion size; processed meats were not defined	Colon and rectum	Processed meats (g/day), continuous variables Processed meat Trend-test *P* value: 0.001	NR	1.070 (1.035–1.107)	Olives, red meat, organ meat, cherries/ strawberries, oranges, raw tomatoes, yogurt, fresh juice
Levi et al. (2004) Canton of Vaud, Switzerland 1992– 2002	Cases: 323; hospital-based colorectal cancer cases Controls: 611; hospital-based, identified at same hospitals of cases, with conditions unrelated to smoking or alcohol and long-term modification of diet Exposure assessment method: questionnaire; validated, administered in person, and included 79 items; processed meat was raw ham, boiled ham, salami, and sausages	Colon and rectum	Processed meat intake (servings/wk), quartiles < 0.8 0.8–1.5 1.6–3.9 > 4.0 Trend-test *P* value: < 0.001	 36 46 111 130	 1.00 1.03 (0.61–1.75) 1.82 (1.12–2.95) 2.53 (1.50–4.27)	Education, tobacco smoking, alcohol drinking, total energy intake, fruit and vegetable intake, BMI, physical activity
Murtaugh et al. (2004) California and Utah, USA 1997–2001	Cases: 952; population-based rectal cancer cases, identified through a cancer registry and online pathology reports from the Kaiser Permanente Northern California Cancer Registry Controls: 1205; controls were randomly selected from membership lists, social security lists, drivers' licence lists; frequency-matched to cases by sex and 5-y age groups Exposure assessment method: Questionnaire; validated, administered in person, and included >800 items; processed meat was bacon, sausages, and cold cuts; cooking methods were assessed, and interactions with *NAT2* phenotype and *GSTM1* genotypes were assessed	Rectum	Processed meat (servings/wk), men: < 0.6 ≥ 0.6 to < 1.6 ≥ 1.6 Trend-test *P* value: < 0.05 Processed meat (servings/wk), women: < 0.2 ≥ 0.2 to < 0.9 ≥ 0.9 Trend-test *P* value: < 0.05	 172 149 235 87 140 162	 1.00 0.95 (0.71–1.28) 18 (0.87–1.61) 1.00 1.21 (0.85–1.72) 1.23 (0.84–1.81)	Age, BMI, energy intake, dietary fibre, calcium, lifetime physical activity, usual number of cigarettes smoked

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2007) Canada 1994–1997	Cases: 1723; identified via the National Enhanced Cancer Surveillance System (NECSS), including the provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Nova Scotia, Newfoundland, Ontario, Prince Edward Island Controls: 3097; population-based controls from each province, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; validated FFQ with 70 items, administered by mail; processed meat was hot dogs, lunch meat, smoked meat, bacon, and sausage	Proximal colon	Processed meat intake (servings/wk), quartiles; men			10-yr age group, province, BMI, strenuous activity, total energy intake
			Q1	68	1.0	
			Q2	92	1.4 (0.9–2.0)	
			Q3	121	1.9 (1.3–2.7)	
			Q4	99	1.6 (1.0–2.4)	
			Trend-test *P* value: 0.01			
			Processed meat intake (servings/wk), quartiles; women			
			Q1	70	1.0	
			Q2	108	1.3 (0.9–1.9)	
			Q3	68	1.2 (0.8–1.8)	
			Q4	105	1.5 (1.0–2.3)	
			Trend-test *P* value: 0.06			
		Distal colon	Processed meat intake (servings/wk), quartiles; men:			
			Q1	112	1.0	
			Q2	130	1.4 (0.9–2.0	
			Q3	177	1.9 (1.3–2.7)	
			Q4	159	1.6 (1.0–2.4)	
			Trend-test *P* value: 0.01			
			Processed meat intake (servings/wk), quartiles; women:			
			Q1	80	1.0	
			Q2	126	1.5 (1.0–2.3)	
			Q3	98	1.8 (1.2–2.7)	
			Q4	110	1.5 (1.0–2.2)	
			Trend-test *P* value: 0.08			
		Proximal colon	Bacon intake (highest vs lowest tertile, servings/wk); men:			
			T1	95	1.0	
			T2	190	1.5 (1.1–2.1)	
			T3	56	1.5 (1.0–2.2)	
			Trend-test *P* value: 0.04			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2007) Canada 1994–1997 (cont.)		Proximal colon	Bacon intake (highest vs lowest tertile, servings/wk); women:			
			T1	NR	1.0	
			T2	NR	1.3 (1.0–1.8)	
			T3	NR	2.2 (1.4–3.3)	
			Trend-test *P* value: 0.001			
		Distal colon	Bacon intake (highest vs lowest tertile, servings/wk); men:			
			T1	NR	1.0	
			T2	NR	1.3 (1.0–1.6)	
			T3	NR	1.4 (1.0–1.9)	
			Trend-test *P* value: 0.05			
			Bacon intake (highest vs lowest tertile, servings/wk); women:			
			T1	NR	1.0	
			T2	NR	(0.9–1.6)	
			T3	NR	(1.2–2.8)	
			Trend-test *P* value: 0.01			
Kimura et al. (2007) Fukuoka, Japan 2000–2003	Cases: 840; hospital-based, cases admitted to hospitals in Fukuoka and three adjacent areas Controls: 833; population-based controls from 15 different areas, sampled based on frequency of age and sex of cases Exposure assessment method: questionnaire; validated, administered in person, and included 148 items; definition of processed meat was not provided	Colon and rectum	Processed meat quintiles (median, g/day)			Age, sex, residential area, BMI, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium, dietary fibre
			Q1 (0.4)	152	1.00	
			Q2 (2.5)	149	1.03 (0.74–1.43)	
			Q3 (4.9)	160	1.09 (0.79–1.52)	
			Q4 (8.2)	151	1.07 (0.77–1.49)	
			Q5 (14.9)	170	1.15 (0.83–1.60)	
			Trend-test *P* value: 0.40			
		Proximal colon	Processed meat (g/day), quintiles			
			Q1	40	1.00	
			Q2	27	0.82 (0.47–1.44)	
			Q3	35	1.12 (0.65–1.92)	
			Q4	33	1.04 (0.60–1.80)	
			Q5	42	1.20 (0.72–2.03)	
			Trend-test *P* value: 0.33			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kimura et al. (2007) Fukuoka, Japan 2000–2003 (cont.)		Distal colon	Processed meat (g/day), quintiles			
			Q1	48	1.00	
			Q2	49	1.10 (0.68–1.78)	
			Q3	57	1.30 (0.81–2.08)	
			Q4	49	1.15 (0.71–1.86)	
			Q5	59	1.32 (0.82–2.11)	
			Trend-test *P* value: 0.27			
		Rectum	Processed meat (g/day), quintiles			
			Q1	59	1.00	
			Q2	70	1.20 (0.78–1.84)	
			Q3	64	1.08 (0.69–1.67)	
			Q4	68	1.21 (0.78–1.87)	
			Q5	66	1.14 (0.73–1.77)	
			Trend-test *P* value: 0.61			
Squires et al. (2010) Newfoundland and Labrador, Canada 1999–2003	Cases: 518; population-based colorectal cases, identified through a cancer registry Controls: 686; population-based, identified through random digit dialling; frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation of local foods, administered by mail, and included 169 items. Pickled meat was meats preserved in brine solution (e.g. trimmed navel beef, cured pork riblets); assessed cooking methods	Colon and rectum	Pickled meat (g/day), tertiles, men:			Age; BMI; smoking status; level of education; intake of vegetables, fruits, folic acid, cholesterol, dietary fibre, saturated fat, alcohol; caloric intake; level of physical activity; NSAID use; presence of inflammatory bowel disease
			T1 (< 1)	139	1.00	
			T2 (1–3)	37	1.64 (0.89–3.02)	
			T3 (> 3)	132	2.07 (1.37–3.15)	
			Pickled meat (g/day), tertiles, women:			
			T1 (< 1)	96	1.00	
			T2 (1–3)	24	1.03 (0.49–2.17)	
			T3 (> 3)	90	2.51 (1.45–4.32)	

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Williams et al. (2010) North Carolina, USA 2001–2006	Cases: 945; population-based distal colorectal cancer cases, identified through the North Carolina Central Cancer Registry; African Americans were oversampled Controls: 959; population-based, selected from the North Carolina Department of Motor Vehicles or Centers for Medicare and Medicaid Services Exposure assessment method: questionnaire; validated, administered in person, and included portion size and frequency; processed meat was sausage, bacon, hot dogs, and all cold cuts (i.e. luncheon meats made from beef, veal, ham, pork, chicken, and turkey)	Distal colon and rectum	Processed meat (quartile median, g/day) in Caucasians			Age, sex, education, BMI, family history, NSAID use, physical activity, calcium, fibre, total energy
			Q1 (3.4)	131	1.00	
			Q2 (9.6)	178	1.15 (0.82–1.62)	
			Q3 (19.1)	208	1.43 (1.02–2.02)	
			Q4 (37.7)	203	1.16 (0.80–1.68)	
			Trend-test *P* value: 0.57			
			Processed meat (quartile median, g/day) in African Americans			
			Q1 (12.2)	44	1.00	
			Q2 (12.2)	85	1.47 (0.76–2.85)	
			Q3 (24.9)	42	0.54 (0.24–1.18)	
			Q4 (42.7)	54	0.86 (0.38–1.96)	
			Trend-test *P* value: 0.94			
De Stefani et al. (2012a) Montevideo, Uruguay 1996–2004	Cases: 361; hospital-based colorectal cases; patients with low socioeconomic status Controls: 2532; Hospital-based from the same hospitals as cases, with conditions unrelated to smoking and drinking Exposure assessment method: questionnaire; not validated, included 64 items, and administered in person; processed meat was bacon, sausage, mortadella, salami, saucisson, hot dog, ham, and air-dried and salted lamb	Colon	Processed meat (g/day), tertiles, men:			Age; residence; BMI; smoking status; smoking cessation; number of cigarettes smoked per day among current smokers; alcohol drinking; mate consumption; total energy, total vegetables and fruits, total white meat, red meat intakes
			≤ 11.4	NR	1.00	
			11.5–28.2	NR	1.76 (0.94–3.28)	
			≥ 28.3	NR	2.01 (1.07–3.76)	
			Trend-test *P* value: 0.03			
			Processed meat (g/day), tertiles, women:			
			≤ 11.4	NR	1.00	
			11.5–28.2	NR	2.25 (1.19–4.23)	
			≥ 28.3	NR	3.53 (1.93–6.46)	
			Trend-test *P* value: <0.0001			
		Rectum	Processed meat (g/day), tertiles, men:			
			≤ 11.4	NR	1.00	
			11.5–28.2	NR	1.47 (0.85–2.54)	
			≥28.3	NR	1.76 (1.03–3.01)	
			Trend-test *P* value: 0.03			
			Processed meat (g/day), tertiles, women:			
			≤ 11.4	NR	1.00	
			11.5–28.2	NR	2.44 (1.17–5.09)	
			≥ 28.3	NR	3.18 (1.54–6.57)	
			Trend-test *P* value: 0.001			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Miller et al. (2013) Pennsylvania, USA 2007–2011	Cases: 989; incident cases, identified through the Pennsylvania State Cancer Registry Controls: 1033; identified through random digit dialling; frequency-matched to cases by age, sex, and ethnicity Exposure assessment method: questionnaire; validated, in-person FFQ with 137 items; meat-cooking module was used with the CHARRED database to estimate carcinogens; processed red meat was bacon, sausage, cold cuts, beef jerky, corned beef, hot dogs, ham, and processed meats added to mixed dishes [There were no data for processed meat including processed poultry.]	Colon and rectum	Processed red meat intake (g/1000 kcal)			Age, sex, BMI, past NSAID use, total energy, total fruits and vegetables, total poultry
			Q1 (< 2.8)	170	1.00	
			Q2 (2.8–5.5)	181	0.99 (0.73–1.34)	
			Q3 (5.6–9.4)	195	1.09 (0.81–1.49)	
			Q4 (9.5–17.6)	218	1.18 (0.87–1.61)	
			Q5 (> 17.6)	225	1.18 (0.87–1.62)	
			Trend-test *P* value: 0.223			
		Colon	Processed red meat intake (g/1000 kcal)			
			Q1 (< 2.8)	125	1.00	
			Q2 (2.8–5.5)	120	0.91 (0.65–1.28)	
			Q3 (5.6–9.4)	142	1.13 (0.81–1.57)	
			Q4 (9.5–17.6)	149	1.15 (0.82–1.61)	
			Q5 (> 17.6)	157	1.21 (0.86–1.70)	
			Trend-test *P* value: 0.157			
		Rectum	Processed red meat intake (g/1000 kcal)			
			Q1 (< 2.8)	42	1.00	
			Q2 (2.8–5.5)	59	1.28 (0.81–2.01)	
			Q3 (5.6–9.4)	53	1.12 (0.70–1.79)	
			Q4 (9.5–17.6)	68	1.35 (0.86–2.13)	
			Q5 (> 17.6)	67	1.22 (0.77–1.95)	
			Trend-test *P* value: 0.613			
		Proximal colon	Total nitrites plus nitrates (µg/1000 kcal)			
			Q1 (< 114.6)	77	1.00	
			Q2 (114.6–197.0)	75	1.05 (0.71–1.56)	
			Q3 (197.1–310.2)	86	1.25 (0.85–1.86)	
			Q4 (310.3–496.6)	76	1.06 (0.71–1.58)	
			Q5 (> 496.6)	102	1.57 (1.06–2.34)	
			Trend-test *P* value: 0.023			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Rosato et al. (2013) Italy and Switzerland 1985–2009	Cases: 329; hospital-based cases with young-onset colorectal cancer (< 45 yr) Controls: 1361; hospital-based, identified from the same hospitals as cases; conditions unrelated to colorectal cancer risk factors or dietary modifications Exposure assessment method: questionnaire; validated and administered in person; processed meat was not defined	Colon and rectum: young-onset colorectal cancer	Processed meat			Age, sex, centre, study, year of interview, education, family history, alcohol, energy intake
			Low	69	1.00	
			Medium	115	1.18 (0.84–1.65)	
			High	145	1.56 (1.11–2.20)	
			Trend-test *P* value: 0.008			
Joshi et al. (2015) USA and Canada 1997–2002	Cases: 3350; population-based, identified through cancer registries in Ontario, Canada; Hawaii, California, Arizona, North Carolina, New Hampshire, Colorado, Minnesota, USA; cases with familial cases included Controls: 3504; cancer-free siblings of the cases (*n* = 1759), unaffected spouses of the cases (*n* = 138), and population-based controls (*n* = 1607) Exposure assessment method: questionnaire; validated, administered by mail, included 200 items, included portion size and frequency of intake, and used the CHARRED database to estimate carcinogens; considered cooking methods Processed meat was reported as total processed meat (including processed red meat and poultry)	Colon and rectum	Processed meat (g/1000 kcal per day)			Age, BMI, sex, ethnicity, saturated fat, dietary fibre, centre, vegetables, physical activity, total caloric intake
			Q1 (0–4.43)	593	1.0	
			Q2 (4.43–7.35)	643	1.1 (0.9–1.2)	
			Q3 (7.36–10.62)	640	1.0 (0.9–1.2)	
			Q4 (10.63–15.29)	654	1.0 (0.8–1.2)	
			Q5 (15.29–152.04)	820	1.2 (1.0–1.4)	
			Trend-test *P* value: 0.054			
			Sausages and lunchmeats (g/1000 kcal per day)			
			Q1 (0–0.08)	582	1.0	
			Q2 (0.08–0.14)	657	1.1 (0.9–1.3)	
			Q3 (0.14–0.22)	706	1.2 (1.0–1.4)	
			Q4 (0.22–0.32)	654	1.0 (0.9–1.2)	
			Q5 (0.32–3.86)	751	1.2 (1.0–1.4)	
			Trend-test *P* value: 0.187			
			Sausages and lunchmeats (g/1000 kcal per day); MMR-proficient			
			Q1 (0–0.08)	138	1.0	
			Q2 (0.08–0.14)	148	1.0 (0.7–1.3)	
			Q3 (0.14–0.22)	194	1.2 (1.0–1.6)	
			Q4 (0.22–0.32)	179	1.1 (0.8–1.4)	
			Q5 (0.32–3.86)	217	1.3 (1.0–1.7)	
			Trend-test *P* value: 0.029			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Sausages and lunchmeats (g/1000 kcal per day); MMR-deficient			
			Q1 (0–0.08)	44	1.0	
			Q2 (0.08–0.14)	58	1.3 (0.8–1.9)	
			Q3 (0.14–0.22)	56	1.2 (0.8–1.9)	
			Q4 (0.22–0.32)	40	0.9 (0.6–1.4)	
			Q5 (0.32–3.86)	45	1.0 (0.6–1.6)	
			Trend-test *P* value: 0.408			
			Test of heterogeneity, MMR-proficient vs MMR-deficient ($P = 0.069$)			
			Pan-fried sausage (g/1000 kcal per day)			
			Q1 (0–0)	1271	1.0	
			Q2 (0.01–0.02)	643	1.1 (1.0–1.3)	
			Q3 (0.020–0.04)	619	1.1 (0.9–1.2)	
			Q4 (0.04–1.32)	781	1.2 (1.0–1.3)	
			Trend-test *P* value: 0.041			
		Colon	Pan-fried sausage (g/1000 kcal per day)			
			Q1 (0–0)	789	1.0	
			Q2 (0.01–0.02)	371	1.1 (0.9–1.3)	
			Q3 (0.20–0.04)	356	1.0 (0.8–1.2)	
			Q4 (0.04–1.32)	456	1.1 (0.9–1.3)	
			Trend-test *P* value: 0.371			
		Rectum	Pan-fried sausage (g/1000 kcal per day)			
			Q1 (0–0)	302	1.0	
			Q2 (0.01–0.02)	204	1.3 (1.1–1.6)	
			Q3 (0.20–0.04)	177	1.2 (1.0–1.5)	
			Q4 (0.04–1.32)	213	1.4 (1.1–1.7)	
			Trend-test *P* value: 0.004			
			Test of heterogeneity, colon vs rectum ($P = 0.053$)			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Pan-fried spam or ham (g/1000 kcal per day)			
			Q1 (0–0)	2097	1.0	
			Q2 (0.01–0.02)	395	1.0 (0.9–1.2)	
			Q3 (0.20–0.04)	403	1.1 (0.9–1.3)	
			Q4 (0.04–0.99)	425	1.2 (1.0–1.4)	
			Trend-test *P* value: 0.048			
			Pan-fried spam or ham (g/1000 kcal per day); MMR-proficient			
			Q1 (0–0)	524	1.0	
			Q2 (0.01–0.02)	106	1.3 (1.0–1.7)	
			Q3 (0.20–0.04)	110	1.4 (1.1–1.8)	
			Q4 (0.04–0.99)	128	1.6 (1.2–2.0)	
			Trend-test *P* value: <0.001			
			Pan-fried spam or ham (g/1000 kcal per day); MMR-deficient			
			Q1 (0–0)	173	1.0	
			Q2 (0.01–0.02)	18	0.6 (0.4–1.0)	
			Q3 (0.20–0.04)	30	1.1 (0.7–1.6)	
			Q4 (0.04–0.99)	19	0.8 (0.5–1.3)	
			Trend-test *P* value: 0.461			
			Test of heterogeneity, MMR-proficient vs MMR-deficient ($P = 0.026$)			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Pan-fried bacon (g/1000 kcal per day)			
			Q1 (0–0)	1094	1.0	
			Q2 (0.01–0.03)	664	1.0 (0.8–1.1)	
			Q3 (0.03–0.05)	720	1.0 (0.9–1.2)	
			Q4 (0.05–1.43)	841	1.0 (0.9–1.2)	
			Trend-test *P* value: 0.61			
			Grilled sausage (g/1000 kcal per day)			
			Q1 (0–0)	2222	1.0	
			Q2 (0.01–0.02)	410	1.1 (0.9–1.3)	
			Q3 (0.02–0.03)	327	0.9 (0.8–1.1)	
			Q4 (0.03–0.99)	357	1.0 (0.9–1.2)	
			Trend-test *P* value: 0.903			

BaP, benzo[*a*]pyrene; BMI, body mass index; CHARRED, Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease; CI, confidence interval; FFQ, food frequency questionnaire; GI, gastrointestinal; h, hour; HAA, heterocyclic aromatic amine; ICD, International Classification of Diseases; MMR, mismatch repair; mo, month; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; wk, week; yr, year

References

Abu Mweis SS, Tayyem RF, Shehadah I, Bawadi HA, Agraib LM, Bani-Hani KE et al. (2015). Food groups and the risk of colorectal cancer: results from a Jordanian case-control study. *Eur J Cancer Prev*, 24(4):313–20. doi:10.1097/CEJ.0000000000000089 PMID:25415835

Alexander DD, Miller AJ, Cushing CA, Lowe KA (2010). Processed meat and colorectal cancer: a quantitative review of prospective epidemiologic studies. *Eur J Cancer Prev*, 19(5):328–41. doi:10.1097/CEJ.0b013e32833b48fa PMID:20495462

Alexander DD, Weed DL, Miller PE, Mohamed MA (2015). Red meat and colorectal cancer: a quantitative update on the state of the epidemiologic science. *J Am Coll Nutr*, 34(6):521–43. doi:10.1080/07315724.2014.992553 PMID:25941850

Ananthakrishnan AN, Du M, Berndt SI, Brenner H, Caan BJ, Casey G et al. (2015). Red meat intake, NAT2, and risk of colorectal cancer: a pooled analysis of 11 studies. *Cancer Epidemiol Biomarkers Prev*, 24(1):198–205. doi:10.1158/1055-9965.EPI-14-0897 PMID:25342387

Andersen V, Holst R, Vogel U (2013). Systematic review: diet-gene interactions and the risk of colorectal cancer. *Aliment Pharmacol Ther*, 37(4):383–91. doi:10.1111/apt.12180 PMID:23216531

Andersen V, Ostergaard M, Christensen J, Overvad K, Tjønneland A, Vogel U (2009). Polymorphisms in the xenobiotic transporter Multidrug Resistance 1 (MDR1) and interaction with meat intake in relation to risk of colorectal cancer in a Danish prospective case-cohort study. *BMC Cancer*, 9(1):407. doi:10.1186/1471-2407-9-407 PMID:19930591

Angstadt AY, Berg A, Zhu J, Miller P, Hartman TJ, Lesko SM et al. (2013). The effect of copy number variation in the phase II detoxification genes UGT2B17 and UGT2B28 on colorectal cancer risk. *Cancer*, 119(13):2477–85. doi:10.1002/cncr.28009 PMID:23575887

Arafa MA, Waly MI, Jriesat S, Al Khafajei A, Sallam S (2011). Dietary and lifestyle characteristics of colorectal cancer in Jordan: a case-control study. *Asian Pac J Cancer Prev*, 12(8):1931–6. PMID:22292627

Balder HF, Vogel J, Jansen MC, Weijenberg MP, van den Brandt PA, Westenbrink S et al. (2006). Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev*, 15(4):717–25. doi:10.1158/1055-9965.EPI-05-0772 PMID:16614114

Barrett JH, Smith G, Waxman R, Gooderham N, Lightfoot T, Garner RC et al. ; Colorectal Cancer Study Group(2003). Investigation of interaction between N-acetyltransferase 2 and heterocyclic amines as potential risk factors for colorectal cancer. *Carcinogenesis*, 24(2):275–82. doi:10.1093/carcin/24.2.275 PMID:12584178

Benito E, Obrador A, Stiggelbout A, Bosch FX, Mulet M, Muñoz N et al. (1990). A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer*, 45(1):69–76. doi:10.1002/ijc.2910450114 PMID:2298506

Berndt SI, Platz EA, Fallin MD, Thuita LW, Hoffman SC, Helzlsouer KJ (2006). Genetic variation in the nucleotide excision repair pathway and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*, 15(11):2263–9. doi:10.1158/1055-9965.EPI-06-0449 PMID:17119055

Bernstein AM, Song M, Zhang X, Pan A, Wang M, Fuchs CS et al. (2015). Processed and unprocessed red meat and risk of colorectal cancer: analysis by tumor location and modification by time. *PLoS One*, 10(8):e0135959. doi:10.1371/journal.pone.0135959 PMID:26305323

Bidoli E, Franceschi S, Talamini R, Barra S, La Vecchia C (1992). Food consumption and cancer of the colon and rectum in north-eastern Italy. *Int J Cancer*, 50(2):223–9. doi:10.1002/ijc.2910500211 PMID:1730516

Bostick RM, Potter JD, Kushi LH, Sellers TA, Steinmetz KA, McKenzie DR et al. (1994). Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control*, 5(1):38–52. doi:10.1007/BF01830725 PMID:8123778

Boutron-Ruault MC, Senesse P, Faivre J, Chatelain N, Belghiti C, Méance S (1999). Foods as risk factors for colorectal cancer: a case-control study in Burgundy (France). *Eur J Cancer Prev*, 8(3):229–35. doi:10.1097/00008469-199906000-00011 PMID:10443952

Brevik A, Joshi AD, Corral R, Onland-Moret NC, Siegmund KD, Le Marchand L et al. (2010). Polymorphisms in base excision repair genes as colorectal cancer risk factors and modifiers of the effect of diets high in red meat. *Cancer Epidemiol Biomarkers Prev*, 19(12):3167–73. doi:10.1158/1055-9965.EPI-10-0606 PMID:21037106

Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruïne AP et al. (2005). Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer*, 92(7):1310–20. doi:10.1038/sj.bjc.6602491 PMID:15812479

Butler LM, Duguay Y, Millikan RC, Sinha R, Gagné J-F, Sandler RS et al. (2005). Joint effects between UDP-glucuronosyltransferase 1A7 genotype and dietary carcinogen exposure on risk of colon cancer. *Cancer Epidemiol Biomarkers Prev*, 14(7):1626–32. doi:10.1158/1055-9965.EPI-04-0682 PMID:16030093

Butler LM, Millikan RC, Sinha R, Keku TO, Winkel S, Harlan B et al. (2008a). Modification by N-acetyltransferase 1 genotype on the association between dietary heterocyclic amines and colon cancer in a multiethnic study. *Mutat Res*, 638(1-2):162–74. doi:10.1016/j.mrfmmm.2007.10.002 PMID:18022202

Butler LM, Wang R, Koh WP, Yu MC (2008b). Prospective study of dietary patterns and colorectal cancer

among Singapore Chinese. *Br J Cancer*, 99(9):1511–6. doi:10.1038/sj.bjc.6604678 PMID:18813309

Butler LM, Sinha R, Millikan RC, Martin CF, Newman B, Gammon MD et al. (2003). Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. *Am J Epidemiol*, 157(5):434–45. doi:10.1093/aje/kwf221 PMID:12615608

Carr PR, Walter V, Brenner H, Hoffmeister M (2016). Meat subtypes and their association with colorectal cancer: Systematic review and meta-analysis. *Int J Cancer*, 138(2):293–302. doi:10.1002/ijc.29423 PMID:25583132

Centonze S, Boeing H, Leoci C, Guerra V, Misciagna G (1994). Dietary habits and colorectal cancer in a low-risk area. Results from a population-based case-control study in southern Italy. *Nutr Cancer*, 21(3):233–46. doi:10.1080/01635589409514322 PMID:8072877

Chan AT, Tranah GJ, Giovannucci EL, Willett WC, Hunter DJ, Fuchs CS (2005). Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. *Int J Cancer*, 115(4):648–52. doi:10.1002/ijc.20890 PMID:15700302

Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E et al. (2011). Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *PLoS One*, 6(6):e20456. doi:10.1371/journal.pone.0020456 PMID:21674008

Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD et al. (2005). Meat consumption and risk of colorectal cancer. *JAMA*, 293(2):172–82. doi:10.1001/jama.293.2.172 PMID:15644544

Chen J, Stampfer MJ, Hough HL, Garcia-Closas M, Willett WC, Hennekens CH et al. (1998). A prospective study of N-acetyltransferase genotype, red meat intake, and risk of colorectal cancer. *Cancer Res*, 58(15):3307–11. PMID:9699660

Chen K, Fan CH, Jin MJ, Song L, Xu H, He HQ et al. (2006). [A case-control study on the association between the genetic polymorphism of sulfotransferase 1A1, diet and susceptibility of colorectal cancer] *Zhonghua Zhong Liu Za Zhi*, 28(9):670–3. PMID:17274372

Chen Z, Wang PP, Woodrow J, Zhu Y, Roebothan B, Mclaughlin JR et al. (2015). Dietary patterns and colorectal cancer: results from a Canadian population-based study. *Nutr J*, 14(1):8. doi:10.1186/1475-2891-14-8 PMID:25592002

Chiu BC, Ji BT, Dai Q, Gridley G, McLaughlin JK, Gao YT et al. (2003). Dietary factors and risk of colon cancer in Shanghai, China. *Cancer Epidemiol Biomarkers Prev*, 12(3):201–8. PMID:12646508

Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA (2008). Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*, 17(11):3098–107. doi:10.1158/1055-9965.EPI-08-0341 PMID:18990750

Cross AJ, Ferrucci LM, Risch A, Graubard BI, Ward MH, Park Y et al. (2010). A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. *Cancer Res*, 70(6):2406–14. doi:10.1158/0008-5472.CAN-09-3929 PMID:20215514

Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R (2007). A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med*, 4(12):e325. doi:10.1371/journal.pmed.0040325 PMID:18076279

da Silva TD, Felipe AV, de Lima JM, Oshima CT, Forones NM (2011). N-Acetyltransferase 2 genetic polymorphisms and risk of colorectal cancer. *World J Gastroenterol*, 17(6):760–5. doi:10.3748/wjg.v17.i6.760 PMID:21390146

Dales LG, Friedman GD, Ury HK, Grossman S, Williams SR (1979). A case-control study of relationships of diet and other traits to colorectal cancer in American blacks. *Am J Epidemiol*, 109(2):132–44. doi:10.1093/oxfordjournals.aje.a112668 PMID:425952

De Stefani E, Boffetta P, Ronco AL, Deneo-Pellegrini H, Correa P, Acosta G et al. (2012a). Processed meat consumption and risk of cancer: a multisite case-control study in Uruguay. *Br J Cancer*, 107(9):1584–8. doi:10.1038/bjc.2012.433 PMID:23011480

De Stefani E, Ronco AL, Boffetta P, Deneo-Pellegrini H, Correa P, Acosta G et al. (2012b). Nutrient-derived dietary patterns and risk of colorectal cancer: a factor analysis in Uruguay. *Asian Pac J Cancer Prev*, 13(1):231–5. doi:10.7314/APJCP.2012.13.1.231 PMID:22502675

Destefani E, Deneopellegrini H, Mendilaharsu M, Ronco A (1997). Meat intake, heterocyclic amines and risk of colorectal cancer. *Int J Oncol*, 10(3):573–80. PMID:21533415

Di Maso M, Talamini R, Bosetti C, Montella M, Zucchetto A, Libra M et al. (2013). Red meat and cancer risk in a network of case-control studies focusing on cooking practices. *Ann Oncol*, 24(12):3107–12. doi:10.1093/annonc/mdt392 PMID:24121119

Egeberg R, Olsen A, Christensen J, Halkjær J, Jakobsen MU, Overvad K et al. (2013). Associations between red meat and risks for colon and rectal cancer depend on the type of red meat consumed. *J Nutr*, 143(4):464–72. doi:10.3945/jn.112.168799 PMID:23427329

English DR, MacInnis RJ, Hodge AM, Hopper JL, Haydon AM, Giles GG (2004). Red meat, chicken, and fish consumption and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*, 13(9):1509–14. PMID:15342453

Evans RC, Fear S, Ashby D, Hackett A, Williams E, Van Der Vliet M et al. (2002). Diet and colorectal cancer: an investigation of the lectin/galactose hypothesis. *Gastroenterology*, 122(7):1784–92. doi:10.1053/gast.2002.33659 PMID:12055585

Faivre J, Boutron MC, Senesse P, Couillault C, Belighiti C, Meny B (1997). Environmental and familial risk factors in relation to the colorectal adenoma–carcinoma sequence: results of a case-control study in Burgundy (France). *Eur J Cancer Prev*, 6(2):127–31. PMID:9237060

Fernandez E, D'Avanzo B, Negri E, Franceschi S, La Vecchia C (1996). Diet diversity and the risk of colorectal cancer in northern Italy. *Cancer Epidemiol Biomarkers Prev*, 5(6):433–6. PMID:8781738

Fernandez E, La Vecchia C, D'Avanzo B, Negri E, Franceschi S (1997). Risk factors for colorectal cancer in subjects with family history of the disease. *Br J Cancer*, 75(9):1381–4. doi:10.1038/bjc.1997.234 PMID:9155063

Figueiredo JC, Hsu L, Hutter CM, Lin Y, Campbell PT, Baron JA et al.; CCFR; GECCO (2014). Genome-wide diet-gene interaction analyses for risk of colorectal cancer. *PLoS Genet*, 10(4):e1004228. doi:10.1371/journal.pgen.1004228 PMID:24743840

Flood A, Velie EM, Sinha R, Chaterjee N, Lacey JV Jr, Schairer C et al. (2003). Meat, fat, and their subtypes as risk factors for colorectal cancer in a prospective cohort of women. *Am J Epidemiol*, 158(1):59–68. doi:10.1093/aje/kwg099 PMID:12835287

Forones NM, de Lima JM, de Souza LG, da Silva ID (2008). Cyclin D1 A870G polymorphism in Brazilian colorectal cancer patients. *J Gastrointest Cancer*, 39(1-4):118–23. doi:10.1007/s12029-009-9057-z PMID:19373442

Franceschi S, Favero A, La Vecchia C, Negri E, Conti E, Montella M et al. (1997). Food groups and risk of colorectal cancer in Italy. *Int J Cancer*, 72(1):56–61. doi:10.1002/(SICI)1097-0215(19970703)72:1<56::AID-IJC8>3.0.CO;2-3 PMID:9212223

Freedman AN, Michalek AM, Marshall JR, Mettlin CJ, Petrelli NJ, Black JD et al. (1996). Familial and nutritional risk factors for p53 overexpression in colorectal cancer. *Cancer Epidemiol Biomarkers Prev*, 5(4):285–91. PMID:8722220

Fung TT, Hu FB, Wu K, Chiuve SE, Fuchs CS, Giovannucci E (2010). The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets and colorectal cancer. *Am J Clin Nutr*, 92(6):1429–35. doi:10.3945/ajcn.2010.29242 PMID:21097651

Gaard M, Tretli S, Løken EB (1996). Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. *Eur J Cancer Prev*, 5(6):445–54. PMID:9061275

Ganesh B, Talole SD, Dikshit R (2009). A case-control study on diet and colorectal cancer from Mumbai, India. *Cancer Epidemiol*, 33(3-4):189–93. doi:10.1016/j.canep.2009.07.009 PMID:19717354

Gay LJ, Mitrou PN, Keen J, Bowman R, Naguib A, Cooke J et al. (2012). Dietary, lifestyle and clinicopathological factors associated with APC mutations and promoter methylation in colorectal cancers from the EPIC-Norfolk study. *J Pathol*, 228(3):405–15. doi:10.1002/path.4085 PMID:22864938

Gerhardsson de Verdier M, Hagman U, Peters RK, Steineck G, Overvik E (1991). Meat, cooking methods and colorectal cancer: a case-referent study in Stockholm. *Int J Cancer*, 49(4):520–5. doi:10.1002/ijc.2910490408 PMID:1917152

Gerhardsson de Verdier M, Hagman U, Steineck G, Rieger A, Norell SE (1990). Diet, body mass and colorectal cancer: a case-referent study in Stockholm. *Int J Cancer*, 46(5):832–8. doi:10.1002/ijc.2910460514 PMID:2172171

Ghadirian P, Lacroix A, Maisonneuve P, Perret C, Potvin C, Gravel D et al. (1997). Nutritional factors and colon carcinoma: a case-control study involving French Canadians in Montréal, Quebec, Canada. *Cancer*, 80(5):858–64. doi:10.1002/(SICI)1097-0142(19970901)80:5<858::AID-CNCR5>3.0.CO;2-H PMID:9307184

Gialamas SP, Petridou ET, Tseleni-Balafouta S, Spyridopoulos TN, Matsoukis IL, Kondi-Pafiti A et al. (2011). Serum adiponectin levels and tissue expression of adiponectin receptors are associated with risk, stage, and grade of colorectal cancer. *Metabolism*, 60(11):1530–8. doi:10.1016/j.metabol.2011.03.020 PMID:21632074

Gilsing AM, Schouten LJ, Goldbohm RA, Dagnelie PC, van den Brandt PA, Weijenberg MP (2015). Vegetarianism, low meat consumption and the risk of colorectal cancer in a population based cohort study. *Sci Rep*, 5(1):13484. doi:10.1038/srep13484 PMID:26316135

Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC (1994). Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res*, 54(9):2390–7. PMID:8162586

Goldbohm RA, van den Brandt PA, van 't Veer P, Brants HA, Dorant E, Sturmans F et al. (1994). A prospective cohort study on the relation between meat consumption and the risk of colon cancer. *Cancer Res*, 54(3):718–23. PMID:8306333

Guesmi F, Zoghlami A, Sghaier D, Nouira R, Dziri C (2010). [Alimentary factors predisposing to colorectal cancer risk: a prospective epidemiologic study] *Tunis Med*, 88(3):184–9. PMID:20415192

Guo X, Liu J, You L, Li G, Huang Y, Li Y (2015). Association between adiponectin polymorphisms and the risk of colorectal cancer. *Genet Test Mol Biomarkers*, 19(1):9–13. doi:10.1089/gtmb.2014.0238 PMID:25489716

Hansen RD, Sørensen M, Tjønneland A, Overvad K, Wallin H, Raaschou-Nielsen O et al. (2007). XPA A23G, XPC Lys939Gln, XPD Lys751Gln and XPD Asp312Asn polymorphisms, interactions with smoking, alcohol and dietary factors, and risk of colorectal cancer. *Mutat Res*, 619(1-2):68–80. doi:10.1016/j.mrfmmm.2007.02.002 PMID:17363013

Helmus DS, Thompson CL, Zelenskiy S, Tucker TC, Li L (2013). Red meat-derived heterocyclic amines increase risk of colon cancer: a population-based case-control

study. *Nutr Cancer*, 65(8):1141–50. doi:10.1080/01635581.2013.834945 PMID:24168237

Hu J, La Vecchia C, Morrison H, Negri E, Mery L; Canadian Cancer Registries Epidemiology Research Group (2011). Salt, processed meat and the risk of cancer. *Eur J Cancer Prev*, 20(2):132–9. doi:10.1097/CEJ.0b013e3283429e32 PMID:21160428

Hu J, Morrison H, Mery L, DesMeules M, Macleod M, Group CCRER; Canadian Cancer Registries Epidemiology Research Group (2007). Diet and vitamin or mineral supplementation and risk of colon cancer by subsite in Canada. *Eur J Cancer Prev*, 16(4):275–91. doi:10.1097/01.cej.0000228411.21719.25 PMID:17554200

Hu JF, Liu YY, Yu YK, Zhao TZ, Liu SD, Wang QQ (1991). Diet and cancer of the colon and rectum: a case-control study in China. *Int J Epidemiol*, 20(2):362–7. doi:10.1093/ije/20.2.362 PMID:1917235

Hu X, Feng F, Li X, Yuan P, Luan R, Yan J et al. (2015). Gene polymorphisms related to insulin resistance and gene-environment interaction in colorectal cancer risk. *Ann Hum Biol*, 42(6):560–8. PMID:26203767

Hu X, Yuan P, Yan J, Feng F, Li X, Liu W et al. (2013). Gene polymorphisms of ADIPOQ +45T>G, UCP2 -866G>A, and FABP2 Ala54Thr on the risk of colorectal cancer: a matched case-control study. *PLoS One*, 8(6):e67275. doi:10.1371/journal.pone.0067275 PMID:23826253

Hu XQ, Yuan P, Luan RS, Li XL, Liu WH, Feng F et al. (2014). Calpain-10 SNP43 and SNP19 polymorphisms and colorectal cancer: a matched case-control study. *Asian Pac J Cancer Prev*, 14(11):6673–80. doi:10.7314/APJCP.2013.14.11.6673 PMID:24377587

Hutter CM, Chang-Claude J, Slattery ML, Pflugeisen BM, Lin Y, Duggan D et al. (2012). Characterization of gene-environment interactions for colorectal cancer susceptibility loci. *Cancer Res*, 72(8):2036–44. doi:10.1158/0008-5472.CAN-11-4067 PMID:22367214

Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M (2009). The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. *Int J Cancer*, 125(1):171–80. doi:10.1002/ijc.24343 PMID:19350627

Iscovich JM, L'Abbé KA, Castelleto R, Calzona A, Bernedo A, Chopita NA et al. (1992). Colon cancer in Argentina. I: Risk from intake of dietary items. *Int J Cancer*, 51(6):851–7. doi:10.1002/ijc.2910510603 PMID:1639534

Järvinen R, Knekt P, Hakulinen T, Rissanen H, Heliövaara M (2001). Dietary fat, cholesterol and colorectal cancer in a prospective study. *Br J Cancer*, 85(3):357–61. doi:10.1054/bjoc.2001.1906 PMID:11487265

Jedrychowski W, Maugeri U, Pac A, Sochacka-Tatara E, Galas A (2008). Protective effect of fish consumption on colorectal cancer risk. Hospital-based case-control study in Eastern Europe. *Ann Nutr Metab*, 53(3-4):295–302. doi:10.1159/000195770 PMID:19169007

Joshi AD, Corral R, Siegmund KD, Haile RW, Le Marchand L, Martínez ME et al. (2009). Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. *Carcinogenesis*, 30(3):472–9. doi:10.1093/carcin/bgn260 PMID:19029193

Joshi AD, Kim A, Lewinger JP, Ulrich CM, Potter JD, Cotterchio M et al. (2015). Meat intake, cooking methods, dietary carcinogens, and colorectal cancer risk: findings from the Colorectal Cancer Family Registry. *Cancer Med*, 4(6):936–52. doi:10.1002/cam4.461 PMID:25846122

Juarranz Sanz M, Soriano Llora T, Calle Purón ME, Martínez Hernández D, González Navarro A, Domínguez Rojas V (2004). Influencia de la dieta en la aparición del cáncer colorrectal en una población de Madrid. *Rev Clin Esp*, 204(7):355–61. doi:10.1016/S0014-2565(04)71484-8 PMID:15274780

Kabat GC, Miller AB, Jain M, Rohan TE (2007). A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer*, 97(1):118–22. doi:10.1038/sj.bjc.6603837 PMID:17551493

Kampman E, Slattery ML, Bigler J, Leppert M, Samowitz W, Caan BJ et al. (1999). Meat consumption, genetic susceptibility, and colon cancer risk: a United States multicenter case-control study. *Cancer Epidemiol Biomarkers Prev*, 8(1):15–24. PMID:9950235

Kampman E, Verhoeven D, Sloots L, van 't Veer P (1995). Vegetable and animal products as determinants of colon cancer risk in Dutch men and women. *Cancer Causes Control*, 6(3):225–34. doi:10.1007/BF00051794 PMID:7612802

Kantor ED, Hutter CM, Minnier J, Berndt SI, Brenner H, Caan BJ et al. (2014). Gene-environment interaction involving recently identified colorectal cancer susceptibility Loci. *Cancer Epidemiol Biomarkers Prev*, 23(9):1824–33. doi:10.1158/1055-9965.EPI-14-0062 PMID:24994789

Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E (1997). Prospective study of diet and female colorectal cancer: the New York University Women's Health Study. *Nutr Cancer*, 28(3):276–81. doi:10.1080/01635589709514588 PMID:9343837

Keku TO, Millikan RC, Martin C, Rahkra-Burris TK, Sandler RS (2003). Family history of colon cancer: what does it mean and how is it useful? *Am J Prev Med*, 24(2):170–6. doi:10.1016/S0749-3797(02)00590-1 PMID:12568823

Kim JI, Park YJ, Kim KH, Kim JI, Song BJ, Lee MS et al. (2003). hOGG1 Ser326Cys polymorphism modifies the significance of the environmental risk factor for colon cancer. *World J Gastroenterol*, 9(5):956–60. doi:10.3748/wjg.v9.i5.956 PMID:12717837

Kimura Y, Kono S, Toyomura K, Nagano J, Mizoue T, Moore MA et al. (2007). Meat, fish and fat intake in relation to subsite-specific risk of colorectal cancer:

The Fukuoka Colorectal Cancer Study. *Cancer Sci*, 98(4):590–7. doi:10.1111/j.1349-7006.2007.00425.x PMID:17425596

Kotake K, Koyama Y, Nasu J, Fukutomi T, Yamaguchi N (1995). Relation of family history of cancer and environmental factors to the risk of colorectal cancer: a case-control study. *Jpn J Clin Oncol*, 25(5):195–202. PMID:7474407

Kune S, Kune GA, Watson LF (1987). Case-control study of dietary etiological factors: the Melbourne Colorectal Cancer Study. *Nutr Cancer*, 9(1):21–42. doi:10.1080/01635588709513908 PMID:3027675

Kuriki K, Hamajima N, Chiba H, Kanemitsu Y, Hirai T, Kato T et al. (2005). Increased risk of colorectal cancer due to interactions between meat consumption and the CD36 gene A52C polymorphism among Japanese. *Nutr Cancer*, 51(2):170–7. doi:10.1207/s15327914nc5102_7 PMID:15860439

Kuriki K, Hirose K, Matsuo K, Wakai K, Ito H, Kanemitsu Y et al. (2006). Meat, milk, saturated fatty acids, the Pro12Ala and C161T polymorphisms of the PPARgamma gene and colorectal cancer risk in Japanese. *Cancer Sci*, 97(11):1226–35. doi:10.1111/j.1349-7006.2006.00314.x PMID:16965392

Küry S, Buecher B, Robiou-du-Pont S, Scoul C, Sébille V, Colman H et al. (2007). Combinations of cytochrome P450 gene polymorphisms enhancing the risk for sporadic colorectal cancer related to red meat consumption. *Cancer Epidemiol Biomarkers Prev*, 16(7):1460–7. doi:10.1158/1055-9965.EPI-07-0236 PMID:17627011

La Vecchia C, D'Avanzo B, Negri E, Franceschi S (1991). History of selected diseases and the risk of colorectal cancer. *Eur J Cancer*, 27(5):582–6. doi:10.1016/0277-5379(91)90223-Z PMID:1828966

La Vecchia C, Ferraroni M, Mezzetti M, Enard L, Negri E, Franceschi S et al. (1996). Attributable risks for colorectal cancer in northern Italy. *Int J Cancer*, 66(1):60–4. doi:10.1002/(SICI)1097-0215(19960328)66:1<60::AID-IJC11>3.0.CO;2-F PMID:8608968

Larsson SC, Adami HO, Giovannucci E, Wolk A (2005b). Re: Heme iron, zinc, alcohol consumption, and risk of colon cancer. *J Natl Cancer Inst*, 97(3):232–3, author reply 233–4. doi:10.1093/jnci/dji032 PMID:15687367

Larsson SC, Orsini N, Wolk A (2006). Processed meat consumption and stomach cancer risk: a meta-analysis. *J Natl Cancer Inst*, 98(15):1078–87. doi:10.1093/jnci/djj301 PMID:16882945

Larsson SC, Rafter J, Holmberg L, Bergkvist L, Wolk A (2005a). Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. *Int J Cancer*, 113(5):829–34. doi:10.1002/ijc.20658 PMID:15499619

Le Marchand L, Donlon T, Seifried A, Wilkens LR (2002a). Red meat intake, CYP2E1 genetic polymorphisms, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*, 11(10 Pt 1):1019–24. PMID:12376502

Le Marchand L, Hankin JH, Pierce LM, Sinha R, Nerurkar PV, Franke AA et al. (2002b). Well-done red meat, metabolic phenotypes and colorectal cancer in Hawaii. *Mutat Res*, 506-507:205–14. doi:10.1016/S0027-5107(02)00167-7 PMID:12351160

Le Marchand L, Hankin JH, Wilkens LR, Pierce LM, Franke A, Kolonel LN et al. (2001). Combined effects of well-done red meat, smoking, and rapid N-acetyltransferase 2 and CYP1A2 phenotypes in increasing colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*, 10(12):1259–66. PMID:11751443

Le Marchand L, Wilkens LR, Hankin JH, Kolonel LN, Lyu LC (1997). A case-control study of diet and colorectal cancer in a multiethnic population in Hawaii (United States): lipids and foods of animal origin. *Cancer Causes Control*, 8(4):637–48. doi:10.1023/A:1018406716115 PMID:9242481

Lee DH, Anderson KE, Harnack LJ, Folsom AR, Jacobs DR Jr (2004). Heme iron, zinc, alcohol consumption, and colon cancer: Iowa Women's Health Study. *J Natl Cancer Inst*, 96(5):403–7. doi:10.1093/jnci/djh047 PMID:14996862

Lee HP, Gourley L, Duffy SW, Estève J, Lee J, Day NE (1989). Colorectal cancer and diet in an Asian population–a case-control study among Singapore Chinese. *Int J Cancer*, 43(6):1007–16. doi:10.1002/ijc.2910430609 PMID:2731998

Lee SA, Shu XO, Yang G, Li H, Gao YT, Zheng W (2009). Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. *Nutr Cancer*, 61(2):194–205. doi:10.1080/01635580802419780 PMID:19235035

Levi F, Pasche C, La Vecchia C, Lucchini F, Franceschi S (1999). Food groups and colorectal cancer risk. *Br J Cancer*, 79(7-8):1283–7. doi:10.1038/sj.bjc.6690206 PMID:10098773

Levi F, Pasche C, Lucchini F, Bosetti C, La Vecchia C (2004). Processed meat and the risk of selected digestive tract and laryngeal neoplasms in Switzerland. *Ann Oncol*, 15(2):346–9. doi:10.1093/annonc/mdh060 PMID:14760132

Lin J, Zhang SM, Cook NR, Lee IM, Buring JE (2004). Dietary fat and fatty acids and risk of colorectal cancer in women. *Am J Epidemiol*, 160(10):1011–22. doi:10.1093/aje/kwh319 PMID:15522858

Little J, Sharp L, Masson LF, Brockton NT, Cotton SC, Haites NE et al. (2006). Colorectal cancer and genetic polymorphisms of CYP1A1, GSTM1 and GSTT1: a case-control study in the Grampian region of Scotland. *Int J Cancer*, 119(9):2155–64. doi:10.1002/ijc.22093 PMID:16823842

Loh YH, Mitrou PN, Bowman R, Wood A, Jeffery H, Luben RN et al. (2010). MGMT Ile143Val polymorphism, dietary factors and the risk of breast, colorectal and prostate cancer in the European Prospective Investigation into Cancer and Nutrition

(EPIC)-Norfolk study. *DNA Repair (Amst)*, 9(4):421–8. doi:10.1016/j.dnarep.2010.01.002 PMID:20096652

Lohsoonthorn P, Danvivat D (1995). Colorectal cancer risk factors: a case-control study in Bangkok. *Asia Pac J Public Health*, 8(2):118–22. doi:10.1177/101053959500800211 PMID:9037809

Lüchtenborg M, Weijenberg MP, de Goeij AF, Wark PA, Brink M, Roemen GM et al. (2005). Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: a prospective cohort study (The Netherlands). *Cancer Causes Control*, 16(9):1041–54. doi:10.1007/s10552-005-0239-0 PMID:16184469

Macquart-Moulin G, Riboli E, Cornée J, Charnay B, Berthezène P, Day N (1986). Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer*, 38(2):183–91. doi:10.1002/ijc.2910380207 PMID:3015806

Mahfouz EM, Sadek RR, Abdel-Latief WM, Mosallem FA-H, Hassan EE (2014). The role of dietary and lifestyle factors in the development of colorectal cancer: case control study in Minia, Egypt. *Cent Eur J Public Health*, 22(4):215–22. doi:10.21101/cejph.a3919 PMID:25622477

Manousos O, Day NE, Trichopoulos D, Gerovassilis F, Tzonou A, Polychronopoulou A (1983). Diet and colorectal cancer: a case-control study in Greece. *Int J Cancer*, 32(1):1–5. doi:10.1002/ijc.2910320102 PMID:6862688

McCann SE, Randall E, Marshall JR, Graham S, Zielezny M, Freudenheim JL (1994). Diet diversity and risk of colon cancer in western New York. *Nutr Cancer*, 21(2):133–41. doi:10.1080/01635589409514311 PMID:8058524

Miller PE, Lazarus P, Lesko SM, Cross AJ, Sinha R, Laio J et al. (2013). Meat-related compounds and colorectal cancer risk by anatomical subsite. *Nutr Cancer*, 65(2):202–26. doi:10.1080/01635581.2013.756534 PMID:23441608

Morita M, Le Marchand L, Kono S, Yin G, Toyomura K, Nagano J et al. (2009). Genetic polymorphisms of CYP2E1 and risk of colorectal cancer: the Fukuoka Colorectal Cancer Study. *Cancer Epidemiol Biomarkers Prev*, 18(1):235–41. doi:10.1158/1055-9965.EPI-08-0698 PMID:19124503

Mrkonjic M, Chappell E, Pethe VV, Manno M, Daftary D, Greenwood CM, Gallinger S, Zanke BW, Knight JA, Bapat B. (2009). Association of apolipoprotein E polymorphisms and dietary factors in colorectal cancer 100(12):1966–1974.

Murtaugh MA, Ma KN, Sweeney C, Caan BJ, Slattery ML (2004). Meat consumption patterns and preparation, genetic variants of metabolic enzymes, and their association with rectal cancer in men and women. *J Nutr*, 134(4):776–84. doi:10.1093/jn/134.4.776 PMID:15051825

Murtaugh MA, Sweeney C, Ma KN, Caan BJ, Slattery ML (2005). The CYP1A1 genotype may alter the association of meat consumption patterns and preparation with the risk of colorectal cancer in men and women. *J Nutr*, 135(2):179–86. doi:10.1093/jn/135.2.179 PMID:15671210

Murtaugh MA, Sweeney C, Ma KN, Potter JD, Caan BJ, Wolff RK et al. (2006). Vitamin D receptor gene polymorphisms, dietary promotion of insulin resistance, and colon and rectal cancer. *Nutr Cancer*, 55(1):35–43. doi:10.1207/s15327914nc5501_5 PMID:16965239

Muscat JE, Wynder EL (1994). The consumption of well-done red meat and the risk of colorectal cancer. *Am J Public Health*, 84(5):856–8. doi:10.2105/AJPH.84.5.856 PMID:8179063

Nashar RM, Almurshed KS (2008). Colorectal cancer: a case control study of dietary factors, king faisal specialist hospital and researh center, riyadh, saudi arabia. *J Family Community Med*, 15(2):57–64. PMID:23012168

Navarro A, Díaz MP, Muñoz SE, Lantieri MJ, Eynard AR (2003). Characterization of meat consumption and risk of colorectal cancer in Cordoba, Argentina. *Nutrition*, 19(1):7–10. doi:10.1016/S0899-9007(02)00832-8 PMID:12507631

Navarro A, Muñoz SE, Lantieri MJ, del Pilar Diaz M, Cristaldo PE, de Fabro SP et al. (2004). Meat cooking habits and risk of colorectal cancer in Córdoba, Argentina. *Nutrition*, 20(10):873–7. doi:10.1016/j.nut.2004.06.008 PMID:15474875

Negri E, Bosetti C, La Vecchia C, Levi F, Tomei F, Franceschi S (1999). Allergy and other selected diseases and risk of colorectal cancer. *Eur J Cancer*, 35(13):1838–41. doi:10.1016/S0959-8049(99)00209-9 PMID:10674000

Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M et al. (2005). Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst*, 97(12):906–16. doi:10.1093/jnci/dji164 PMID:15956652

Norat T, Lukanova A, Ferrari P, Riboli E (2002). Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer*, 98(2):241–56. doi:10.1002/ijc.10126 PMID:11857415

Nöthlings U, Yamamoto JF, Wilkens LR, Murphy SP, Park SY, Henderson BE et al. (2009). Meat and heterocyclic amine intake, smoking, NAT1 and NAT2 polymorphisms, and colorectal cancer risk in the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev*, 18(7):2098–106. doi:10.1158/1055-9965.EPI-08-1218 PMID:19549810

Nowell S, Coles B, Sinha R, MacLeod S, Luke Ratnasinghe D, Stotts C et al. (2002). Analysis of total meat intake and exposure to individual heterocyclic amines in a

case-control study of colorectal cancer: contribution of metabolic variation to risk. *Mutat Res*, 506-507:175–85. doi:10.1016/S0027-5107(02)00164-1 PMID:12351157

Oba S, Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N et al. (2006). The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. *Cancer Lett*, 244(2):260–7. doi:10.1016/j.canlet.2005.12.037 PMID:16519996

Ollberding NJ, Wilkens LR, Henderson BE, Kolonel LN, Le Marchand L (2012). Meat consumption, heterocyclic amines and colorectal cancer risk: the Multiethnic Cohort Study. *Int J Cancer*, 131(7):E1125–33. doi:10.1002/ijc.27546 PMID:22438055

Pham NM, Mizoue T, Tanaka K, Tsuji I, Tamakoshi A, Matsuo K et al.; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan (2014). Meat consumption and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*, 44(7):641–50. doi:10.1093/jjco/hyu061 PMID:24842864

Phillips RL (1975). Role of life-style and dietary habits in risk of cancer among seventh-day adventists. *Cancer Res*, 35(11 Pt. 2):3513–22. PMID:1192416

Pickle LW, Greene MH, Ziegler RG, Toledo A, Hoover R, Lynch HT et al. (1984). Colorectal cancer in rural Nebraska. *Cancer Res*, 44(1):363–9. PMID:6690049

Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D et al. (1999). Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control*, 10(5):387–96. doi:10.1023/A:1008962219408 PMID:10530608

Pimenta CA, Latini FR, DE Lima JM, DA Silva TD, Felipe AV, DE Lima Pazine VM et al. (2014). Study of the polymorphisms of cyclooxygenase-2 (-765G>C) and 5-lipoxygenase (1708G>A) in patients with colorectal cancer. *Oncol Lett*, 7(2):513–8. doi:10.3892/ol.2013.1732 PMID:24396479

Ping Y, Ogushi Y, Okada Y, Haruki Y, Okazaki I, Ogawa T (1998). Lifestyle and colorectal cancer: A case-control study. *Environ Health Prev Med*, 3(3):146–51. doi:10.1007/BF02931705 PMID:21432494

Pou SA, Díaz MP, Osella AR (2012). Applying multilevel model to the relationship of dietary patterns and colorectal cancer: an ongoing case-control study in Córdoba, Argentina. *Eur J Nutr*, 51(6):755–64. doi:10.1007/s00394-011-0255-7 PMID:21990003

Pou SA, Niclis C, Aballay LR, Tumas N, Román MD, Muñoz SE et al. (2014). [Cancer and its association with dietary patterns in Córdoba (Argentina)] *Nutr Hosp*, 29(3):618–28. PMID:24559007

Qiao L, Feng Y (2013). Intakes of heme iron and zinc and colorectal cancer incidence: a meta-analysis of prospective studies. *Cancer Causes Control*, 24(6):1175–83. doi:10.1007/s10552-013-0197-x PMID:23568532

Ramzi NH, Chahil JK, Lye SH, Munretnam K, Sahadevappa KI, Velapasamy S et al. (2014). Role of genetic & environment risk factors in the aetiology of colorectal cancer in Malaysia. *Indian J Med Res*, 139(6):873–82. PMID:25109722

Roberts-Thomson IC, Ryan P, Khoo KK, Hart WJ, McMichael AJ, Butler RN (1996). Diet, acetylator phenotype, and risk of colorectal neoplasia. *Lancet*, 347(9012):1372–4. doi:10.1016/S0140-6736(96)91012-0 PMID:8637343

Rosato V, Bosetti C, Levi F, Polesel J, Zucchetto A, Negri E et al. (2013). Risk factors for young-onset colorectal cancer. *Cancer Causes Control*, 24(2):335–41. doi:10.1007/s10552-012-0119-3 PMID:23224326

Rouillier P, Senesse P, Cottet V, Valléau A, Faivre J, Boutron-Ruault MC (2005). Dietary patterns and the adenomacarcinoma sequence of colorectal cancer. *Eur J Nutr*, 44(5):311–8. doi:10.1007/s00394-004-0525-8 PMID:15316829

Ruder EH, Thiébaut AC, Thompson FE, Potischman N, Subar AF, Park Y et al. (2011). Adolescent and mid-life diet: risk of colorectal cancer in the NIH-AARP Diet and Health Study. *Am J Clin Nutr*, 94(6):1607–19. doi:10.3945/ajcn.111.020701 PMID:22071715

Saebø M, Skjelbred CF, Brekke Li K, Bowitz Lothe IM, Hagen PC, Johnsen E et al. (2008). CYP1A2 164 A–>C polymorphism, cigarette smoking, consumption of well-done red meat and risk of developing colorectal adenomas and carcinomas. *Anticancer Res*, 28:4C: 2289–95. PMID:18751408

Sandhu MS, White IR, McPherson K (2001). Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev*, 10(5):439–46. PMID:11352852

Satia JA, Keku T, Galanko JA, Martin C, Doctolero RT, Tajima A et al. (2005). Diet, lifestyle, and genomic instability in the North Carolina Colon Cancer Study. *Cancer Epidemiol Biomarkers Prev*, 14(2):429–36. doi:10.1158/1055-9965.EPI-04-0486 PMID:15734969

Satia JA, Tseng M, Galanko JA, Martin C, Sandler RS (2009). Dietary patterns and colon cancer risk in Whites and African Americans in the North Carolina Colon Cancer Study. *Nutr Cancer*, 61(2):179–93. doi:10.1080/01635580802419806 PMID:19235034

Satia-Abouta J, Galanko JA, Martin CF, Ammerman A, Sandler RS (2004). Food groups and colon cancer risk in African-Americans and Caucasians. *Int J Cancer*, 109(5):728–36. doi:10.1002/ijc.20044 PMID:14999782

Sato Y, Nakaya N, Kuriyama S, Nishino Y, Tsubono Y, Tsuji I (2006). Meat consumption and risk of colorectal cancer in Japan: the Miyagi Cohort Study. *Eur J Cancer Prev*, 15(3):211–8. doi:10.1097/01.cej.0000197455.87356.05 PMID:16679863

Sellers TA, Bazyk AE, Bostick RM, Kushi LH, Olson JE, Anderson KE et al. (1998). Diet and risk of colon

cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). *Cancer Causes Control*, 9(4):357–67. doi:10.1023/A:1008886715597 PMID:9794167

Seow A, Yuan JM, Sun CL, Van Den Berg D, Lee HP, Yu MC (2002). Dietary isothiocyanates, glutathione S-transferase polymorphisms and colorectal cancer risk in the Singapore Chinese Health Study. *Carcinogenesis*, 23(12):2055–61. doi:10.1093/carcin/23.12.2055 PMID:12507929

Shannon J, White E, Shattuck AL, Potter JD (1996). Relationship of food groups and water intake to colon cancer risk. *Cancer Epidemiol Biomarkers Prev*, 5(7):495–502. PMID:8827352

Silva TD, Felipe AV, Pimenta CA, Barão K, Forones NM (2012). CYP2E1 RsaI and 96-bp insertion genetic polymorphisms associated with risk for colorectal cancer. *Genet Mol Res*, 11(3):3138–45. doi:10.4238/2012.September.3.2 PMID:23007992

Singh PN, Fraser GE (1998). Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol*, 148(8):761–74. doi:10.1093/oxfordjournals.aje.a009697 PMID:9786231

Skjelbred CF, Saebø M, Hjartåker A, Grotmol T, Hansteen IL, Tveit KM et al. (2007). Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. *BMC Cancer*, 7(1):228. doi:10.1186/1471-2407-7-228 PMID:18093316

Slattery ML, Berry TD, Potter J, Caan B (1997). Diet diversity, diet composition, and risk of colon cancer (United States). *Cancer Causes Control*, 8(6):872–82. doi:10.1023/A:1018416412906 PMID:9427430

Slattery ML, Curtin K, Anderson K, Ma KN, Edwards S, Leppert M et al. (2000). Associations between dietary intake and Ki-ras mutations in colon tumors: a population-based study. *Cancer Res*, 60(24):6935–41. PMID:11156393

Slattery ML, Curtin K, Ma K, Edwards S, Schaffer D, Anderson K et al. (2002a). Diet activity, and lifestyle associations with p53 mutations in colon tumors. *Cancer Epidemiol Biomarkers Prev*, 11(6):541–8. PMID:12050095

Slattery ML, Curtin K, Ma K, Schaffer D, Potter J, Samowitz W (2002b). GSTM-1 and NAT2 and genetic alterations in colon tumors. *Cancer Causes Control*, 13(6):527–34. doi:10.1023/A:1016376016716 PMID:12195642

Slattery ML, Edwards SL, Samowitz W (1998). Stage of colon cancer at diagnosis: implications for risk factor associations? *Int J Epidemiol*, 27(3):382–7. doi:10.1093/ije/27.3.382 PMID:9698124

Slattery ML, Levin TR, Ma K, Goldgar D, Holubkov R, Edwards S (2003). Family history and colorectal cancer: predictors of risk. *Cancer Causes Control*, 14(9):879–87. doi:10.1023/B:CACO.0000003840.94591.76 PMID:14682445

Sørensen M, Autrup H, Olsen A, Tjønneland A, Overvad K, Raaschou-Nielsen O (2008). Prospective study of NAT1 and NAT2 polymorphisms, tobacco smoking and meat consumption and risk of colorectal cancer. *Cancer Lett*, 266(2):186–93. doi:10.1016/j.canlet.2008.02.046 PMID:18372103

Spencer EA, Key TJ, Appleby PN, Dahm CC, Keogh RH, Fentiman IS et al. (2010). Meat, poultry and fish and risk of colorectal cancer: pooled analysis of data from the UK dietary cohort consortium. *Cancer Causes Control*, 21(9):1417–25. doi:10.1007/s10552-010-9569-7 PMID:20437091

Squires J, Roebothan B, Buehler S, Sun Z, Cotterchio M, Younghusband B et al. (2010). Pickled meat consumption and colorectal cancer (CRC): a case-control study in Newfoundland and Labrador, Canada. *Cancer Causes Control*, 21(9):1513–21. doi:10.1007/s10552-010-9580-z PMID:20506038

Sriamporn S, Wiangnon S, Suwanrungruang K, Rungsrikaji D, Sukprasert A, Thipsuntornsak N et al. (2007). Risk factors for colorectal cancer in northeast Thailand: lifestyle related. *Asian Pac J Cancer Prev*, 8(4):573–7. PMID:18260731

Steck SE, Butler LM, Keku T, Antwi S, Galanko J, Sandler RS et al. (2014). Nucleotide excision repair gene polymorphisms, meat intake and colon cancer risk. *Mutat Res*, 762:24–31. doi:10.1016/j.mrfmmm.2014.02.004 PMID:24607854

Steinmetz KA, Potter JD (1993). Food-group consumption and colon cancer in the Adelaide Case-Control Study. II. Meat, poultry, seafood, dairy foods and eggs. *Int J Cancer*, 53(5):720–7. doi:10.1002/ijc.2910530503 PMID:8449595

Tabatabaei SM, Fritschi L, Knuiman MW, Boyle T, Iacopetta BJ, Platell C et al. (2011). Meat consumption and cooking practices and the risk of colorectal cancer. *Eur J Clin Nutr*, 65(6):668–75. doi:10.1038/ejcn.2011.17 PMID:21364608

Tajima K, Tominaga S (1985). Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res*, 76(8):705–16. PMID:3930448

Takachi R, Tsubono Y, Baba K, Inoue M, Sasazuki S, Iwasaki M et al.; Japan Public Health Center-Based Prospective Study Group (2011). Red meat intake may increase the risk of colon cancer in Japanese, a population with relatively low red meat consumption. *Asia Pac J Clin Nutr*, 20(4):603–12. PMID:22094846

Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F et al. (2000). Red meat intake and cancer risk: a study in Italy. *Int J Cancer*, 86(3):425–8. doi:10.1002/(SICI)1097-0215(20000501)86:3<425::AID-IJC19>3.0.CO;2-S PMID:10760833

Theodoratou E, Campbell H, Tenesa A, McNeill G, Cetnarskyj R, Barnetson RA et al. (2008). Modification of the associations between lifestyle, dietary

factors and colorectal cancer risk by APC variants. *Carcinogenesis*, 29(9):1774–80. doi:10.1093/carcin/bgn082 PMID:18375958

Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ et al. (2002). Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. *Cancer Causes Control*, 13(4):383–93. doi:10.1023/A:1015236701054 PMID:12074508

Tranah GJ, Bugni J, Giovannucci E, Ma J, Fuchs C, Hines L et al. (2006). O6-methylguanine-DNA methyltransferase Leu84Phe and Ile143Val polymorphisms and risk of colorectal cancer in the Nurses' Health Study and Physicians' Health Study (United States). *Cancer Causes Control*, 17(5):721–31. doi:10.1007/s10552-006-0005-y PMID:16633920

Turner F, Smith G, Sachse C, Lightfoot T, Garner RC, Wolf CR et al. (2004). Vegetable, fruit and meat consumption and potential risk modifying genes in relation to colorectal cancer. *Int J Cancer*, 112(2):259–64. doi:10.1002/ijc.20404 PMID:15352038

Tuyns AJ, Kaaks R, Haelterman M (1988). Colorectal cancer and the consumption of foods: a case-control study in Belgium. *Nutr Cancer*, 11(3):189–204. doi:10.1080/01635588809513986 PMID:3405870

Vlajinac H, Adanja B, Jarebinski M (1987). Case-control study of the relationship of diet and colon cancer. *Arch Geschwulstforsch*, 57(6):493–8. PMID:3435228

Wakai K, Hirose K, Matsuo K, Ito H, Kuriki K, Suzuki T et al. (2006). Dietary risk factors for colon and rectal cancers: a comparative case-control study. *J Epidemiol*, 16(3):125–35. doi:10.2188/jea.16.125 PMID:16710081

Wang J, Joshi AD, Corral R, Siegmund KD, Marchand LL, Martinez ME et al. (2012). Carcinogen metabolism genes, red meat and poultry intake, and colorectal cancer risk. *Int J Cancer*, 130(8):1898–907. doi:10.1002/ijc.26199 PMID:21618522

Wei EK, Colditz GA, Giovannucci EL, Fuchs CS, Rosner BA (2009). Cumulative risk of colon cancer up to age 70 years by risk factor status using data from the Nurses' Health Study. *Am J Epidemiol*, 170(7):863–72. doi:10.1093/aje/kwp210 PMID:19723749

Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC et al. (2004). Comparison of risk factors for colon and rectal cancer. *Int J Cancer*, 108(3):433–42. doi:10.1002/ijc.11540 PMID:14648711

Welfare M, Monesola Adeokun A, Bassendine MF, Daly AK (1999). Polymorphisms in GSTP1, GSTM1, and GSTT1 and susceptibility to colorectal cancer. *Cancer Epidemiol Biomarkers Prev*, 8(4 Pt 1):289–92. PMID:10207630

Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE (1990). Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med*, 323(24):1664–72. doi:10.1056/NEJM199012133232404 PMID:2172820

Williams CD, Satia JA, Adair LS, Stevens J, Galanko J, Keku TO et al. (2010). Associations of red meat, fat, and protein intake with distal colorectal cancer risk. *Nutr Cancer*, 62(6):701–9. doi:10.1080/01635581003605938 PMID:20661817

Wohlleb JC, Hunter CF, Blass B, Kadlubar FF, Chu DZ, Lang NP (1990). Aromatic amine acetyltransferase as a marker for colorectal cancer: environmental and demographic associations. *Int J Cancer*, 46(1):22–30. doi:10.1002/ijc.2910460107 PMID:2365498

Yeh CC, Hsieh LL, Tang R, Chang-Chieh CR, Sung FC (2003). Risk factors for colorectal cancer in Taiwan: a hospital-based case-control study. *J Formos Med Assoc*, 102(5):305–12. PMID:12874668

Yeh CC, Hsieh LL, Tang R, Chang-Chieh CR, Sung FC (2005). MS-920: DNA repair gene polymorphisms, diet and colorectal cancer risk in Taiwan. *Cancer Lett*, 224(2):279–88. doi:10.1016/j.canlet.2005.01.029 PMID:15914278

Zaridze D, Filipchenko V, Kustov V, Serdyuk V, Duffy S (1992). Diet and colorectal cancer: results of two case-control studies in Russia. *Eur J Cancer*, 29A(1):112–5. PMID:1445726

Zhang B, Li X, Nakama H, Zhang X, Wei N, Zhang X et al. (2002). A case-control study on risk of changing food consumption for colorectal cancer. *Cancer Invest*, 20(4):458–63. doi:10.1081/CNV-120002145 PMID:12094540

Zhang X, Giovannucci EL, Smith-Warner SA, Wu K, Fuchs CS, Pollak M et al. (2011). A prospective study of intakes of zinc and heme iron and colorectal cancer risk in men and women. *Cancer Causes Control*, 22(12):1627–37. doi:10.1007/s10552-011-9839-z PMID:21909950

Zhivotovskiy AS, Kutikhin AG, Azanov AZ, Yuzhalin AE, Magarill YA, Brusina EB (2012). Colorectal cancer risk factors among the population of South-East Siberia: a case-control study. *Asian Pac J Cancer Prev*, 13(10):5183–8. doi:10.7314/APJCP.2012.13.10.5183 PMID:23244132

2.3 Cancer of the stomach

The Working Group focused their review on studies that clearly defined red meat or processed meat (see Section 1 and Section 2.1). Studies were excluded if: (1) risk estimates were presented for total meat (red and processed meat combined) intake; (2) the type of meat was not defined or included white meat; (3) fewer than 100 cases were reported, due to the limited statistical power, as a large database of high-quality studies were available; (4) a more recent report from the same study was available; (5) risk estimates, adjusted for important confounders, were not available (crude estimates were not considered to be informative); (6) dietary patterns were the focus; and (7) outcomes were assessed using mortality data.

Several cohort and case–control studies, conducted in areas all over the world, have reported on the association between red and processed meat intake and cancer of the stomach. Important confounders for the assessment of this association are age, tobacco smoking, socioeconomic status (or education), and energy intake. Infection with *Helicobacter pylori* is a risk factor for cancer of the stomach, although its role in the association between intake of red or processed meat and cancer of the stomach is unclear. Salt intake may also be a confounder, as there is evidence that it increases the risk of cancer of the stomach, and it is also present in preserved or salted (processed) meat; however, it is difficult to distinguish the effect of salt from that of preserved meat.

2.3.1 Cohort studies

(a) Red meat

See Table 2.3.1 (web only; available at: http://publications.iarc.fr/564)

Of the publications on cohort studies that reported on the association between red meat and gastric cancer in the USA, Europe, Japan, and China, positive associations were reported in two studies: the EPIC cohort, which followed up 521 457 participants (González et al., 2006), and a case–control study of 226 gastric non-cardia cancer (GNCA) cases and 451 controls nested within the Shanghai Men's Health Study (SMHS) cohort (Epplein et al., 2014). [The Working Group noted that the strengths of the EPIC study (González et al., 2006) were its large size and analysis by subsite, histological type, and *H. pylori* infection. For the study nested within the Shanghai cohort (Epplein et al., 2014), the Working Group noted that this population had over 90% prevalence of CagA-positive *H. pylori* infection. In addition, socioeconomic status (or education) was not included as a covariate, and the items included in red meat were not detailed.]

Several other studies reported no association, or relative risks greater than one, but with wide confidence intervals that included the null value, between red meat consumption and gastric cancer. These studies included a cohort of 13 250 people older than 15 years from the Fukuoka Prefecture in Japan (Ngoan et al., 2002); a population-based cohort of 61 433 Swedish women (Larsson et al., 2006); the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC Study), which included 42 513 men and 57 777 women (Iso et al., 2007); the NIH-AARP study cohort of 494 979 individuals Cross et al. (2011); and a cohort of 120 852 men and women in the NLCS (Keszei et al., 2012). [The Working Group noted that processed meat was included in the definition of red meat in the NIH-AARP study.]

(b) Processed meat

See Table 2.3.2

Studies investigating the association between consumption of total processed meat, specific processed meat are presented below. Of the reviewed papers, we excluded papers reporting fewer than 100 cases (e.g. Kneller et al., 1991; Knekt et al., 1999; Khan et al., 2004). Studies focusing on dietary pattern (e.g. Pham et al., 2010), studies

from mortality data (e.g. McCullough et al., 2001, Ngoan et al.., 2002; Tokui et al., 2005; Iso et al., 2007), studies that were overlapping or updated (Cross et al., 2007) were excluded. Finally, seven studies were included.

Among 7990 American men of Japanese ancestry in a cohort study in which 150 cases of gastric cancer were observed, Nomura et al. (1990) reported an age-adjusted relative risk of 1.3 (95% CI, 0.9–2.0) for the highest versus the lowest frequency of intake of ham and sausage. [The Working Group noted that only age was adjusted. Smoking status was related to gastric cancer, but was not adjusted for. No subsite analysis was conducted.]

In a cohort of 11 907 randomly selected Japanese residents of Hawaii, USA, with an average follow-up period of 14.8 years, 108 observed cases of gastric cancer (44 women, 64 men) were identified, and no association was observed between processed meat consumption and incidence of gastric cancer (Galanis et al., 1998). The adjusted odds ratios for the highest frequency compared with the lowest frequency of consumption were 1.0 (95% CI, 0.5–1.9; 20 exposed cases) and 1.2 (95% CI, 0.6–2.4; 15 exposed cases) for men and women, respectively. [The Working Group noted that the case number was small, especially for women. An FFQ was used with only 13 items. No subsite analysis was conducted.]

González et al. (2006) examined the association between processed meat consumption and risk of gastric cancer in the EPIC study. The adjusted hazard ratio for the association with processed meat intake (highest vs lowest quintile) was 1.62 (95% CI, 1.08–2.41; P_{trend} = 0.02), which was more apparent in non-cardia cancer (HR, 1.92; 95% CI, 1.11–3.33; P_{trend} = 0.01) than in cardia cancer (HR, 1.14; 95% CI, 0.52–2.49; P_{trend} = 0.91). No difference was seen by histological type. When *H. pylori* infection was considered in the case–control data set nested in the present study, *H. pylori* antibody status did not appear to modify the association. [The Working Group noted that it was defined that white meat was not included. The population size was large, and detailed information on subsite, histological type, and *H. pylori* was available.]

In a population-based cohort of 61 433 Swedish women, Larsson et al. (2006) found a positive association between long-term processed meat consumption (using two surveys 10 years apart) and gastric cancer risk. During 18 years of follow-up, 156 incident cases of gastric cancer were diagnosed. The multivariate-adjusted hazard ratio for the highest versus the lowest serving per week of total processed meat was 1.66 (95% CI, 1.13–2.45; 67 exposed cases). [The Working Group noted that using a survey from two time points enabled the effect of long-term exposure to be seen. The number of cases was small. No subsite analysis was conducted.]

In the NIH-American Association of Retired Persons (NIH-AARP Diet and Health Study cohort of 494 979 individuals, aged 50–71 years, Cross et al. (2011) investigated intake of processed meat and meat cooking by-products with accrued 454 gastric cardia cancers (GCAs) and 501 GNCAs. After adjusting for important confounders, no association was observed between processed meat consumption and GCA and GNCA. For the highest versus the lowest quintile, the hazard ratios were 0.82 (95% CI, 0.59–1.14; P_{trend} = 0.285) and 1.09 (95% CI, 0.81–1.48; P_{trend} = 0.329), respectively. Nitrate and nitrite were not associated with gastric cancer. [The Working Group noted that this was a large study with a large number of cases, both for GCA and GNCA.]

In the Netherlands Cohort Study (NLCS), Keszei et al. (2012) reported on the association between intake of processed meat and gastric cancer risk in both men and women, after adjusting for important confounders. The case–cohort study consisted of 120 852 men and women, and after 16.3 years of follow-up, 163 GCAs and 489 GNCAs were observed. The

definition of processed meat included all meat items that had undergone some form of preservation, including cold cuts, croquettes, and all types of sausages. For the highest compared with the lowest category, the relative risks of intake of processed meat for GCA and GNCA were 1.49 (95% CI, 0.81–2.75; P_{trend} = 0.34; 32 exposed cases) and 1.19 (95% CI, 0.78–1.79; P_{trend} = 0.36; 77 exposed cases), respectively, in men. [The Working Group noted that the number of cases for gastric cancer of the cardia was small. A detailed FFQ with 150 items was used.]

Epplein et al. (2014) investigated the interaction between preserved meat, comprising intake of smoked meat, salted meat, and "Chinese" sausage, and *H. pylori* infection among 226 GNCA cases and 451 controls nested within the Shanghai Men's Health Study (SMHS prospective cohort. Overall, after adjusting for important confounders, including age, education, smoking, and total energy, preserved meat intake was not associated with gastric cancer. For the highest compared with the lowest category of intake, the relative risk of preserved meat was 1.01 (95% CI, 0.66–1.55; P_{trend} = 0.99). An effect modification by *H. pylori* was not apparent ($P_{interaction}$ = 0.09). [The Working Group noted that information on *H. pylori* infection was available. This was a study in a population with over 90% prevalence of CagA-positive *H. pylori* infection. Socioeconomic status or education was not adjusted for. Processed meat intake was low in the study population.]

2.3.2 Case–control studies

(a) Red meat

See Table 2.3.3 (web only; available at: http://publications.iarc.fr/564)

The Working Group reviewed 20 reports from case–control studies of gastric cancer reporting on the association with consumption of red meat (La Vecchia et al., 1987; Kono et al., 1988; Ward et al., 1997; De Stefani et al., 1998; Ji et al., 1998; Tavani et al., 2000; Palli et al., 2001; Takezaki et al., 2001; Chen et al., 2002; Huang et al., 2004; Lissowska et al., 2004; Wu et al., 2007; Hu et al., 2008; Navarro Silvera et al., 2008; Pourfarzi et al., 2009; Gao et al., 2011; Wang et al., 2012, 2014; Ward et al., 2012; Zamani et al., 2013). Although odds ratios greater than one were reported in all but three studies (Kono et al., 1988; Ji et al., 1998; Huang et al., 2004), the studies had several methodological limitations, including low precision power resulting from a small number of cases, use of an FFQ that may not have been validated, lack of adjustment for important confounders (e.g. smoking, total energy intake), inclusion of processed meat in the definition of red meat, and issues with the selection of hospital-based controls. Few studies reported analyses by subsite. The Working Group put more emphasis on two well-designed population-based case–control studies from the USA (Wu et al., 2007) and Canada (Hu et al., 2008) that used validated FFQs and adjusted for important confounders.

(b) Processed meat

The Working Group reviewed several case–control studies of gastric cancer that reported on the association with consumption of processed meat. Few studies were hospital-based (Lee et al., 1990; Boeing et al., 1991b; De Stefani et al., 1998, 2012; Huang et al., 2004), and the majority were population-based (Risch et al., 1985; La Vecchia et al., 1987; Sanchez-Diez et al., 1992; Ward & López-Carrillo, 1999; Palli et al., 2001; Takezaki et al., 2001; Chen et al., 2002; Nomura et al., 2003; Lissowska et al., 2004; Wu et al., 2007; Navarro Silvera et al., 2008; Pourfarzi et al., 2009; Hu et al., 2011; Ward et al., 2012).

(i) Hospital-based case–control studies

See Table 2.3.4

Several hospital-based case–control studies of gastric cancer were conducted in Taipei, Taiwan, China (Lee et al., 1990), Germany (Boeing et al., 1991a, b), Uruguay (De Stefani et al., 1998, 2012), and Japan (Huang et al., 2004). All but two

studies (Huang et al., 2004; De Stefani et al., 1998) reported increased risks of gastric cancer associated with processed meat consumption in multivariable models. The possibility of selection bias (due to the selection of hospital-based controls that may have been admitted for conditions leading to modifications in diet), recall bias, and confounding (due to inadequate adjustment for potential confounding variables) could not be ruled out.

(ii) Population-based case–control studies

See Table 2.3.5

Several population-based case–control studies of gastric cancer that reported on processed meat consumption were identified from Canada (Risch et al., 1985; Hu et al., 2011), Italy (La Vecchia et al., 1987; Palli et al., 2001), Poland (Boeing et al., 1991a; Lissowska et al., 2004), Spain (Sanchez-Diez et al., 1992), Mexico (Ward & López-Carrillo, 1999), China (Takezaki et al., 2001), the Islamic Republic of Iran (Pourfarzi et al., 2009), and the USA, specifically Nebraska (Chen et al., 2002; Ward et al., 1997, 2012), Hawaii (Nomura et al., 2003), Los Angeles (Wu et al., 2007), Connecticut, New Jersey, and western Washington state (Navarro Silvera et al., 2008).

Nearly all the studies reported odds ratios above one, although chance, bias, and confounding could not be ruled out as possible explanations for the observed excesses due to study limitations, including inadequate adjustment for potential confounders (e.g. tobacco smoking, total energy intake), recall bias, and information bias (e.g. large amount of information obtained from proxy respondents).

However, no association between processed meat and gastric cancer was reported in a population-based case–control study from 1988 to 1994 in Nebraska, USA (Ward et al., 2012): the multivariate odds ratio for the highest versus the lowest quartile of processed meat consumption was 0.97 (95% CI, 0.51–1.85; P_{trend} = 0.87; 46 exposed cases). Although, in a previous study, Ward et al. (1997) reported a positive association between processed meat and gastric cancer based on servings per day (P_{trend} = 0.06). The 2012 publication conducted a more accurate analysis, estimating grams per day and considering adequate confounding factors. [The Working Group noted that the response rate was high. No subsite analysis was conducted.]

2.3.3 Meta-analyses

(a) Red meat

Among the meta-analyses published on gastric cancer and meat consumption, Song et al. (2014) was the most recent and comprehensive, including 18 studies (4 cohort studies, 14 case–control studies) and 1 228 327 subjects, published between 1997 and 2013. Two case–control studies, Wang et al. (2012) and Navarro Silvera et al. (2008) were not included in the meta-analysis. [Therefore, the Working Group did not place great weight on the meta-analysis.] In the meta-analysis, high–red meat intake was found to be associated with an increased risk of gastric cancer. The summary relative risk of gastric cancer for the highest compared with the lowest categories was 1.37 (95% CI, 1.18–1.59; $P_{heterogeneity}$ < 0.001; I^2 = 67.6%). A significant association was also observed with population-based case–control studies (RR, 1.58; 95% CI, 1.22–2.06; $P_{heterogeneity}$ < 0.001; I^2 = 73.0%) and hospital-based case–control studies (RR, 1.63; 95% CI, 1.38–1.92; $P_{heterogeneity}$ = 0.284; I^2 = 19.1%), but not with cohort studies (RR, 1.00; 95% CI, 0.83–1.20; $P_{heterogeneity}$ = 0.158; I^2 = 33.9%). A significant association was also shown in the subgroup analysis by geographical area (Asia, Europe), publication year (≥ 2000), sample size (< 1000, ≥ 1000), and study quality score. The dose–response analysis revealed that gastric cancer was associated with a 17% increased risk per 100 g/day increment of red meat intake (RR, 1.17; 95% CI, 1.05–1.32). [The Working Group noted that the dose–response

analysis did not distinguish between cohort and case–control studies.]

(b) Processed meat

The most recent and comprehensive meta-analysis on the association between processed meat and gastric cancer was reported by Larsson et al. (2006). The meta-analysis included seven prospective cohort studies and 14 case–control studies. The summary relative risks of gastric cancer for the highest compared with the lowest categories of red meat intake were 1.24 (95% CI, 0.98–1.56; $P_{\text{heterogeneity}} = 0.04$) for cohort studies and 1.63 (95% CI, 1.31–2.01; $P_{\text{heterogeneity}} = 0.06$) for case–control studies. In an exposure–response analysis, the meta-relative risks for gastric cancer were 1.15 (95% CI, 1.04–1.27) for cohort studies and 1.38 (95% CI, 1.19–1.60) for case–control studies per 30 g/day increment of processed meat intake. An elevated risk was also observed for the highest compared with the lowest categories of intake of specific items of processed meat. For bacon, the relative risks were 1.38 (1.12–1.71) for cohort studies and 1.37 (1.06–1.78) for case–control studies, and for sausage, the relative risks were 1.26 (0.92–1.72) for cohort studies and 1.49 (1.09–2.03) for case–control studies. [The Working Group noted that one case–control study in Paraguay (Rolón et al., 1995) was not included. Specific items of processed meat such as ham, bacon, or sausage were analysed separately from processed meat.]

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Nomura et al. (1990) Hawaii, USA 1965–October 1986 Cohort study	7990; men of Japanese ancestry, born between 1919–1990, residing on the Hawaiian island of Oahu Exposure assessment method: questionnaire; FFQ for food and 24-h dietary recall for nutrients	Stomach	Risk by frequency for ham, bacon, and sausage			Age
			≤ 1 time/wk	71	1.0	
			2–4 times/wk	43	1.0 (0.7–1.4)	
			≥ 5 times/wk	36	1.3 (0.9–2.0)	
Galanis et al. (1998) Hawaii, USA (Japanese residents) 1975–1994 Cohort study	11 907 (5610 men, 6297 women); randomly selected Japanese residents of Hawaii Exposure assessment method: questionnaire; FFQ	Stomach	Risk by frequency for processed meats			Age, years of education, Japanese place of birth, sex
			Men and women:			
			None	34	1.0	
			1–2 times/wk	39	0.9 (0.6–1.4)	
			≥ 3 times/wk	35	1.0 (0.6–1.7)	
			Trend-test *P* value: 0.37			
		Stomach	Risk by frequency for processed meats			Age, years of education, Japanese place of birth, cigarette smoking, alcohol intake status
			Men:			
			None	18	1.0	
			1–2 times/wk	26	1.1 (0.6–2.0)	
			≥ 3 times/wk	20	1.0 (0.5–1.9)	
			Trend-test *P* value: 0.58			
		Stomach	Risk by frequency for processed meats			Age, years of education, Japanese place of birth
			Women:			
			None	16	1.0	
			1–2 times/wk	13	0.7 (0.3–1.4)	
			≥ 3 times/wk	15	1.2 (0.6–2.4)	
			Trend-test *P* value: 0.77			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
González et al. (2006) Ten European countries: Denmark (Aarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Greece, Italy (Florence, Turin, Varese, Naples, Ragusa), the Netherlands (Bilthoven, Utrecht), Norway, Spain (Granada, Murcia, Asturias, Navarre, San Sebastián), Sweden (Malmö, Umeå), and the United Kingdom (Norfolk, Oxford) 1992–1999/2002 (depending on the study centre) Cohort study	521 457; aged 35–70 yr, usually from the general population Exposure assessment method: questionnaire; FFQ	Stomach	Processed meat (quartiles)			Centre and age at EPIC study entry, and adjusted by sex, height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, alcohol intake, energy intake, vegetable intake, citrus fruit intake, and non-citrus fruit intake; red meat, poultry, and processed meat intakes were mutually adjusted
			Q1	NR	1.00	
			Q2	NR	1.10 (0.76–1.58)	
			Q3	NR	1.16 (0.79–1.69)	
			Q4	NR	1.62 (1.08–2.41)	
			Continuous, observed	NR	1.18 (0.97–1.43)	
			Continuous, calibrated	NR	1.64 (1.07–2.51)	
			Trend-test *P* value: 0.02			
		Stomach/cardia adenocarcinoma	Processed meat(quartiles)			
			Q1	NR	1.00	
			Q2	NR	1.19 (0.61–2.34)	
			Q3	NR	1.04 (0.51–2.12)	
			Q4	NR	1.14 (0.52–2.49)	
			Continuous, observed	NR	0.89 (0.59–1.34)	
			Continuous, calibrated	NR	0.76 (0.29–1.96)	
			Trend-test *P* value: 0.91			
		Stomach/ non-cardia adenocarcinoma	Processed meat (quartiles)			
			Q1	NR	1.00	
			Q2	NR	1.02 (0.60–1.71)	
			Q3	NR	1.02 (0.59–1.77)	
			Q4	NR	1.92 (1.11–3.33)	
			Continuous, observed	NR	1.36 (1.06–1.74)	
			Continuous, calibrated	NR	2.45 (1.43–4.21)	
			Trend-test *P* value: 0.01			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
González et al. (2006) (cont.)		Stomach/ adenocarcinoma	Processed meat (nested case–control study)			
			H. pylori antibody status: Negative	40	0.45 (0.05–4.01)	
			Positive	201	2.00 (1.06–3.79)	
			Trend-test *P* value: 0.48			
		Stomach/cardia adenocarcinoma	Processed meat (nested case–control study)			
			H. pylori antibody status: Negative	22	0.86 (0.03–27.0)	
			Positive	47	1.62 (0.47–5.55)	
			Trend-test *P* value: 0.42			
		Stomach/ non-cardia adenocarcinoma	Processed meat (nested case–control study)			
			H. pylori antibody status: Negative	12	0.002 (0.001–62.6)	
			Positive	113	2.67 (1.20–5.93)	
			Trend-test *P* value: 0.25			
Larsson et al. (2006) Uppsala and Västmanland counties, central Sweden Recruitment, 1987–1990; end of follow-up, 2004 Cohort study	61 433; women born in 1914 and 1948 Exposure assessment method: questionnaire; FFQ, age-specific portion sizes (mean of weighed and recorded food data of 213 random samples unpublished)	Stomach	Processed meat (servings/wk)			Age, education, BMI, energy, alcohol, fruits, vegetables
			< 1.5	51	1.00	
			1.5–2.9	38	1.46 (0.95–2.25)	
			≥ 3.0	67	1.66 (1.13–2.45)	
			Trend-test *P* value: 0.01			
		Stomach	Bacon or side pork (servings/wk)			
			0	52	1.00	
			0.1–0.4	66	1.27 (0.88–1.85)	
			≥ 0.5	38	1.55 (1.00–2.41)	
			Trend-test *P* value: 0.05			
		Stomach	Sausage or hot dogs (servings/wk)			
			< 0.4	24	1.00	
			0.4–0.9	55	1.44 (0.89–2.35)	
			≥ 1.0	77	1.50 (0.93–2.41)	
			Trend-test *P* value: 0.13			
		Stomach	Ham or salami (servings/wk)			
			< 0.4	45	1.00	
			0.4–1.4	46	0.97 (0.65–1.51)	
			≥ 1.5	65	1.48 (0.99–2.22)	
			Trend-test *P* value: 0.03			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2011) California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan), USA End of 2006 Cohort study	494 979; men and women aged 50–71 yr; enrolled in 1995–1996. The following individuals were excluded: duplicates and participants who died or moved before the baseline questionnaire was received or withdrew from the study, who did not return the baseline questionnaire, whose baseline questionnaire was filled in by someone else on their behalf, who had prevalent cancer according to the cancer registry or self-report, and who had extreme daily total energy intake Exposure assessment method: questionnaire; dietary intake of various food items was assessed through a 124-item FFQ (usual frequency of consumption and portion size information of foods over the previous 12 mo). Portion sizes and daily nutrient intakes were calculated from the 1994–1996 USA Department of Agriculture's Continuing Survey of Food Intakes by Individuals. "Processed meat" was bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs, and low-fat hot dogs made from poultry; meat added to complex food mixtures, such as pizza, chilli, lasagne, and stew, contributed to the relevant meat type	Stomach/cardia adenocarcinoma	Processed meat (quintile median, µg/1000 kcal)			Age, sex, BMI, education, ethnicity, tobacco smoking, alcohol drinking, usual physical activity at work, vigorous physical activity, daily intake of fruits, daily intake of vegetables, daily intake of saturated fat, daily intake of calories
			Q1 (1.7)	68	1.00	
			Q2 (4.5)	78	0.89 (0.64–1.24)	
			Q3 (7.8)	93	0.91 (0.66–1.26)	
			Q4 (12.6)	108	0.92 (0.67–1.28)	
			Q5 (23.2)	107	0.82 (0.59–1.14)	
			All processed meats, continuous (per 10 g/1000 kcal)	NR	1.00 (0.92–1.09)	
			Trend-test *P* value: 0.285			
		Stomach/ non-cardia adenocarcinoma	Processed meat (quintile median, µg/1000 kcal)			
			Q1 (1.7)	93	1.00	
			Q2 (4.5)	81	0.87 (0.64–1.18)	
			Q3 (7.8)	105	1.10 (0.82–1.47)	
			Q4 (12.6)	105	1.04 (0.77–1.41)	
			Q5 (23.2)	117	1.09 (0.81–1.48)	
			All processed meats, continuous (per 10 g/1000 kcal)	NR	1.02 (0.94–1.11)	
			Trend-test *P* value: 0.329			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2011) California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan), USA End of 2006 Cohort study	303 156; men and women aged 5–71 yr; enrolled in 1995–1996. The following individuals were excluded: duplicates and participants who died or moved before the risk factor questionnaire was received or withdrew from the study, who did not return the risk factor questionnaire, whose risk factor questionnaire was filled in by someone else on their behalf, who had prevalent cancer according to the cancer registry or self-report, and who had extreme daily total energy intake Exposure assessment method: questionnaire; dietary intake of various food items was assessed through a 124-item FFQ (usual frequency of consumption and portion size information of foods over the previous 12 mo). Portion sizes and daily nutrient intakes were calculated from the 1994-1996 USA Department of Agriculture's Continuing Survey of Food Intakes by Individuals. A risk factor questionnaire sent 6 mo later elicited detailed information on meat intake and cooking preferences. Nitrate and nitrite intake from processed meat was estimated using a database of measured values from 10 types of processed meats, which represented 90% of processed meats consumed in the USA	Stomach/ stomach cardia adenocarcinoma	Nitrate (quintile median, µg/1000 kcal)			Age, sex, BMI, education, ethnicity, tobacco smoking, alcohol drinking, usual physical activity at work, vigorous physical activity, daily intake of fruits, daily intake of vegetables, daily intake of saturated fat, daily intake of calories
			Q1 (24.9)	39	1.00	
			Q2 (66.9)	57	1.17 (0.77–1.77)	
			Q3 (112.7)	36	0.64 (0.40–1.02)	
			Q4 (174.5	61	0.94 (0.61–1.45)	
			Q5 (298.0)	62	0.81 (0.52–1.25)	
			All nitrates, continuous (per 100 µg/1000 kcal)	NR	0.99 (0.90–1.09)	
			Trend-test *P* value: 0.259			
		Stomach/cardia adenocarcinoma	Nitrite (quintile median, µg/1000 kcal)			
			Q1 (12.1)	44	1.00	
			Q2 (34.6)	40	0.72 (0.47–1.11)	
			Q3 (61.4)	55	0.88 (0.58–1.32)	
			Q4 (102.9)	61	0.87 (0.58–1.31)	
			Q5 (199.2)	55	0.71 (0.47–1.08)	
			All nitrites, continuous (per 100 µg/1000 kcal)	NR	0.89 (0.77–1.03)	
			Trend-test *P* value: 0.25			
		Stomach/ non-cardia adenocarcinoma	Nitrate (quintile median, µg/1000 kcal)			
			Q1 (24.2)	50	1.00	
			Q2 (66.9)	48	0.90 (0.60–1.35)	
			Q3 (112.7)	50	0.89 (0.59–1.33)	
			Q4 (174.5)	56	0.91 (0.61–1.37)	
			Q5 (298.0)	73	1.04 (0.69–1.55)	
			All nitrates, continuous (per 100 µg/1000 kcal)	NR	1.01 (0.92–1.10)	
			Trend-test *P* value: 0.578			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2011) (cont.)		Stomach/ non-cardia adenocarcinoma	Nitrite (quintile median, µg/1000 kcal)			
			Q1 (12.1)	54	1.00	
			Q2 (34.6)	44	0.77 (0.51–1.15)	
			Q3 (61.4)	48	0.79 (0.53–1.18)	
			Q4 (102.9)	67	1.04 (0.71–1.52)	
			Q5 (199.2)	64	0.93 (0.63–1.37)	
			All nitrite, continuous (per 100 µg/1000 kcal)	NR	1.02 (0.91–1.15)	
			Trend-test *P* value: 0.615			
Keszei et al. (2012) The Netherlands 1986–2002 Cohort study	120 852 individuals were recruited, and finally, 3923 sub-cohort members were used in the analysis (case–cohort design); the sample was selected from 204 municipal population registries throughout the Netherlands by sex-stratified random sampling Exposure assessment method: questionnaire; FFQ	Stomach/cardia adenocarcinoma	Processed meat intake			Age, smoking status, years of cigarette smoking, number of cigarettes smoked per day, total energy intake, BMI, alcohol intake, vegetable intake), fruit intake, levels of education, non-occupational physical activity
			Men:			
			Q1	23	1.00	
			Q2	34	1.51 (0.86–2.64)	
			Q3	21	0.89 (0.47–1.68)	
			Q4	29	1.26 (0.71–2.24)	
			Q5	32	1.49 (0.81–2.75)	
			Continuous (50 g/day increment)	139	1.15 (0.71–1.86)	
			Trend-test *P* value: 0.34			
		Stomach/ non-cardia adenocarcinoma	Processed meat intake (quintiles)			
			Men:			
			Q1	62	1.00	
			Q2	65	1.05 (0.71–1.56)	
			Q3	59	0.96 (0.64–1.44)	
			Q4	66	1.09 (0.73–1.63)	
			Q5	77	1.19 (0.78–1.79)	
			Trend-test *P* value: 0.36			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Keszei et al. (2012) The Netherlands 1986–2002 Cohort study (cont.)		Stomach/cardia adenocarcinoma	Processed meat intake			
			Women:			
			T1	7	1.00	
			T2	8	1.19 (0.41–3.44)	
			T3	9	1.12 (0.36–3.47)	
			Continuous (50 g/day increment)	24	0.70 (0.14–3.47)	
			Trend-test *P* value: 0.89			
		Stomach/ non-cardia adenocarcinoma	Processed meat intake (tertiles)			
			Women:			
			T1	51	1.00	
			T2	56	1.21 (0.81–1.81)	
			T3	53	1.11 (0.73–1.70)	
			Trend-test *P* value: 0.7			
Epplein et al. (2014) Shanghai, China Recruitment, 2002–2006; follow-up, 2009 Nested case–control study	Cases: 226 incident cases; permanent residents of urban Shanghai Controls: 451; permanent residents of urban Shanghai Exposure assessment method: questionnaire; validated FFQ; frequency of intake and not amount; preserved meat was smoked meat, salted meat, and Chinese sausage	Stomach/ non-cardia adenocarcinoma	Processed meat intake (times/mo), tertiles			Age, smoking, history of gastritis, regular aspirin use, total energy intake, high-risk *H. pylori* infection
			T1 (≤ 0.20)	71	1.00	
			T2 (0.21–1.42)	81	1.13 (0.74–1.72)	
			T3 (1.42)	74	1.01 (0.66–1.55)	
			Trend-test *P* value: 0.99			
		Stomach/ non-cardia adenocarcinoma	Processed meat intake (times/mo) in low risk residents (0–4 seropositive results to 6 *H. pylori* proteins), tertiles			
			T1	37	1.00	
			T2	29	0.96 (0.53–1.72)	
			T3	20	0.79 (0.41–1.51)	
			Trend-test *P* value: 0.49			
		Stomach/ non-cardia adenocarcinoma	Processed meat intake (times/mo) in high risk residents (seropositive results to 6 *H. pylori* proteins), tertiles			
			T1	34	1.00	
			T2	52	1.42 (0.80–2.52)	
			T3	54	1.34 (0.76–2.36)	
			Trend-test *P* value: 0.09			

BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; h, hour; ICD, International Classification of Diseases; mo, month; NR, not reported; wk, week; yr, year

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lee et al. (1990) Taipei City, Taiwan, China NA	Cases: 210; serial patients with stomach cancer from four major teaching hospitals in Taipei City Controls: 810; hospital controls, group-matched to cases by hospital, age, and sex, were recruited from among ophthalmic patients in study hospitals Exposure assessment method: questionnaire	Stomach	Salted meat consumption, before age 20			Adjusted for only risk factors significantly associated with stomach cancer in univariate analysis
			< 1 meal/mo	129	1.00	
			2–5 meals/mo	50	1.24	
			≥ 6 meals/mo	31	2.90	
			Salted meat consumption, between ages 20 and 39			
			< 1 meal/mo	137	1.00	
			2–5 meals/mo	55	1.26	
			≥ 6 meals/mo	18	3.26	
			Cured meat consumption, before age 20			
			< 1 meal/mo	31	1.00	
			2–5 meals/mo	156	1.61	
			≥ 6 meals/mo	23	1.72	
			Cured meat consumption, between ages 20 and 39			
			< 1 meal/mo	23	1.00	
			2–5 meals/mo	146	2.04	
			≥ 6 meals/mo	41	2.31	
			Salted meat consumption (frequency/mo)			
			< 1 meal/mo	266	1.00	
			2–5 meals/mo	105	1.48	
			≥ 6 meals/mo	49	3.18	
Boeing et al. (1991b) Germany 1985–1988	Cases: 143; the local coordinators identified all patients younger than 80 yr with histologically confirmed incident stomach cancer admitted to hospitals, and organized interviews in the hospitals, which were conducted by trained interviewers	Stomach	Processed meat, tertile 1 (lowest)	NR	1.00	Adjusted for age, sex, hospital, raw vegetables, citrus fruit, cheese, wholemeal bread
			Processed meat, tertile 2	NR	1.37 (0.82–2.31)	
			Processed meat, tertile 3 (highest)	NR	2.21 (1.32–3.71)	
			χ^2 for trend = 9.46	NR	–	

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Boeing et al. (1991b) Germany 1985–1988 (cont.)	Controls: 579; one group of controls consisted of patients from the hospitals, usually two controls of the same sex for each case and of comparable age; patients with a history of chronic atrophic gastritis or intestinal metaplasia were not considered to be eligible as controls; another type of control group consisted of visitors to the hospitals, who were approached directly by the interviewers during their temporary stay at the hospital; the interviewers were advised to keep their selection of visitor controls within age limits similar to those of the cases Exposure assessment method: questionnaire		Smoking of meat at home, no	68	1.00	Adjusted for age, sex, hospital
			Smoking of meat at home, yes (other wood)	57	0.88 (0.59–1.34)	
			Smoking of meat at home, yes (specifying spruce)	18	3.19 (1.50–6.75)	
			Nitrate (quintiles)			Age, sex, hospital, vitamin C, carotene, calcium
			Q1	NR	1.00	
			Q2	NR	0.93 (0.53–1.64)	
			Q3	NR	0.61 (0.32–1.19)	
			Q4	NR	0.61 (0.30–1.27)	
			Q5	NR	1.26 (0.59–2.70)	

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Boeing et al. (1991a) Poland (nine university hospitals) 1986–1990	Cases: 741 (including 374 carcinoma intestinalis and 259 carcinoma of the diffuse-type cases); consecutive incident cases of gastric cancer (adenocarcinoma), histologically confirmed (histological diagnosis from the surgical excision or, if the patient was not operable, endoscopy-based diagnosis using the obtained biopsy material) Controls: 741; hospital-based controls admitted to the hospital surgical wards for other reasons, matched to the cases by sex and age (≥ 5 yr) Exposure assessment method: questionnaire; dietary intake measured by an FFQ including 43 single-food items; frequency was estimated on a scale of six categories (ranging from "never" to "everyday"), but "no efforts were made to quantify food consumption"; tertiles based on the distribution of frequency categories among the controls were used in the analysis; "processed meat" was estimated by the items "sausages" and "ham of good quality"	Stomach/ adenocarcinoma (all)	Sausages			Age, sex, occupation, education, residency, fruit and vegetable score, non-white bread, cheese score
			Tertile 1 (low)	388	1.00	
			Tertile 2	266	1.20 (0.95–1.51)	
			Tertile 3 (high)	87	1.55 (1.07–2.26)	
			Trend-test *P* value: 0.01			
		Stomach/ adenocarcinoma (intestinal type)	Sausages			
			Tertile 1 (low)	NR	1.00	
			Tertile 2	NR	1.09 (0.79–1.52)	
			Tertile 3 (high)	NR	1.74 (1.00–3.01)	
			Trend-test *P* value: 0.09			
		Stomach/ adenocarcinoma (diffuse type)	Sausages			
			Tertile 1 (low)	NR	1.00	
			Tertile 2	NR	1.19 (0.79–1.79)	
			Tertile 3 (high)	NR	1.63 (0.85–3.15)	
			Trend-test *P* value: 0.13			
		Stomach/ adenocarcinoma (all)	Ham			
			Tertile 1 (low)	313	1.00	
			Tertile 2	268	0.89	
			Tertile 3 (high)	160	0.87	
			Trend-test *P* value: 0.29			

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (1998) Montevideo, Uruguay 1993–1996	Cases: 340; all newly diagnosed and microscopically confirmed patients with gastric cancer admitted to the four major hospitals in Montevideo Controls: 698; all controls were selected from the same hospitals and in the same period as the cases; controls were aged 25–84 yr, free of conditions related to digestive tract or nutritional disorders, and free of conditions related to tobacco and alcohol consumption Exposure assessment method: questionnaire	Stomach	Nitrite Processed meat	NR NR	0.53 (0.42–0.67) 0.96 (0.79–1.17)	Age, sex, residence, urban/rural status, tobacco duration, total alcohol consumption, mate drinking; red meat, barbecued meat, salted meat, processed meat, vegetables, and fruits were also included in the model

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Huang et al. (2004) Nagoya, Japan 1988–1998	Cases: 1988; of a total of 80 420 first-visit outpatients who visited the Aichi Cancer Center Hospital between January 1988 and June 1998; 8057 outpatients were excluded due to interviewer absence, inadmissible age (younger than 18 yr), or visit for a consultation; the questionnaire was finally administered to 72 363 subjects; among them, 71 277 (98.5%) completed the questionnaire adequately; after linkage between questionnaire data and medical data, 9032 subjects (12.7%) were excluded, as the cancer history of at least one of their parents or siblings was unknown Controls: 50 706; first-visit non-cancer subjects were regarded as the referent group Exposure assessment method: questionnaire; FFQ	Stomach	Risk by frequency for sausage			Age, sex
			≥ 3 times/wk vs < 3 times/wk, without gastric cancer family history	NR	1.03 (0.86–1.22)	
			≥ 3 times/wk vs < 3 times/wk, with gastric cancer family history	NR	0.87 (0.61–1.26)	

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (2012) Uruguay 1996–2004	Cases: 234 274; incident cases of stomach cancer (n = 274) diagnosed in the four major hospitals in Montevideo and microscopically confirmed (C15) Controls: 2532; hospital-based controls (from the same hospitals) with conditions unrelated to tobacco smoking and alcohol drinking Exposure assessment method: questionnaire; dietary intake measured by an FFQ including 64 food items (quantities recorded as servings/wk) and tested for reproducibility with good results; "processed meat" was bacon, sausage, mortadella, salami, saucisson, hot dog, ham, and air-dried and salted lamb; intakes were energy-adjusted by the residual method	Stomach	Processed meat by type *Men*			Age, residence, BMI, smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, alcohol drinking, mate consumption, total energy intake, total vegetable and fruit intake, total white meat and red meat intake.
			Bacon	NR	0.64 (0.49–0.83)	
			Sausage	NR	1.02 (0.86–1.21)	
			Mortadella	NR	0.99 (0.87–1.14)	
			Salami	NR	0.99 (0.86–1.15)	
			Saucisson	NR	1.22 (1.03–1.44)	
			Hot dog	NR	1.49 (1.30–1.70)	
			Ham	NR	0.96 (0.81–1.14)	
			Salted meat	NR	1.02 (0.87–1.19)	
			Processed meat by type *Women*			
			Bacon	NR	0.72 (0.46–1.13)	
			Sausage	NR	1.16 (0.88–1.53)	
			Mortadella	NR	1.25 (1.01–1.56)	
			Salami	NR	0.76 (0.58–0.99)	
			Saucisson	NR	1.48 (1.07–2.04)	
			Hot dog	NR	1.50 (1.23–1.83)	
			Ham	NR	1.24 (1.03–1.44)	
			Salted meat	NR	0.62 (0.36–1.07)	
			Processed meat *Men*			
			T1 (< 11.4 g/day)	NR	1.00	
			T2 (11.5–28.2 g/day)	NR	1.60 (1.02–2.49)	
			T3 (≥ 28.3 g/day)	NR	1.93 (1.25–2.98)	
			Trend-test P value: 0.003			
			Processed meat *Women*			
			T1 (< 11.4 g/day)	NR	1.00	
			T2 (11.5–28.2 g/day)	NR	3.07 (1.58–5.98)	
			T3 (≥ 28.3 g/day)	NR	4.51 (2.34–8.70)	
			Trend-test P value: 0.0001			

BMI, body mass index; CI, confidence intervals; FFQ, food frequency questionnaire; mo, month; NA, not available; NR, not reported

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Risch et al. (1985) Toronto, Winnipeg, and St John's, Canada 1979–1982	Cases: 246; aged 35–79 yr with newly diagnosed gastric cancer; all cases were histologically verified Controls: 246; randomly selected population controls; individually matched by age, sex, and area of residence Exposure assessment method: questionnaire	Stomach	Smoked meats (per 100 g/day increase)	246	2.22 (1.19–4.15)	Total food consumption and ethnicity
			Nitrite (1 mg/day)	246	1.71 (1.24–2.37)	
			Nitrate (100 g/day)	246	0.66 (0.54–0.81)	
			Dimethylnitrosamine (10 µg/day)	246	0.94 (0.14–6.13)	
			Smoked meats (per 100 g/day increase)	246	3.92 (1.76–8.75)	Matched by age, sex, area of residence, and adjusted for total food consumption, ethnicity, and consumption of grains, chocolate, fibrous foods, eggs, and public water supply

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
La Vecchia et al. (1987) Greater Milan area, Italy January 1985–June 1986	Cases: 206; incident cases of histologically confirmed gastric cancer diagnosed within the year preceding the interview and admitted to the National Cancer Institute, to several university clinics (chiefly surgery), and to the Ospedale Maggiore in Milan Controls: 474; hospital-based controls who were admitted to the Ospedale Maggiore in Milan and to several university clinics; patients admitted for malignant disorders, any disease of the digestive tract, or any condition related to consumption of alcohol or tobacco that might have resulted in modification of the diet were excluded Exposure assessment method: questionnaire; dietary intake was based on an FFQ including 29 food items; individuals were asked to indicate the frequency of consumption of these items per week before the onset of the disease that led to hospital admission and to recall any major change in frequency of intake of the same foods during the 10-yr period preceding the diagnosis; items related to processed meat were "raw ham", "ham", "salami and other sausages", and "canned meat"	Stomach	Raw ham intake (frequency)			Age, sex
			Low	75	1.00	
			Intermediate	37	0.62	
			High	94	1.04	
			Salami and other sausages intake (frequency)			
			Low	114	1.00	
			Intermediate	31	0.56	
			High	61	1.27	
			Canned meat intake (frequency)			
			Low	187	1.00	
			Intermediate	15	0.95	
			High	4	0.77	

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Sanchez-Diez et al. (1992) Province of León, Spain 1975–1986	Cases: 109; total cases diagnosed between 1975 and 1986 at a specific study site Controls: 123; all people born locally or who had been living in the area for the past 10 yr; one control was randomly selected and matched by year of birth, sex, and municipality of residence Exposure assessment method: questionnaire	Stomach	Homemade sausages, not consumed	13	1.00	Matched by year of birth, sex, municipality of residence
			Homemade sausages, daily consumption	42	3.34 (1.51–7.37)	
			Smoked sausages, not consumed	9	1.00	
			Smoked sausages, daily consumption	40	3.55 (1.59–7.94)	
Ward & López-Carrillo (1999) Mexico City, Mexico 1989–1990	Cases: 220; 267 newly diagnosed cases of gastric cancer in patients aged 20 yr and older were identified between 1989 and 1990 at 15 metropolitan area hospitals in Mexico City; these cases represented approximately 80% of those reported to the Mexican Cancer Registry in the same period; 22 (8.2%) of the identified cases were unavailable for interview; a further 20 cases (7.5%) were excluded because the pathology material could not be obtained, and five cases (1.9%) were excluded because their tumours were not adenocarcinomas of the stomach Controls: 752; controls were an age-stratified random sample of Mexico City metropolitan area residents selected from the 1986–1987 household sampling frame of the Mexican National Survey for Health and Nutrition Exposure assessment method: questionnaire	Stomach/ adenocarcinoma	Processed meat intake (times/wk)			Age, sex, total calories, chilli pepper consumption, added salt, history of peptic ulcer, cigarette smoking, socioeconomic status
			< 1	25	1.0	
			1–2	67	2.0 (1.0–3.8)	
			3–5	68	2.8 (1.4–5.7)	
			≥ 6	60	3.2 (1.5–6.6)	
			Trend-test *P* value: 0.002			
		Stomach/ adenocarcinoma (intestinal)	Processed meat intake (times/wk)			
			< 1	NR	1.0	
			1–2	NR	2.2 (0.9–5.2)	
			3–5	NR	2.6 (1.0–6.4)	
			≥ 6	NR	2.6 (1.0–7.0)	
		Stomach/ adenocarcinoma (diffuse)	Processed meat intake (times/wk)			
			< 1	NR	1.0	
			1–2	NR	1.1 (0.5–2.8)	
			3–5	NR	1.8 (0.7–4.6)	
			≥ 6	NR	2.2 (0.8–6.0)	

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Palli et al. (2001) Florence, Italy 1985–1987	Cases: 382; all gastric cancer cases were histologically confirmed and originally classified according to the Lauren classification by review of all available surgical pathology specimens Controls: 561; computerized lists of residents were used to identify a random sample of eligible population controls Exposure assessment method: questionnaire	Stomach	Cured and canned meat intake, MSI+ Tertile 1 Tertile 2 Tertile 3 Trend-test *P* value: 0.1 Cured and canned meat intake, MSI– Tertile 1 Tertile 2 Tertile 3 Trend-test *P* value: 0.05	 NR NR NR NR NR NR 	 1.0 1.0 (0.5–2.4) 1.0 (0.4–2.6) 1.0 1.2 (0.6–2.3) 1.9 (1.0–3.7) 	Adjusted for non-dietary variables (age, sex, social class, family history of gastric cancer, area of residence, BMI), total energy, consumption tertiles of each food of interest (reference, lowest tertile)
Takezaki et al. (2001) Pizhou, Jiangsu Province, China 1996 (1995 for controls)–2000	Cases: 187 stomach cancer; incident cases of histopathologically confirmed cases of stomach cancer who visited the Pizhou City Municipal Hospital Controls: 333; healthy residents of Pizhou, matched to cases by sex, ethnicity, and age (≤ 2 yr); controls came from three different sources: individuals from a population-based ecological study conducted in 1995–1996; individuals selected between 1995 and 1998 in the general population; individuals selected between 1998 and 2000 Exposure assessment method: questionnaire; food consumption frequency was measured at the time of the interview and 10 yr previously; among the available items, only "salted meat" could be used to estimate "processed meat" consumption; previously used in a case–control and ecological study	Stomach	Salted meat, < 1 time/mo Salted meat, 1–3 times/mo Salted meat, ≥ 1 time/wk Trend-test *P* value: 0.001	NR NR NR	1.00 3.82 (2.24–6.50) 2.36 (1.08–5.15)	Age, sex, smoking, drinking

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Chen et al. (2002) Eastern Nebraska, USA 1 July 1988–31 June 1993	Cases: 124 (distal stomach); incident, histologically confirmed cases of stomach adenocarcinoma, identified from the Nebraska Cancer Registry or 14 participating hospitals covering > 90% of the study population Controls: 449; population-based controls selected from the control group of a previous case–control study conducted in 1986–1987 in the same base population; frequency-matched to the whole distribution of cases by age, sex, and vital status Exposure assessment method: questionnaire; dietary assessment was based on a modified version of the short HHHQ, with the addition of several food items (e.g. for processed meat); subjects were asked to recall frequency of consumption of 54 dietary items before 1985; "processed meat" was bacon; sausage, including breakfast sausage; processed or smoked ham bought from the store; meat that was cured or smoked at home; sandwich meats, such as bologna or salami; and hot dogs	Stomach/distal adenocarcinoma	Processed meat (times/day), quartiles			Age, sex, energy intake, respondent type, BMI, alcohol use, tobacco use, education, family history, vitamin supplement use
			Q1	NR	1.00	
			Q2	NR	1.70 (0.77–3.70)	
			Q3	NR	1.20 (0.55–2.70)	
			Q4	NR	1.70 (0.72–3.90)	

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Nomura et al. (2003) Hawaii, USA 1993–1999	Cases: 658; from eight major hospitals on the Hawaiian Islands and identified by the rapid reporting system of the Hawaii Tumor Registry Controls: 446; controls identified from lists of Oahu residents interviewed by the Health Surveillance Program, which identifies a 1% representative random sample of all households in the state Exposure assessment method: questionnaire	Stomach	Processed meat *Men* T1 T2 T3 Trend-test *P* value: 0.19 Processed meat, Tertiles *Women* T1 T2 T3 Trend-test *P* value: 0.43 Bacon, Tertiles *Men* T1 T2 T3 Trend-test *P* value: 0.36 Bacon *Women* T1 T2 T3 Trend-test *P* value: 0.4	 NR NR NR NR NR NR NR NR NR NR NR NR	 1.0 1.8 (1.0–3.3) 1.7 (0.9–3.3) 1.0 0.6 (0.3–1.3) 0.7 (0.3–1.5) 1.0 1.3 (0.7–2.2) 1.3 (0.7–2.4) 1.0 0.6 (0.3–1.3) 1.1 (0.5–2.3)	Age, ethnicity, smoking, education, history of gastric ulcer, NSAID use, family history of gastric cancer, total calories, intake of other foods and food groups
Lissowska et al. (2004) Warsaw, Poland 1994–1996	Cases: 274; cases consisted of Warsaw residents newly diagnosed with stomach cancer; identified by collaborating physicians in each of the 22 hospitals Controls: 463; controls randomly selected from the general population in Warsaw Exposure assessment method: questionnaire	Stomach	Sausages ,Quartiles (frequency/wk) Q1 Q2 Q3 Q4 Trend-test *P* value: 0.81	 NR NR NR NR	 1.00 1.13 (0.74–1.71) 0.75 (0.48–1.17) 1.23 (0.79–1.93)	Age, sex, education, smoking, calories from food

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Wu et al. (2007) Los Angeles, USA 1992–1997	Cases: 829; all incident cancers were identified by the Los Angeles Cancer Surveillance Program, a population-based tumour registry Controls: 1308; control subjects were individually matched to interviewed case patients by sex, race, and date of birth (± 5 yr) in the neighbourhoods Exposure assessment method: questionnaire	Stomach/cardia adenocarcinoma	Processed meat, quartiles (g/day)			Age, sex, race, birthplace, education, smoking, BMI (kg/m^2), reflux, use of vitamins, total calories
			Q1	NR	1.00	
			Q2	NR	0.84 (0.60–1.30)	
			Q3	NR	0.76 (0.50–1.20)	
			Q4	NR	0.89 (0.60–1.40)	
			Trend-test *P* value: 0.57			
		Stomach/distal adenocarcinoma	Processed meat, quartiles (g/day)			
			Q1	NR	1.00	
			Q2	NR	1.54 (1.10–2.20)	
			Q3	NR	1.22 (0.80–1.80)	
			Q4	NR	1.65 (1.10–2.50)	
			Trend-test *P* value: 0.049			
		Stomach/cardia adenocarcinoma	Processed meat among subjects infected with *H. pylori*, quartiles of intake (g/day)			
			Q1	NR	1.00	
			Q2	NR	1.16 (0.60–2.40)	
			Q3	NR	0.40 (0.20–0.96)	
			Q4	NR	0.57 (0.20–1.30)	
			Trend-test *P* value: 0.08			
		Stomach/distal adenocarcinoma	Processed meat among subjects infected with *H. pylori*, quartiles of intake (g/day)			
			Q1	NR	1.00	
			Q2	NR	2.46 (1.10–5.20)	
			Q3	NR	1.40 (0.60–3.10)	
			Q4	NR	1.97 (0.90–4.50)	
			Trend-test *P* value: 0.3			

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Navarro Silvera et al. (2008) Connecticut, New Jersey and western Washington, USA 1993–early 1995	Cases: 607; incident cases of stomach adenocarcinoma (255 cardia cases, 352 non-cardia cases); this population was part of a larger population of cases also containing cases of cardia and non-cardia gastric adenocarcinoma; gastric cardia adenocarcinoma were considered as the "target cases", whereas non-cardia gastric adenocarcinoma cases were considered as the "comparison case group", which was frequency-matched to the "target group"	Stomach/cardia adenocarcinoma	High-nitrite meats, for an increase in intake of 1 serving/day	NR NR	1.19 (0.74–1.91)	Sex; site; age, "race"; proxy status; income; education; usual BMI; cigarettes per day; consumption of beer, wine, and liquor each; energy intake
		Stomach/ non-cardia adenocarcinoma	High-nitrite meats, for an increase in intake of 1 serving/day	NR NR	1.88 (1.24–2.84)	

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Navarro Silvera et al. (2008) Connecticut, New Jersey and western Washington, USA 1993–early 1995 (cont.)	Controls: 687; population-based controls frequency-matched to the expected distribution of the "target cases" by 5-yr age group, sex (in New Jersey and Washington state), "race" (in New Jersey), and study site; controls aged 30–64 yr were identified by the random digit dialling method, and controls aged 65–79 yr were identified by Health Care Financing Administration rosters Exposure assessment method: questionnaire; an expanded version of an FFQ developed and validated by investigators at the Fred Hutchinson Cancer Research Center was used to assess usual food consumption in the period 3–5 yr before diagnosis (cases) or interview (controls); processed meat was defined as " high-nitrite meats", including smoked turkey lunchmeat; cured, smoked ham lunchmeat; bologna; salami; hot dogs; sausage, not including breakfast sausage; bacon; and breakfast sausage					

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Pourfarzi et al. (2009) Ardabil Province, Iran 2004–2005	Cases: 217; identified from the Ardabil Cancer Registry; cases were eligible if they were in people who had been Ardabil residents for at least 5 yr before diagnosis, were aged older than 18 yr, had not had previous gastric surgery, and had a positive histopathological report of gastric carcinoma; in addition to the cases routinely reported to the cancer registry, active surveillance for gastric cancer was conducted by the cancer registry through all hospitals and clinics, particularly those of three gastroenterologists, to maximize the completeness of case ascertainment Controls: 394; two controls were sought for each case and frequency-matched to the case group by age (5 yr) and sex; controls had to satisfy the same residency and age criteria as cases, and were randomly selected from the community using a computer-based sampling frame that had been created for the annual household survey by the health department; this database was used to select random households, which were then visited by health professionals seeking eligible individuals; if such a person was not available or did not satisfy the inclusion criteria, the immediate neighbour to the right-hand side was visited Exposure assessment method: questionnaire	Stomach	Smoked meats, ≥ 1 time/mo Smoked meats, never Processed meats, ≥ 1 time/mo Processed meats, never	20 189 23 188	0.91 (0.40–2.09) 1.00 1.14 (0.55–2.37) 1.00	Sex, age group, education, family history of gastric cancer, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake, *H. pylori*

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2011) Canada 1994–1997	Cases: 1182; this study involved histologically confirmed cancer cases Controls: 5039; individuals without cancer were selected from a random sample of the population within each province, with an age and sex distribution similar to that of all cancer cases Exposure assessment method: questionnaire	Stomach	Processed meat (servings/wk) ≤ 0.94 0.95–2.41 2.42–5.41 ≥ 5.42 Trend-test *P* value: 0.0001	 NR NR NR NR	 1.0 1.2 (1.0–1.6) 1.3 (1.0–1.7) 1.7 (1.3–2.2)	Age, province, education, BMI, alcohol drinking, smoking, vegetable and fruit intake, total energy
Ward et al. (2012) USA (66 counties in eastern Nebraska) 1 July 1988–30 June 1993	Cases: 154 for stomach; incident cases of adenocarcinoma of the stomach, identified from the Nebraska Cancer Registry and confirmed by histological review Controls: 449; controls randomly selected from a previous population-based case–control study in the same geographical region; matched by race, age, sex, and vital status Exposure assessment method: questionnaire; dietary information was obtained using a short version of the HHHQ; "processed meat" was bacon, sausage, luncheon meats, hot dogs, ham, and home-cured meat	Stomach	Processed meat Q1 (≤ 16.1 g/day) Q2 (16.2–29.6 g/day) Q3 (29.7–52.3 g/day) Q4 (> 52.3 g/day) OR (per 10 g/day) Trend-test *P* value: 0.87	 30 38 40 46 NR	 1.00 0.81 (0.45–1.46) 1.17 (0.66–2.10) 0.97 (0.51–1.85) 1.03 (0.97–1.10)	Age, sex, smoking status,, education, vitamin C, fibre, carbohydrates, total calories

BMI, body mass index; CI, confidence intervals; FFQ, food frequency questionnaire; *H. pylori*, *Helicobacter pylori*; HHHQ, Health Habits and History Questionnaire; mo, month; MSI, microsatellite instability; NR, not reported; OR, odds ratio

References

Boeing H, Jedrychowski W, Wahrendorf J, Popiela T, Tobiasz-Adamczyk B, Kulig A (1991a). Dietary risk factors in intestinal and diffuse types of stomach cancer: a multicenter case-control study in Poland. *Cancer Causes Control*, 2(4):227–33. doi:10.1007/BF00052138 PMID:1873452

Boeing H, Frentzel-Beyme R, Berger M, Berndt V, Göres W, Körner M et al. (1991b). Case-control study on stomach cancer in Germany. *Int J Cancer*, 47(6):858–64. doi:10.1002/ijc.2910470612 PMID:2010228

Chen H, Ward MH, Graubard BI, Heineman EF, Markin RM, Potischman NA et al. (2002). Dietary patterns and adenocarcinoma of the esophagus and distal stomach. *Am J Clin Nutr*, 75(1):137–44. PMID:11756071

Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R (2007). A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med*, 4(12):12 (e 325): e325 doi:10.1371/journal.pmed.0040325 PMID:18076279

Cross AJ, Freedman ND, Ren J, Ward MH, Hollenbeck AR, Schatzkin A et al. (2011). Meat consumption and risk of esophageal and gastric cancer in a large prospective study. *Am J Gastroenterol*, 106(3):432–42. doi:10.1038/ajg.2010.415 PMID:20978481

De Stefani E, Boffetta P, Mendilaharsu M, Carzoglio J, Deneo-Pellegrini H (1998). Dietary nitrosamines, heterocyclic amines, and risk of gastric cancer: a case-control study in Uruguay. *Nutr Cancer*, 30(2):158–62. doi:10.1080/01635589809514656 PMID:9589435

De Stefani E, Boffetta P, Ronco AL, Deneo-Pellegrini H, Correa P, Acosta G et al. (2012). Processed meat consumption and risk of cancer: a multisite case-control study in Uruguay. *Br J Cancer*, 107(9):1584–8. doi:10.1038/bjc.2012.433 PMID:23011480

Epplein M, Zheng W, Li H, Peek RM Jr, Correa P, Gao J et al. (2014). Diet, Helicobacter pylori strain-specific infection, and gastric cancer risk among Chinese men. *Nutr Cancer*, 66(4):550–7. doi:10.1080/01635581.2014.894096 PMID:24666234

Galanis DJ, Kolonel LN, Lee J, Nomura A (1998). Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. *Int J Epidemiol*, 27(2):173–80. doi:10.1093/ije/27.2.173 PMID:9602395

Gao Y, Hu N, Han XY, Ding T, Giffen C, Goldstein AM et al. (2011). Risk factors for esophageal and gastric cancers in Shanxi Province, China: a case-control study. *Cancer Epidemiol*, 35(6):e91–9. doi:10.1016/j.canep.2011.06.006 PMID:21846596

González CA, Jakszyn P, Pera G, Agudo A, Bingham S, Palli D et al. (2006). Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst*, 98(5):345–54. doi:10.1093/jnci/djj071 PMID:16507831

Hu J, La Vecchia C, DesMeules M, Negri E, Mery L, Group CCRE; Canadian Cancer Registries Epidemiology Research Group (2008). Meat and fish consumption and cancer in Canada. *Nutr Cancer*, 60(3):313–24. doi:10.1080/01635580701759724 PMID:18444165

Hu J, La Vecchia C, Morrison H, Negri E, Mery L; Canadian Cancer Registries Epidemiology Research Group (2011). Salt, processed meat and the risk of cancer. *Eur J Cancer Prev*, 20(2):132–9. doi:10.1097/CEJ.0b013e3283429e32 PMID:21160428

Huang XE, Hirose K, Wakai K, Matsuo K, Ito H, Xiang J et al. (2004). Comparison of lifestyle risk factors by family history for gastric, breast, lung and colorectal cancer. *Asian Pac J Cancer Prev*, 5(4):419–27. PMID:15546249

Iso H, Kubota Y; Japan Collaborative Cohort Study for Evaluation of Cancer (2007). Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev*, 8:Suppl: 35–80. PMID:18260705

Ji BT, Chow WH, Yang G, McLaughlin JK, Zheng W, Shu XO et al. (1998). Dietary habits and stomach cancer in Shanghai, China. *Int J Cancer*, 76(5):659–64. doi:10.1002/(SICI)1097-0215(19980529)76:5<659::AID-IJC8>3.0.CO;2-P PMID:9610722

Keszei AP, Schouten LJ, Goldbohm RA, van den Brandt PA (2012). Red and processed meat consumption and the risk of esophageal and gastric cancer subtypes in The Netherlands Cohort Study. *Ann Oncol*, 23(9):2319–26. doi:10.1093/annonc/mdr615 PMID:22351741

Khan MM, Goto R, Kobayashi K, Suzumura S, Nagata Y, Sonoda T et al. (2004). Dietary habits and cancer mortality among middle aged and older Japanese living in hokkaido, Japan by cancer site and sex. *Asian Pac J Cancer Prev*, 5(1):58–65. PMID:15075007

Knekt P, Järvinen R, Dich J, Hakulinen T (1999). Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study. *Int J Cancer*, 80(6):852–6. doi:10.1002/(SICI)1097-0215(19990315)80:6<852::AID-IJC9>3.0.CO;2-S PMID:10074917

Kneller RW, McLaughlin JK, Bjelke E, Schuman LM, Blot WJ, Wacholder S et al. (1991). A cohort study of stomach cancer in a high-risk American population. *Cancer*, 68(3):672–8. doi:10.1002/1097-0142(19910801)68:3<672::AID-CNCR2820680339>3.0.CO;2-T PMID:2065291

Kono S, Ikeda M, Tokudome S, Kuratsune M (1988). A case-control study of gastric cancer and diet in northern Kyushu, Japan. *Jpn J Cancer Res*, 79(10):1067–74. doi:10.1111/j.1349-7006.1988.tb01528.x PMID:3143695

La Vecchia C, Negri E, Decarli A, D'Avanzo B, Franceschi S (1987). A case-control study of diet and gastric cancer

in northern Italy. *Int J Cancer*, 40(4):484–9. doi:10.1002/ijc.2910400409 PMID:3117710

Larsson SC, Bergkvist L, Wolk A (2006). Processed meat consumption, dietary nitrosamines and stomach cancer risk in a cohort of Swedish women. *Int J Cancer*, 119(4):915–9. doi:10.1002/ijc.21925 PMID:16550597

Lee HH, Wu HY, Chuang YC, Chang AS, Chao HH, Chen KY et al. (1990). Epidemiologic characteristics and multiple risk factors of stomach cancer in Taiwan. *Anticancer Res*, 10(4):875–81. PMID:2382983

Lissowska J, Gail MH, Pee D, Groves FD, Sobin LH, Nasierowska-Guttmejer A et al. (2004). Diet and stomach cancer risk in Warsaw, Poland. *Nutr Cancer*, 48(2):149–59. doi:10.1207/s15327914nc4802_4 PMID:15231449

McCullough ML, Robertson AS, Jacobs EJ, Chao A, Calle EE, Thun MJ (2001). A prospective study of diet and stomach cancer mortality in United States men and women. *Cancer Epidemiol Biomarkers Prev*, 10(11):1201–5. PMID:11700269

Navarro Silvera SA, Mayne ST, Risch H, Gammon MD, Vaughan TL, Chow WH et al. (2008). Food group intake and risk of subtypes of esophageal and gastric cancer. *Int J Cancer*, 123(4):852–60. doi:10.1002/ijc.23544 PMID:18537156

Ngoan LT, Mizoue T, Fujino Y, Tokui N, Yoshimura T (2002). Dietary factors and stomach cancer mortality. *Br J Cancer*, 87(1):37–42. doi:10.1038/sj.bjc.6600415 PMID:12085253

Nomura A, Grove JS, Stemmermann GN, Severson RK (1990). A prospective study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption. *Cancer Res*, 50(3):627–31. PMID:2297702

Nomura AM, Hankin JH, Kolonel LN, Wilkens LR, Goodman MT, Stemmermann GN (2003). Case-control study of diet and other risk factors for gastric cancer in Hawaii (United States). *Cancer Causes Control*, 14(6):547–58. doi:10.1023/A:1024887411846 PMID:12948286

Palli D, Russo A, Ottini L, Masala G, Saieva C, Amorosi A et al. (2001). Red meat, family history, and increased risk of gastric cancer with microsatellite instability. *Cancer Res*, 61(14):5415–9. PMID:11454685

Pham TM, Fujino Y, Kikuchi S, Tamakoshi A, Matsuda S, Yoshimura T (2010). Dietary patterns and risk of stomach cancer mortality: the Japan collaborative cohort study. *Ann Epidemiol*, 20(5):356–63. doi:10.1016/j.annepidem.2010.02.002 PMID:20382336

Pourfarzi F, Whelan A, Kaldor J, Malekzadeh R (2009). The role of diet and other environmental factors in the causation of gastric cancer in Iran–a population based study. *Int J Cancer*, 125(8):1953–60. doi:10.1002/ijc.24499 PMID:19569234

Risch HA, Jain M, Choi NW, Fodor JG, Pfeiffer CJ, Howe GR et al. (1985). Dietary factors and the incidence of cancer of the stomach. *Am J Epidemiol*, 122(6):947–59. PMID:2998182

Rolón PA, Castellsagué X, Benz M, Muñoz N (1995). Hot and cold mate drinking and esophageal cancer in Paraguay. *Cancer Epidemiol Biomarkers Prev*, 4(6):595–605. PMID:8547825

Sanchez-Diez A, Hernandez-Mejia R, Cueto-Espinar A (1992). Study of the relation between diet and gastric cancer in a rural area of the Province of Leon, Spain. *Eur J Epidemiol*, 8(2):233–7. doi:10.1007/BF00144806 PMID:1644141

Song P, Lu M, Yin Q, Wu L, Zhang D, Fu B et al. (2014). Red meat consumption and stomach cancer risk: a meta-analysis. *J Cancer Res Clin Oncol*, 140(6):979–92. doi:10.1007/s00432-014-1637-z PMID:24682372

Takezaki T, Gao CM, Wu JZ, Ding JH, Liu YT, Zhang Y et al. (2001). Dietary protective and risk factors for esophageal and stomach cancers in a low-epidemic area for stomach cancer in Jiangsu Province, China: comparison with those in a high-epidemic area. *Jpn J Cancer Res*, 92(11):1157–65. doi:10.1111/j.1349-7006.2001.tb02135.x PMID:11714439

Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F et al. (2000). Red meat intake and cancer risk: a study in Italy. *Int J Cancer*, 86(3):425–8. doi:10.1002/(SICI)1097-0215(20000501)86:3<425::AID-IJC19>3.0.CO;2-S PMID:10760833

Tokui N, Yoshimura T, Fujino Y, Mizoue T, Hoshiyama Y, Yatsuya H et al.; JACC Study Group(2005). Dietary habits and stomach cancer risk in the JACC Study. *J Epidemiol*, 15:Suppl 2: S98–108. doi:10.2188/jea.15.S98 PMID:16127240

Wang XQ, Yan H, Terry PD, Wang JS, Cheng L, Wu WA et al. (2012). Interaction between dietary factors and Helicobacter pylori infection in noncardia gastric cancer: a population-based case-control study in China. *J Am Coll Nutr*, 31(5):375–84. doi:10.1080/07315724.2012.10720447 PMID:23529995

Wang XQ, Terry PD, Cheng L, Yan H, Wang JS, Wu WA et al. (2014). Interactions between pork consumption, CagA status and IL-1B-31 genotypes in gastric cancer. *World J Gastroenterol*, 20(25):8151–7. doi:10.3748/wjg.v20.i25.8151 PMID:25009387

Ward MH, Sinha R, Heineman EF, Rothman N, Markin R, Weisenburger DD et al. (1997). Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference. *Int J Cancer*, 71(1):14–9. doi:10.1002/(SICI)1097-0215(19970328)71:1<14::AID-IJC4>3.0.CO;2-6 PMID:9096659

Ward MH, López-Carrillo L (1999). Dietary factors and the risk of gastric cancer in Mexico City. *Am J Epidemiol*, 149(10):925–32. doi:10.1093/oxfordjournals.aje.a009736 PMID:10342801

Ward MH, Cross AJ, Abnet CC, Sinha R, Markin RS, Weisenburger DD (2012). Heme iron from meat and risk of adenocarcinoma of the esophagus and stomach.

Eur J Cancer Prev, 21(2):134–8. doi:10.1097/CEJ.0b013e32834c9b6c PMID:22044848

Wu AH, Tseng CC, Hankin J, Bernstein L (2007). Fiber intake and risk of adenocarcinomas of the esophagus and stomach. *Cancer Causes Control*, 18(7):713–22. doi:10.1007/s10552-007-9014-8 PMID:17562192

Zamani N, Hajifaraji M, Fazel-tabar Malekshah A, Keshtkar AA, Esmaillzadeh A, Malekzadeh R (2013). A case-control study of the relationship between gastric cancer and meat consumption in Iran. *Arch Iran Med*, 16(6):324–9. PMID:23725064

2.4 Cancer of the pancreas

2.4.1 Cohort studies

Cohort studies on cancer of the pancreas have been conducted in North America, Europe, and Asia. Considering the high mortality rate for cancer of the pancreas, both studies of incidence and mortality were included in the review. Studies investigating the association between consumption of red meat or specific red meats, such as beef, pork, or other meats, are reviewed first, followed by studies on consumption of processed meat or specific processed meat items, such as ham or bacon. Findings for red meat and processed meat combined are presented only when a study did not present data for either type of meat separately.

For studies reporting on more than one type of meat, the descriptive details are given in the section the first time the study is cited, while only the key results are provided for subsequent citations. The Working Group's comments, if any, on the study's strengths and limitations are also presented only the first time a study is cited, unless different issues were noted in each analysis. Studies that did not adjust for important potential confounders for pancreatic cancer, including age, smoking, BMI, and energy intake, are noted.

After reviewing all of the available studies, the Working Group excluded the following groups of publications from further consideration: studies reporting fewer than 100 cases (e.g. Zheng et al., 1993), due to their limited statistical power; studies reporting risk estimates that were not specific for red meat intake (e.g. Yun et al., 2008; Berjia et al., 2014; Hirayama, 1990); and reports on study populations that were included in or updated by subsequent reports (e.g. Khan et al., 2004; Cross et al., 2007; Iso et al., 2007).

(a) Red meat

See Table 2.4.1

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort in Finland (Stolzenberg-Solomon et al., 2002), 27 111 male smokers aged 50–69 years were followed from 1985 to 1997, and 163 developed pancreatic cancer. The median value of red meat intake was 128.7 g/day for non-cases. The adjusted hazard ratio for the highest quintile versus the lowest quintile of consumption was 0.95 (95% CI, 0.58–1.56; P_{trend} = 0.71). Beef and pork also did not show any association. [The Working Group noted that the definition of red meat was not reported. Subjects were male smokers with largely atypical diets, so generalizability of the results was limited.]

In the Nurses' Health Study (NHS), 178 pancreatic cancer cases were observed over 18 years of follow-up in 88 802 women (Michaud et al., 2003). Diet was assessed by questionnaire four times during follow-up. The definition of red meat included processed meat, so those results are not reported here. For the highest versus the lowest quintile of consumption of beef, pork, or lamb as a main dish, the multivariate hazard ratio was 0.75 (95% CI, 0.41–1.40). Updating the dietary exposures reportedly produced similar results, but data were not shown. [The Working Group noted that the sample size was small.]

Nöthlings et al. (2005) observed positive associations between red meat, beef, and pork consumption and pancreatic cancer incidence in 190 545 men from the Multiethnic Cohort Study in Hawaii and California, USA. During 7 years of follow-up, 482 incident pancreatic cancers occurred. For the highest compared with the lowest quintiles, after adjusting for important confounders, the multivariate relative risks for intakes of red meat, beef, and pork were 1.45 (95% CI, 1.19–1.76; $P_{trend} < 0.01$), 1.21 (95% CI, 0.99–1.47; P_{trend} = 0.03), and 1.53 (95% CI, 1.25–1.87; $P_{trend} < 0.01$), respectively. [The Working Group noted that the sample size was large, and the cohort included considerable dietary heterogeneity due to the multi-ethnic background. There was no adjustment for BMI.]

In a population-based cohort of 61 433 Swedish women recruited for mammography screening, Larsson et al. (2006) reported a positive association between long-term red meat consumption, measured by two surveys 10 years apart, and pancreatic cancer risk. During follow-up from 1987 to 2004, 172 incident cases of pancreatic cancer were observed. After adjusting for important confounders, the multivariate hazard ratio for the highest versus the lowest number of servings per week of red meat was 1.73 (95% CI, 0.99–2.98). A dose–response relationship was observed (P_{trend} = 0.01). [The Working Group noted that using surveys from two time points enabled the effect of long-term exposure to be seen. The cohort was restricted to women. The sample size was small.]

In the Japan Collaborative Cohort (JACC) Study, Lin et al. (2006) evaluated the relationship between dietary factors, including meat, and risk of pancreatic cancer death; 46 465 men and 64 327 women aged 40–79 years were followed up, and 300 deaths from pancreatic cancer were recognized. After adjustment, the multivariate relative risks for the highest compared with the lowest category of intake of beef were 2.3 (95% CI, 0.83–6.39; P_{trend} = 0.33; 4 observed deaths) for men and 0.98 (95% CI, 0.14–7.11; P_{trend} = 0.74; 1 observed death) for women. The corresponding results for pork were 1.63 (95% CI, 0.62–4.26; P_{trend} = 0.34; 5 observed deaths) for men and 1.71 (95% CI, 0.71–4.09; P_{trend} = 0.35; 6 observed deaths) for women. [The Working Group noted that, while the total number of deaths was not small, the number of observed deaths among the highest category of intake was small. BMI and total energy were not adjusted.]

In a case–cohort analysis of the Netherlands Cohort Study (NLCS), Heinen et al. (2009) observed no association between intake of red meat or individual red meat items and pancreatic cancer risk. The study consisted of 120 852 men and women, and 350 pancreatic cancer cases, identified during 13 years of follow-up. Meat consumption was assessed using a validated FFQ with 150 items. For the highest compared with the lowest quintile, after adjusting for important confounders, the multivariate relative risks for intakes of red meat, beef, pork, and minced meat were 0.75 (95% CI, 0.52–1.09; P_{trend} = 0.23), 1.20 (95% CI, 0.84–1.72; P_{trend} = 0.61), 0.75 (95% CI, 0.52–1.08; P_{trend} = 0.27), and 0.78 (95% CI, 0.54–1.10; P_{trend} = 0.16), respectively. The corresponding value for intake of liver, categorized into two groups, was 1.05 (95% CI, 0.83–1.33). [The Working Group noted that red meat was clearly defined as not including processed meat. BMI was not adjusted.]

In the Iowa Women's Health Study (IWHS), Inoue-Choi et al. (2011) assessed multiple aspects of dietary intake among 34 642 postmenopausal women. A total of 256 pancreatic cancer cases during the period from 1986 to 2007 were included in the analysis. No statistically significant associations were observed between intake of red meat and pancreatic cancer (HR, 0.97; 95% CI, 0.65–1.44; for the highest vs lowest consumption category; P_{trend} = 0.79). [The Working Group noted that the definition of red meat was not reported. The follow-up was nearly complete. BMI and energy were not adjusted.]

Among the 62 581 subjects randomized to screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the USA (Anderson et al., 2012), 248 cases of exocrine pancreatic cancer were identified during follow-up from 1993 to 2007. The multivariate hazard ratios for the highest versus the lowest quintile of intake of red meat by doneness preference were 0.84 (95% CI, 0.55–1.29; P_{trend} = 0.36) for rare to medium well done and 1.60 (95% CI, 1.01–2.54; P_{trend} = 0.04) for well to very well done. When quintiles 1–4 were combined, the corresponding values for the highest quintile of "red barbecued meat" [definition not reported] were 0.79 (95% CI, 0.55–1.13; 39 exposed cases) for rare to medium well done and 1.35 (95% CI, 1.00–1.83; 56 exposed cases) for well to very well

done. Pancreatic cancer was significantly associated with consumption of fried (HR, 1.74; 95% CI, 1.05–2.90) and grilled or barbecued pork chops (HR, 1.80; 95% CI, 1.04–3.13), but not with any other cooking method or preference of doneness for pork chops, hamburger, or steak. [The Working Group noted that BMI was not adjusted. The definitions of red meat and barbecued meat were not reported.]

Rohrmann et al. (2013) examined the association between meat consumption and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. A total of 477 202 EPIC participants from 10 European countries recruited between 1992 and 2000 were included in the analysis. Eight hundred and sixty-five non-endocrine pancreatic cancer cases were observed during follow-up to 2008. After adjusting for important confounders, no significant association between consumption of red meat and pancreatic cancer was observed; the multivariate relative risk for the fourth compared with the first quantile of intake was 1.07 (95% CI, 0.83–1.38). [The Working Group took note of the large international study encompassing diverse diets.]

(b) Processed meat

See Table 2.4.2 (web only; available at: http://publications.iarc.fr/564)

In the ATBC Study cohort (Stolzenberg-Solomon et al., 2002), the median value of processed meat intake was 61.2 g/day. After adjusting for important confounders, no association was observed for processed meat (highest vs lowest quintile multivariate HR,1.04; 95% CI, 0.66–1.65).

In the NHS, the adjusted hazard ratio for the highest versus the lowest quintile of processed meat consumption was 1.28 (95% CI, 0.86–1.92; $P_{trend} = 0.10$) (Michaud et al., 2003) Analyses using dietary exposures updated during follow-up produced similar results. [The Working Group noted that repeated surveys enabled changes in diet to be considered, and exposure updates did not alter the results. BMI was not adjusted.]

Nöthlings et al. (2005) observed a positive association between processed meat consumption and pancreatic cancer incidence in the Multiethnic Cohort Study. For the highest compared with the lowest quintile, after adjusting for important confounders, the multivariate relative risk for intake of processed meat was 1.68 (95% CI, 1.35–2.07; $P_{trend} < 0.01$).

In a population-based cohort of 61 433 Swedish women, Larsson et al. (2006) found no association between pancreatic cancer risk and processed meat consumption at baseline or in the long term, measured using two surveys 10 years apart. For long-term processed meat consumption, the multivariate hazard ratio for the highest versus the lowest number of servings per week was 0.94 (95% CI, 0.61–1.44; $P_{trend} = 0.70$). Results for baseline consumption were similar. [The Working Group noted that using surveys from two time points enabled the effect of long-term exposure to be seen. The cohort was restricted to women.]

In the JACC Study (Lin et al., 2006), for the highest compared with the lowest category, the multivariate relative risks for intakes of ham and sausage were 1.82 (95% CI, 0.62–4.26; $P_{trend} = 0.34$; 7 observed deaths) for men and 0.93 (95% CI, 0.29–2.99; $P_{trend} = 0.63$; 3 observed deaths) for women.

In the NLCS (Heinen et al., 2009), for the highest compared with the lowest category of processed meat intake, the multivariate relative risk was 0.93 (95% CI, 0.65–1.35; $P_{trend} = 0.97$; 70 exposed cases). [A detailed validated FFQ with 150 items was used.] Among subjects randomized to screening in the PLCO trial in the USA (Anderson et al., 2012), the multivariate hazard ratio for the highest versus the lowest tertile of bacon/sausage consumption by doneness preference was 0.99 (95% CI, 0.73–1.35) for crisp or charred compared with cooked to a lesser degree of doneness. [The Working Group noted that

BMI was not adjusted. Information on cooking method preferences was available.]

In the EPIC study, Rohrmann et al. (2013) did not find a significant relation between consumption of processed meat and pancreatic cancer (multivariate RR per 50 g/day increase, 0.93; 95% CI, 0.71–1.23).

During follow-up of the NIH-AARP cohort, until 2006, where 2193 pancreatic cancer cases were identified, Jiao et al. (2015) investigated the joint associations between pancreatic cancer and processed meat consumption and intake of advanced glycation end products (AGEPs). The multivariate hazard ratio for the highest compared with the lowest quintile of processed meat consumption was 1.03 (95% CI, 0.92–1.37; P_{trend} = 0.28). Further adjustment for AGEPs did not alter the results.

(c) Red meat and processed meat combined

Coughlin et al. (2000), in a cohort of 483 109 men and 619 199 women from the Cancer Prevention Study (CPS) II (CPS-II), confirmed 3751 pancreatic cancer deaths during follow-up from 1982 to 1996. The red meat variable used in the analysis included processed meat items. The multivariate-adjusted hazard ratios for the highest versus the lowest quintile for this variable were 1.1 (95% CI, 0.9–1.2) in men and 0.9 (95% CI, 0.8–1.0) in women. [The Working Group noted that this was a large study with a low percentage of men and women lost to follow-up. Red meat and processed meat were combined.]

Based on a follow-up of the NIH-AARP study cohort from 1995 to 2000 with 836 cases, Stolzenberg-Solomon et al. (2007) reported a statistically significant association between pancreatic cancer risk and red meat consumption for men (adjusted HR, 1.42; 95% CI, 1.05–1.91; highest vs lowest category of consumption), but not for women (HR, 0.69 ; 95% CI, 0.83–1.35) or for both sexes combined (HR, 1.06; 95% CI, 0.83–1.35). [The Working Group noted that the red meat variable included processed items.]

Jiao et al. (2015) investigated the risk of pancreatic cancer associated with red meat consumption and intake of AGEPs in the same cohort. For the highest compared with the lowest quintile of intake among men, the multivariate hazard ratios for red meat and red meat cooked at a high temperature were 1.35 (95% CI, 1.07–1.70; P_{trend} = 0.05) and 1.18 (95% CI, 0.89–1.56; P_{trend} = 0.01), respectively. The hazard ratios were attenuated and no longer significant after further adjustment for AGEPs. Data on the association between meat consumption and pancreatic cancer risk were not reported for women. [The Working Group noted that this was a large study, but the definition of red meat may have included processed meat items, as per the report based on follow-up through 2000.]

2.4.2 Case–control studies

Case–control studies on cancer of the pancreas have been conducted in North America, Europe, and Asia. Considering the high mortality rate for cancer of the pancreas, both studies of incidence and mortality data were included in the review. The studies were considered based on the quality of reporting of the type of meat, study design issues (e.g. population- vs hospital-based design), sample size, and exposure assessment, including validation of dietary questionnaires and inclusion of relevant confounders. Studies that did not adjust for important potential confounders (see Section 2.4.1) are noted.

As for cohort studies, case–control studies that investigated the association with consumption of total red meat or specific red meats are presented first, followed by studies that investigated the association with consumption of processed meat. Study details and Working Group comments are provided only the first time a study is cited, unless important differences were noted.

After reviewing all of the available studies, studies with fewer than 100 cases (e.g. Kadlubar

et al., 2009; Luckett et al., 2012), papers reporting only dietary patterns (e.g. Bosetti et al., 2013; Chan et al., 2013) or preserved processed items including eggs (e.g. Ji et al., 1995), and overlapping studies of the same population (e.g. Hu et al., 2011) were excluded from further consideration. Studies that did not report pertinent odds ratios (e.g. Li et al., 2007) were excluded when only crude odds ratios could be calculated from the data presented.

(a) Red meat

See Table 2.4.3

Lyon et al. (1993) reported the results of a population-based case–control study of cancer of the exocrine pancreas conducted from 1984 to 1987 in Utah, USA; 149 cases of pancreatic cancer were identified from the Utah Cancer Registry, and 363 controls were identified by random digit dialling or health insurance records of those older than 65 years. Dietary intake data were collected from a 32-item FFQ administered to proxy respondents for cases and controls. Red meat was defined as beef and pork. The multivariate odds ratios for the highest versus the lowest level of red meat consumption were 1.41 (95% CI, 0.72–2.75; P_{trend} = 0.30) in men and 1.44 (95% CI, 0.65–3.20; P_{trend} = 0.45) in women. [The Working Group noted that the study was small, and BMI and energy were not adjusted.]

Ji et al. (1995) reported findings for red meat consumption in a population-based case–control study conducted from 1990 to 1993 in Shanghai, China. Pancreatic cancer cases (n = 451) were identified by a rapid reporting system. Controls (n = 1552) were selected Shanghai residents, frequency-matched to cases by sex and age. Interviews with next of kin were conducted for 38% of cases and 10% of controls. Usual meat intake over the previous 5 years was ascertained from an 86-item questionnaire. The multivariate odds ratios for the highest versus the lowest quartile of red meat consumption were 0.73 (95% CI, 0.47–1.12; P_{trend} = 0.24) in men and 1.24 (95% CI, 0.73–2.13; P_{trend} = 0.86) in women. [The Working Group noted that processed meat was not included. This study was large, but a substantial number of case and control interviews were performed with next of kin. BMI and energy were not adjusted. No validation data for FFQ were reported.]

In a population-based case–control study, conducted from 1995 to 1999 in California, USA, Chan et al. (2007), reported the results of red meat consumption. Dietary intake of red meat was collected from a validated, 131-item SQFFQ. Cases were 532 pancreatic cancer patients from the Northern California Cancer Center. Controls were 1701 area residents identified by random digit dialling, and frequency-matched to cases by sex and age. Compared with a frequency of < 1 time/month, the multivariate odds ratios for ≥ 2 times/week frequency of beef or lamb intake as a main dish and pork intake as a main dish were 2.2 (95% CI, 1.0–4.5; 14 exposed cases) and 0.6 (95% CI, 0.3–1.1; P_{trend} = 0.2; 11 exposed cases), respectively. Results for total red meats, including processed red meats, were also reported. [The Working Group noted that the study design was sound.]

Hu et al. (2008) reported the results of a population-based case–control study of pancreatic cancer conducted from 1994 to 1997 in eight Canadian provinces. Dietary intake of red meat was collected from a mailed, validated questionnaire with 69 items. Cases were 628 individuals identified from provincial cancer registries. Controls were 5039 individuals selected from a random sample within the provinces. The multivariate odds ratio for the highest versus the lowest quartile of frequency of red meat consumption was 1.1 (95% CI, 0.9–1.5; P_{trend} = 0.31). [The Working Group noted that the sample size was large, and a validated FFQ was used.]

In a population-based case–control study, Anderson et al. (2009) reported the results of red meat consumption from 2003 to 2007 in Canada. Dietary intake of red meat was collected

from a mailed FFQ. Cases were 422 pancreatic cancer patients identified by the Ontario Cancer Registry. Controls were 312 subjects recruited through random digit dialling. The age-adjusted odds ratio for > 3 servings/week versus ≤ 1 serving/week of red meat consumption was 1.49 (95% CI, 0.98–2.28). Adjusting for other factors, such as smoking and education, did not alter the results. [The Working Group noted that the exact definition of red meat was not reported. This study was large, but the questionnaire was not validated. BMI and energy were not adjusted.]

Tavani et al. (2000), using data from a hospital-based case–control study of several cancers in northern Italy in 1983–1996, reported results for red meat consumption and pancreatic cancer. Cases were 362 hospital patients younger than 75 years with confirmed pancreatic cancer. Controls were 7990 patients younger than 75 years admitted to the same network of hospitals as the cancer cases for acute non-cancer conditions. Dietary intake of red meat over the previous 2 years was collected by FFQ, which defined red meat as beef, veal, or pork, excluding processed items. The multivariate odds ratio for the highest (≥ 7 times/week) versus the lowest (≤ 3 times/week) level of red meat consumption was 1.6 (95% CI, 1.2–2.1). [The participation of cases and controls was similar and almost complete. The questionnaire was not tested for validity, but reproducibility was reported to be satisfactory. BMI and energy were not adjusted.] Similar findings were reported in an earlier paper based on the same study (Soler et al., 1998), which also provided data for liver consumption (OR, 1.43; 95% CI, 1.01–1.99). [The Working Group noted that the study population appeared to overlap with those studied by Soler et al. (1998), Tavani et al. (2000), Polesel et al. (2010), and Di Maso et al. (2013).]

Polesel et al. (2010) reported the results of a hospital-based case–control study of pancreatic cancer conducted from 1991 to 2008 in northern Italy. [The study population appeared to overlap with that studied by Tavani et al. (2000).] Cases were 326 men and women with incident pancreatic cancer. Controls were 652 hospital patients admitted for acute conditions. Dietary intake of red meat was collected from a validated questionnaire with 78 items. Cooking methods were assessed for all meats combined. After adjusting for important potential confounders, the multivariate odds ratio for the highest versus the lowest quintile of red meat consumption was 1.99 (95% CI, 1.18–3.36). Data were also reported for pork and processed meat combined (multivariate OR, 1.25; 95% CI, 0.85–1.84; $P_{trend} = 0.27$). [The definition of red meat was not reported. and data were not reported for pork and processed meat separately. The Working Group judged the data on cooking methods to be uninformative, as they were reported only for all meats combined. The response rate was high for both cases and controls.]

Di Maso et al. (2013) also reported results of a hospital-based case–control study that partially overlapped with that of Tavani et al. (2000). Red meat was defined as including beef, veal, pork, horse meat, and meat sauces. The multivariate odds ratio for pancreatic cancer was 1.51 (95% CI, 1.25–1.82) per 50 g/day increment. Associations with red meat cooked in different ways were also examined, with no significant heterogeneity identified between meats cooked by roasting/grilling, boiling/stewing, and frying/pan-frying. [The Working Group noted that the results of later, overlapping studies were similar to those reported by Tavani et al. (2000), and the Tavani et al. study had a large number of cases and controls, and the definition of red meat was clearly described and did not include processed meat.]

(b) Processed meat

See Table 2.4.4 (web only; available at: http://publications.iarc.fr/564)

Lyon et al. (1993), in a population-based case–control study of cancer of the exocrine pancreas

in Utah, USA (previously described in Section 2.4.2(a)), assessed dietary intake of nitrated meats (bacon, sausages, and hot dogs) with a standardized questionnaire. The multivariate odds ratios for the highest versus the lowest level of nitrated meat consumption were 2.77 (95% CI, 1.34–5.72; $P_{trend} < 0.001$) in men and 1.08 (95% CI, 0.48–2.42; $P_{trend} = 0.15$) in women.

In a population-based case–control study in Japan from 1987 to 1992, Ohba et al. (1996) reported on the association with ham and sausage consumption. Cases were 141 pancreatic cancer patients identified from hospitals. Controls were 282 subjects randomly selected from telephone books. Dietary data were collected from an FFQ, which was administered in person to cases and by mail to controls. Only the univariate odds ratio was reported for consumption of ham/sausage > 3 times/week (OR, 0.89; 95% CI, 0.44–1.77). [The Working Group noted that this study had several limitations: sample size was small, data collection methods were different for cases and controls; questionnaire was not validated, and only univariate analysis was conducted for processed meats.]

In a population-based case–control study in California, USA (Chan et al., 2007) (as previously described in Section 2.4.2(a)), the multivariate odds ratios for intake ≥ 2 times/week versus < 1 time/month of sausage, kielbasa, salami, bologna, other processed meat sandwiches, beef or pork hot dogs were 1.8 (95% CI, 1.3–2.6) and 1.9 (95% CI, 1.3–3.0), respectively. For intake of bacon ≥ 4 times/week, the odds ratio was 1.9 (95% CI, 1.0–3.5), and for intake of beef or pork hot dogs ≥ 1 time/week, the odds ratio was 1.1 (95% CI, 0.8–1.4; $P_{trend} = 0.9$).

In a population-based case–control study of pancreatic cancer in eight Canadian provinces [previously described in Section 2.4.2(a)], Hu et al. (2008) reported that the multivariate odds ratio for the highest versus the lowest level of processed meat consumption was 1.4 (95% CI, 1.0–1.9; $P_{trend} = 0.01$).

In a hospital-based case–control study, Mizuno et al. (1992) reported the results of ham/sausage consumption and pancreatic cancer incidence from 1989 to 1990 in seven cooperating hospitals in Japan. Cases were 124 pancreatic cancer patients identified in seven cooperating hospitals in Japan. Controls were 124 sex- and age-matched patients with non-cancer conditions. Information was collected by questionnaire, but details were not reported. The sex- and age-adjusted odds ratio for consuming ham/sausage ≥ 3 times/week was 1.05 (95% CI, 0.54–2.04). [The Working Group noted that this study was small. Details of dietary assessment were not reported, and only age and sex were adjusted.]

A hospital-based case–control study in northern Italy by Soler et al. (1998), partially overlapping with studies by Tavani et al. (2000), Polesel et al. (2010), and Di Maso et al. (2013), reported a multivariate odds ratio for the highest versus the lowest frequency of ham and sausage consumption of 1.64 (95% CI, 1.24–2.18). [The Working Group took note of the high participation of cases and controls. BMI and energy were not adjusted.]

(c) Red meat and processed meat combined

Anderson et al. (2002) reported the results of a population-based case–control study of pancreatic cancer conducted from 1994 to 1998 in the upper Midwestern USA. Cases were 193 (approximately 30% participation rate) patients recruited from hospitals. Controls were 674 (59% response rate) subjects selected from drivers' licence lists or USA Health Care Financing Administration records. Dietary intake of red meat was collected from in-person interviews using an FFQ. After adjusting for potential confounders, the multivariate odds ratios for the highest versus the lowest quintile of consumption for red and processed meat combined were 2.2 (95% CI, 1.4–3.4) for grilled or barbecued meats, 1.4 (95% CI, 0.7–2.6) for fried meats, and 0.7 (95% CI, 0.4–1.2) for

broiled meats. [The Working Group noted that red meat and processed meat were combined. Detailed information on the cooking methods was available. This study had limited power, and BMI and energy were not adjusted.]

2.4.3 Meta-analyses

Associations between pancreatic cancer and consumption of red meat and processed meat were estimated in two meta-analyses published in 2012: Larsson & Wolk (2012), focused on prospective studies, and Paluszkiewicz et al. (2012), considered both cohort and case–control studies.

Larsson & Wolk (2012), in a meta-analysis based on 11 prospective studies with 6643 cases identified through PubMed and Embase searches through November 2011, reported on red and processed meat consumption. An increase in red meat consumption of 120 g/day was associated with a meta-relative risk of 1.13 (95% CI, 0.93–1.39; $P_{\text{heterogeneity}} < 0.001$; 11 studies). For processed meat, the relative risk for a 50 g/day increase in consumption was 1.19 (95% CI, 1.04–1.36; $P_{\text{heterogeneity}} = 0.46$; 7 studies). [The Working Group noted that there were no studies missing. Studies considering specific items of red or processed meat were also included. No evidence of publication bias was found.]

Paluszkiewicz et al. (2012) included cohort studies and case–control studies identified through MEDLINE, PubMed, Cochrane Library, Embase, CANCERLIT, Scopus, and Google Scholar through 2010. Six cohort studies and four case–control studies provided data for red meat. For the highest versus the lowest category of red meat intake, a statistically significant increased risk was observed for case–control studies (OR, 1.48; 95% CI, 1.25–1.76; $P_{\text{heterogeneity}} = 0.7716$), but not for cohort studies (RR, 1.14; 95% CI, 0.94–1.38; $P_{\text{heterogeneity}} = 0.004$). Analyses for processed meat were not reported. [The Working Group noted that several electronic databases were searched for relevant studies. Study quality was assessed, but how quality scores were used in the analysis was not reported. No analyses of sensitivity or publication bias were reported.]

Two large prospective studies were published since these meta-analyses, both showing no association overall between red or processed meat consumption and pancreatic cancer risk (Rohrmann et al., 2013; Jiao et al., 2015). However, results in Jiao et al. (2015) were positive for red meat before adjusting for AGEP consumption.

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Coughlin et al. (2000) USA 1982–1996	483 109 men and 619 199 women; American Cancer Society volunteers Exposure assessment method: questionnaire; four-page, self-administered questionnaire; total red meat included beef, pork, ham, hamburgers, liver, sausages, bacon, and smoked meats	Pancreas	Red meat, quartiles Men: Q1 Q2 Q3 Q4 Red meat, quartiles Women: Q1 Q2 Q3 Q4	 454 425 461 447 421 458 314 345	 1.0 1.1 (0.9–1.2) 1.1 (0.9–1.2) 1.1 (0.9–1.2) 1.0 1.0 (0.9–1.1) 0.9 (0.7–1.0) 0.9 (0.8–1.0)	Age, race, education, family history of pancreatic cancer, history of gallstones, BMI, smoking, alcohol, citrus fruits and juices, vegetables, history of diabetes mellitus
Stolzenberg-Solomon et al. (2002) Finland 1985–1997	27 111; male smokers aged 50–69 yr Exposure assessment method: questionnaire; 200-item dietary history questionnaire	Pancreas	Red meat (g/day) ≤ 93.0 > 93.0 to ≤ 117.3 > 117.3 to ≤ 141.6 > 141.6 to ≤ 175.6 ≥ 175.6 Trend-test *P* value: 0.71 Beef (g/day) ≤ 10.8 > 10.8 to ≤ 17.5 > 17.5 to ≤ 25.1 > 25.1 to ≤ 36.8 ≥ 36.8 Trend-test *P* value: 0.28 Pork (g/day) ≤ 25.2 > 25.2 to ≤ 33.1 > 33.1 to ≤ 41.2 > 41.2 to ≤ 52.5 ≥ 52.5 Trend-test *P* value: 0.96	 NR NR NR NR NR NR NR NR NR NR NR NR NR NR NR	 1.00 0.88 (0.54–1.44) 0.84 (0.51–1.39) 1.28 (0.81–2.01) 0.95 (0.58–1.56) 1.00 1.09 (0.66–1.81) 1.11 (0.67–1.83) 1.19 (0.73–1.96) 1.30 (0.79–2.12) 1.00 1.00 (0.61–1.61) 0.99 (0.61–1.60) 0.94 (0.57–1.53) 1.01 (0.62–1.64)	Age, smoking, total energy

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Michaud et al. (2003) USA 1980–1998	88 802; female registered nurses aged 30–55 yr from the USA Exposure assessment method: questionnaire; validated FFQ, assessed dietary intake in 1980, 1984, 1986, and 1990 using an SQFFQ (61 items in 1980, 131 items other years)	Pancreas	Beef, pork, or lamb as main dish (frequency)			Smoking, BMI, diabetes, total energy intake, physical activity, height, menopausal status
			Baseline consumption: < 3 times/mo	29	1.00	
			1 time/wk	60	0.97 (0.62–1.51)	
			2–4 times/wk	67	0.89 (0.56–1.42)	
			≥ 5 times/wk	22	0.75 (0.41–1.40)	
			Trend-test *P* value: 0.33			
			Beef, pork, or lamb as sandwich or mixed dish (frequency)			
			Baseline consumption: < 3 times/mo	21	1.00	
			1 time/wk	57	1.13 (0.68–1.86)	
			2–4 times/wk	55	0.91 (0.55–1.52)	
			≥ 5 times/week	45	0.95 (0.55–1.62)	
			Trend-test *P* value: 0.60			
Nöthlings et al. (2005) USA 1993–2001	190 545; African American, Latino, Japanese American, native Hawaiian, and Caucasian residents of Hawaii and California, aged 45–75 yr Exposure assessment method: questionnaire; quantitative FFQ	Pancreas	Red meat (quintile median, g/1000 kcal per day)			Sex, time in study, age at cohort entry, ethnicity, history of diabetes mellitus, familial history of pancreatic cancer, smoking status, energy intake
			4.5	86	1.00	
			11.0	95	1.06 (0.87–1.29)	
			16.8	113	1.27 (1.05–1.54)	
			23.4	83	1.03 (0.84–1.26)	
			35.0	105	1.45 (1.19–1.76)	
			Trend-test *P* value: 0.01			
			Beef (quintile median, g/1000 kcal per day)			
			3.1	93	1.00	
			7.7	103	1.01 (0.84–1.22)	
			11.8	103	1.08 (0.89–1.30)	
			16.7	89	1.02 (0.84–1.24)	
			25.9	94	1.21 (0.99–1.47)	
			Trend-test *P* value: 0.03			

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Nöthlings et al. (2005) USA 1993–2001 (cont.)			Pork (quintile median, g/1000 kcal per day)			
			0.4	75	1.00	
			1.8	87	1.14 (0.93–1.40)	
			3.5	95	1.12 (0.91–1.39)	
			5.7	112	1.44 (1.18–1.76)	
			9.7	113	1.53 (1.25–1.87)	
			Trend-test *P* value: 0.01			
Larsson et al. (2006) Sweden 1987–2004	61 433; women born between 1914 and 1948 and residing in Uppsala and Västmanland counties, central Sweden Exposure assessment method: questionnaire; 67- and 96-item FFQ; "red meat" was minced meat (hamburgers, meatballs, meatloaf, etc.); casserole with beef, pork, or veal; and whole beef (steaks, roasts, etc.)	Pancreas	Red meat (servings/wk)			Age, BMI, smoking, alcohol intake, education, total energy intake, folate, processed meat, poultry, eggs
			Baseline consumption: < 1.5	38	1.00	
			1.5 to < 2.5	32	1.15 (0.70–1.89)	
			2.5 to < 4.0	76	1.30 (0.85–2.00)	
			≥ 4.0	26	1.33 (0.77–2.31)	
			Trend-test *P* value: 0.07			
			Red meat (servings/wk)			
			Updated average consumption: < 1.5	31	1.00	
			1.5 to < 2.5	42	1.62 (1.00–2.64)	
			2.5 to < 4.0	70	1.34 (0.85–2.13)	
			≥ 4.0	29	1.73 (0.99–2.98)	
			Trend-test *P* value: 0.01			
Lin et al. (2006) Japan 1988–1999	110 792 (46 465 men, 64 327 women); Japanese residing in 45 areas throughout Japan Exposure assessment method: questionnaire; 33-item FFQ	Pancreas	Beef (frequency)			Age, area, pack-years of smoking
			Men: 0–2 times/mo	65	1.00	
			1–4 times/wk	25	0.60 (0.37–0.99)	
			Almost every day	4	2.30 (0.83–6.39)	
			Trend-test *P* value: 0.33			

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lin et al. (2006) Japan 1988–1999 (cont.)			Beef (frequency)			
			Women: 0–2 times/mo	61	1.00	
			1–4 times/wk	35	1.10 (0.69–1.74)	
			Almost every day	1	0.98 (0.14–7.11)	
			Trend-test *P* value: 0.74			
			Pork (frequency)			
			Men: 0–2 times/mo	34	1.00	
			1–4 times/wk	67	1.15 (0.74–1.80)	
			Almost every day	5	1.63 (0.62–4.26)	
			Trend-test *P* value: 0.34			
			Pork (frequency)			
			Women: 0–2 times/mo	39	1.00	
			1–4 times/wk	71	1.11 (0.69–1.67)	
			Almost every day	6	1.71 (0.71–4.09)	
			Trend-test *P* value: 0.35			
Stolzenberg-Solomon et al. (2007) USA 1995–2000	537 302; National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study Exposure assessment method: questionnaire	Pancreas	Red meat consumption (highest vs lowest category)			Smoking, energy-adjusted saturated fat
			Men	147	1.42 (1.05–1.91)	
			Women	47	0.69 (0.45–1.05)	

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Heinen et al. (2009) The Netherlands 1986–1999	120 852; men and women aged 55–69 yr at enrolment Exposure assessment method: questionnaire; 150-item FFQ	Pancreas	Red meat, quintiles			Sex, age, energy intake, smoking, alcohol, diabetes, hypertension, vegetable and fruit intake
			Q1	70	1.00	
			Q2	69	0.98 (0.69–1.39)	
			Q3	67	0.93 (0.65–1.34)	
			Q4	84	1.14 (0.80–1.61)	
			Q5	60	0.75 (0.52–1.09)	
			Trend-test *P* value: 0.23			
			Beef, quintiles			
			Q1	65	1.00	
			Q2	75	1.16 (0.81–1.66)	
			Q3	70	0.99 (0.69–1.42)	
			Q4	56	0.81 (0.56–1.18)	
			Q5	84	1.20 (0.84–1.72)	
			Trend-test *P* value: 0.61			
			Pork, quintiles			
			Q1	76	1.00	
			Q2	64	0.85 (0.60–1.22)	
			Q3	70	0.89 (0.63–1.26)	
			Q4	80	1.01 (0.72–1.43)	
			Q5	60	0.75 (0.52–1.08)	
			Trend-test *P* value: 0.27			
			Minced meat, quintiles			
			Q1	75	1.00	
			Q2	65	0.79 (0.56–1.13)	
			Q3	84	1.02 (0.73–1.43)	
			Q4	61	0.75 (0.52–1.07)	
			Q5	65	0.78 (0.54–1.10)	
			Trend-test *P* value: 0.16			
			Liver (g/day)			
			> 0	130	1.05 (0.83–1.33)	

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Inoue-Choi et al. (2011) Iowa, USA 1986–2007	34 642; postmenopausal women aged 55 to 69 yr Exposure assessment method: questionnaire; FFQ	Pancreas	Red meat (mean, servings/wk)			Age, race, education, alcohol intake, smoking, physical activity
			2.0	54	1.00	
			3.5	43	0.85 (0.57–1.28)	
			5.0	52	0.99 (0.67–1.47)	
			7.0	55	1.06 (0.72–1.55)	
			9.0	52	0.97 (0.65–1.44)	
			Trend-test *P* value: 0.79			
Anderson et al. (2012) USA 1993–2007	62,581; women and men aged 55–74 yr Exposure assessment method: FFQ (170 questions)	Pancreas	Red meat, rare to medium well done			Age, sex, education, diabetes, dietary fat intake, cigarette smoking history, race
			Q1	53	1.00	
			Q2	57	1.11 (0.76–1.63)	
			Q3	43	0.81 (0.54–1.21)	
			Q4	50	0.91 (0.61–1.34)	
			Q5	45	0.84 (0.55–1.29)	
			Trend-test *P* value: 0.364			
			Red meat, well to very well done			
			Q1	39	1.00	
			Q2	58	1.52 (1.01–2.29)	
			Q3	47	1.25 (0.81–1.92)	
			Q4	49	1.37 (0.88–2.12)	
			Q5	55	1.60 (1.01–2.54)	
			Trend-test *P* value: 0.039			
			Red barbecued meat, rare to medium well done			
			Q1–Q4	209	1.00	
			Q5	39	0.79 (0.55–1.13)	
			Red barbecued meat, well to very well done			
			Q1–Q4	192	1.00	
			Q5	56	1.35 (1.00–1.83)	
			Pork chops, cooking method			
			Do not eat	19	1.00	
			Baked	67	1.44 (0.86–2.40)	
			Oven-broiled	31	1.78 (1.00–3.17)	
			Pan-fried	86	1.74 (1.05–2.90)	
			Grilled or barbecued	42	1.80 (1.04–3.13)	

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Anderson et al. (2012) USA 1993–2007 (cont.)			Hamburger, cooking method			
			Do not eat	11	1.00	
			Oven-broiled	23	1.11 (0.54–2.30)	
			Pan-fried	75	1.32 (0.69–2.51)	
			Grilled or barbecued	133	1.43 (0.77–2.67)	
			Steak, cooking method			
			Do not eat	20	1.00	
			Oven-broiled	76	1.15 (0.70–1.89)	
			Pan-fried	32	1.10 (0.62–1.94)	
			Grilled or barbecued	119	0.93 (0.57–1.50)	
			Hamburger, doneness preference			
			Do not eat	10	1.00	
			Rare or medium rare	26	1.40 (0.67–2.93)	
			Medium	38	0.88 (0.43–1.78)	
			Medium well done	60	1.04 (0.53–2.06)	
			Well done	99	1.32 (0.68–2.55)	
			Very well done	15	1.39 (0.62–3.11)	
			Steak, doneness preference			
			Do not eat	13	1.00	
			Rare or medium rare	72	1.43 (0.79–2.61)	
			Medium	55	0.99 (0.54–1.83)	
			Medium well done	61	1.16 (0.64–2.13)	
			Well done	35	1.19 (0.62–2.26)	
			Very well done	12	1.68 (0.76–3.70)	
Rohrmann et al. (2013) Europe 1992–2008	477 202; European Prospective Investigation into Cancer and Nutrition (EPIC) participants from 10 European countries Exposure assessment method: questionnaire	Pancreas	Red meat intake (g/day)			Area, sex, age, height, weight, physical activity index, smoking, education, history of diabetes mellitus, total energy
			0 to < 20	176	1.00	
			20 to < 40	215	1.01 (0.82–1.24)	
			40 to < 80	291	0.99 (0.80–1.22)	
			≥ 80	183	1.07 (0.83–1.38)	
			Per 50 g observed	865	1.05 (0.94–1.17)	
			Per 50 g calibrated	865	1.03 (0.93–1.14)	

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Rohrmann et al. (2013) Europe 1992–2008 (cont.)			Red meat intake (g/day)			
			Men: 0 to < 20	58	1.00	
			20 to < 40	84	1.01 (0.71–1.43)	
			40 to < 80	134	0.95 (0.67–1.35)	
			≥ 80	120	0.94 (0.63–1.40)	
			Trend-test *P* value: 0.53			
			Red meat intake (g/day)			
			Women: 0 to < 20	118	1.00	
			20 to < 40	131	1.01 (0.78–1.31)	
			40 to < 80	157	1.00 (0.76–1.32)	
			≥ 80	63	1.23 (0.87–1.75)	
Jiao et al. (2015) USA 1995–2006	567 169; members of the National Institutes of Health – American Association of Retired Persons (NIH-AARP) aged 50–71 yr, in six states Exposure assessment method: questionnaire; 124-item, 12-mo FFQ	Pancreas	Red meat intake (g/1000 kcal)			Age, race, education, diabetes, smoking status, first-degree family history of cancer, BMI, alcohol consumption, carbohydrate intake, saturated fat
			Men: 0–30.2	242	1.00	
			30.3–51.8	268	1.19 (0.99–1.42)	
			51.9–76.6	282	1.09 (0.90–1.32)	
			76.7–115.5	302	1.17 (0.95–1.43)	
			115.6–972.8	313	1.35 (1.07–0.70)	
			Trend-test *P* value: 0.05			
			Red meat cooked at high temperatures (g/1000 kcal)			
			Men: 0–9.2	245	1.00	
			9.3–18.0	255	0.87 (0.69–1.10)	
			18.1–29.7	294	1.23 (0.98–1.54)	
			29.8–49.2	300	1.01 (0.78–1.30)	
			49.3–693.7	313	1.18 (0.89–1.56)	
			Trend-test *P* value: 0.01			

BMI, body mass index; CVI, confidence interval; FFQ, food frequency questionnaire; mo, month; NR, not reported; SQFFQ, semi-quantitative food frequency questionnaire; wk, week; yr, year

Table 2.4.3 Case–control studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Lyon et al. (1993) Utah, USA 1984–1987	Cases: 149; Utah Cancer Registry Controls: 363; random digit dialling and health care financing records Exposure assessment method: questionnaire; 32-item FFQ; red meat included beef and pork	Pancreas	Red meat Men: Low	30	1.00	Age, smoking, consumption of coffee and alcohol
			Medium	16	0.64 (0.30–1.37)	
			High	41	1.41 (0.72–2.75)	
			Trend-test *P* value: 0.3			
			Red meat Women: Low	16	1.00	
			Medium	23	1.05 (0.47–2.34)	
			High	21	1.44 (0.65–3.20)	
			Trend-test *P* value: 0.45			
Ji et al. (1995) Shanghai, China 1990–1993	Cases: 451; rapid reporting system; residents in Shanghai aged 30–74 yr Controls: 1552; Shanghai general population, frequency-matched by age and sex Exposure assessment method: questionnaire; 86-item FFQ; no validation data were reported	Pancreas	Red meat (servings/mo) Men: ≤ 13.7	NR	1.00	Age. income, smoking, green tea drinking (females only), response status
			13.8–22.5	NR	0.64 (0.42–0.99)	
			22.6–37.7	NR	0.76 (0.50–1.15)	
			≥ 37.8	NR	0.73 (0.47–1.12)	
			Trend-test *P* value: 0.24			
			Red meat (servings/mo) Women: ≤ 10.7	NR	1.00	
			10.7–19.8	NR	1.34 (0.81–2.21)	
			19.9–33.1	NR	0.83 (0.47–1.43)	
			≥ 33.0	NR	1.24 (0.73–2.13)	
			Trend-test *P* value: 0.86			

Table 2.4.3 Case–control studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Tavani et al. (2000) Italy 1983–1996	Cases: 362; patients at several hospitals aged < 75 yr Controls: 7990; patients aged < 75 yr in the same network of hospitals for acute non-cancer conditions Exposure assessment method: questionnaire; FFQ with approximately 40 foods; red meat defined as beef, veal, and pork, excluding canned and preserved	Pancreas	Red meat consumption (median, times/wk) 3 5 7 Trend-test *P* value: ≤ 0.01	 115 120 127	 1.0 1.2 (0.9–1.6) 1.6 (1.2–2.1)	Age; year of recruitment; sex; education; smoking habits; alcohol, fat, fruit, and vegetable intakes
Anderson et al. (2002) USA 1994–1998	Cases: 193; incident cases aged ≥ 20 yr from area hospitals and clinics Controls: 674; aged ≥ 20 yr from drivers' licence and health care financing records; matched by age, sex, and race Exposure assessment method: questionnaire; in-person FFQ; "red meat" included bacon, sausage, and ham	Pancreas	Grilled/barbecued red meat (g/day) 0 0.9–3.5 3.7–10.7 10.8–88.0 Trend-test *P* value: < .001 Fried red meat (g/day) 0–1.1 1.2–4.6 4.7–11.5 11.7–24.1 24.2–192.6 Trend-test *P* value: 0.90 Broiled red meat (g/day) 0–0.49 0.50–4.90 5.00–11.70 12.00–171.10 Trend-test *P* value: 0,08	 77 14 36 66 25 26 55 44 43 102 31 28 32	 1.0 1.4 (0.7–2.7) 1.2 (0.7–1.9) 2.2 (1.4–3.4) 1.0 1.1 (0.6–2.0) 1.9 (1.1–3.3) 1.6 (0.9–2.8) 1.4 (0.7–2.6) 1.0 0.9 (0.5–1.4) 0.7 (0.4–1.1) 0.7 (0.4–1.2)	Age, sex, smoking, education, race, diabetes, red meat cooked by other methods

Table 2.4.3 Case–control studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Chan et al. (2007) USA 1995–1999	Cases: 532; from Northern California Cancer Center and aged 21–85 yr Controls: 1701; general population, identified by random digit dialling; matched by age and sex Exposure assessment method: questionnaire; validated, 131-item FFQ; red meat included bacon and other processed meats	Pancreas	Beef or lamb as main dish (frequency)			Age, sex, energy intake, BMI, race, education, smoking, diabetes
			< 1 time/mo	107	1.0	
			1–3 times/mo	175	1.2 (0.9–1.6)	
			1 time/wk	127	1.1 (0.8–1.5)	
			2–4 times/wk	102	1.4 (1.0–2.0)	
			≥ 5 times/wk	14	2.2 (1.0–4.5)	
			Trend-test *P* value: 0.03			
			Pork as main dish (frequency)			
			< 1 time/mo	132	1.0	
			1–3 times/mo	113	0.9 (0.7–1.2)	
			1 time/wk	57	0.9 (0.6–1.4)	
			≥ 2 times/wk	11	0.6 (0.3–1.1)	
			Trend-test *P* value: 0.2			
			Hamburger (frequency)			
			< 1 time/mo	230	1.0	
			1–3 times/mo	134	1.1 (0.8–1.4)	
			1 time/wk	92	1.3 (1.0–1.7)	
			≥ 2 times/wk	70	1.7 (1.2–2.4)	
			Trend-test *P* value: 0.005			
Hu et al. (2008) Canada 1994–1997	Cases: 628; aged 20–76 yr from provincial cancer registries Controls: 5039; random sample within provinces, frequency-matched by age and sex Exposure assessment method: questionnaire; Block FFQ, short version (69 items)	Pancreas	Red meat (servings/wk)			Age, province, education, BMI, sex, alcohol use, smoking, total vegetable and fruit intake, total energy intake
			Q1	NR	1.0	
			Q2	NR	1.2 (0.9–1.5)	
			Q3	NR	1.3 (1.0–1.7)	
			Q4	NR	1.1 (0.9–1.5)	
			Trend-test *P* value: 0.31			

Table 2.4.3 Case–control studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Anderson et al. (2009) Canada 2003–2007	Cases: 422; Ontario Cancer Registry Controls: 312; random digit dialling Exposure assessment method: questionnaire; mailed questionnaire, but a full FFQ was not administered; validity was not reported	Pancreas	Red meat (servings/wk) ≤ 1 2–3 > 3	 99 151 131	 1.00 1.16 (0.78–1.72) 1.49 (0.98–2.28)	Age
Polesel et al. (2010) Italy 1991–2008	Cases: 326; incident cases admitted to major general hospitals Controls: 652; hospital patients with various acute conditions, matched by study centre, sex, and age Exposure assessment method: questionnaire; 78-item FFQ on average weekly consumption in the past 2 yr; meat-cooking methods assessed, but definition of red meat was not specified	Pancreas	Red meat (median, servings/wk) 1.00 2.25 3.25 4.25 6.25 Trend-test *P* value: 0.01 Pork and processed meat (median, servings/wk) 1.50 3.00 5.00 Trend-test *P* value: 0.27	 43 51 51 84 97 89 115 122	 1.00 1.26 (0.75–2.12) 1.69 (0.98–2.91) 1.79 (1.09–2.96) 1.99 (1.18–3.36) 1.00 1.18 (0.81–1.73) 1.25 (0.85–1.84)	Year of interview, education, tobacco smoking, alcohol drinking, self-reported history of diabetes, BMI, total energy, study centre, age, sex
Di Maso et al. (2013) Italy, Switzerland 1991–2009	Cases: 326; incident cases from major hospitals Controls: 652; patients in the same hospitals with acute conditions Exposure assessment method: questionnaire; validated FFQ; red meat included beef, veal, pork, horse meat, and meat sauces	Pancreas	Red meat intake (g/day) < 60 60–89 ≥ 90 Increase of 50 g/day Trend-test *P* value: < 0.01	 96 96 134 326	 1.00 1.42 (0.98–2.07) 2.18 (1.51–3.16) 1.51 (1.25–1.82)	Study centre, age, sex, education, year, BMI, tobacco, alcohol, fruit and vegetable consumption

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; mo, month; NR, not reported; wk, week; yr, year

References

Anderson KE, Sinha R, Kulldorff M, Gross M, Lang NP, Barber C et al. (2002). Meat intake and cooking techniques: associations with pancreatic cancer. *Mutat Res*, 506-507:225–31. doi:10.1016/S0027-5107(02)00169-0 PMID:12351162

Anderson KE, Mongin SJ, Sinha R, Stolzenberg-Solomon R, Gross MD, Ziegler RG et al. (2012). Pancreatic cancer risk: associations with meat-derived carcinogen intake in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort. *Mol Carcinog*, 51(1):128–37. doi:10.1002/mc.20794 PMID:22162237

Anderson LN, Cotterchio M, Gallinger S (2009). Lifestyle, dietary, and medical history factors associated with pancreatic cancer risk in Ontario, Canada. *Cancer Causes Control*, 20(6):825–34. doi:10.1007/s10552-009-9303-5 PMID:19194662

Berjia FL, Poulsen M, Nauta M (2014). Burden of diseases estimates associated to different red meat cooking practices. *Food Chem Toxicol*, 66:237–44. doi:10.1016/j.fct.2014.01.045 PMID:24491261

Bosetti C, Bravi F, Turati F, Edefonti V, Polesel J, Decarli A et al. (2013). Nutrient-based dietary patterns and pancreatic cancer risk. *Ann Epidemiol*, 23(3):124–8. doi:10.1016/j.annepidem.2012.12.005 PMID:23332711

Chan JM, Wang F, Holly EA (2007). Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control*, 18(10):1153–67. doi:10.1007/s10552-007-9054-0 PMID:17805983

Chan JM, Gong Z, Holly EA, Bracci PM (2013). Dietary patterns and risk of pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area. *Nutr Cancer*, 65(1):157–64. doi:10.1080/01635581.2012.725502 PMID:23368926

Coughlin SS, Calle EE, Patel AV, Thun MJ (2000). Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control*, 11(10):915–23. doi:10.1023/A:1026580131793 PMID:11142526

Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R (2007). A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med*, 4(12):12 (e 325): e325 doi:10.1371/journal.pmed.0040325 PMID:18076279

Di Maso M, Talamini R, Bosetti C, Montella M, Zucchetto A, Libra M et al. (2013). Red meat and cancer risk in a network of case-control studies focusing on cooking practices. *Ann Oncol*, 24(12):3107–12. doi:10.1093/annonc/mdt392 PMID:24121119

Heinen MM, Verhage BA, Goldbohm RA, van den Brandt PA (2009). Meat and fat intake and pancreatic cancer risk in the Netherlands Cohort Study. *Int J Cancer*, 125(5):1118–26. doi:10.1002/ijc.24387 PMID:19452526

Hirayama T (1990). [A large scale cohort study on the effect of life styles on the risk of cancer by each site] *Gan No Rinsho*, (Spec No):233–42. PMID:2313877

Hu J, La Vecchia C, DesMeules M, Negri E, Mery L, Group CCRE; Canadian Cancer Registries Epidemiology Research Group (2008). Meat and fish consumption and cancer in Canada. *Nutr Cancer*, 60(3):313–24. doi:10.1080/01635580701759724 PMID:18444165

Hu J, La Vecchia C, Morrison H, Negri E, Mery L; Canadian Cancer Registries Epidemiology Research Group (2011). Salt, processed meat and the risk of cancer. *Eur J Cancer Prev*, 20(2):132–9. doi:10.1097/CEJ.0b013e3283429e32 PMID:21160428

Inoue-Choi M, Flood A, Robien K, Anderson K (2011). Nutrients, food groups, dietary patterns, and risk of pancreatic cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*, 20(4):711–4. doi:10.1158/1055-9965.EPI-11-0026 PMID:21278328

Iso H, Kubota Y; Japan Collaborative Cohort Study for Evaluation of Cancer (2007). Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev*, 8:Suppl: 35–80. PMID:18260705

Ji BT, Chow WH, Gridley G, Mclaughlin JK, Dai Q, Wacholder S et al. (1995). Dietary factors and the risk of pancreatic cancer: a case-control study in Shanghai China. *Cancer Epidemiol Biomarkers Prev*, 4(8):885–93. PMID:8634662

Jiao L, Stolzenberg-Solomon R, Zimmerman TP, Duan Z, Chen L, Kahle L et al. (2015). Dietary consumption of advanced glycation end products and pancreatic cancer in the prospective NIH-AARP Diet and Health Study. *Am J Clin Nutr*, 101(1):126–34. doi:10.3945/ajcn.114.098061 PMID:25527756

Kadlubar S, Anderson JP, Sweeney C, Gross MD, Lang NP, Kadlubar FF et al. (2009). Phenotypic CYP2A6 variation and the risk of pancreatic cancer. *JOP*, 10(3):263–70. PMID:19454817

Khan MM, Goto R, Kobayashi K, Suzumura S, Nagata Y, Sonoda T et al. (2004). Dietary habits and cancer mortality among middle aged and older Japanese living in Hokkaido, Japan by cancer site and sex. *Asian Pac J Cancer Prev*, 5(1):58–65. PMID:15075007

Larsson SC, Håkanson N, Permert J, Wolk A (2006). Meat, fish, poultry and egg consumption in relation to risk of pancreatic cancer: a prospective study. *Int J Cancer*, 118(11):2866–70. doi:10.1002/ijc.21732 PMID:16385571

Larsson SC, Wolk A (2012). Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. *Br J Cancer*, 106(3):603–7. doi:10.1038/bjc.2011.585 PMID:22240790

Li D, Day RS, Bondy ML, Sinha R, Nguyen NT, Evans DB et al. (2007). Dietary mutagen exposure and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*, 16(4):655–61. doi:10.1158/1055-9965.EPI-06-0993 PMID:17416754

Lin Y, Kikuchi S, Tamakoshi A, Yagyu K, Obata Y, Inaba Y et al. (2006). Dietary habits and pancreatic cancer risk in a cohort of middle-aged and elderly Japanese. *Nutr Cancer*, 56(1):40–9. doi:10.1207/s15327914nc5601_6 PMID:17176216

Luckett BG, Su LJ, Rood JC, Fontham ET (2012). Cadmium exposure and pancreatic cancer in south Louisiana. *J Environ Public Health*, 2012:180186. doi:10.1155/2012/180186 PMID:23319964

Lyon JL, Slattery ML, Mahoney AW, Robison LM (1993). Dietary intake as a risk factor for cancer of the exocrine pancreas. *Cancer Epidemiol Biomarkers Prev*, 2(6):513–8. PMID:8268766

Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS (2003). Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. *Am J Epidemiol*, 157(12):1115–25. doi:10.1093/aje/kwg098 PMID:12796048

Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K et al. (1992). A multi-institute case-control study on the risk factors of developing pancreatic cancer. *Jpn J Clin Oncol*, 22(4):286–91. PMID:1434027

Nöthlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN (2005). Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. *J Natl Cancer Inst*, 97(19):1458–65. doi:10.1093/jnci/dji292 PMID:16204695

Ohba S, Nishi M, Miyake H (1996). Eating habits and pancreas cancer. *Int J Pancreatol*, 20(1):37–42. PMID:8872522

Paluszkiewicz P, Smolińska K, Dębińska I, Turski WA (2012). Main dietary compounds and pancreatic cancer risk. The quantitative analysis of case-control and cohort studies. *Cancer Epidemiol*, 36(1):60–7. doi:10.1016/j.canep.2011.05.004 PMID:22018953

Polesel J, Talamini R, Negri E, Bosetti C, Boz G, Lucenteforte E et al. (2010). Dietary habits and risk of pancreatic cancer: an Italian case-control study. *Cancer Causes Control*, 21(4):493–500. doi:10.1007/s10552-009-9480-2 PMID:20091114

Rohrmann S, Linseisen J, Nöthlings U, Overvad K, Egeberg R, Tjønneland A et al. (2013). Meat and fish consumption and risk of pancreatic cancer: results from the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*, 132(3):617–24. doi:10.1002/ijc.27637 PMID:22610753

Soler M, Chatenoud L, La Vecchia C, Franceschi S, Negri E (1998). Diet, alcohol, coffee and pancreatic cancer: final results from an Italian study. *Eur J Cancer Prev*, 7(6):455–60. doi:10.1097/00008469-199812000-00005 PMID:9926293

Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D (2002). Prospective study of diet and pancreatic cancer in male smokers. *Am J Epidemiol*, 155(9):783–92. doi:10.1093/aje/155.9.783 PMID:11978580

Stolzenberg-Solomon RZ, Cross AJ, Silverman DT, Schairer C, Thompson FE, Kipnis V et al. (2007). Meat and meat-mutagen intake and pancreatic cancer risk in the NIH-AARP cohort. *Cancer Epidemiol Biomarkers Prev*, 16(12):2664–75. doi:10.1158/1055-9965.EPI-07-0378 PMID:18086772

Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F et al. (2000). Red meat intake and cancer risk: a study in Italy. *Int J Cancer*, 86(3):425–8. doi:10.1002/(SICI)1097-0215(20000501)86:3<425::AID-IJC19>3.0.CO;2-S PMID:10760833

Yun YH, Lim MK, Won YJ, Park SM, Chang YJ, Oh SW et al. (2008). Dietary preference, physical activity, and cancer risk in men: national health insurance corporation study. *BMC Cancer*, 8(1):366 doi:10.1186/1471-2407-8-366 PMID:19077256

Zheng T, Boyle P, Willett WC, Hu H, Dan J, Evstifeeva TV et al. (1993). A case-control study of oral cancer in Beijing, People's Republic of China. Associations with nutrient intakes, foods and food groups. *Eur J Cancer B Oral Oncol*, 29B(1):45–55. doi:10.1016/0964-1955(93)90010-C PMID:8180577

2.5 Cancer of the prostate

2.5.1 Cohort studies

See Table 2.5.1 (red meat) and Table 2.5.2 (processed meat, web only; available at: http://publications.iarc.fr/564)

The quality of the studies was evaluated based on sample size, quality of reporting of the type of meat, consideration of relevant confounders, study design issues (e.g. population- vs hospital-based design, response rates), and exposure assessment, including validation of dietary questionnaires. The Working Group considered total energy intake, BMI, and race as important potential confounders. Cancer of the prostate poses a special problem compared with other sites because there is a broad range of clinical behaviours, and the classification is not uniform across studies (e.g. grade, stage, Gleason score, or other definitions of clinical aggressiveness). In addition, the widespread use of prostate-specific antigen (PSA) testing, which may be associated with dietary habits, further complicates the interpretation of epidemiological findings.

More than 20 cohort studies have reported on the intake of red meat or processed meat and the incidence or mortality (when incident cases were also considered) from prostate cancer, spanning from 1984 to 2011. The Americas, Asia, and Europe were represented, with studies from Japan, Norway, the Netherlands, the United Kingdom, and the USA.

The most informative cohorts were published by Schuurman et al. (1999), Michaud et al. (2001), Cross et al. (2005) (PLCO randomized trial), Rodriguez et al. (2006), Park et al. (2007), Allen et al. (2008), Koutros et al. (2008), Agalliu et al. (2011), and Major et al. (2011), and several of these studies were included in a pooled analysis of 15 prospective cohort studies (Wu et al., 2016).

Studies with fewer than 100 exposed cases are not described further in the text or tables (e.g. Gann et al., 1994; Giovannucci et al., 1993; Loh et al., 2010; Phillips & Snowdon, 1983; Richman et al., 2011; Rohrmann et al., 2007; Sander et al., 2011; Snowdon et al., 1984; Veierød et al., 1997; Wu et al., 2006).

(a) Pooling Project of Prospective Studies of Diet and Cancer

The Pooling Project of Prospective Studies of Diet and Cancer (DCPP) (Wu et al., 2016) pooled data from 15 of the prospective cohorts conducted globally (Ahn et al., 2008; Neuhouser et al., 2007; Rohrmann et al., 2007; Rodriguez et al., 2006; Larsson et al., 2009; Allen et al., 2008; Michaud et al., 2001; Kurahashi et al., 2008; Muller et al., 2009; Park et al., 2007; Schuurman et al., 1999; Sinha et al., 2009; Kristal et al., 2010; Cross et al., 2005). The individual studies included in the DCPP are not described in detail in the text and tables because the analysis was superseded by Wu et al. (2016).

Among over 700 000 men, 52 683 incident cases of prostate cancer, including 4924 advanced cases, were identified. Methods of ascertainment of meat intake and outcome measures were harmonized across cohorts (all dietary instruments were validated). Median intakes of red meat ranged from 10.3 g/day in a Japanese cohort to 109 g/day in a Melbourne cohort.

A modest positive association was found between the highest category of red meat consumption and prostate tumours identified as advanced stage at diagnosis (RR, 1.19; 95% CI, 1.01–1.40; P_{trend} = 0.07; $P_{heterogeneity}$ = 0.47). For processed meat, the corresponding relative risk was 1.17 (95% CI, 0.99–1.39; P_{trend} = 0.10; $P_{heterogeneity}$ = 0.94). Positive associations between red meat, and inverse associations between poultry intake, and advanced cancers were limited to North American studies.

(b) Studies not included in the pooling project

Among a cohort of farmers in the Agricultural Health Study in the USA involved in pesticide application, Koutros et al. (2008)

reported on the 668 prostate cancer cases that were identified, including 140 with advanced-stage prostate cancer. The response rate was low (about 50%). Slight increases in incident prostate cancer risk were noticed with quintiles of red meat intake, with no dose–response relationship (P_{trend} = 0.76). Doneness was associated with risk. For the second tertile of intake of well-done meat (median, 40.6 g/day), the relative risk was 1.12 (95% CI, 0.92–1.37), and for the third tertile of intake of well-done meat (median, 80.3 g/day), it was 1.26 (95% CI, 1.02–1.54; P_{trend} = 0.03). When this was limited to advanced cases, the relative risk for the second versus the first tertile (40.6 vs 18.0 g/day) was 1.63 (95% CI, 1.06–2.52), and for the third tertile versus the first tertile (median, 80.3 g/day), it was 1.97 (95% CI, 1.26–3.08; P_{trend} = 0.004). [Red meat was not clearly defined; doneness was for total meat.]

Major et al. (2011) conducted a study on African Americans within the NIH-AARP study. Levels of HAAs and polycyclic aromatic hydrocarbons (PAHs) from meats were ascertained by linking data to the NCI Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease (CHARRED) database. Haem iron intake was estimated. No association between incident prostate cancer and red meat intake was found, except for red meat cooked at high temperatures: the relative risk for the second (median, 11.40 g per 1000 kcal) versus the first tertile (3.49 g per 1000 kcal) was 1.18 (95% CI, 1.0–1.38), and for the third tertile (median, 24.74 g per 1000 kcal), it was 1.22 (95% CI, 1.03–1.44). The relative risk of the estimated exposure to the mutagen DiMeIQx for the second tertile (median, 0.93 ng per 1000 kcal) was 1.15 (95% CI, 0.93–1.42), and for the third tertile, it was 1.3 (95% CI, 1.05–1.61; P_{trend} = 0.02). No associations were observed with intake of other HAAs. The results for processed meat were inconclusive. [The Working Group noted that red meat included all types of beef and pork.]

Agalliu et al. (2011) described a nested case–cohort study in a Canadian cohort, with 702 cases and 1979 controls (subcohort), who were alumni of the University of Alberta. Elevated relative risks were reported for red meat, but none reached statistical significance, except Q5 (median, 3.1 oz [~87.8 g/day]) vs Q1 (median, 0.7 oz [~19.8 g/day]); the relative risk was 1.44 (95% CI, 1.06–1.95). There was no dose–response relationship. [The Working Group noted that red meat was not defined.]

2.5.2 Case–control studies

See Table 2.5.3 (red meat) and Table 2.5.4 (processed meat, web only; available at: http://publications.iarc.fr/564)

More than 20 case–control studies were considered, six with a population-based design. The Working Group considered first the population-based studies that tended to be more informative, given the uncertainty in the choice of hospital controls, who were affected by diseases that could have possibly had an impact on dietary habits. Studies with fewer than 100 cases were excluded (see details below).

(a) Population-based studies

Slattery et al. (1990) was not considered here because meat intake was considered together with estimated intake of saturated fats. Studies by Nowell et al. (2004) and Ukoli et al. (2009) were excluded because numbers were small, or dietary assessment was limited.

Norrish et al. (1999) conducted a population-based study in New Zealand that included 317 cases and 480 controls randomly selected from electoral rolls. They used a 107-item FFQ. An association was found with intake of browned beef steaks. The odds ratios were 1.36 (95% CI, 0.84–2.18) for medium/lightly browned and 1.68 (95% CI, 1.02–2.77) for well browned. Similar, but not statistically significant, associations were found in advanced cases. The researchers also

looked separately at other types of red meats, including pork, lamb, and minced beefand, processed meats including sausage, and bacon, with null results.

Wright et al. (2011) conducted a population-based study that included 1754 cases and 1645 controls identified by random digit dialling. Response rates were high (78%) in cases and lower (67%) in controls. Detailed clinical data were obtained for the cases. Disease aggressiveness was based on a composite variable incorporating Gleason score stage and PSA, where more aggressive cases were defined by a Gleason score of ≥ 7, non-localized stage, or PSA > 20 ng/mL at the time of diagnosis. A positive association was found with increasing servings per day (1 serving/day) of red meat. The odds ratios were 1.21 (95% CI, 0.97–1.51) for 0.59–1.09 servings/day and 1.43 (95% CI, 1.11–1.84) for > 1.09 servings/day. [The definition of red meat was unclear.] Similar associations were found among less and more aggressive cancer cases.

Joshi et al. (2012) conducted a study in the USA, with 717 localized and 1140 advanced incident cases, in a multiethnic population. Controls were selected with a "neighbourhood walking algorithm" or randomly from a health care financing organization. [The degree of selection bias with this type of procedure was uncertain, as selection was conditioned by local characteristics, such as the social structure of the neighbourhood and the nature of the financing organization.] The response rate was not given. Accurate dietary histories were collected with a modified version of the Block FFQ. No association with red meat intake was found, except when hamburgers cooked at high temperatures were considered, and only among advanced cases. The odds ratios were 1.3 (95% CI, 1.0–1.6) for low frequency (< 4.4 g/1000 kcal) versus never, 1.4 (95% CI, 1.0–1.8) for medium frequency (≥ 4.4 to < 7.9 g/1000 kcal), and 1.7 (95% CI, 1.3–2.2) for high frequency (≥ 7.9 g/1000 kcal). Associations were particularly strong for pan-fried red meat; subgroup analyses and multiple comparisons were considered. Previously, John et al. (2011) had reported on the San Francisco Bay Area portion of this study (John et al., 2011). In that study, advanced prostate cancer cases showed an association with increasing tertiles of total red meat intake versus no intake. The odds ratios were 1.1 (95% CI, 0.68–1.79), 1.65 (95% CI, 1.02–2.65), and 1.53 (95% CI, 0.93–2.49; P_{trend} = 0.02). Similar associations with advanced cases were found for hamburgers, steaks, and processed meat. The odds ratios for processed meat (increasing tertiles versus no intake) were 1.25 (95% CI, 0.85–1.83), 1.15 (95% CI, 0.77–1.71), and 1.57 (95% CI, 1.04–2.36), again with no clear dose–response. This study also examined cooking methods and meat mutagens.

(b) Hospital-based studies

The following hospital-based studies were given less weight for different reasons: Bashir et al. (2014), as no details given on the choice of controls; Li et al. (2014), as no response rates and limited exposure assessment; Mahmood et al. (2012), as no details on exposure assessment and no response rates; Punnen et al. (2011), as no response rates, no adjustment for total energy intake, and only cases with Gleason ≥ 7 included; Rodrigues et al. (2011), as no response rates and no adjustment for energy intake; Román et al. (2014), as no response rates and source of controls not identified; Rosato et al. (2014), as no response rates and results not given for meat as such; Salem et al. (2011), as diagnoses in controls not specified and poor dietary history; Sonoda et al. (2004), as no response rates and limited adjustment for confounders; Subahir et al. (2009), as diseases of controls not specified and no response rates; Sung et al. (1999), as no response rates, unclear adjustment for confounders, and limited dietary history; Walker et al. (2005), as no response rates for controls and only dietary patterns examined; and De Stefani et al. (1995), as the distinction between red and white meat was unclear. These

studies are not further described in the text and tables.

Deneo-Pellegrini et al. (1999) described a study in Uruguay with cancer-free controls, with small numbers. For red meat and for processed meat, the slightly elevated odds ratios were not statistically significant. An update of the same study was published by the same authors with similar results (Deneo-Pellegrini et al. (2012).

Aune et al. (2009) conducted a hospital-based study on multiple cancers in Uruguay, with 345 histologically confirmed cases. A 64-item FFQ validated was used. An association was found with red meat. The odds ratio for the second (150 to < 250 g/day) versus the first (0 to < 150 g/day) tertile was 1.56 (95% CI, 1.15–2.13), and the odds ratio for the third (250–600 g/day) versus the first tertile was 1.87 (95% CI, 1.08–3.21; P_{trend} = 0.001). No association was found with processed meat. [The Working Group noted that the results were adjusted for energy intake, BMI, and numerous other risk factors.]

Among those given less priority, Punnen et al. (2011) is worth mentioning because of the relatively large size of the study (466 cases). They found an association with an increasing intake of grilled beef. The odds ratios were 1.5 (95% CI, 1.03–2.19) for low intake versus none, 1.69 (95% CI, 1.19–2.38) for medium intake versus none, and 1.61 (95% CI, 1.13–2.28) (P_{trend} = 0.004) for high intake versus none. The odds ratios with increasing intake of grilled hamburgers versus no intake were 1.41 (95% CI, 0.99–2.01), 1.58 (95% CI, 1.11–2.24), and 1.86, (95% CI, 1.28–2.71; P_{trend} = 0.001).

Di Maso et al. (2013) published results based on data from a large hospital-based study in Italy (1294 cases, non-neoplastic controls). They reported slightly elevated odds ratios for red meat, which were not statistically significant.

(c) Other studies

Amin et al. (2008), in Canada, recruited 1356 subjects with increased PSA undergoing a prostate biopsy, comparing those with a cancer diagnosis with the others. All men were asked to respond to a self-administered, validated FFQ (included only 12 food groups) before the procedure; the procedure was a biopsy administered after a rising serum PSA level or a suspicious digital rectal examination. Increased odds ratios with intake of red meat (including ham and sausages) were found, with an apparent dose–response relationship across quintiles. The odds ratio for Q4 (5 servings/week) versus Q1 (1 serving/week) was 2.31 (95% CI, 1.32–2.46), and for Q5 (data missing or unavailable) versus Q1, it was 2.91 (95% CI, 1.56–4.87; P_{trend} = 0.027). [The Working Group noted that there was apparently a low response rate among controls. This study was of interest because both cases and controls had high PSA. That is, screening was not a source of confounding, the FFQ was administered when PSA was measured, and the identification of cases occurred after, so recall bias could be reasonably ruled out. Red meat included ham and sausages and so corresponded to red meat and processed meat combined.]

Table 2.5.1 Cohort studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Koutros et al. (2008) USA Recruitment, 1993–1997 Cohort study	23 080 men, 197 017 person-years, 668 prostate cancer cases (140 advanced); Agricultural Health Study included 57 311 licenced pesticide applicators from Iowa and North Carolina; 23 080 available for analysis Exposure assessment method: questionnaire; frequency of intake of hamburgers, beef steaks, chicken, pork chops/ham steaks, and bacon/sausage in the last 12 mo; doneness of total meat and cooking methods [red meat was not clearly defined]	Prostate: incident cases	Red meat (median, g/day)			Age, state of residence, race, smoking, family history of prostate cancer
			Q1 (23.2)	145	1.00	
			Q2 (42.5)	143	1.28 (1.15–1.62)	
			Q3 (60.9)	121	1.15 (0.90–1.48)	
			Q4 (81.6)	109	1.16 (0.90–1.50)	
			Q5 (122.3)	95	1.11 (0.84–1.46)	
			Trend-test *P* value: 0.76			
		Prostate: incident cases	Doneness level, well- and very well-done total meat (median, g/day)			
			T1 (18.0)	187	1.00	
			T2 (40.6)	212	1.12 (0.92–1.37)	
			T3 (80.3)	214	1.26 (1.02–1.54)	
			Trend-test *P* value: 0.03			
		Prostate: (aggressive/ advanced)	Doneness level, very well-done total meat (median, g/day)			
			T1 (18.0)	35	1.00	
			T2 (40.6)	51	1.63 (1.06–2.52)	
			T3 (80.3)	54	1.97 (1.26–3.08)	
			Trend-test *P* value: 0.004			
		Prostate: incident cases	Doneness level, rare or medium total meat (median, g/day)			
			T1 (0)	239	1.00	
			T2 (18.0)	205	1.06 (0.87–1.29)	
			T3 (63.0)	169	1.04 (0.84–1.29)	
			Trend-test *P* value: 0.8			

Table 2.5.1 Cohort studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Agalliu et al. (2011) Canada 1995–1998 Cohort study	702 cases and 1979 controls (subcohort); prospective cohort of 73 909 men and women, mainly alumni of the University of Alberta, (34 291 men) Exposure assessment method: questionnaire; 166 food items and validated; red meat was not defined	Prostate	Quintiles of red meat intake [median, g/day]			Age, race, BMI, physical activity, education
			Q1 [19.8]	108	1.00	
			Q2 [36. 8]	124	1.10 (0.80–1.50)	
			Q3 [48.2]	151	1.33 (0.98–1.80)	
			Q4 [62.3]	128	1.18 (0.87–1.61)	
			Q5 [87.8]	150	1.44 (1.06–1.95)	
			Trend-test *P* value: 0.04			
		Prostate (aggressive/ advanced)	Quintiles of red meat intake [median, g/day]			
			Q1 [19.8]	28	1.00	
			Q2 [36.8]	40	1.44 (0.85–2.43)	
			Q3 [48.2]	37	1.30 (0.76–2.23)	
			Q4 [62.3]	32	1.17 (0.67–2.03)	
			Q5 [87.8]	36	1.38 (0.80–2.39)	
			Trend-test *P* value: 0.10			
Major et al. (2011) USA Enrolment, 1995–1996 Cohort study	Prospective cohort of 7949 men; from National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study; men and women aged 50–57 yr; 556 401 people, including 9304 African American men (after exclusions, 7949) Exposure assessment method: questionnaire; 124-item FFQ on previous 12 mo; "red meat" included all types of beef and pork	Prostate	Quintiles of red meat (median intake, g/1000 kcal)			Age, BMI, smoking, education, marital status, alcohol consumption, health status, family history of prostate cancer, family history of diabetes, fruit intake
			Q1 (8.42)	244	1.00	
			Q2 (19.35)	225	0.99 (0.82–1.19)	
			Q3 (29.17)	226	1.05 (0.87–1.26)	
			Q4 (40.32)	213	1.01 (0.83–1.24)	
			Q5 (60.92)	181	0.92 (0.75–1.14)	
			Trend-test *P* value: 0.48			
		Prostate	Tertiles of red meat cooked at high temperatures (median intake, g/1000 kcal)			
			T1 (3.49)	365	1.00	
			T2 (11.40)	373	1.18 (1.00–1.38)	
			T3 (24.74)	351	1.22 (1.03–1.44)	
			Trend-test *P* value: 0.04			

Table 2.5.1 Cohort studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Major et al. (2011) USA Enrolment, 1995–1996 Cohort study (cont.)		Prostate	Tertiles of red meat cooked at low temperatures (median intake, g/1000 kcal)			
			T1 (6.63)	405	1.00	
			T2 (15.36)	368	0.91 (0.78–1.06)	
			T3 (29.06)	316	0.84 (0.71–0.99)	
			Trend-test *P* value: 0.05			
		Prostate: advanced cases	Tertiles of red meat cooked at high temperatures (median intake, g/1000 kcal)			
			T1 (3.49)	34	1.00	
			T2 (11.40)	35	1.23 (0.74–2.06)	
			T3 (24.74)	39	1.44 (0.83–2.47)	
			Trend-test *P* value: 0.20			
Wu et al. (2016) International pooled cohort consortium 1985–2009 Cohort study	842 149 men; consortium of 15 cohort studies (52 683 incident prostate cancer cases, including 4924 advanced cases) Exposure assessment method: questionnaire	Prostate (aggressive/ advanced)	Quintiles of red meat intake (g/day)			Marital status, race, education, BMI, height, alcohol intake, total energy intake, smoking status, family history of prostate cancer, physical activity, history of diabetes, multivitamin use
			Q1 (< 20)	NR	1.00	
			Q2 (20 to < 40)	NR	1.02 (0.89–1.16)	
			Q3 (40 to < 60)	NR	1.11 (0.96–1.27)	
			Q4 (60 to < 100)	NR	1.05 (0.91–1.21)	
			Q5 (≥ 100)	NR	1.19 (1.01–1.40)	
			Trend-test *P* value: 0.07			

BMI, body mass index; FFQ, food frequency questionnaire; mo, month; NR, not reported; yr, year

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Deneo-Pellegrini et al. (1999) Uruguay 1994–1997	Cases: 175; localized cancers, 25%; regional cancers, 72%; disseminated cancers, 3% Controls: 233; hospital patients with conditions unrelated to diet, mainly mild surgical conditions, and no cancers Exposure assessment method: questionnaire; 64 food items; red meat was beef and lamb	Prostate	Red meat, quartiles Q1 Q2 Q3 Q4 Trend-test *P* value: 0.17	 32 61 36 46	 1.0 1.5 (0.9–2.7) 1.7 (0.9–3.3) 1.7 (0.8–3.4)	Age, residence, urban/rural, education, family history, BMI, energy intake
Norrish et al. (1999) New Zealand 1996–1997	Cases: 317; population-based, histologically confirmed cases Controls: 480; controls were randomly selected from electoral rolls and matched by age Exposure assessment method: questionnaire; self-administered, 107-item FFQ	Prostate Prostate: advanced cases	Beef steak doneness Medium or lightly browned vs never eaten Well done or well browned vs never eaten Trend-test *P* value: 0.03 Beef steak doneness Medium or lightly browned vs never eaten Well done or well browned vs never eaten Trend-test *P* value: 0.16	 163 123 NR NR	 1.36 (0.84–2.18) 1.68 (1.02–2.77) 1.38 (0.78–2.42) 1.56 (0.86–2.81)	Age, socioeconomic status, total NSAIDs, total energy intake
Amin et al. (2008) Canada 2003–2006	Cases: 386 men; cohort of 1356 subjects with increased PSA who underwent prostate biopsy; cases were those with cancer at biopsy Controls: 268 men; controls had high PSA, but non-malignant lesions at biopsy Exposure assessment method: questionnaire; self-administered FFQ with 12 food groups; repeated questionnaires among 50 subjects to validate the FFQ and exclude recall bias	Prostate	Red meat, ham, and sausages; quintiles Q1 Q2 Q3 Q4 Q5 Trend-test *P* value: 0.027	 NR NR NR NR NR	 1.00 1.55 (0.85–1.69) 1.97 (0.74–2.73) 2.31 (1.32–2.46) 2.91 (1.56–4.87)	Age, ethnicity, education, family history, smoking, alcohol, sexually transmitted infection, cystitis

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Aune et al. (2009) Uruguay 1996–2004	Cases: 345; recruited in four major hospitals in Montevideo Controls: 2032; controls had non-neoplastic diseases not related to smoking or drinking, and no recent changes in dietary habits Exposure assessment method: questionnaire; 64 food items; FFQ tested for reproducibility (correlation coefficient between two assessments was 0.77 for red meat); red meat was defined as fresh meat, including lamb and beef	Prostate	Red meat (g/day), tertiles T1 (0 to < 150) T2 (150 to < 250) T3 (250–600) Trend-test *P* value: 0.001	 125 179 41	 1.00 1.56 (1.15–2.13) 1.87 (1.08–3.21)	Residence; age; education; income; interviewer; smoking; alcohol; intake of grains and fatty foods, fruits and vegetables; energy intake; BMI; other dietary habits
John et al. (2011) USA 1997–2000	Cases: 726; population-based, aged 40–70 yr; non-Hispanic, whites and African Americans; SEER codes 41–85 Controls: 527; controls identified with random digit dialling and randomly selected from the rosters of beneficiaries of the Health Care Financing Administration; frequency-matched by age and ethnicity Exposure assessment method: questionnaire; 74-item food questionnaire; red meat was all types of beef and pork	Prostate: advanced cases	Hamburgers (g/1000 kcal per day), tertiles No red meat consumed T1 T2 T3 Trend-test *P* value: 0.005	 42 144 150 195	 1.00 1.21 (0.75–1.95) 1.33 (0.82–2.14) 1.79 (1.10–2.92)	Age, race, socioeconomic status, family history, BMI, calorie intake, fat, fruits, vegetables
		Prostate: advanced cases	Red meat (g/1000kcal per day), tertiles No red meat consumed T1 T2 T3 Trend-test *P* value: 0.02	 42 128 190 171	 1.00 1.10 (0.68–1.79) 1.65 (1.02–2.65) 1.53 (0.93–2.49)	
		Prostate: localized cases	Red meat (g/1000kcal per day), tertiles No red meat consumed T1 T2 T3 Trend-test *P* value: 0.62	 58 156 157 156	 1.00 0.71 (0.39–1.27) 1.12 (0.63–2.01) 0.91 (0.49–1.69)	

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Punnen et al. (2011) USA 2001–2004	Cases: 466; hospital-based. incident histologically confirmed cases; only aggressive cases (Gleason score ≥ 7) Controls: 511; controls were men older than 50 yr undergoing medical examination, with PSA < 4; frequency-matched by age, ethnicity, and medical centre Exposure assessment method: questionnaire; SQFFQ; estimation of exposure to mutagens	Prostate	Grilled beef intake			Age, ethnicity, medical centre, family history, smoking, BMI, prior history of PSA testing, education level, n-3 fatty acid intake
			Low intake vs none	85	1.50 (1.03–2.19)	
			Medium vs none	124	1.69 (1.19–2.38)	
			High vs none	129	1.61 (1.13–2.28)	
			Trend-test *P* value: 0.004			
			Grilled hamburger intake			
			Low vs none	106	1.41 (0.99–2.01)	
			Medium vs none	126	1.58 (1.11–2.24)	
			High vs none	120	1.86 (1.28–2.71)	
			Trend-test *P* value: 0.001			
Wright et al. (2011) USA 1993–1996	Cases: 1754; population-based study; cases identified from the SEER Registries Controls: 1645; population controls identified by random digit telephone dialling and matched by age Exposure assessment method: questionnaire; self-administered FFQ on usual dietary intake during 3–5 yr before the reference date; [red meat not clearly defined]	Prostate	Red meat (servings/day)			Age, PSA screening history, BMI, total caloric intake
			≤ 0.58	NR	1.00	
			0.59–1.09	NR	1.21 (0.97–1.51)	
			> 1.09	NR	1.43 (1.11–1.84)	
			Trend-test *P* value: <0.01			
		Prostate: less aggressive cancer	Red meat (servings/day)			
			≤ 0.58	NR	1.00	
			0.59–1.09	NR	1.11 (0.87–1.42)	
			> 1.09	NR	1.38 (1.05–1.82)	
			Trend-test *P* value: 0.02			
		Prostate: more aggressive cancer	Red meat (servings/day)			
			≤ 0.58	NR	1.00	
			0.59–1.09	NR	1.43 (1.06–1.96)	
			> 1.09	NR	1.55 (1.10–2.20)	
			Trend-test *P* value: 0.01			

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Deneo-Pellegrini et al. (2012) Uruguay 1996–2004	Cases: 326; hospital-based study; localized cancers, 25%; regional cancers, 72%; and disseminated cancers, 3% Controls: 652; hospital controls; conditions not related to smoking, drinking and no recent dietary changes (minor surgical conditions); matched 2:1 on age and residence Exposure assessment method: questionnaire; 64 food items; red meat was beef and lamb	Prostate	T1 T2 T3 Trend-test *P* value: 0.17	95 119 112	1.00 1.28 (0.90–1.81) 1.28 (0.90–1.82)	Age, residence, urban/rural, BMI, education, family history, energy intake, other types of meats
Joshi et al. (2012) USA 1997–1998	Cases: 717 localized, 1140 advanced; multiethnic, population-based; incident cases identified through cancer registries Controls: 1096; controls selected with neighbourhood walk algorithm or randomly selected from the Health Care Financing Administration Exposure assessment method: questionnaire; red meat was all types of beef and pork, hamburgers, and steak	Prostate: advanced cases	High-temperature cooked hamburger (g/1000 kcal/day) Never/rarely (0) Low (> 0 to < 4.4) Medium (≥ 4.4 to < 7.9) High (> 7.9) Trend-test *P* value: < 0.001	 501 310 145 183	 1.0 1.3 (1.0–1.6) 1.4 (1.0–1.8) 1.7 (1.3–2.2)	Age, BMI, caloric intakes, family history, fat intake, alcohol, smoking, fruit intake, vegetable intake
		Prostate: advanced cases	Red meat (g/1000 kcal per day), quintiles Q1 (≥ 0 to < 4.6) Q2 (≥ 4.6 to < 8.9) Q3 (≥ 8.9 to < 14.4) Q4 (≥ 14.4 to < 23.3) Q5 (≥ 23.3) Trend-test *P* value: 0.667	 209 200 250 257 223	 1.0 0.9 (0.7–1.2) 1.2 (0.9–1.5) 1.1 (0.8–1.5) 1.0 (0.8–1.4)	

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2012) USA 1997–1998 (cont.)		Prostate: localized cases	Red meat (g/1000 kcal per day), quintiles			
			Q1 (≥ 0 to < 4.6)	124	1.0	
			Q2 (≥ 4.6 to < 8.9)	142	1.2 (0.8–1.6)	
			Q3 (≥ 8.9 to < 14.4)	140	1.1 (0.8–1.5)	
			Q4 (≥ 14.4 to < 23.3)	141	1.0 (0.7–1.4)	
			Q5 (≥ 23.3)	168	1.1 (0.8–1.6)	
			Trend-test *P* value: 0.822			
		Prostate: advanced cases	High-temperature cooked red meat (g/1000 kcal per day)			
			Never/rarely (0)	133	1.0	
			Low (> 0 to < 9.4)	457	1.1 (0.9–1.5)	
			Medium (≥ 9.4 to < 16.9)	274	1.4 (1.0–1.9)	
			High (≥ 16.9)	275	1.4 (1.0–1.9)	
			Trend-test *P* value: 0.026			
		Prostate: advanced cases	Well-done red meat (g/1000 kcal per day)			
			Never/rarely (0)	392	1.0	
			Low (> 0 to < 6.1)	355	1.2 (0.9–1.4)	
			Medium (≥ 6.1 to < 11.0)	161	1.1 (0.8–1.4)	
			High (≥ 11.0)	231	1.4 (1.1–1.8)	
			Trend-test *P* value: 0.013			
		Prostate: advanced cases	Pan-fried red meat (g/1000 kcal per day)			
			Never/rarely (0)	538	1.0	
			Low (> 0.0 to < 5.0)	297	1.2 (1.0–1.5)	
			Medium (≥ 5.0 to < 9.8)	137	1.2 (0.9–1.6)	
			High (≥ 9.8)	167	1.3 (1.0–1.8)	
			Trend-test *P* value: 0.035			

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Di Maso et al. (2013) Italy and Switzerland 1991–2002	Cases: 1294; hospitalized incident cases Controls: 11 656; hospital controls; non-neoplastic conditions unrelated to alcohol, diet, and tobacco; frequency-matched to cases Exposure assessment method: questionnaire; red meat was beef, veal, pork, horse meat, and half of the first course, including meat sauce (e.g. lasagne, pasta/rice with bologna sauce)	Prostate	Red meat (g/day) 60–89 vs < 60 ≥ 90 vs < 60 Trend-test *P* value: 0.14	 385 453	 1.17 (0.96–1.42) 1.15 (0.96–1.39)	Centre, age, education, BMI, smoking, alcohol, vegetable intake, fruit intake
		Prostate	Increase of 50 g/day	NR	1.07 (0.97–1.18)	

BMI, body mass index; FFQ, food frequency questionnaire; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology, and End Results; SQFFQ, semi-quantitative food frequency questionnaire; yr, year

References

Agalliu I, Kirsh VA, Kreiger N, Soskolne CL, Rohan TE (2011). Oxidative balance score and risk of prostate cancer: results from a case-cohort study. *Cancer Epidemiol*, 35(4):353–61. doi:10.1016/j.canep.2010.11.002 PMID:21145797

Ahn J, Moslehi R, Weinstein SJ, Snyder K, Virtamo J, Albanes D (2008). Family history of prostate cancer and prostate cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. *Int J Cancer*, 123(5):1154–9. doi:10.1002/ijc.23591 PMID:18546266

Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A et al. (2008). Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer*, 98(9):1574–81. doi:10.1038/sj.bjc.6604331 PMID:18382426

Amin M, Jeyaganth S, Fahmy N, Bégin LR, Aronson S, Jacobson S et al. (2008). Dietary habits and prostate cancer detection: a case-control study. *Can Urol Assoc J*, 2(5):510–5. doi:10.5489/cuaj.918 PMID:18953447

Aune D, De Stefani E, Ronco A, Boffetta P, Deneo-Pellegrini H, Acosta G et al. (2009). Meat consumption and cancer risk: a case-control study in Uruguay. *Asian Pac J Cancer Prev*, 10(3):429–36. PMID:19640186

Bashir MN, Ahmad MR, Malik A (2014). Risk factors of prostate cancer: a case-control study in Faisalabad, Pakistan. *Asian Pac J Cancer Prev*, 15(23):10237–40. doi:10.7314/APJCP.2014.15.23.10237 PMID:25556453

Cross AJ, Peters U, Kirsh VA, Andriole GL, Reding D, Hayes RB et al. (2005). A prospective study of meat and meat mutagens and prostate cancer risk. *Cancer Res*, 65(24):11779–84. doi:10.1158/0008-5472.CAN-05-2191 PMID:16357191

De Stefani E, Fierro L, Barrios E, Ronco A (1995). Tobacco, alcohol, diet and risk of prostate cancer. *Tumori*, 81(5):315–20. PMID:8804446

Deneo-Pellegrini H, De Stefani E, Ronco A, Mendilaharsu M (1999). Foods, nutrients and prostate cancer: a case-control study in Uruguay. *Br J Cancer*, 80(3-4):591–7. doi:10.1038/sj.bjc.6690396 PMID:10408871

Deneo-Pellegrini H, Ronco AL, De Stefani E, Boffetta P, Correa P, Mendilaharsu M et al. (2012). Food groups and risk of prostate cancer: a case-control study in Uruguay. *Cancer Causes Control*, 23(7):1031–8. doi:10.1007/s10552-012-9968-z PMID:22544454

Di Maso M, Talamini R, Bosetti C, Montella M, Zucchetto A, Libra M et al. (2013). Red meat and cancer risk in a network of case-control studies focusing on cooking practices. *Ann Oncol*, 24(12):3107–12. doi:10.1093/annonc/mdt392 PMID:24121119

Gann PH, Hennekens CH, Sacks FM, Grodstein F, Giovannucci EL, Stampfer MJ (1994). Prospective study of plasma fatty acids and risk of prostate cancer. *J Natl Cancer Inst*, 86(4):281–6. doi:10.1093/jnci/86.4.281 PMID:8158682

Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CG et al. (1993). A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst*, 85(19):1571–9. doi:10.1093/jnci/85.19.1571 PMID:8105097

John EM, Stern MC, Sinha R, Koo J (2011). Meat consumption, cooking practices, meat mutagens, and risk of prostate cancer. *Nutr Cancer*, 63(4):525–37. doi:10.1080/01635581.2011.539311 PMID:21526454

Joshi AD, Corral R, Catsburg C, Lewinger JP, Koo J, John EM et al. (2012). Red meat and poultry, cooking practices, genetic susceptibility and risk of prostate cancer: results from a multiethnic case-control study. *Carcinogenesis*, 33(11):2108–18. doi:10.1093/carcin/bgs242 PMID:22822096

Koutros S, Cross AJ, Sandler DP, Hoppin JA, Ma X, Zheng T et al. (2008). Meat and meat mutagens and risk of prostate cancer in the Agricultural Health Study. *Cancer Epidemiol Biomarkers Prev*, 17(1):80–7. doi:10.1158/1055-9965.EPI-07-0392 PMID:18199713

Kristal AR, Arnold KB, Neuhouser ML, Goodman P, Platz EA, Albanes D et al. (2010). Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. *Am J Epidemiol*, 172(5):566–77. doi:10.1093/aje/kwq148 PMID:20693267

Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane AS; Japan Public Health Center-Based Prospective Study Group (2008). Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. *Cancer Epidemiol Biomarkers Prev*, 17(4):930–7. doi:10.1158/1055-9965.EPI-07-2681 PMID:18398033

Larsson SC, Akesson A, Wolk A (2009). Dietary acrylamide intake and prostate cancer risk in a prospective cohort of Swedish men. *Cancer Epidemiol Biomarkers Prev*, 18(6):1939–41. doi:10.1158/1055-9965.EPI-09-0280 PMID:19505926

Li ML, Lin J, Hou JG, Xu L, Cui XG, Xu XX et al. (2014). Environmental and psycho-social factors related to prostate cancer risk in the Chinese population: a case-control study. *Biomed Environ Sci*, 27(9):707–17. PMID:25256860

Loh YH, Mitrou PN, Bowman R, Wood A, Jeffery H, Luben RN et al. (2010). MGMT Ile143Val polymorphism, dietary factors and the risk of breast, colorectal and prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study. *DNA Repair (Amst)*, 9(4):421–8. doi:10.1016/j.dnarep.2010.01.002 PMID:20096652

Mahmood S, Qasmi G, Ahmed A, Kokab F, Zahid MF, Afridi MI et al. (2012). Lifestyle factors associated with the risk of prostate cancer among Pakistani men. *J Ayub Med Coll Abbottabad*, 24(2):111–5. PMID:24397069

Major JM, Cross AJ, Watters JL, Hollenbeck AR, Graubard BI, Sinha R (2011). Patterns of meat intake and risk of prostate cancer among African-Americans in a large prospective study. *Cancer Causes Control*, 22(12):1691–8. doi:10.1007/s10552-011-9845-1 PMID:21971816

Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willet WC, Giovannucci E (2001). A prospective study on intake of animal products and risk of prostate cancer. *Cancer Causes Control*, 12(6):557–67. doi:10.1023/A:1011256201044 PMID:11519764

Muller DC, Severi G, Baglietto L, Krishnan K, English DR, Hopper JL et al. (2009). Dietary patterns and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*, 18(11):3126–9. doi:10.1158/1055-9965.EPI-09-0780 PMID:19861522

Neuhouser ML, Barnett MJ, Kristal AR, Ambrosone CB, King I, Thornquist M et al. (2007). (n-6) PUFA increase and dairy foods decrease prostate cancer risk in heavy smokers. *J Nutr*, 137(7):1821–7. doi:10.1093/jn/137.7.1821 PMID:17585037

Norrish AE, Ferguson LR, Knize MG, Felton JS, Sharpe SJ, Jackson RT (1999). Heterocyclic amine content of cooked meat and risk of prostate cancer. *J Natl Cancer Inst*, 91(23):2038–44. doi:10.1093/jnci/91.23.2038 PMID:10580030

Nowell S, Ratnasinghe DL, Ambrosone CB, Williams S, Teague-Ross T, Trimble L et al. (2004). Association of SULT1A1 phenotype and genotype with prostate cancer risk in African-Americans and Caucasians. *Cancer Epidemiol Biomarkers Prev*, 13(2):270–6. doi:10.1158/1055-9965.EPI-03-0047 PMID:14973106

Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN (2007). Fat and meat intake and prostate cancer risk: the multiethnic cohort study. *Int J Cancer*, 121(6):1339–45. doi:10.1002/ijc.22805 PMID:17487838

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

Punnen S, Hardin J, Cheng I, Klein EA, Witte JS (2011). Impact of meat consumption, preparation, and mutagens on aggressive prostate cancer. *PLoS One*, 6(11):e27711. doi:10.1371/journal.pone.0027711 PMID:22132129

Richman EL, Kenfield SA, Stampfer MJ, Giovannucci EL, Chan JM (2011). Egg, red meat, and poultry intake and risk of lethal prostate cancer in the prostate-specific antigen-era: incidence and survival. *Cancer Prev Res (Phila)*, 4(12):2110–21. doi:10.1158/1940-6207.CAPR-11-0354 PMID:21930800

Rodrigues IS, Kuasne H, Losi-Guembarovski R, Fuganti PE, Gregório EP, Kishima MO et al. (2011). Evaluation of the influence of polymorphic variants CYP1A1 2B, CYP1B1 2, CYP3A4 1B, GSTM1 0, and GSTT1 0 in prostate cancer. *Urol Oncol*, 29(6):654–63. doi:10.1016/j.urolonc.2010.01.009 PMID:20884258

Rodriguez C, McCullough ML, Mondul AM, Jacobs EJ, Chao A, Patel AV et al. (2006). Meat consumption among Black and White men and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev*, 15(2):211–6. doi:10.1158/1055-9965.EPI-05-0614 PMID:16492907

Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ (2007). Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control*, 18(1):41–50. doi:10.1007/s10552-006-0082-y PMID:17315319

Román MD, Niclis C, Tumas N, Díaz MP, Osella AR, Muñoz SE (2014). Tobacco smoking patterns and differential food effects on prostate and breast cancers among smokers and nonsmokers in Córdoba, Argentina. *Eur J Cancer Prev*, 23(4):310–8. doi:10.1097/CEJ.0000000000000044 PMID:24871563

Rosato V, Edefonti V, Bravi F, Bosetti C, Bertuccio P, Talamini R et al. (2014). Nutrient-based dietary patterns and prostate cancer risk: a case-control study from Italy. *Cancer Causes Control*, 25(4):525–32. doi:10.1007/s10552-014-0356-8 PMID:24515125

Salem S, Salahi M, Mohseni M, Ahmadi H, Mehrsai A, Jahani Y et al. (2011). Major dietary factors and prostate cancer risk: a prospective multicenter case-control study. *Nutr Cancer*, 63(1):21–7. PMID:21161822

Sander A, Linseisen J, Rohrmann S (2011). Intake of heterocyclic aromatic amines and the risk of prostate cancer in the EPIC-Heidelberg cohort. *Cancer Causes Control*, 22(1):109–14. doi:10.1007/s10552-010-9680-9 PMID:21103922

Schuurman AG, van den Brandt PA, Dorant E, Goldbohm RA (1999). Animal products, calcium and protein and prostate cancer risk in The Netherlands Cohort Study. *Br J Cancer*, 80(7):1107–13. doi:10.1038/sj.bjc.6690472 PMID:10362125

Sinha R, Park Y, Graubard BI, Leitzmann MF, Hollenbeck A, Schatzkin A et al. (2009). Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the United States. *Am J Epidemiol*, 170(9):1165–77. doi:10.1093/aje/kwp280 PMID:19808637

Slattery ML, Schumacher MC, West DW, Robison LM, French TK (1990). Food-consumption trends between adolescent and adult years and subsequent risk of prostate cancer. *Am J Clin Nutr*, 52(4):752–7. doi:10.1093/ajcn/52.4.752 PMID:2403069

Snowdon DA, Phillips RL, Choi W (1984). Diet, obesity, and risk of fatal prostate cancer. *Am J Epidemiol*, 120(2):244–50. doi:10.1093/oxfordjournals.aje.a113886 PMID:6465122

Sonoda T, Nagata Y, Mori M, Miyanaga N, Takashima N, Okumura K et al. (2004). A case-control study of diet and prostate cancer in Japan: possible

protective effect of traditional Japanese diet. *Cancer Sci*, 95(3):238–42. doi:10.1111/j.1349-7006.2004.tb02209.x PMID:15016323

Subahir MN, Shah SA, Zainuddin ZM (2009). Risk factors for prostate cancer in Universiti Kebangsaan Malaysia Medical Centre: a case-control study. *Asian Pac J Cancer Prev*, 10(6):1015–20. PMID:20192575

Sung JF, Lin RS, Pu YS, Chen YC, Chang HC, Lai MK (1999). Risk factors for prostate carcinoma in Taiwan: a case-control study in a Chinese population. *Cancer*, 86(3):484–91. doi:10.1002/(SICI)1097-0142(19990801)86:3<484::AID-CNCR17>3.0.CO;2-P PMID:10430257

Ukoli FA, Taher K, Egbagbe E, Lomotey M, Oguike T, Akumabor P et al. (2009). Association of self-reported consumption of cooked meat, fish, seafood and eggs with prostate cancer risk among Nigerians. *Infect Agent Cancer*, 4:Suppl 1: S6. doi:10.1186/1750-9378-4-S1-S6 PMID:19208211

Veierød MB, Laake P, Thelle DS (1997). Dietary fat intake and risk of prostate cancer: a prospective study of 25,708 Norwegian men. *Int J Cancer*, 73(5):634–8. doi:10.1002/(SICI)1097-0215(19971127)73:5<634::AID-IJC4>3.0.CO;2-Y PMID:9398038

Walker M, Aronson KJ, King W, Wilson JW, Fan W, Heaton JP et al. (2005). Dietary patterns and risk of prostate cancer in Ontario, Canada. *Int J Cancer*, 116(4):592–8. doi:10.1002/ijc.21112 PMID:15825170

Wright JL, Neuhouser ML, Lin DW, Kwon EM, Feng Z, Ostrander EA et al. (2011). AMACR polymorphisms, dietary intake of red meat and dairy and prostate cancer risk. *Prostate*, 71(5):498–506. doi:10.1002/pros.21267 PMID:20945498

Wu K, Hu FB, Willett WC, Giovannucci E (2006). Dietary patterns and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev*, 15(1):167–71. doi:10.1158/1055-9965.EPI-05-0100 PMID:16434606

Wu K, Spiegelman D, Hou T, Albanes D, Allen NE, Berndt SI et al. (2016). Associations between unprocessed red and processed meat, poultry, seafood and egg intake and the risk of prostate cancer: A pooled analysis of 15 prospective cohort studies. *Int J Cancer*, 138(10):2368–82. doi:10.1002/ijc.29973 PMID:26685908

2.6 Cancer of the breast

2.6.1 Cohort studies

More details of the cohort studies can be found in Table 2.6.1 and Table 2.6.2 (web only; available at: http://publications.iarc.fr/564).

Intake of red and processed meat was evaluated in relation to cancer of the breast in cohort studies conducted in the USA, Canada, the Netherlands, the United Kingdom, Sweden, Denmark, and France, as well as in the EPIC study, which included multiple European countries, and in a cohort consortium of eight studies in North America and Europe. Important potential confounders for breast cancer included age, alcohol intake, reproductive factors (such as age at menarche, parity, age at first birth, use of oral contraceptives, age at menopause), use of postmenopausal hormones among postmenopausal women, family history of breast cancer, obesity, and energy intake. Studies that did not adjust for these covariates are noted. Recent publications with more reliable exposure assessment, more adequate adjustment for potential confounders, and longer follow-up time were included in the evaluation.

Studies were considered uninformative and not included in the evaluation if they assessed meat intake without specifying the types of meats included (e.g. Mills et al., 1988; van den Brandt et al., 1990; Vatten et al., 1990; Knekt et al., 1994; Gaard et al., 1995). In addition, studies that evaluated breast cancer in relation to dietary patterns, rather than the consumption of red or processed meat (e.g. Männistö et al., 2005; Cottet et al., 2009; Butler et al., 2010; Couto et al., 2013), or had a low number of cases (Byrne et al., 1996) were excluded from further review.

Mills et al., (1989) evaluated individual red meat items, "beef index", and breast cancer in a low-risk cohort of 20 341 Californian, Seventh-Day Adventist women aged 25–99 years. The beef index was the sum of intake from individual red meat items, including beef hamburger, beef steak, and other beef/veal. During a mean follow-up of 6 years (1976–1982), 215 primary breast cancer cases were histologically verified. The relative risk for the top (≥ 1 time/week) versus the bottom (never) category of the beef index was 1.05 (95% CI, 0.75–1.47). Intake of red meat (i.e. beef hamburger, beef steak, and other beef/veal) was not associated with breast cancer. [Alcohol and caloric intake were not adjusted for in statistical analyses. This study was part of the Pooling Project of Prospective Studies by Missmer et al., (2002). A smaller number of cases were included in the pooling project (160 cases).]

Toniolo et al. (1994) conducted a nested case–control study of 180 breast cancer cases and 829 controls from the first 6 years of follow-up (median follow-up time, 22.2 months) in the New York University Women's Health Study (NYUWHS) cohort. The study originally included 14 291 women aged 35–65 years enrolled between 1985 and 1991. Diet was assessed with a 71–food item, validated Block FFQ. The relative risk for the top versus the bottom quintile of meat intake was 1.87 (95% CI, 1.09–3.21; P_{trend} = 0.01). [The Working Group noted the relatively small sample size. In addition, the study did not specify red meat. Meat included beef, veal, lamb, or pork preparations or processed luncheon meats (ham, cold cuts, turkey rolls), that is, unprocessed and processed red meat and processed white meat. Alcohol intake was not adjusted for. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). A larger number of cases were included in the pooling project (385 cases).]

The Iowa Women's Health Study (IWHS) cohort included 41 836 postmenopausal (age, 55–69 years) women. Five nested case–control studies of the cohort were included (Zheng et al., 1998; Zheng et al., 1999; Deitz et al., 2000; Zheng et al., 2001; Zheng et al., 2002). These studies are described in more detail below.

Zheng et al. (1998) conducted a nested case–control study of 273 cases and 657 controls nested within the IWHS. All eligible subjects were asked to complete a self-administered FFQ on meat intake habits during the reference year. The questionnaire included questions on usual intake and preparation of 15 meats. A doneness score was also calculated to describe the eating preferences of the participants based on their responses to colour photographs. The study found a positive dose–response relationship between doneness of red and processed meat and breast cancer risk. The odds ratios for very well-done meat versus rare or medium-done meat were 1.54 (95% CI, 0.96–2.47) for hamburger, 2.21 (95% CI, 1.30–3.77) for beef steak, and 1.64 (95% CI, 0.92–2.93) for bacon. Women who consumed these three meats consistently very well done had an odds ratio of 4.62 (95% CI, 1.36–15.70; P_{trend} = 0.001) compared with women who consumed the meats rare or medium done. In addition, compared with women in the lowest tertile of intake of these three types of meats with a doneness level of rare/medium, those who were in the top tertile of intake with a doneness level of consistently very well done had an odds ratio of 3.01 (95% CI, 1.47–6.17). [The Working Group noted that there was a statistically significant positive association between intake of red meat and risk of breast cancer (P_{trend} = 0.02), with a 78% elevated risk observed for the highest versus the lowest tertile of intake group; however, red meat included processed meat. Reproductive factors and alcohol intake were not adjusted for in statistical analyses. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). A much larger number of cases were included in the pooling project (1130 cases).]

Deitz et al. (2000) used a subset of the nested case–control study data from the IWHS (174 cases, 387 controls) with DNA samples, and evaluated doneness score and red meat [which included processed meat] intake and breast cancer by *NAT2* polymorphism. Polymorphisms in the *NAT2* gene may result in a rapid, intermediate, and slow acetylation phenotype. The study found that a higher intake of red meat was suggestively positively associated with breast cancer among women with the *NAT2* rapid/intermediate type (OR, 1.7; 95% CI, 0.9–3.4; for the highest vs lowest tertile of intake), but not associated with breast cancer among those with the *NAT2* slow type (OR, 0.9; 95% CI, 0.5–1.7; for the same comparison). However, the *P* value for interaction by *NAT2* genotype was not significant (*P* = 0.91). For the association between doneness score and breast cancer, there was a borderline significant interaction by *NAT2* genotype (*P* = 0.06). Compared with women who reported consuming hamburger, beef steak, and bacon rare/medium (doneness score, 3/4), those who reported consuming these meats very well done (doneness score, 9) had odds ratios of 3.9 (95% CI, 0.8–18.9; P_{trend} = 0.22) for the *NAT2* slow genotype and 7.6 (95% CI, 1.1–50.4; P_{trend} = 0.003) for the *NAT2* rapid/intermediate type. [The Working Group noted that the sample size was much more limited than the original study by Zheng et al. (1999) because a large number of the subjects had buccal cell samples instead of blood samples, and *NAT2* amplification was successful only in 9% (79/878) of buccal cell DNA samples. Sample size was too small to evaluate the interaction with genetic polymorphisms. Only age was adjusted for. Red meat included processed meat.]

A similar study using a subset of the nested case–control study data from the IWHS was conducted to evaluate the association between doneness of red meat and breast cancer risk stratified by *SULT1A1* polymorphism (Zheng et al., 2001). The study included 156 cases and 332 controls, with blood samples. The association between doneness of red meat [which included processed meat] and breast cancer appeared to differ by the polymorphism, although the *P* value for interaction was not significant (*P* = 0.40). Compared with participants consuming rare/medium-

done red meat, those who consistently consumed well-done red meat had relative risks of 3.6 (95% CI, 1.4–9.3; P_{trend} = 0.01) for the *SULT1A1* Arg/Arg genotype, 1.8 (95% CI, 0.9–3.8; P_{trend} = 0.10) for the Arg/His genotype, and 1.0 (95% CI, 0.3–3.7; P_{trend} = 0.98) for the His/His genotype. [The Working Group noted that the sample size was too small to evaluate the interaction with genetic polymorphisms, and most of the categories had fewer than 20 cases. Age, waist:hip ratio, and number of live births were adjusted for. Red meat included processed meat.]

Zheng et al. (2002) also evaluated a similar interaction between meat doneness level and breast cancer risk by *GSTM1* and *GSTT1* polymorphisms in a nested case–control study in the IWHS (202 cases, 481 controls; with blood samples and genotyping for *GSTM1*). The association between doneness of red meat and breast cancer did not vary by *GSTT1* genotype. However, there was a significant interaction by *GSTM1* genotype ($P_{interaction}$ = 0.04). Compared with women who consumed rare/medium-done meat and had the *GSTM1* genotype, those who consistently consumed well- or very well-done meat and had the *GSTM1* null genotype had a relative risk of 2.5 (95% CI, 1.3–4.5). [The Working Group noted that the sample size was too small to evaluate the interaction with genetic polymorphisms. Age, waist: hip ratio, number of live births, and family history were adjusted for. Red meat included processed meat.]

Voorrips et al. (2002) evaluated red meat and processed meat intake and breast cancer in the Netherlands Cohort Study on Diet and Cancer (NLCS), among a cohort of 62 573 women aged 55–69 years. Diet was assessed with a validated FFQ with 150 food items. Red meat, which was presented as "fresh meat", included beef and pork, and did not include processed meat. Subjects were classified into quintiles or categories of consumption (g/day), based on the distribution in the control group of 1598 women. During a mean follow-up of 6 years, 941 breast cancer cases were documented. The relative risk for the top (median, 145 g/day) versus the bottom (median, 45 g/day) quintile of red meat intake was 0.98 (95% CI, 0.73–1.33) for breast cancer. The relative risk for the top (median, 13 g/day) versus the bottom (median, 0 g/day) category of processed meat intake was 0.93 (95% CI, 0.67–1.29) for breast cancer. Intake of beef and pork was also not associated with breast cancer. [The Working Group noted that assessment and adjustment of information on postmenopausal hormone use was not mentioned. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). Almost the same number of cases was included in the pooling project (937 cases).]

Missmer et al. (2002) conducted a pooled analysis of eight prospective cohort studies (Adventist Health Study (AHS); Canadian National Breast Screening Study (CNBSS); IWHS; NLCS; New York State Cohort, (NYSC); New-York University Women's Health Study (NYUWHS); Nurses' Health Study (NHS); and Sweden Mammography Cohort (SMC)) from North America and western Europe, which used validated FFQs. A total of 7379 breast cancer cases diagnosed during up to 15 years of follow-up were included. Pooled multivariate-adjusted relative risks for an increase of 100 g/day in red meat intake were 0.98 (95% CI, 0.93–1.04) in all women, 0.97 (95% CI, 0.79–1.20) in premenopausal women, and 0.97 (95% CI, 0.91–1.03) in postmenopausal women. None of the red meat items, including ground beef, organ products or processed meats, bacon products, sausage products, and hot dogs, were associated with breast cancer risk. [The Working Group noted that red meat included both fresh and processed red meat, blood pudding, liver, and kidney.]

Holmes et al. (2003) evaluated red meat and processed meat intake and breast cancer among 88 647 women included in the NHS. Diet was assessed using a 61–food item FFQ at baseline and a 116–food item FFQ since 1984. Both FFQs were validated. FFQs were sent to the women

multiple times during follow-up. Red meats included hamburger, beef/pork/lamb as a main dish, beef/pork/lamb in sandwiches or mixed dishes, hot dogs, bacon, and other processed meats. Between 1980 and 1998, 4107 cases of invasive breast cancer were identified. There was no association between intake of red meat or processed meat and breast cancer. The relative risk for the top (≥ 1.32 servings/day) versus the bottom (≤ 0.55 servings/day) quintile of red meat intake was 0.94 (95% CI, 0.84–1.05). The relative risk for the top (≥ 0.46 servings/day) versus the bottom (≤ 0.10 servings/day) quintile of processed meat intake was 0.94 (95% CI, 0.85–1.05). The associations were similar by menopausal status. [The study was limited by the definition of red meat, which included processed meat. Fung et al. (2005) evaluated the same cohort, with a shorter follow-up period (1984–2000) and a smaller number of cases (3026 cases), and was not considered. Similarly, Wu et al. (2010) evaluated the consumption of mutagens from meats cooked at a high temperature in an NHS subcohort, with a shorter follow-up period (1996–2006) and fewer cases (2317 cases), and was not considered. The NHS was part of the Pooling Project of Prospective Studies by Missmer et al. 2002. A smaller number of cases were included in the pooling project (2661 cases).]

van der Hel et al. (2004) evaluated red meat and processed meat intake in relation to breast cancer in a nested case–control study of 229 cases (average age, 48 years) and 264 controls, with blood samples, nested within a Dutch prospective study. Controls were frequency-matched by age, town, and menopausal status. Meat consumption was recorded at baseline with the use of a validated, self-administered FFQ. Red meat intake in grams per day was calculated by adding up intakes of beef and pork. There was no association between red meat or processed meat intake and breast cancer risk. Compared with women who had a red meat intake of < 30 g/day, women who were in the high-intake category of ≥ 45 g/day had an odds ratio of 1.32 (95% CI, 0.84–2.08). Compared with women with a processed meat intake of < 20 g/day, those who were in the high-intake category of ≥ 35 g/day had an odds ratio of 1.08 (95% CI, 0.60–1.70). When polymorphisms related to metabolism of HAAs, including *NAT1, NAT2, GSTM1, GSTT1*, were evaluated, there was a positive association with *GSTM1* null genotype. When the association with red meat intake was stratified by *GSTM1* polymorphism, no interaction was observed. [The Working Group noted that the sample size was too limited to evaluate the interaction with genetic polymorphisms. Family history of breast cancer and postmenopausal hormone use were not adjusted for in the multivariate analysis.]

Kabat et al., (2007) evaluated red meat and haem iron intake and breast cancer in the CNBSS, a randomized controlled trial of screening for breast cancer involving women aged 40–59 years. Diet was assessed with a validated FFQ with 86 food items. During a mean follow-up of 16.4 years, 2491 breast cancer cases (1171 premenopausal cases, 993 postmenopausal cases) were included. The relative risk for the top (≥ 40.30 g/day) versus the bottom (< 14.25 g/day) quintile of red meat intake was 0.98 (95% CI, 0.86–1.12) for breast cancer. The relative risk for the top (> 2.95 mg/day) versus the bottom (< 1.58 mg/day) quintile of haem iron intake was 1.03 (95% CI, 0.90–1.18) for breast cancer. The results were similar by menopausal status. [The Working Group noted that red meat was not defined. Although this study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002), which evaluated red meat intake, only 419 breast cancer cases, with a shorter follow-up period (5 years), were included in the pooling project.]

Taylor et al. (2007) evaluated red meat and processed meat intake and breast cancer in the United Kingdom Women's Cohort Study (UKWCS) in 678 cases (283 premenopausal cases, 395 postmenopausal cases). Diet was assessed

between 1995 and 1998 using a 217-item, postal FFQ developed from that of the EPIC study. Red meat consisted of beef, pork, lamb, and other red meats included in mixed dishes, such as meat lasagne, moussaka, ravioli, and filled pasta with sauce. Processed meat consisted of bacon, ham, corned beef, spam, luncheon meats, sausages, pies, pasties, sausage rolls, liver pâté, salami, and meat pizza. Higher intakes of both red meat and processed meat were associated with an elevated risk of breast cancer. Compared with non-consumers, those who were in the high-intake category had a hazard ratio of 1.41 (95% CI, 1.11–1.81) for red meat (> 57 g/day) and 1.39 (95% CI, 1.09–1.78) for processed meat (> 20 g/day). When the association was evaluated by menopausal status, the hazard ratios for the highest versus the lowest quartile of intake were 1.32 (95% CI, 0.93–1.88; 61 cases) among premenopausal women and 1.56 (95% CI, 1.09–2.23; 106 cases) among postmenopausal women for red meat. [The Working Group noted that family history of breast cancer and alcohol intake were not adjusted for.]

Egeberg et al. (2008) conducted a nested case–control study among 24 697 postmenopausal women included in the Diet, Cancer and Health cohort study (1993–2000) in Denmark. The study included 378 breast cancer cases and 378 matched controls. Meat consumption was estimated from a 192-item, validated FFQ, completed at baseline, covering the participants' habitual diet during the preceding 12 months. Intake of red meat in grams per day was calculated by adding up intakes of beef, veal, pork, lamb, and offal. [Intake of processed meat included processed fish, and was not reviewed.] Compared with women whose red meat intake was < 50 g/day, those who consumed > 80 g/day had a relative risk of 1.65 (95% CI, 1.09–2.50; $P_{trend} = 0.03$). The associations were also stratified by *NAT1* and *NAT2* polymorphisms. There was no significant interaction by *NAT1* polymorphism, but there was a significant interaction by *NAT2* polymorphism for red meat intake ($P_{interaction} = 0.04$). The relative risks per 25 g/day increase in red meat intake were 1.37 (95% CI, 1.07–1.76) for the *NAT2* intermediate/fast acetylator phenotype and 1.00 (95% CI, 0.85–1.18) for the *NAT2* slow acetylator phenotype. [The Working Group noted that sample size was limited in some of the stratified analyses by *NAT* polymorphisms. Caloric intake and family history of breast cancer were not adjusted for in the multivariate analysis.]

Kabat et al. (2009) evaluated the association between red meat intake and meat preparation in relation to breast cancer among postmenopausal women only in the NIH-AARP study. Diet was assessed with the NCI Diet History Questionnaire (DHQ), a self-administered, validated FFQ with 124 food items. [Red meat included many types of processed meats, and data are not reported here.] Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs, and low-fat hot dogs made from poultry. During a follow-up of 8 years, 3818 breast cancer cases were documented. Processed meat was not associated with breast cancer risk. The relative risk for the top (> 12.5 g/1000 kcal) versus the bottom (≤ 2.2 g/1000 kcal) quintile of processed meat intake was 1.0 (95% CI, 0.90–1.12) for breast cancer. Cooking methods (grilled or barbecued meat, pan-fried meat, oven-broiled meat, sautéed meat, baked meat, or microwaved meat) and meat doneness levels (rare/medium-done cooked meat or well/very well-done cooked meat) were not associated with breast cancer risk. [The Working Group noted that an earlier publication of the NIH-AARP cohort that had a shorter follow-up and inferior adjustment for potential confounders of breast cancer (Cross et al., 2007) was not considered. Evaluation of cooking methods and doneness levels included poultry.]

Larsson et al. (2009) evaluated red meat intake and breast cancer in the SMC, which was established in 1987–1990 in central Sweden. Diet was assessed with a 67– and 96–food item FFQ at baseline and in 1997, respectively. During a mean follow-up of 17.4 years, 2952 breast cancer cases were ascertained. For overall breast cancer, the relative risks for the top (≥ 98 g/day) versus the bottom (< 46 g/day) quintile of intake were 0.98 (95% CI, 0.86–1.12) for red meat, 1.08 (95% CI, 0.96–1.22) for processed meat, 1.10 (95% CI, 0.90–1.34) for estrogen receptor (ER)+/progesterone receptor (PR)+ tumours, 0.86 (95% CI, 0.60–1.23) for ER+/PR– tumours, and 1.12 (95% CI, 0.70–1.79) for ER–/PR– tumours. [The Working Group noted that red meat included all fresh and minced pork, beef, and veal. Processed meats included ham, bacon, sausages, salami, processed meat cuts, liver pâté, and blood sausages. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). However, a much smaller number of cases were included in the pooling project (1320 cases).]

Ferrucci et al., (2009) evaluated red meat and processed meat intake and cooking methods and doneness levels, and breast cancer risk in the Prostate, Lung, Colorectal and Ovarian (PLCO) trial, a multicentre, randomized controlled trial in women aged 55–74 years who were recruited in 1993–2001. Diet was assessed with by the NCI Diet history Questionnaire (DHQ), a self-administered, validated FFQ with 124 food items. During a mean follow-up of 5.5 years, 1205 breast cancer cases were documented. [Red meat included processed meat, and data are not reported here.] Processed meat included bacon, cold cuts, hams, hot dogs, and sausage. The hazard ratio for the top (> 11.6 g/1000 kcal; median, 16.9 g/1000 kcal) versus the bottom (≤ 2.4 g/1000 kcal; median, 1.4 g/1000 kcal) quintile of processed meat intake was 1.12 (95% CI, 0.92–1.36; P_{trend} = 0.22). Intake of steak, hamburger, sausage, bacon, and pork chops was not associated with breast cancer. The hazard ratios for the top versus the bottom quintile were 1.03 (95% CI, 0.84–1.27) for pan-fried meat, 1.10 (95% CI, 0.90–1.34) for grilled meat, 1.09 (95% CI, 0.90–1.32) for well/very well-done meat, and 1.20 (95% CI, 0.99–1.45) for grilled/pan-fried well/very well-done meat. [The Working Group noted that red meat included processed meat.]

Pala et al. (2009) evaluated the association between red meat and processed meat and breast cancer in the EPIC study. Information on diet was collected from 319 826 women aged 20–70 years in 1992–2003. Diet was assessed by using country-specific (Italy and Sweden centre-specific) validated FFQs designed to capture habitual consumption of food over the preceding year. Red meat consisted of fresh, minced, and frozen beef, veal, pork, and lamb. Processed meats were mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, or heating, and included ham, bacon, sausages, blood sausages, liver pâté, salami, mortadella, tinned meat, and others. A total of 7119 invasive breast cancer cases were documented during a median of 8.8 years of follow-up. A higher intake of processed meat, but not red meat, was associated with a modest elevated risk of breast cancer. The hazard ratio for the highest (median, 84.6 g/day) compared with the lowest (median, 1.4 g/day) quintile of red meat consumption was 1.06 (95% CI, 0.98–1.14; P_{trend} = 0.19). The hazard ratio for the highest (median, 56.5 g/day) compared with the lowest (median, 1.7 g/day) quintile of processed meat consumption was 1.10 (95% CI, 1.00–1.20; P_{trend} = 0.07). The positive association was limited to postmenopausal breast cancer (3673 postmenopausal cases vs 1699 premenopausal cases). The corresponding hazard ratios were 1.13 (95% CI, 1.00–1.28; P_{trend} = 0.06) for postmenopausal women and 0.99 (95% CI, 0.82–1.19; P_{trend} = 0.72) for premenopausal women. [The Working Group noted that family history of breast cancer was not adjusted for.]

Loh et al. (2010) evaluated the association between red and processed meat intake and breast cancer stratified by *MGMT* Ile143Val polymorphism in the EPIC-Norfolk study in 276 cases and 1498 controls. There was no significant interaction with the polymorphism. [The Working Group noted that the sample size was too small to evaluate the interaction with genetic polymorphisms.]

Lee et al. (2013) conducted a nested case–control study within the NHS to evaluate the interaction between red meat intake and *NAT2* acetylator genotype and cytochrome P450 1A2–164 A/C (*CYP1A2*) polymorphism. The study included 579 cases and 981 matched controls. There was no interaction between *NAT2* acetylator genotype or *CYP1A2* polymorphism and red meat intake in relation to breast cancer. [The Working Group noted that the study was limited by the definition of red meat, which included processed meat. Holmes et al. (2003) evaluated red meat intake in the same cohort.]

Genkinger et al. (2013) evaluated breast cancer among African American women from the Black Women's Health Study (BWHS). The study included a total of 1268 cases, among 52 062 women, identified during 12 years of follow-up. Diet during the past year was estimated from a 68-item, modified Block FFQ completed at baseline in 1995. In 2001, a modified version of the 1995 FFQ, which asked about 85 food items, was administered to collect updated dietary information. The 1995 FFQ ascertained the intake of 13 meat items; the 2001 FFQ asked about 15 meat items. Intakes of red meat or processed meat were not associated with breast cancer. Compared with women with a red meat intake of < 100 g/week, those who consumed ≥ 400 g/week had a relative risk of 1.02 (95% CI, 0.83–1.24; P_{trend} = 0.83). Compared with women with a processed meat intake of < 100 g/week, those who consumed ≥ 200 g/week had a relative risk of 0.99 (95% CI, 0.82–1.20; P_{trend} = 0.96). The associations were similar by menopausal status. [The Working Group noted that information on the definitions of red meat and processed meat, and validation of the FFQs was not provided.]

The study by Pouchieu et al. (2014) was based on the SU.VI.MAX, a randomized, double-blind, placebo-controlled trial of a combination of low-dose antioxidants (ascorbic acid, vitamin E, β-carotene, selenium, and zinc), conducted from 1994 to 2002. The study included 190 cases, among 4684 women aged 35–60 years at baseline, identified during a median of 11.3 years of follow-up (1994–2007). Participants completed a dietary record every 2 months, in which they declared all foods and beverages consumed during periods of 24 hours. These dietary records were randomly distributed between week and weekend days, and over seasons to take into account intra-individual variability. Dietary records from the first 2 years of follow-up were used in the study. Portion sizes were assessed using a validated picture booklet, and the amounts consumed from composite dishes were estimated using French recipes validated by food and nutrition professionals. Red meat consisted of fresh, minced, and frozen beef, veal, pork, and lamb. Processed meats were mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, or heating, and included ham, bacon, sausages, blood sausages, liver pâté, salami, mortadella, tinned meat, and others. There was no association between baseline intake of either red meat or processed meat and breast cancer in the whole population. The relative risks for the top versus the bottom quartile of intake were 1.19 (95% CI, 0.79–1.80; P_{trend} = 0.3) for red meat (< 24.9 vs > 63.7 g/day) and 1.45 (95% CI, 0.92–2.27; P_{trend} = 0.03) for processed meat (< 16.4 vs > 43.5 g/day). However, processed meat intake was positively associated with breast cancer risk in the placebo group, but not in the treatment group. The relative risks for the highest compared with the lowest quartile of processed meat consumption were 2.46 (95% CI, 1.28–4.72; P_{trend} = 0.001) in the placebo group and 0.86

(95% CI, 0.45–1.63; P_{trend} = 0.7) in the antioxidant-supplemented group ($P_{interaction}$ = 0.06). [The Working Group took note of the relatively small number of cases. No information was provided on the number of cases in each red meat intake category. Adjustment of lipid intake would be an overadjustment. Some reproductive factors were not adjusted for.]

Farvid et al. (2014) also evaluated early-adulthood total red meat intake and breast cancer in the NHS II. The study included 2830 cases, among 88 803 premenopausal women aged 26–45 years, identified during 20 years of follow-up. Diet was assessed by validated FFQ, with approximately 130 food items. The study found that a higher total red meat (i.e red meat and processed read meat) intake was associated with an elevated risk of breast cancer. The relative risk for the top (median, 1.50 servings/day) versus the bottom (median, 0.14 servings/day) quintile of intake was 1.22 (95% CI, 1.06–1.40; P_{trend} = 0.01). The association was similar by menopausal status, but not statistically significant. [The Working Group noted that the study was limited by the definition of red meat, which included processed meat. Earlier studies of the cohort by Cho et al. (2003) and Cho et al. (2006) were not evaluated.]

Farvid et al. (2015) also evaluated the association between adolescent total red meat intake and breast cancer risk in the NHS II. A subcohort of 44 231 women aged 33–52 years, who filled in a special 124-item FFQ about diet during high school, were followed up for 13 years, and 1132 breast cancer cases were documented. Total red meat intake included unprocessed red meat (hamburger, beef, lamb, pork, and meatloaf) and processed red meat items (hot dog, bacon, and other processed meats such as sausage, salami, and bologna). There was a positive association between adolescent total red meat intake and premenopausal breast cancer. The relative risk for the top (median, 2.43 servings/day) versus the bottom (median, 0.7 servings/day) quintile of total red meat intake was 1.43 (95% CI, 1.05–1.94; P_{trend} = 0.007). The positive association was similar, but significant only for processed meat (RR, 1.29; 95% CI, 0.98–1.70; P_{trend} = 0.02) when intakes of red meat and processed meat were evaluated separately. The association with premenopausal breast cancer was stronger among those with ER+/PR+ breast cancer than among those with ER–/PR– breast cancer; the relative risks per 1 serving/day of total red meat were 1.23 (95% CI, 1.06–1.44) for ER+/PR+ breast cancer and 1.18 (95% CI, 0.87–1.60) for ER–/PR– breast cancer. Haem iron intake was not associated with breast cancer risk. [The Working Group noted that the relative risks for breast cancer by quintile of processed meat and red meat intake in premenopausal, postmenopausal, and all women were reported in tables. A limitation was that the adolescent dietary intake was reported when women were 33–52 years of age. An earlier study by Linos et al. (2008) was not evaluated.]

2.6.2 Case–control studies

Case–control studies on the association between breast cancer and consumption of red meat (see Table 2.6.3, web only) or processed meat (see Table 2.6.4, web only) have been conducted in North America, Latin America, Europe, North Africa, and Asia (these tables are available online at: http://publications.iarc.fr/564). These studies are organized according to the definition of red meat or processed meat, and within these categories, by publication year and study design. Important potential confounders for breast cancer include age, alcohol intake, reproductive factors, use of postmenopausal hormones among postmenopausal women, family history of breast cancer, obesity, and energy intake. Studies that did not adjust for these covariates are noted. In addition, studies with low participation rates (< 50%) in cases or controls, or with large differences in the participation rates of cases and controls are noted because this may have led to selection bias.

Studies that met several exclusion criteria were considered to be uninformative for this evaluation and were not considered further. Studies that evaluated meat intake without providing data specifically for red meat or processed meat were excluded (e.g. Hirayama, 1978; Kinlen, 1982; Talamini et al., 1984; Kato et al., 1992; Malik et al., 1993; Holmberg et al., 1994; Trichopoulou et al., 1995; Núñez et al., 1996; Potischman et al., 1998; Han et al., 2004; Lee et al., 2004; Ko et al., 2013; Bessaoud et al., 2008; Dos Santos Silva et al., 2002; La Vecchia et al., 1987). Similarly, studies that evaluated breast cancer in relation to dietary patterns instead of evaluating red or processed meat were excluded (e.g. Cui et al., 2007; Wu et al., 2009; Cade et al., 2010; Cho et al., 2010; Ronco et al., 2010; Buck et al., 2011; Zhang et al., 2011; Bessaoud et al., 2012; Jordan et al., 2013; Mourouti et al., 2014; Pou et al., 2014). Other reasons for exclusion were small sample size (about < 100 breast cancer cases) (e.g. Phillips, 1975; Kikuchi et al., 1990; Ingram et al., 1991; Morales Suárez-Varela et al., 1998; Delfino et al., 2000; Lima et al., 2008; Di Pietro et al., 2007; Landa et al., 1994), and the availability of updated or more complete data from the same population (Lee et al., 1991; Levi et al., 1993; Ronco et al., 1996; Favero et al., 1998).

(a) Red meat and/or processed meat

(i) Population-based studies

Lubin et al. (1981) conducted a study in Canada with 577 cases and 826 controls. The study evaluated intake of beef and pork. Women who consumed beef daily had a relative risk of 1.53 (95% CI, 1.1–2.1) compared with women who consumed beef < 3 times/week in the age-adjusted analysis. Similarly, compared with women who consumed pork ≤ 1 day/month, those who consumed it ≥ 1 time/week had a relative risk of 2.16 (95% CI, 1.6–2.9) in the age-adjusted analysis. [The Working Group noted that the response rate was much lower among controls. The FFQ was not validated. Only age was adjusted for in statistical analyses.]

Hislop et al. (1986) evaluated intake of beef and pork and breast cancer in British Columbia, Canada. A total of 846 cases (74% participation rate) and 862 controls (79% participation rate) were included. Eligible cases included women younger than 70 years who were registered in the British Columbia Cancer Registry during 1980–1982. A pool of controls, frequency-matched on age, was created from the neighbours or acquaintances of the cases. Diet was assessed with a mailed, self-administered questionnaire for four different age periods. Compared with a beef intake of less than once daily, those who consumed beef daily had an odds ratio of 1.47 (95% CI, 1.12–1.92). Compared with a pork intake of less than once weekly, those who consumed pork weekly had an odds ratio of 1.13 (95% CI, 0.92–1.39). [The Working Group noted that diet was not assessed with a validated and standardized assessment tool. Odds ratios were adjusted for age only. The evaluation of intake was dichotomous only.]

Toniolo et al. (1989) evaluated intake of cured meat [i.e. processed meat] and offal and breast cancer in Italy. A total of 250 cases (91% participation rate) and 499 controls (86% participation rate) were included. Women younger than 75 years who resided in the province of Vercelli were included. Cases were women with microscopically confirmed invasive breast cancer who were free of local or distant metastases, except in the regional lymph nodes. Controls were female residents who were frequency-matched to the cases within 10-year age strata in an approximately 2:1 ratio. Diet was assessed with a dietary history method. The relative risk for the top versus the bottom intake of cured meat [i.e. processed meat] was 1.3. [The Working Group noted that diet was assessed with a validated assessment tool. Odds ratios were adjusted for age and caloric intake only, and 95% confidence intervals were not provided.]

Matos et al. (1991) conducted a population-based study in Argentina that included 196 cases recruited in 1979–1981 and 205 controls selected from friends and sanguineous family members of the cases. The study evaluated beef consumption based on cooking methods (barbecued, deep-fried, baked, boiled, stewed). None of the associations were significant. [The Working Group noted that the study had a modest sample size, and did not report the response rate among controls. The FFQ was not validated. Only age, age at first birth, and years of schooling were adjusted for in the statistical analysis. The consumption of beef was adjusted for other meat items, and the way of cooking for the other ways of cooking.]

Ambrosone et al. (1998) conducted a population-based case–control study of diet and breast cancer in New York, USA, with 740 cases and 810 controls. Controls younger than 65 years were randomly selected from the New York State Motor Vehicle Registry, and those 65 years and over were identified from Health Care Financing Administration lists. Of the premenopausal women contacted, 66% of eligible cases and 62% of eligible controls participated, and of the postmenopausal women contacted, 54% of cases and 44% of controls participated. An FFQ with the usual portion sizes of over 300 foods was administered to assess usual intake 2 years before the interview. Processed meat included ham, hot dogs, sausages, bacon, and cold cuts. The study found that intake of beef or pork was not associated with breast cancer risk in either premenopausal or postmenopausal women. Processed meat intake was non-significantly associated with premenopausal breast cancer; intake of > 48 g/day compared with < 14 g/day was associated with an odds ratio of 1.4 (95% CI, 0.9–2.3; $P_{trend} = 0.09$). [The Working Group noted the low response rate, especially among controls, which might have led to selection bias. There was no description of validation of the FFQ. Caloric intake was not adjusted for.]

Hermann et al. (2002) evaluated diet and breast cancer among women up to 50 years of age [thus, probably almost all of them were premenopausal women] in Germany (355 cases, 838 controls). Cases were women with a diagnosis of incident in situ or invasive breast cancer (35% participation rate). Controls were matched by exact age and study region, and were selected from a random list of residents provided by the population registries (37% participation rate). Diet was assessed with a 176-item FFQ similar to the FFQ used in the German part of the EPIC study, which was validated in other populations. The study found that the highest quartile of intake of red meat (≥ 65 g/day) was associated with an increased risk of breast cancer of up to 85% (OR, 1.85; 95% CI, 1.23–2.78; $P_{trend} = 0.016$) compared with the lowest quartile of intake (1–21 g/day). The odds ratios for the highest intake categories (≥ 33 g/day for beef, ≥ 39 g/day for pork, and ≥ 73 g/day for processed meat) were 1.58 (95% CI, 1.06–2.36; $P_{trend} = 0.04$), 1.47 (95% CI, 0.98–2.21; $P_{trend} = 0.07$), and 1.29 (95% CI, 0.86–1.95; $P_{trend} = 0.17$) for beef, pork, and processed meat, respectively. [The Working Group noted the modest sample size, and the median time between diagnosis of breast cancer and FFQ administration was 209 days for the cases, which led to a low response rate. This study overlapped with Brandt et al. (2004).]

Using essentially the same data set, Brandt et al. (2004) evaluated the association with breast cancer risk, stratified by the allelic length of the epidermal growth factor receptor (*EGFR*) gene CA simple sequence repeat. The sample size was further reduced to 311 cases and 689 controls, after excluding those with no genetic data. The positive association between red meat intake and breast cancer appeared to be limited to those with the long/long allele of *EGFR* (OR for red meat intake of ≥ 65 vs < 22 g/day, 10.68; 95% CI, 1.57–72.58; $P_{trend} = 0.03$) and those with the short/short allele of *EGFR* (OR for the same comparison, 1.86; 95% CI, 1.06–3.27; $P_{trend} = 0.02$), but

was not shown among those with the short/long allele of *EGFR*. Processed meat was not evaluated. [The Working Group noted that the sample size for the evaluation of the long/long allele of *EGFR* was limited, with six cases in the reference category. Caloric intake was not adjusted for. The data set was also used in (Hermann et al., 2002).]

Steck et al. (2007) evaluated the lifetime intakes of grilled or barbecued and smoked meats [i.e. processed meats] among 1508 cases and 1556 controls in a population-based case–control study in Long Island, New York, USA. Cases (82% eligible) were identified through the pathology/cytology records of 33 institutions, and lived in Nassau County and Suffolk County. Controls (63% eligible) were identified using random digit dialling and Centers for Medicare & Medicaid Services rosters. Meat intake was assessed as part of an in-home questionnaire administered by a trained interviewer. The consumption patterns of four categories of grilled/barbecued and smoked meats over each decade of life since the teenage years were examined. The participants also completed a Block FFQ, which included approximately 100 food items, that assessed diet in the previous year. The associations were evaluated by menopausal status. In postmenopausal women, compared with those who consumed grilled/barbecued red meat (beef, pork, and lamb) ≤ 630 times over their lifetime, those who consumed grilled/barbecued red meat ≥ 2163 times over their lifetime had an odds ratio of 1.32 (95% CI, 1.01–1.72; $P_{trend} = 0.10$). Compared with those who consumed smoked ham, pork, and lamb [i.e. processed meat] ≤ 810 times over their lifetime, those who consumed smoked ham, pork, and lamb ≥ 2278 times over their lifetime had an odds ratio of 1.30 (95% CI, 0.99–1.69; $P_{trend} = 0.22$). However, there was no association among premenopausal women, probably because the sample size was much smaller among premenopausal women. [The Working Group noted that the much lower response rate in controls was a limitation that might have led to selection bias. In addition, although energy intake was adjusted for, only a limited number of breast cancer risk factors were adjusted for.]

Fu et al. (2011) used the Nashville Breast Health Study (the USA). The study included 2386 (62% response rate) newly diagnosed primary breast cancer (invasive ductal or ductal carcinoma in situ) cases between the ages of 25 and 75 years. The majority of the participants were residents of the Nashville metropolitan area. The study included 1703 controls (71% response rate), which had virtually identical criteria to the cases. Of the controls, 87% were identified by random digit dialling households, and the remaining controls were mostly identified among women who received a screening mammography with a normal finding. Interviewer-administered telephone interviews were used to obtained information on usual intake frequency, portion size, cooking method, and doneness of 11 meats in the previous year before the interviews (for controls) or cancer diagnosis (for cases). All participants who completed questions on food doneness had a photograph booklet in front of them during the telephone interview. Red meat included hamburgers, cheeseburgers, beef patties, beef steaks, pork chops, ham steaks, and ribs (short ribs or spare ribs). Processed meat included bacon, sausage, and hot dogs/frankfurters. Compared with those in the lowest quartile of intake, those in the highest quartile of intake had odds ratios of 1.7 (95% CI, 1.3–2.4; $P_{trend} < 0.001$) for red meat and 1.7 (95% CI, 1.2–2.3; $P_{trend} < 0.001$) for well-done red meat among postmenopausal women. Corresponding odds ratios were 1.3 (95% CI, 0.9–2.0; $P_{trend} = 0.031$) for red meat and 1.5 (95% CI, 1.1–2.2; $P_{trend} = 0.017$) for well-done red meat among premenopausal women. The results for individual processed meat items, but not for total processed meats, were presented. Compared with those in the lowest quartile of intake, those in the highest quartile of intake had odds ratios of 1.2 (95% CI, 1.0–1.4; $P_{trend} = 0.006$) for bacon, 1.0 (95% CI, 0.7–1.3; $P_{trend} = 0.612$) for sausage,

and 1.0 (95% CI, 0.8–1.3; P_{trend} = 0.633) for hot dogs/frankfurters. [The Working Group noted that the FFQ was not validated and that red meat included some processed meat (e.g. ham).]

Chandran et al. (2013), in the USA, evaluated ethnic disparities with red and processed meat intake and breast cancer in African Americans (803 cases, 889 controls) and Caucasians (755 cases, 701 controls). Controls were identified by random digit dialling of residential telephone and cell phone numbers. Diet was assessed with an FFQ with approximately 125 food items, which was validated in other USA populations. Processed meat included lunchmeats, as well as bacon, sausages, bratwursts, chorizo, salami, and hot dogs. For Caucasian women, the odds ratios for the top versus the bottom quartile of intake were 1.48 (95% CI, 1.07–2.04; P_{trend} = 0.07) for processed meat (> 15.19 vs ≤ 2.35 g/1000 kcal per day) and 1.40 (95% CI, 1.01–1.94; P_{trend} = 0.29) for red meat (> 24.70 vs ≤ 4.14 g/1000 kcal per day). For African American women, the odds ratios for the top versus the bottom quartile of intake were 1.21 (95% CI, 0.89–1.64; P_{trend} = 0.18) for processed meat (> 15.19 vs ≤ 2.35 g/1000 kcal per day) and 0.84 (95% CI, 0.61–1.14; P_{trend} = 0.28) for red meat (> 24.70 vs ≤ 4.14 g/1000 kcal per day). The results supported an association between red meat or processed meat consumption and increased breast cancer risk in Caucasian women. However, in African American women, only processed meat consumption was positively associated with breast cancer. [The Working Group concluded that the strengths of the study included the large sample of African American women, and evaluation by menopausal status and hormone receptor status. In addition, an extensive list of covariates was adjusted for. Limitations included the much lower response rate in controls, which may have led to selection bias and limited statistical power in some subgroup analyses. In addition, alcohol intake was not adjusted for in statistical analyses.]

Mourouti et al. (2015) evaluated red meat and processed meat in 250 cases and 250 controls from Greece. Breast cancer patients that visited the pathology–oncology clinics of five major general hospitals in Athens, Greece, were recruited as cases (average age, 56 years). Controls were selected from the same catchment area, and had a participation rate of 88%. Diet was assessed with a validated SQFFQ with 86 questions. Red meat included beef, lamb, veal, and pork. Processed meat included cured and smoked meats, ham, bacon, sausages, and salami. The study found a positive association with processed meat intake, but not with red meat intake. Compared with non-consumers, women who consumed processed meat 1–2 times/week and women who consumed processed meat ≥ 6 times/week had odds ratios of 2.65 (95% CI, 1.36–5.14) and 2.81 (95% CI, 1.13–6.96), respectively ($P < 0.05$). Compared with women who consumed red meat ≤ 1 time/week, those who consumed red meat 8–10 times/week had an odds ratio of 0.99 (95% CI, 0.31–3.12). [The Working Group noted that the study had a modest sample size, but did not adjust for caloric intake, alcohol intake, and reproductive factors.]

(ii) Hospital-based studies

Richardson et al. (1991) conducted a hospital-based case–control study in southern France that included 409 cases and 515 controls. Cases were women between 28 and 66 years of age with histologically confirmed primary carcinoma of the breast. Controls were women of the same age group who were admitted for the first time to a nearby hospital or hospitalized for general surgery in a large clinic. Among the 932 people interviewed, all cases joined, but eight controls refused to join the study. A dietary history questionnaire of similar design to the one described in Block (1982) with 55 food items was used to assess diet. The study found a non-significant positive association between processed pork meat intake and breast cancer (OR, 1.4;

95% CI, 0.9–2.0; intake of > 87.5 vs ≤ 25 g/week). [The Working Group noted that no description was provided whether the dietary history questionnaire was validated. Information on caloric intake was not available for adjustment in statistical analyses.]

Franceschi et al. (1995) conducted a hospital-based case–control study in Italy in 1991–1994. The study included 2569 cases and 2588 controls. Cases were women with first histologically confirmed cancer of the breast, diagnosed no later than 1 year before the interview, and with no previous diagnoses of cancer at other sites. Controls were patients with no history of cancer admitted to major teaching and general hospitals in the same catchment area of the cases for acute non-neoplastic, non-gynaecological conditions, unrelated to hormonal or digestive tract diseases, or to long-term modifications of diet. Diet was measured with a 79–food item, validated FFQ. Red meat included steak, roast beef, lean ground beef, boiled beef, beef or veal stew, wiener schnitzel, liver, and pasta with meat sauce and with meat filling. Pork and processed meats included pork chop, prosciutto, ham, salami, and sausages. Compared with those in the lowest quintile of red meat intake (≤ 2.0 servings/week), participants in the highest quintile of red meat intake (> 5.3 servings/week) had an odds ratio of 1.09 (95% CI, 0.90–1.31). Compared with those in the lowest quintile of pork and processed meat intake (≤ 1.0 servings/week), participants in the highest quintile of pork and processed meat intake (> 4.5 servings/week) had an odds ratio of 1.09 (95% CI, 0.89–1.33). The participation rate of cases and controls was > 95%. In addition, a limited number of breast cancer risk factors (age and parity) were adjusted for. This study was included in a later analysis of case–control studies conducted in Italy and Switzerland (Di Maso et al. 2013). [The Working Group noted that, in this study, pork (i.e. red meat) was included in processed meat, and red meat did not include pork.]

Tavani et al. (2000) conducted a large hospital-based study of red meat intake and multiple cancer sites in Italy that included 3412 breast cancer cases. Controls (n = 7990) were selected among those who were admitted to the same network of hospitals as the cases. Controls with a wide spectrum of acute non-neoplastic conditions were accrued. A structured questionnaire asked about the frequency of intake of approximately 40 foods and total red meat consumption per week. Red meat included beef, veal, and pork, and excluded canned and preserved meat. Compared with those who consumed ≤ 3 portions/week of red meat, women who consumed > 6 portions/week of red meat had an odds ratio of 1.2 (95% CI, 1.1–1.4). [The Working Group noted that the participation rate of cases and controls was > 95%. The questionnaire asking about food intake was not validated. Processed meat was not evaluated separately. Caloric intake was not adjusted for in statistical analyses.]

Di Maso et al. (2013) evaluated data with information on cooking practices from a network of case–control studies conducted in Italy and Switzerland between 1991 and 2009. Multiple cancer sites were evaluated in relation to red meat intake and intake by cooking method (roasting/grilling, boiling/stewing, frying/pan-frying). For breast cancer analysis, 3034 cases and 11 656 controls were included. Trained personnel administered a structured questionnaire to cases and controls during hospitalization. Subjects' usual diet in the 2 years before diagnosis (or hospital admission for controls) was investigated using an FFQ that included specific food items on weekly consumption of red meat according to different cooking methods (i.e. boiling/stewing, roasting/grilling, or frying/pan-frying). Serving size was defined as an average serving in the Italian diet. Red meat included beef, veal, pork, horse meat, and half of the first course, including meat sauce (e.g. lasagne, pasta/rice with bologna sauce), and did not include processed meat. The

FFQ was tested for validity. Compared with those who consumed < 60 g/day of red meat, those who consumed ≥ 90 g/day of red meat had an odds ratio of 1.18 (95% CI, 1.04–1.33; P_{trend} < 0.01). The odds ratios per 50 g/day increase in red meat intake were 1.14 (95% CI, 1.02–1.28) for pre- and perimenopausal women and 1.10 (95% CI, 1.01–1.19) for postmenopausal women ($P_{interaction}$ = 0.55). Among the cooking methods, roasting/grilling conferred the highest risk (OR, 1.20; 95% CI, 1.08–1.34) for an increase of 50 g/day of red meat. [The Working Group noted that the study included Franceschi et al. (1995), previously reported in this section.]

(b) Red meat and processed meat combined or not clearly defined

(i) Population-based studies

Ewertz and Gill (1990) evaluated intake of individual red meat items and breast cancer in Denmark. A total of 1474 cases (88% participation rate) and 1322 age-matched controls (79% participation rate) were included. Cases were recruited from the Danish Cancer Registry and the nationwide clinical trial of the Danish Breast Cancer Cooperative Group (DBCG). Controls were an age-stratified random sample of the general female population, selected from the central population register. Diet was assessed with an FFQ with 21 food items. Intake of lean pork, medium-fat pork, fatty pork, and liver was evaluated. The relative risk for the top versus the bottom quartile of intake of medium-fat pork was 1.34 (95% CI, 1.05–1.71). No other items were significantly related to breast cancer. [The Working Group noted that diet was assessed 1 year after the diagnosis among cases. Information on validation of the FFQ was not provided. Odds ratios were adjusted for age at diagnosis and place of residence only.]

Goodman et al. (1992) evaluated bacon, sausage, liver and pork, and other meats, including spam, luncheon meats, beef, and lamb, but not red meat or processed meat intake in 272 postmenopausal breast cancer cases and 296 controls in Hawaii, USA. The study selected 43 different food items that largely contribute to the intake of fat and animal protein in Japanese and Caucasian women. A dose–response relation with breast cancer risk and sausage intake was suggested (P_{trend} < 0.01). The odds ratio for high (> 60 g/week) versus low (none) sausage intake was 1.7 (95% CI, 1.2–2.4). [The Working Group noted the modest sample size. In addition, there was no separate evaluation of red meat or processed meat. Caloric intake was not adjusted for. Age, ethnicity, age at first birth, and age at menopause were adjusted for, but other breast cancer risk factors were not adjusted for.]

Witte et al. (1997) conducted a family-matched case–control study including cases from a multicentre genetic epidemiology study of breast cancer conducted in the USA and Canada in 1989. Survivors of bilateral premenopausal breast cancer with at least one sister who was alive in 1989 were included, and one or more of the sisters served as controls. A total of 140 cases and 222 unaffected sisters of the cases were included. Cases and controls were mailed a 61-item SQFFQ to assess diet a median time of > 13 years after diagnosis. Red meat was not positively associated with breast cancer risk (OR, 0.6; 95% CI, 0.3–1.3) for the highest versus the lowest quartile (14.1 vs 4.5 servings/week) of intake. [The Working Group noted that the sample size was small. Red meat was not defined.]

Männistö et al. (1999) evaluated intake of beef and pork [i.e. red meat] and breast cancer in Finland. The subjects were participants in the Kuopio Breast Cancer Study who lived in the catchment area of the Kuopio University Hospital in 1990–1995. A total of 310 cases aged 25–75 years (81% participation rate), and 454 controls (72% participation rate) from the Finnish National Population Register and 506 controls (92% participation rate) who were referred to the same examinations as the cases

and subsequently found healthy were included. Diet was assessed with a validated FFQ with 110 food items. Among premenopausal women, the odds ratios for the top versus the bottom quintile (> 77 vs < 37 g/day) of intake of beef and pork [red meat] were 0.6 (95% CI, 0.3–1.4) versus population controls and 0.5 (95% CI, 0.3–1.2) versus referral controls. Among postmenopausal women (top vs bottom quintile, > 68 vs < 29 g/day), the corresponding odds ratios were 0.9 (95% CI, 0.5–1.7) and 1.0 (95% CI, 0.5–2.0). [The Working Group noted that caloric intake was not adjusted for in statistical analyses.]

Shannon et al. (2003) conducted a population-based case–control study of diet and postmenopausal breast cancer in western Washington, USA, with 441 cases and 370 controls. Diet was assessed by FFQ with 95 food items. The study found that red meat was, but processed meat was not, associated with an elevated breast cancer risk. The odds ratio for the top quartile (> 0.82 servings/day) compared with the bottom quartile (≤ 0.29 servings/day) of intake was 2.03 (95% CI, 1.28–3.22; $P_{trend} = 0.002$) for red meat intake. [The Working Group noted that red meat and processed meat were not defined. The response rate was low, especially among controls (50%). In addition, the FFQ might not have been validated because there was no description of validation.]

Shannon et al. (2005) evaluated intake of red meat and processed meat and breast cancer in China. The study was nested within a randomized trial of breast self-examination. A total of 378 cases (85% participation rate) and 1070 age- and menstrual status–matched controls (64–82% participation rate) were included. Diet was assessed with an interviewer-administered FFQ with 115 food items. Red meat included beef, pork, pork chops, spare ribs, pig trotters, ham, pork liver, beef, other red meats, organ meat (except liver), and lamb or mutton. The odds ratio for the top (≥ 6.1 servings/week) versus the bottom (≤ 3.0 servings/week) quartile of red meat intake was 1.24 (95% CI, 0.77–1.99). The odds ratio for the top (≥ 2 servings/month) versus the bottom (≤ 0.5 servings/month) quartile of cured meat intake was 1.2 (95% CI, 0.82–1.74). Red meat or cured meat [i.e. processed meat] intake was not associated with breast cancer risk. [The Working Group noted that, although the study was based on a prospective clinical trial study, there was no follow-up of participants after dietary assessment, which was based on the status of the cases and controls, and for cases, was conducted before biopsy, and thus, was considered as a case–control study. The statistical analysis was adjusted for age, total energy intake, and breastfeeding only. Red meat included ham, which is a processed meat.]

Mignone et al. (2009) used data from the Collaborative Breast Cancer Study (CBCS) in the USA. The study included 2686 cases and 3508 community controls. Recent incident invasive breast cancer cases were identified through their respective state cancer registries. Community controls were selected at random (within age strata) from lists of licenced drivers and Medicare beneficiaries with no history of breast cancer. Detailed questions on red meat consumption and cooking practices in the recent past (approximately 5 years before diagnosis in the cases or a comparable time referent in the controls) were collected. Women were asked to report on the degree of doneness for red meat. Compared with women who consumed red meat < 2 servings/week, those who consumed ≥ 5 servings/week had an odds ratio of 0.98 (95% CI, 0.81–1.18) in the multivariate analysis among all women. Corresponding odds ratios were 0.82 (95% CI, 0.60–1.13) among premenopausal women and 1.02 (95% CI, 0.80–1.31) among postmenopausal women. [The Working Group noted that the study did not appear to utilize the full FFQ. Red meat was not clearly defined, but presumably did not include processed meat because processed meat items were not described

as assessed. Caloric intake was not adjusted for in the multivariate analysis.]

Rabstein et al. (2010) in Germany included 1020 cases and 1047 population-based controls. Women with a histopathologically confirmed breast cancer diagnosis within 6 months before enrolment were included (88% response rate). Current residence in the study region, age not more than 80 years, and Caucasians were selected. Controls were frequency-matched to cases by year of birth in 5-year classes with the same inclusion criteria as cases. The study evaluated red meat intake and breast cancer by hormone receptor status and *NAT2* polymorphism. Regular (> 1 time/week) consumption of red meat was associated with an elevated risk of breast cancer compared with rare (< 1 time/month) consumption (OR, 1.59, 95% CI, 1.11–1.99). The positive association was similar by hormone receptor status; the corresponding odds ratios were 1.33 (95% CI, 0.95–1.87) for ER+ cases (n = 601), 1.71 (95% CI, 0.95–3.09) for ER– cases (n = 169), 1.42 (95% CI, 1.00–2.00) for PR+ cases (n = 569), and 1.43 (95% CI, 0.85–2.41) for PR– cases (n = 195). The association was also similar by *NAT2* acetylation status ($P_{interaction}$ = 0.16); the corresponding odds ratios were 1.71 (95% CI, 1.15–2.55) for slow acetylators (n = 569) and 1.73 (95% CI, 1.15–2.61) for fast acetylators (n = 439). [The Working Group concluded that the study lacked information on the dietary assessment, the validation study of the dietary assessment tool, and the definition of red meat.]

The population-based Shanghai Breast Cancer Study was analysed by Dai et al. (2002), Kallianpur et al. (2008), and Bao et al. (2012). The study consisted of a phase 1 (1996–1998) and phase 2 (2002–2004). Cases were identified through the rapid case ascertainment system of the Shanghai Cancer Registry and were permanent residents of urban Shanghai (age, 25–70 years); 1602 eligible breast cancer cases were identified during phase 1, and 2388 cases were identified during phase 2 (86% participant rate). Controls were randomly selected from women in the Shanghai Resident Registry and frequency-matched to cases by age in 5-year intervals (78% participation rate). Diet was measured with a validated, 76–food item FFQ that included 19 animal foods.

Dai et al. (2002) published the association between red meat intake and breast cancer using phase 1 subjects (1459 cases, 1556 controls). Red meat included pork, beef, and lamb. Red meat intake and breast cancer risk were evaluated and stratified by the deep-frying cooking method (never, ever, well done). The positive association between red meat intake and breast cancer appeared to be stronger in those who used ever or well-done deep-frying cooking method than in those who never used this cooking method. After adjusting for total energy and other potential confounders, the odds ratios for > 87 g/day of red meat compared with < 29 g/day of red meat were 1.49 (95% CI, 1.04–2.15) for never-users of the deep-frying cooking method, 1.78 (95% CI, 1.24–2.55) for ever-users of the deep-fried cooking method, and 1.92 (95% CI, 1.30–2.83) for well-done users of the deep-frying cooking method. [The Working Group noted that no information was provided on whether red meat included processed meat. Alcohol intake was not adjusted for in statistical analyses.]

Bao et al. (2012) used subjects from phases 1 and 2 of the Shanghai Breast Cancer Study (3443 cases, 3474 controls). Red meat was positively associated with breast cancer. Compared with women who consumed ≤ 26 g/day of red meat, those who consumed ≥ 82 g/day of red meat had an odds ratio of 1.45 (95% CI, 1.22–1.72; P_{trend} < 0.0001). Corresponding odds ratios were 1.51 (1.20–1.90) for ER+/PR+, 1.55 (1.16–2.07) for ER–/PR–, 1.81 (95% CI, 1.15–2.84) for ER+/PR–, and 1.29 (95% CI, 0.81–2.03) ER–/PR+ breast cancers (for ER+/PR+ and ER–/PR– , $P_{heterogeneity}$ = 0.57). [The Working Group noted that no information was provided on whether red meat included processed meat.]

Kallianpur et al. (2008) evaluated iron intake in the phase 1 and 2 population (3452 cases, 3474 controls). After adjusting for known risk factors, including total energy intake, animal-derived (largely haem) iron intake was positively associated with breast cancer risk ($P_{trend} < 0.01$). The odds ratio for the top versus the bottom quartile of intake was 1.50 (95% CI, 1.19–1.88). The association was similar by menopausal status. [The Working Group noted that no information was provided on whether red meat included processed meat. Alcohol intake was not adjusted for in statistical analyses.]

(ii) Hospital-based studies

Lee et al. (1992) conducted a study among Singapore Chinese women, comprising 200 cases (93% response rate) and 420 hospital-based controls (94% response rate). Diet was assessed by interview using a 90–food item FFQ. Red meat intake was associated with breast cancer in premenopausal women (109 cases), but not in postmenopausal women (91 cases). The odds ratios for the highest versus the lowest tertile of red meat intake (≥ 48.6 vs < 22.0 g/day) was 2.6 (95% CI, 1.3–4.9) in premenopausal women and 1.2 (95% CI, 0.6–2.4) in postmenopausal women. [The Working Group noted that red meat intake was mostly pork, but also included beef and mutton; it was not specified whether processed meat was excluded. The study had a modest sample size. The FFQ was not validated in this population.]

De Stefani et al. (1997) conducted a hospital-based case–control study in Uruguay in 1994–1996 that included 352 breast cancer cases (96% participation) and 382 controls (98% participation). The study used an FFQ with 64 items that was not validated. The study found an increased risk of breast cancer was associated with a higher beef intake and lamb intake. The odds ratios were 3.84 (95% CI, 2.09–7.05) for beef and 2.38 (95% CI, 1.27–4.47) for lamb for the top versus the bottom quartile of intake (≥ 365 vs ≤ 154 servings/year) and for the third versus the first tertile of intake (< 12 vs > 53 servings/year), respectively. The results were not similar by menopausal status since P_{trend} was significant only among postmenopausal women. Processed meat was not associated with breast cancer risk. [The Working Group noted that this was a hospital-based study with a small sample size. The FFQ was not validated. Adjustment of fat intake in the multivariate analysis would have been an overadjustment. Red meat included processed meat, so data are not presented here.]

A hospital-based case–control study of breast cancer was conducted in Guangdong, China, with 438 cases (96% response rate) and 438 controls (98% response rate) by Zhang et al. (2009). Diet was assessed with an 81–food item, validated FFQ. Processed meat included sausage, ham, bacon, and hot dog. The odds ratio for the highest quartile of intake was 1.44 (95% CI, 0.97–2.15; $P_{trend} = 0.07$) for processed meat. [The Working Group took note of the high participation rate. Alcohol intake was not adjusted for in statistical analyses. Red meat included processed meat, so data are not given here.]

Kruk (2007), in Poland, evaluated 858 cases and 1085 controls aged 28–78 years, and evaluated the association between red meat intake and breast cancer. Cases were identified from the Szczecin Regional Cancer Registry and were diagnosed with histologically confirmed invasive cancer. Controls were frequency-matched by age (5-year age group) and place of residence. Most controls (853) were selected among patients admitted to ambulatories in the same area as the cases to control for health. The remaining 232 controls were selected from hospital patients. Diet was assessed by FFQ, which was modified from the Block (the USA) and Franceschi (Italy) FFQs to include 18 main, Polish-specific food groups. Kruk & Marchlewicz (2013) described that red meat included pork, beef, or lamb that was broiled, fried, or canned. The study presented the results by menopausal status (310

premenopausal, 548 postmenopausal cases). The positive association between red meat intake and breast cancer risk was significant in premenopausal women and was suggestive, but not significant, among postmenopausal women. The odds ratios comparing those who consumed 0 servings/week of red meat with those who consumed ≥ 5 servings/week of red meat were 2.96 (95% CI, 1.49–5.91; P_{trend} = 0.009) among premenopausal women and 1.51 (95% CI, 0.89–2.57; P_{trend} = 0.65) among postmenopausal women. [The Working Group noted that the study had low response rates among cases. The FFQ was not validated. Caloric intake was not adjusted for. Kruk & Marchlewicz used the same data set and stratified the association by physical activity level. Red meat included processed meat.]

Kruk & Marchlewicz (2013) used the same data set as Kruk (2007), and evaluated the association between red meat and processed meat intake and breast cancer stratified by lifetime physical activity. A positive association between processed meat intake and breast cancer was only significant among those with low lifetime physical activity. The odds ratio comparing those who consumed ≤ 2 servings/week of processed meat with those who consumed ≥ 7 servings/week of processed meat was 1.78 (95% CI, 1.04–3.59) among women with < 105 metabolic equivalent hours per week of physical activity. Separate results were not presented by menopausal status. [The Working Group noted that the study had low response rates among cases. The FFQ was not validated. Caloric intake was not adjusted for. It was unclear whether the reported data were the result of a true effect modification by physical activity because the statistically significant subgroup had the largest sample size, and the *P* value for interaction was not calculated. Red meat included canned red meat (i.e. processed meat), so data are not reported here.]

Ronco et al. (2012) conducted a hospital-based case–control study (253 cases, 497 controls) and evaluated multiple risk factors for premenopausal breast cancer in Uruguay. Red meat included beef, barbecue, and milanesas (a typical form of fried meat in Uruguay). The study found that a high consumption of red meat, which was based on two food items, was associated with a higher risk of breast cancer (OR, 2.2; 95% CI, 1.35–3.60). [The Working Group concluded that the limitations were that this was a hospital-based study with a relatively small sample size. In addition, the study used a limited and non-validated FFQ, had no category cut-points for red meat intake, and made no adjustment for caloric intake in statistical analyses.]

Laamiri et al. (2014) reported that both red meat and processed meat intake were strongly positively associated with breast cancer among 400 cases and 400 controls from Morocco. Cases were recruited from the National Institute of Oncology. Controls were recruited at the institute after they had undergone a mammography that showed no signs of breast cancer. Diet was measured by FFQ. The odds ratios were 4.61 [95% CI, 2.26–9.44] for red meat intake and 9.78 [95% CI, 4.73–20.24] for processed meat intake. [The Working Group concluded that the study lacked information on response rates, details of items collected in the FFQ, validation study of the dietary assessment tool, and definition of red meat and processed meat, as well as the increment unit for the odds ratios, which appeared to treat red meat and processed meat as continuous variables. The study also did not adjust for alcohol intake, caloric intake, and reproductive factors.]

References

Ambrosone CB, Freudenheim JL, Sinha R, Graham S, Marshall JR, Vena JE et al. (1998). Breast cancer risk, meat consumption and N-acetyltransferase (NAT2) genetic polymorphisms. *Int J Cancer*, 75(6):825–30. doi:10.1002/(SICI)1097-0215(19980316)75:6<825::AID-IJC2>3.0.CO;2-X PMID:9506525

Bao PP, Shu XO, Zheng Y, Cai H, Ruan ZX, Gu K et al. (2012). Fruit, vegetable, and animal food intake and

breast cancer risk by hormone receptor status. *Nutr Cancer*, 64(6):806–19. doi:10.1080/01635581.2012.707277 PMID:22860889

Bessaoud F, Daurès JP, Gerber M (2008). Dietary factors and breast cancer risk: a case control study among a population in Southern France. *Nutr Cancer*, 60(2):177–87. doi:10.1080/01635580701649651 PMID:18444149

Bessaoud F, Tretarre B, Daurès JP, Gerber M (2012). Identification of dietary patterns using two statistical approaches and their association with breast cancer risk: a case-control study in Southern France. *Ann Epidemiol*, 22(7):499–510. doi:10.1016/j.annepidem.2012.04.006 PMID:22571994

Block G (1982). A review of validations of dietary assessment methods. *Am J Epidemiol*, 115(4):492–505. doi:10.1093/oxfordjournals.aje.a113331 PMID:7041631

Brandt B, Hermann S, Straif K, Tidow N, Buerger H, Chang-Claude J (2004). Modification of breast cancer risk in young women by a polymorphic sequence in the egfr gene. *Cancer Res*, 64(1):7–12. doi:10.1158/0008-5472.CAN-03-2623 PMID:14729599

Buck K, Vrieling A, Flesch-Janys D, Chang-Claude J (2011). Dietary patterns and the risk of postmenopausal breast cancer in a German case-control study. *Cancer Causes Control*, 22(2):273–82. doi:10.1007/s10552-010-9695-2 PMID:21110223

Butler LM, Wu AH, Wang R, Koh WP, Yuan JM, Yu MC (2010). A vegetable-fruit-soy dietary pattern protects against breast cancer among postmenopausal Singapore Chinese women. *Am J Clin Nutr*, 91(4):1013–9. doi:10.3945/ajcn.2009.28572 PMID:20181808

Byrne C, Ursin G, Ziegler RG (1996). A comparison of food habit and food frequency data as predictors of breast cancer in the NHANES I/NHEFS cohort. *J Nutr*, 126(11):2757–64. PMID:8914946

Cade JE, Taylor EF, Burley VJ, Greenwood DC (2010). Common dietary patterns and risk of breast cancer: analysis from the United Kingdom Women's Cohort Study. *Nutr Cancer*, 62(3):300–6. doi:10.1080/01635580903441246 PMID:20358467

Chandran U, Zirpoli G, Ciupak G, McCann SE, Gong Z, Pawlish K et al. (2013). Racial disparities in red meat and poultry intake and breast cancer risk. *Cancer Causes Control*, 24(12):2217–29. doi:10.1007/s10552-013-0299-5 PMID:24091794

Cho E, Spiegelman D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA et al. (2003). Premenopausal fat intake and risk of breast cancer. *J Natl Cancer Inst*, 95(14):1079–85. doi:10.1093/jnci/95.14.1079 PMID:12865454

Cho E, Chen WY, Hunter DJ, Stampfer MJ, Colditz GA, Hankinson SE et al. (2006). Red meat intake and risk of breast cancer among premenopausal women. *Arch Intern Med*, 166(20):2253–9. doi:10.1001/archinte.166.20.2253 PMID:17101944

Cho YA, Kim J, Shin A, Park KS, Ro J (2010). Dietary patterns and breast cancer risk in Korean women. *Nutr Cancer*, 62(8):1161–9. doi:10.1080/01635581.2010.514660 PMID:21058205

Cottet V, Touvier M, Fournier A, Touillaud MS, Lafay L, Clavel-Chapelon F et al. (2009). Postmenopausal breast cancer risk and dietary patterns in the E3N-EPIC prospective cohort study. *Am J Epidemiol*, 170(10):1257–67. doi:10.1093/aje/kwp257 PMID:19828509

Couto E, Sandin S, Löf M, Ursin G, Adami HO, Weiderpass E (2013). Mediterranean dietary pattern and risk of breast cancer. *PLoS One*, 8(2):e55374. doi:10.1371/journal.pone.0055374 PMID:23390532

Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R (2007). A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med*, 4(12):e325. doi:10.1371/journal.pmed.0040325 PMID:18076279

Cui X, Dai Q, Tseng M, Shu XO, Gao YT, Zheng W (2007). Dietary patterns and breast cancer risk in the shanghai breast cancer study. *Cancer Epidemiol Biomarkers Prev*, 16(7):1443–8. doi:10.1158/1055-9965.EPI-07-0059 PMID:17623805

Dai Q, Shu XO, Jin F, Gao YT, Ruan ZX, Zheng W (2002). Consumption of animal foods, cooking methods, and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*, 11(9):801–8. PMID:12223422

De Stefani E, Ronco A, Mendilaharsu M, Guidobono M, Deneo-Pellegrini H (1997). Meat intake, heterocyclic amines, and risk of breast cancer: a case-control study in Uruguay. *Cancer Epidemiol Biomarkers Prev*, 6(8):573–81. PMID:9264269

Deitz AC, Zheng W, Leff MA, Gross M, Wen WQ, Doll MA et al. (2000). N-Acetyltransferase-2 genetic polymorphism, well-done meat intake, and breast cancer risk among postmenopausal women. *Cancer Epidemiol Biomarkers Prev*, 9(9):905–10. PMID:11008907

Delfino RJ, Sinha R, Smith C, West J, White E, Lin HJ et al. (2000). Breast cancer, heterocyclic aromatic amines from meat and N-acetyltransferase 2 genotype. *Carcinogenesis*, 21(4):607–15. doi:10.1093/carcin/21.4.607 PMID:10753193

Di Maso M, Talamini R, Bosetti C, Montella M, Zucchetto A, Libra M et al. (2013). Red meat and cancer risk in a network of case-control studies focusing on cooking practices. *Ann Oncol*, 24(12):3107–12. doi:10.1093/annonc/mdt392 PMID:24121119

Di Pietro PF, Medeiros NI, Vieira FG, Fausto MA, Belló-Klein A (2007). Breast cancer in southern Brazil: association with past dietary intake. *Nutr Hosp*, 22(5):565–72. PMID:17970540

Dos Santos Silva I, Mangtani P, McCormack V, Bhakta D, Sevak L, McMichael AJ (2002). Lifelong vegetarianism and risk of breast cancer: a population-based case-control study among South Asian migrant women living in England. *Int J Cancer*, 99(2):238–44. doi:10.1002/ijc.10300 PMID:11979439

Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I et al. (2008). Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. *Eur J Cancer Prev*, 17(1):39–47. doi:10.1097/CEJ.0b013e32809b4cdd PMID:18090909

Ewertz M, Gill C (1990). Dietary factors and breast-cancer risk in Denmark. *Int J Cancer*, 46(5):779–84. doi:10.1002/ijc.2910460505 PMID:2228305

Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC (2014). Dietary protein sources in early adulthood and breast cancer incidence: prospective cohort study. *BMJ*, 348:g3437. doi:10.1136/bmj.g3437 PMID:24916719

Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC (2015). Adolescent meat intake and breast cancer risk. *Int J Cancer*, 136(8):1909–20. doi:10.1002/ijc.29218 PMID:25220168

Favero A, Parpinel M, Franceschi S (1998). Diet and risk of breast cancer: major findings from an Italian case-control study. *Biomed Pharmacother*, 52(3):109–15. doi:10.1016/S0753-3322(98)80088-7 PMID:9755803

Ferrucci LM, Cross AJ, Graubard BI, Brinton LA, McCarty CA, Ziegler RG et al. (2009). Intake of meat, meat mutagens, and iron and the risk of breast cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Br J Cancer*, 101(1):178–84. doi:10.1038/sj.bjc.6605118 PMID:19513076

Franceschi S, Favero A, La Vecchia C, Negri E, Dal Maso L, Salvini S et al. (1995). Influence of food groups and food diversity on breast cancer risk in Italy. *Int J Cancer*, 63(6):785–9. doi:10.1002/ijc.2910630606 PMID:8847134

Fu Z, Deming SL, Fair AM, Shrubsole MJ, Wujcik DM, Shu XO et al. (2011). Well-done meat intake and meat-derived mutagen exposures in relation to breast cancer risk: the Nashville Breast Health Study. *Breast Cancer Res Treat*, 129(3):919–28. doi:10.1007/s10549-011-1538-7 PMID:21537933

Fung TT, Hu FB, Holmes MD, Rosner BA, Hunter DJ, Colditz GA et al. (2005). Dietary patterns and the risk of postmenopausal breast cancer. *Int J Cancer*, 116(1):116–21. doi:10.1002/ijc.20999 PMID:15756679

Gaard M, Tretli S, Løken EB (1995). Dietary fat and the risk of breast cancer: a prospective study of 25,892 Norwegian women. *Int J Cancer*, 63(1):13–7. doi:10.1002/ijc.2910630104 PMID:7558440

Genkinger JM, Makambi KH, Palmer JR, Rosenberg L, Adams-Campbell LL (2013). Consumption of dairy and meat in relation to breast cancer risk in the Black Women's Health Study. *Cancer Causes Control*, 24(4):675–84. doi:10.1007/s10552-013-0146-8 PMID:23329367

Goodman MT, Nomura AM, Wilkens LR, Hankin J (1992). The association of diet, obesity, and breast cancer in Hawaii. *Cancer Epidemiol Biomarkers Prev*, 1(4):269–75. PMID:1303126

Han DF, Ma J, Zhou X, Qiu H, Fang L, Huang S (2004). [A case-control study on the risk of female breast cancer in Wuhan area] *Zhonghua Liu Xing Bing Xue Za Zhi*, 25(3):256–60. PMID:15200943

Hermann S, Linseisen J, Chang-Claude J (2002). Nutrition and breast cancer risk by age 50: a population-based case-control study in Germany. *Nutr Cancer*, 44(1):23–34. doi:10.1207/S15327914NC441_4 PMID:12672638

Hirayama T (1978). Epidemiology of breast cancer with special reference to the role of diet. *Prev Med*, 7(2):173–95. doi:10.1016/0091-7435(78)90244-X PMID:674105

Hislop TG, Coldman AJ, Elwood JM, Brauer G, Kan L (1986). Childhood and recent eating patterns and risk of breast cancer. *Cancer Detect Prev*, 9(1-2):47–58. PMID:3731194

Holmberg L, Ohlander EM, Byers T, Zack M, Wolk A, Bergström R et al. (1994). Diet and breast cancer risk. Results from a population-based, case-control study in Sweden. *Arch Intern Med*, 154(16):1805–11. doi:10.1001/archinte.1994.00420160038005 PMID:8053747

Holmes MD, Colditz GA, Hunter DJ, Hankinson SE, Rosner B, Speizer FE et al. (2003). Meat, fish and egg intake and risk of breast cancer. *Int J Cancer*, 104(2):221–7. doi:10.1002/ijc.10910 PMID:12569578

Ingram DM, Nottage E, Roberts T (1991). The role of diet in the development of breast cancer: a case-control study of patients with breast cancer, benign epithelial hyperplasia and fibrocystic disease of the breast. *Br J Cancer*, 64(1):187–91. doi:10.1038/bjc.1991.268 PMID:1854621

Jordan I, Hebestreit A, Swai B, Krawinkel MB (2013). Dietary patterns and breast cancer risk among women in northern Tanzania: a case-control study. *Eur J Nutr*, 52(3):905–15. doi:10.1007/s00394-012-0398-1 PMID:22729968

Kabat GC, Miller AB, Jain M, Rohan TE (2007). Dietary iron and heme iron intake and risk of breast cancer: a prospective cohort study. *Cancer Epidemiol Biomarkers Prev*, 16(6):1306–8. doi:10.1158/1055-9965.EPI-07-0086 PMID:17548704

Kabat GC, Cross AJ, Park Y, Schatzkin A, Hollenbeck AR, Rohan TE et al. (2009). Meat intake and meat preparation in relation to risk of postmenopausal breast cancer in the NIH-AARP diet and health study. *Int J Cancer*, 124(10):2430–5. doi:10.1002/ijc.24203 PMID:19165862

Kallianpur AR, Lee SA, Gao YT, Lu W, Zheng Y, Ruan ZX et al. (2008). Dietary and lifestyle predictors of age at natural menopause and reproductive span in the Shanghai Women's Health Study. *Breast Cancer Res Treat*, 107(1):123–32. doi:10.1007/s10549-007-9538-3 PMID:17431764

Kato I, Miura S, Kasumi F, Iwase T, Tashiro H, Fujita Y et al. (1992). A case-control study of breast cancer among Japanese women: with special reference to family history and reproductive and dietary factors. *Breast Cancer Res Treat*, 24(1):51–9. doi:10.1007/BF01832358 PMID:1463872

Kikuchi S, Okamoto N, Suzuki T, Kawahara S, Nagai H, Sakiyama T et al. (1990). [A case control study of breast cancer, mammary cyst and dietary, drinking or smoking habit in Japan] *Gan No Rinsho*, (Spec No):365–9. doi:10.1002/ijc.2910590608 PMID:2313891

Kinlen LJ (1982). Meat and fat consumption and cancer mortality: A study of strict religious orders in Britain. *Lancet*, 1(8278):946–9. doi:10.1016/S0140-6736(82)91943-2 PMID:6122780

Knekt P, Steineck G, Järvinen R, Hakulinen T, Aromaa A (1994). Intake of fried meat and risk of cancer: a follow-up study in Finland. *Int J Cancer*, 59(6):756–60. doi:10.1002/ijc.2910590608 PMID:7989114

Ko KP, Kim SW, Ma SH, Park B, Ahn Y, Lee JW et al. (2013). Dietary intake and breast cancer among carriers and noncarriers of BRCA mutations in the Korean Hereditary Breast Cancer Study. *Am J Clin Nutr*, 98(6):1493–501. doi:10.3945/ajcn.112.057760 PMID:24153343

Kruk J (2007). Association of lifestyle and other risk factors with breast cancer according to menopausal status: a case-control study in the Region of Western Pomerania (Poland). *Asian Pac J Cancer Prev*, 8(4):513–24. PMID:18260721

Kruk J, Marchlewicz M (2013). Dietary fat and physical activity in relation to breast cancer among Polish women. *Asian Pac J Cancer Prev*, 14(4):2495–502. doi:10.7314/APJCP.2013.14.4.2495 PMID:23725163

La Vecchia C, Decarli A, Franceschi S, Gentile A, Negri E, Parazzini F (1987). Dietary factors and the risk of breast cancer. *Nutr Cancer*, 10(4):205–14. doi:10.1080/01635588709513958 PMID:2829140

Laamiri FZ, Bouayad A, Otmani A, Ahid S, Mrabet M, Barkat A (2014). Dietery factor obesity microenvironnement and breast cancer. *Gland Surg*, 3(3):165–73. PMID:25207209

Landa MC, Frago N, Tres A (1994). Diet and the risk of breast cancer in Spain. *Eur J Cancer Prev*, 3(4):313–20. doi:10.1097/00008469-199407000-00003 PMID:7950885

Larsson SC, Bergkvist L, Wolk A (2009). Long-term meat intake and risk of breast cancer by oestrogen and progesterone receptor status in a cohort of Swedish women. *Eur J Cancer*, 45(17):3042–6. doi:10.1016/j.ejca.2009.04.035 PMID:19464165

Lee CY, Ko IS, Kim HS, Lee WH, Chang SB, Min JS et al. (2004). Development and validation study of the breast cancer risk appraisal for Korean women. *Nurs Health Sci*, 6(3):201–7. doi:10.1111/j.1442-2018.2004.00193.x PMID:15291768

Lee HJ, Wu K, Cox DG, Hunter D, Hankinson SE, Willett WC et al. (2013). Polymorphisms in xenobiotic metabolizing genes, intakes of heterocyclic amines and red meat, and postmenopausal breast cancer. *Nutr Cancer*, 65(8):1122–31. doi:10.1080/01635581.2013.824991 PMID:24099317

Lee HP, Gourley L, Duffy SW, Estéve J, Lee J, Day NE (1991). Dietary effects on breast-cancer risk in Singapore. *Lancet*, 337(8751):1197–200. doi:10.1016/0140-6736(91)92867-2 PMID:1673746

Lee HP, Gourley L, Duffy SW, Estève J, Lee J, Day NE (1992). Risk factors for breast cancer by age and menopausal status: a case-control study in Singapore. *Cancer Causes Control*, 3(4):313–22. doi:10.1007/BF00146884 PMID:1617118

Levi F, La Vecchia C, Gulie C, Negri E (1993). Dietary factors and breast cancer risk in Vaud, Switzerland. *Nutr Cancer*, 19(3):327–35. doi:10.1080/01635589309514263 PMID:8346081

Lima FE, Latorre MR, Costa MJ, Fisberg RM (2008). Diet and cancer in Northeast Brazil: evaluation of eating habits and food group consumption in relation to breast cancer. *Cad Saude Publica*, 24(4):820–8. doi:10.1590/S0102-311X2008000400012 PMID:18392359

Linos E, Willett WC, Cho E, Colditz G, Frazier LA (2008). Red meat consumption during adolescence among premenopausal women and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*, 17(8):2146–51. doi:10.1158/1055-9965.EPI-08-0037 PMID:18669582

Loh YH, Mitrou PN, Bowman R, Wood A, Jeffery H, Luben RN et al. (2010). MGMT Ile143Val polymorphism, dietary factors and the risk of breast, colorectal and prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study. *DNA Repair (Amst)*, 9(4):421–8. doi:10.1016/j.dnarep.2010.01.002 PMID:20096652

Lubin JH, Burns PE, Blot WJ, Ziegler RG, Lees AW, Fraumeni JF Jr (1981). Dietary factors and breast cancer risk. *Int J Cancer*, 28(6):685–9. doi:10.1002/ijc.2910280605 PMID:7333703

Malik IA, Sharif S, Malik F, Hakimali A, Khan WA, Badruddin SH (1993). Nutritional aspects of mammary carcinogenesis: a case-control study. *J Pak Med Assoc*, 43(6):118–20. PMID:8411614

Männistö S, Pietinen P, Virtanen M, Kataja V, Uusitupa M (1999). Diet and the risk of breast cancer in a case-control study: does the threat of disease have an influence on recall bias? *J Clin Epidemiol*, 52(5):429–39. doi:10.1016/S0895-4356(99)00010-4 PMID:10360338

Männistö S, Dixon LB, Balder HF, Virtanen MJ, Krogh V, Khani BR et al. (2005). Dietary patterns and breast cancer risk: results from three cohort studies in the DIETSCAN project. *Cancer Causes Control*, 16(6):725–33. doi:10.1007/s10552-005-1763-7 PMID:16049811

Matos EL, Thomas DB, Sobel N, Vuoto D (1991). Breast cancer in Argentina: case-control study with special reference to meat eating habits. *Neoplasma*, 38(3):357–66. PMID:1857455

Mignone LI, Giovannucci E, Newcomb PA, Titus-Ernstoff L, Trentham-Dietz A, Hampton JM et al. (2009). Meat consumption, heterocyclic amines, NAT2, and

the risk of breast cancer. *Nutr Cancer*, 61(1):36–46. doi:10.1080/01635580802348658 PMID:19116874

Mills PK, Annegers JF, Phillips RL (1988). Animal product consumption and subsequent fatal breast cancer risk among Seventh-day Adventists. *Am J Epidemiol*, 127(3):440–53. doi:10.1093/oxfordjournals.aje.a114821 PMID:3341351

Mills PK, Beeson WL, Phillips RL, Fraser GE (1989). Dietary habits and breast cancer incidence among Seventh-day Adventists. *Cancer*, 64(3):582–90. doi:10.1002/1097-0142(19890801)64:3<582::AID-CNCR2820640304>3.0.CO;2-V PMID:2743252

Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL et al. (2002). Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. *Int J Epidemiol*, 31(1):78–85. doi:10.1093/ije/31.1.78 PMID:11914299

Morales Suárez-Varela M, Jiménez López MC, Almenar Cubells D, Llópis González A (1998). [Effect of the ingestion of food and gynecologic risk factors on breast cancer risk in Valencia] *Nutr Hosp*, 13(6):325–9. PMID:9889560

Mourouti N, Kontogianni MD, Papavagelis C, Plytzanopoulou P, Vassilakou T, Malamos N et al. (2014). Adherence to the Mediterranean diet is associated with lower likelihood of breast cancer: a case-control study. *Nutr Cancer*, 66(5):810–7. doi:10.1080/01635581.2014.916319 PMID:24847911

Mourouti N, Kontogianni MD, Papavagelis C, Plytzanopoulou P, Vassilakou T, Psaltopoulou T et al. (2015). Meat consumption and breast cancer: a case-control study in women. *Meat Sci*, 100:195–201. doi:10.1016/j.meatsci.2014.10.019 PMID:25460125

Núñez C, Carbajal A, Belmonte S, Moreiras O, Varela G (1996). [A case control study of the relationship between diet and breast cancer in a sample from 3 Spanish hospital populations. Effects of food, energy and nutrient intake] *Rev Clin Esp*, 196(2):75–81. PMID:8685492

Pala V, Krogh V, Berrino F, Sieri S, Grioni S, Tjønneland A et al. (2009). Meat, eggs, dairy products, and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Am J Clin Nutr*, 90(3):602–12. doi:10.3945/ajcn.2008.27173 PMID:19491385

Phillips RL (1975). Role of life-style and dietary habits in risk of cancer among seventh-day adventists. *Cancer Res*, 35(11 Pt. 2):3513–22. PMID:1192416

Potischman N, Weiss HA, Swanson CA, Coates RJ, Gammon MD, Malone KE et al. (1998). Diet during adolescence and risk of breast cancer among young women. *J Natl Cancer Inst*, 90(3):226–33. doi:10.1093/jnci/90.3.226 PMID:9462680

Pou SA, Niclis C, Aballay LR, Tumas N, Román MD, Muñoz SE et al. (2014). [Cancer and its association with dietary patterns in Córdoba (Argentina)] *Nutr Hosp*, 29(3):618–28. PMID:24559007

Pouchieu C, Deschasaux M, Hercberg S, Druesne-Pecollo N, Latino-Martel P, Touvier M (2014). Prospective association between red and processed meat intakes and breast cancer risk: modulation by an antioxidant supplementation in the SU.VI.MAX randomized controlled trial. *Int J Epidemiol*, 43(5):1583–92. doi:10.1093/ije/dyu134 PMID:24994839

Rabstein S, Brüning T, Harth V, Fischer HP, Haas S, Weiss T et al.; GENICA Network (2010). N-acetyltransferase 2, exposure to aromatic and heterocyclic amines, and receptor-defined breast cancer. *Eur J Cancer Prev*, 19(2):100–9. doi:10.1097/CEJ.0b013e328333fbb7 PMID:19996973

Richardson S, Gerber M, Cenée S (1991). The role of fat, animal protein and some vitamin consumption in breast cancer: a case control study in southern France. *Int J Cancer*, 48(1):1–9. PMID:2019449

Ronco A, De Stefani E, Mendilaharsu M, Deneo-Pellegrini H (1996). Meat, fat and risk of breast cancer: a case-control study from Uruguay. *Int J Cancer*, 65(3):328–31. doi:10.1002/(SICI)1097-0215(19960126)65:3<328::AID-IJC9>3.0.CO;2-1 PMID:8575853

Ronco AL, de Stefani E, Aune D, Boffetta P, Deneo-Pellegrini H, Acosta G et al. (2010). Nutrient patterns and risk of breast cancer in Uruguay. *Asian Pac J Cancer Prev*, 11(2):519–24. PMID:20843144

Ronco AL, De Stefani E, Deneo-Pellegrini H (2012). Risk factors for premenopausal breast cancer: a case-control study in Uruguay. *Asian Pac J Cancer Prev*, 13(6):2879–86. doi:10.7314/APJCP.2012.13.6.2879 PMID:22938477

Shannon J, Cook LS, Stanford JL (2003). Dietary intake and risk of postmenopausal breast cancer (United States). *Cancer Causes Control*, 14(1):19–27. doi:10.1023/A:1022506507984 PMID:12708721

Shannon J, Ray R, Wu C, Nelson Z, Gao DL, Li W et al. (2005). Food and botanical groupings and risk of breast cancer: a case-control study in Shanghai, China. *Cancer Epidemiol Biomarkers Prev*, 14(1):81–90. PMID:15668480

Steck SE, Gaudet MM, Eng SM, Britton JA, Teitelbaum SL, Neugut AI et al. (2007). Cooked meat and risk of breast cancer–lifetime versus recent dietary intake. *Epidemiology*, 18(3):373–82. doi:10.1097/01.ede.0000259968.11151.06 PMID:17435448

Talamini R, La Vecchia C, Decarli A, Franceschi S, Grattoni E, Grigoletto E et al. (1984). Social factors, diet and breast cancer in a northern Italian population. *Br J Cancer*, 49(6):723–9. doi:10.1038/bjc.1984.114 PMID:6547346

Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F et al. (2000). Red meat intake and cancer risk: a study in Italy. *Int J Cancer*, 86(3):425–8. doi:10.1002/

(SICI)1097-0215(20000501)86:3<425::AID-IJC19>3.0.CO;2-S PMID:10760833

Taylor EF, Burley VJ, Greenwood DC, Cade JE (2007). Meat consumption and risk of breast cancer in the UK Women's Cohort Study. *Br J Cancer*, 96(7):1139–46. doi:10.1038/sj.bjc.6603689 PMID:17406351

Toniolo P, Riboli E, Protta F, Charrel M, Cappa AP (1989). Calorie-providing nutrients and risk of breast cancer. *J Natl Cancer Inst*, 81(4):278–86. doi:10.1093/jnci/81.4.278 PMID:2913325

Toniolo P, Riboli E, Shore RE, Pasternack BS (1994). Consumption of meat, animal products, protein, and fat and risk of breast cancer: a prospective cohort study in New York. *Epidemiology*, 5(4):391–7. doi:10.1097/00001648-199407000-00003 PMID:7918807

Trichopoulou A, Katsouyanni K, Stuver S, Tzala L, Gnardellis C, Rimm E et al. (1995). Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. *J Natl Cancer Inst*, 87(2):110–6. doi:10.1093/jnci/87.2.110 PMID:7503842

van den Brandt PA, Goldbohm RA, van Loon AJ, Kok FJ (1990). Cross-sectional versus longitudinal investigations of the diet-cancer relation. *Epidemiology*, 1(5):402–4. doi:10.1097/00001648-199009000-00011 PMID:2078617

van der Hel OL, Peeters PH, Hein DW, Doll MA, Grobbee DE, Ocké M et al. (2004). GSTM1 null genotype, red meat consumption and breast cancer risk (The Netherlands). *Cancer Causes Control*, 15(3):295–303. doi:10.1023/B:-CACO.0000024255.16305.f4 PMID:15090724

Vatten LJ, Solvoll K, Løken EB (1990). Frequency of meat and fish intake and risk of breast cancer in a prospective study of 14,500 Norwegian women. *Int J Cancer*, 46(1):12–5. doi:10.1002/ijc.2910460105 PMID:2365494

Voorrips LE, Brants HA, Kardinaal AF, Hiddink GJ, van den Brandt PA, Goldbohm RA (2002). Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: the Netherlands Cohort Study on Diet and Cancer. *Am J Clin Nutr*, 76(4):873–82. doi:10.1093/ajcn/76.4.873 PMID:12324303

Witte JS, Ursin G, Siemiatycki J, Thompson WD, Paganini-Hill A, Haile RW (1997). Diet and premenopausal bilateral breast cancer: a case-control study. *Breast Cancer Res Treat*, 42(3):243–51. doi:10.1023/A:1005710211184 PMID:9065608

Wu AH, Yu MC, Tseng CC, Stanczyk FZ, Pike MC (2009). Dietary patterns and breast cancer risk in Asian American women. *Am J Clin Nutr*, 89(4):1145–54. doi:10.3945/ajcn.2008.26915 PMID:19211822

Wu K, Sinha R, Holmes MD, Giovannucci E, Willett W, Cho E (2010). Meat mutagens and breast cancer in postmenopausal women–a cohort analysis. *Cancer Epidemiol Biomarkers Prev*, 19(5):1301–10. doi:10.1158/1055-9965.EPI-10-0002 PMID:20447922

Zhang CX, Ho SC, Chen YM, Lin FY, Fu JH, Cheng SZ (2009). Meat and egg consumption and risk of breast cancer among Chinese women. *Cancer Causes Control*, 20(10):1845–53. doi:10.1007/s10552-009-9377-0 PMID:19533390

Zhang CX, Ho SC, Fu JH, Cheng SZ, Chen YM, Lin FY (2011). Dietary patterns and breast cancer risk among Chinese women. *Cancer Causes Control*, 22(1):115–24. doi:10.1007/s10552-010-9681-8 PMID:21080051

Zheng W, Gustafson DR, Sinha R, Cerhan JR, Moore D, Hong CP et al. (1998). Well-done meat intake and the risk of breast cancer. *J Natl Cancer Inst*, 90(22):1724–9. doi:10.1093/jnci/90.22.1724 PMID:9827527

Zheng W, Deitz AC, Campbell DR, Wen WQ, Cerhan JR, Sellers TA et al. (1999). N-acetyltransferase 1 genetic polymorphism, cigarette smoking, well-done meat intake, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 8(3):233–9. PMID:10090301

Zheng W, Xie D, Cerhan JR, Sellers TA, Wen W, Folsom AR (2001). Sulfotransferase 1A1 polymorphism, endogenous estrogen exposure, well-done meat intake, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 10(2):89–94. PMID:11219777

Zheng W, Wen WQ, Gustafson DR, Gross M, Cerhan JR, Folsom AR (2002). GSTM1 and GSTT1 polymorphisms and postmenopausal breast cancer risk. *Breast Cancer Res Treat*, 74(1):9–16. doi:10.1023/A:1016005100958 PMID:12150456

2.7 Cancer of the lung

The quality of the available studies on the association between cancer of the lung and consumption of red and processed meat was evaluated based on sample size, quality of reporting of the type of meat, inclusion of relevant confounders, study design issues (e.g. population- vs hospital-based design, response rates), and exposure assessment, including validation of dietary questionnaires. Adequate control for potential confounding by energy intake and smoking (including details on smoking history, given the strength of the association with cancer of the lung) was considered as key in the evaluation of the association between cancer of the lung and red and processed meat consumption. Studies that did not distinguish clearly between red and white meat were excluded from review, unless otherwise noted. Additional criteria are listed below for case–control studies.

2.7.1 Cohort studies

See Table 2.7.1 and Table 2.7.2 (web only; available at: http://publications.iarc.fr/564)

Six cohort studies were considered informative with respect to the association between cancer of the lung and meat intake. Unlike for other cancer sites, such as the colorectum, there were fewer studies available for the review of cancer of the lung. Therefore, the Working Group included most studies of lung cancer and red or processed meat, with exceptions as noted. The Working Group included one study investigating mortality; given the short survival of lung cancer patients, mortality is a reasonable surrogate for incidence. Balder et al. (2005) was excluded because it referred to a mixed category of "pork, processed meat, and potatoes". The study by Knekt et al. (1994) was excluded because it only reported results for fried meat (did not specify if red or white).

Breslow et al. (2000) studied 20 195 individuals with dietary data from the 1987 National Health Interview Survey, who were then linked to the National Death Index. Baseline diet was assessed with a 59-item FFQ. Food groups, including total meat/poultry/fish, red meats, and processed meats, were analysed after adjustment for age, sex, BMI, smoking, and other variables, but not total energy. There were 158 deaths from lung cancer. Red meat intake was associated with lung cancer mortality. The relative risk was 1.6 (95% CI, 1.0–2.6; P_{trend} = 0.014) for the highest (6.6 servings/week) versus the lowest (0–2.3 servings/week) quartile. No association was found with processed meat (P_{trend} = 0.721). [The Working Group noted that this was a small study based on mortality, with a limited FFQ and no adjustment for total energy.]

Tasevska et al. (2009) studied 278 380 men and 189 596 women from the National Institutes of Health-AARP Diet and Health (NHI-AARP) study. Diet was assessed with a 124-item FFQ. Meat-cooking modalities were investigated, and the CHARRED database was used to estimate the intake of HAAs, benzo[*a*]pyrene (BaP), and haem iron. A high intake of red meat was associated with an increased risk of lung cancer in both men (HR, 1.22; 95% CI, 1.09–1.38; P_{trend} = 0.005) and women (HR, 1.13; 95% CI, 0.97–1.32; P_{trend} = 0.05) for the highest compared with the lowest category of intake. A high intake of processed meat increased the risk only in men (HR, 1.23; 95% CI, 1.10–1.37; P_{trend} = 0.003). In an analysis stratified by smoking status, never-smoking men and women had increased risks with red meat consumption that were not statistically significant. The hazard ratios for the 90th versus the 10th percentile were 1.19 (95% CI, 0.69–2.06; P_{trend} = 0.52) in men and 1.21 (95% CI, 0.76–1.94; P = 0.44) in women for red meat. The relative risk for the highest versus the lowest tertile of intake of well/very well-done meat was 1.20 (95% CI, 1.07–1.35; P_{trend} = 0.002), and for intake of MeIQx, it was 1.20 (95% CI, 1.04–1.38;

P_{trend} = 0.04) in men. Haem iron intake for the highest compared with the lowest quintile was associated with an increased risk of lung carcinoma in both men (HR, 1.25; 95% CI, 1.07–1.45; P_{trend} = 0.02) and women (HR, 1.18; 95% CI, 0.99–1.42; P_{trend} = 0.002).

Linseisen et al. (2011) used the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, with 1822 incident lung cancers, exposure assessment based on a validated FFQ and 24-hour recall, and statistical analyses including adjustment for several smoking variables. With a continuous model, they found a statistically non-significant increase in risk of lung cancer. The relative risks were 1.06 (95% CI, 0.89–1.27) per 50 g increment of red meat and 1.13 (95% CI, 0.95–1.34) for the same amount of processed meat. Some subcohorts included health-conscious or vegetarian subjects [very large size].

Tasevska et al. (2011) used the Prostate, Lung, Colorectal and Ovarian (PLCO) cohort in which lung cancer screening was offered. There were 454 lung cancer cases in men and 328 in women. No information was given on response rates and losses to follow-up. No association was found with red meat or processed meat intake in men in multivariable modelling. Women showed slightly elevated relative risks with increasing quintiles of red meat intake (from ≤ 14.6 to > 42.5 g/1000 kcal): 1.33 (95% CI, 0.91–1.94), 1.60 (95% CI, 1.10–2.33), 1.24 (95% CI, 0.84–1.85), 1.30 (95% CI, 0.87–1.95), with no dose–response (P_{trend} = 0.65; adjusted for total energy intake and several other confounders, including smoking). [The Working Group noted that the study included both screened and non-screened arms, and the authors reported that associations were similar. There was accurate adjustment for smoking variables.]

Gnagnarella et al. (2013) invited asymptomatic volunteers aged 50 years or older who were current smokers or recent quitters, and had smoked at least 20 pack-years, to undergo annual screening with computed tomography. They assessed participants' diet at baseline using a self-administered FFQ that included 188 food items and beverages. During a mean screening period of 5.7 years, 178 of 4336 participants were diagnosed with lung cancer. In the multivariable analysis, red meat consumption was associated with an increased risk of lung cancer [HR for quartile 4 vs quartile 1, 1.73; 95% CI, 1.15–2.61; P_{trend} = 0.003]. [The Working Group noted that this was a relatively small study of heavy smokers.]

Butler et al. (2013) published a study based on data from a prospective cohort study among Chinese in Singapore that included 1004 lung cancer cases. A 165-item FFQ was used. The relative risk for fried meat was 1.13 (95% CI, 0.98–1.31) for the second tertile and 1.09 (95% CI, 0.94–1.27) for the third tertile of intake, but it was not specified whether fried meat was red or white. The corresponding relative risks for adenocarcinomas were 1.31 (95% CI, 1.03–1.68) and 1.36 (95% CI, 1.06–1.74). Risk estimates for fried pork consumption separately showed no clear association. [The Working Group concluded that a limitation was that the fried meat definition included both white and red meat. The strengths were that the study used a validated FFQ, had a large sample size, and adequately controlled for smoking, with 70% of the cohort being non-smokers.]

2.7.2 Case–control studies

See Table 2.7.3 and Table 2.7.4 (web only; available at: http://publications.iarc.fr/564)

The Working Group identified 21 case–control studies on the association between lung cancer and red and processed meat consumption from the USA, Uruguay, Europe, China, and China, Hong Kong Special Administrative Region, India, Canada, Singapore, Pakistan, and Brazil. When there were multiple publications from the same study, only the most recent one was included. Most of these studies were not

originally designed to assess meat consumption, and most of the available papers reported positive associations. The potential for reporting bias (i.e. reporting only statistically significant associations among the many associations that were investigated), therefore, needed to be considered in the evaluation of these findings.

The Working Group subsequently excluded eight case–control studies (most hospital-based) because the type of meat (red or white) was not specified (Suzuki et al., 1994; Phukan et al., 2014), the methods of control selection were unclear (Kubík et al., 2001; Shen et al., 2008; Chiu et al., 2010), the response rates were not given (Dosil-Díaz et al., 2007), or the information on adjustment for confounders was inadequate (Ganesh et al., 2011; Luqman et al., 2014). Brennan et al. (2000) was included, in spite of the lack of distinction between white and red meat, because it was one of the few studies to report estimates for non-smokers only.

Goodman et al. (1992) conducted a population-based study in Hawaii, USA, among 326 cases of histologically confirmed lung cancer and 865 controls. Exposure assessment was good, with an FFQ with 130 items. Results were inconsistent, with an increased risk for sausages, luncheon meat, and bacon in men (weaker and not statistically significant in women) and lack of association for red meat. A strong interaction was found with smoking, with odds ratios rising up to 11.8 (95% CI, 2.3–61.6) for smokers with > 70 pack-years of cigarettes consuming more than the median intake of sausages (men only for squamous cell carcinoma). There was also a statistically significant association with estimated nitrosamine intake. [The Working Group noted that the method of selection of controls changed during the conduction of the study. Strong odds ratios were based on the subgroup analysis.]

The study by Swanson et al. (1992) from China was based on a case–control design nested within an occupational population (a mining company) and a population-based study in a city. The response rate was very high. The accuracy of cancer ascertainment was uncertain, although the authors stated that it was based on pathological examinations. No association with meat intake (almost exclusively pork) was found. [The Working Group noted that there was a very small number of non-smoking cases.]

Sankaranarayanan et al. (1994) conducted a hospital-based study in India, based on 387 cases. Controls were relatives of patients or bystanders. Forty-five items were included in the dietary questionnaire. Strong but statistically unstable associations were reported for beef, with no dose–response. [The Working Group noted that the number of meat eaters in this study was small.]

Sinha et al. (1998) reported on a population-based study from the USA that included 593 cases and 628 controls, drawn from the drivers' licences or health care financing rosters. [The selection of controls was unclear, particularly oversampling of smokers.] A 110-item Health Habits and History Questionnaire (HHHQ) with 15 items related to red meat was used to assess exposure. Information on cooking methods and doneness levels was also obtained. Only women were included. There were statistically significant increases in risk with 10 g/day increments in the consumption of all red meat, well-done red meat, and fried red meat. When comparing the 90th and 10th percentiles, lung cancer risk increased for all red meat (OR, 1.8; 95% CI, 1.2–2.7), for well-done red meat (OR, 1.5; 95% CI, 1.1–2.1), and for fried red meat (OR, 1.5; 95% CI, 1.1–2.0).

Brennan et al. (2000) conducted a multicentre, hospital-based case–control study in non-smokers (defined as having smoked < 400 cigarettes in a lifetime) in Europe with a large samples size (506 cases, 1045 controls); diseases in controls were not specified. There was no association with meat intake, except in small cell carcinomas. Odds ratios were 1.2 (95% CI, 0.3–4.5) and 1.6 (95% CI, 1.1–2.2)

in increasing tertiles (weekly/several times and weekly/daily vs never, respectively). [The Working Group noted that the study was informative because it provided data on non-smokers. However, no distinction between white and red meat was made, and no adjustment for second-hand smoke was made.]

Alavanja et al. (2001) conducted a population-based study in the USA, with 360 cases identified through the Surveillance, Epidemiology, and End Results (SEER) Program and 574 controls sampled from drivers' licences and Medicare rosters (females only). A 70-item FFQ (NCI Block questionnaire) was used. Red meat was defined as hamburger, beef burritos, beef stew, pot pie, meatloaf, beef (fat unspecified), pork (fat unspecified), ham, lunchmeats, bacon, liver, sausage, or hot dogs. [The response rate, particularly in controls, was low.] The researchers found an association with increasing levels of red meat intake. Odds ratios were 1.7 (95% CI, 0.9–3.3) for 3.5–5.5 times/week, 2.0 (95% CI, 1.4–4.0) for 5.6–7.6 times/week, 2.5 (95% CI, 1.2–5.2) for 7.7–9.8 times/week, and 3.3 (95% CI, 1.7–7.6) for > 9.8 times/week (P_{trend} = 0.005). In addition, effect modification by histological type and smoking was considered. The odds ratios for red meat consumption were similar among adenocarcinoma cases (OR, 3.0; 95% CI, 1.1–7.9) and non-adenocarcinoma cases (OR, 3.2; 95% CI, 1.3–8.3), and among lifetime non-smokers and ex-smokers (OR, 2.8; 95% CI, 1.4–5.4) and current smokers (OR, 4.9; 95% CI, 1.1–22.3). [Red meat included processed meat.]

Hu et al. (2002) published the results of a population-based study in Canada in which controls were drawn from an insurance plan or random digit dialling. Only women who never smoked were included. A 70-item FFQ based on the NCI Block questionnaire was used. Overall, 161 cases and 483 controls were included, with a 1:3 case–control ratio. Modest associations were found with red meat (OR, 0.8 for second quartile, 2–3 servings/week; OR, 1.4. for third quartile, 3.1–5 servings/week; OR, 1.4 for fourth quartile, > 5 servings/week; none statistically significant). An increase in risk for processed red meat and bacon was not statistically significant, except for smoked meat (third tertile vs first tertile OR, 2.1; 95% CI, 1.1–4.0). Never-smokers were examined separately with the following results: for red meat, in increasing quartiles of servings/week, OR were 0.8 (95% CI, 0.4–1.5), 1.4 (95% CI, 0.7–2.6), and 1.4 (95% CI, 0.7–2.8), and for smoked meat, in increasing tertiles, 1.3 (95% CI, 0.8–2.3) and 2.1 (95% CI, 1.1–4.0). [The Working Group noted that the study size was small.]

Zatloukal et al. (2003) published the results of a study in the Czech Republic using spouses, relatives, and friends of hospital patients as controls. They found an association between lung cancer and increasing tertiles of intake of red meat, but only for histologies other than adenocarcinoma. The odds ratios were 1.54 (95% CI, 0.89–2.67) for weekly consumption and 1.81 (95% CI, 1.04–3.8) for daily consumption (P_{trend} = 0.04) [subgroup analysis noted].

Kubík et al. (2004) published the results of a hospital-based study in the Czech Republic among non-smoking women only (130 cases; 1022 controls were spouses, friends, or relatives of hospital patients). [Only nine food items were included in the dietary questionnaire.] They found an association with red meat (≥ 1 time/day to ≥ 1 time/week vs ≤ 1 time/week to > 1 time/month ; OR, 2.2; 95% CI, 1.07–4.51).

Lam et al. (2009) published a well-designed population-based study in Italy, with high response rates (87% cases, 72% controls) and large numbers (1903 cases, 2073 controls). Exposure assessment included a 58-item FFQ, with estimation of exposure to mutagens and detailed information on cooking practices. The researchers found increased odds ratios with increasing tertiles of red meat intake, 1.3 (95% CI, 1.1–1.6) and 1.8 (95% CI, 1.5–2.2). The odds ratios with increasing tertiles of processed meat intake were 1.3 (95% CI, 1.1–1.5) and 1.7 (95%

CI, 1.4–2.1). The odds ratios for estimated intake of the mutagen PhIP were 1.1 (95% CI, 0.9–1.4) and 1.5 (95% CI, 1.2–1.8). Never-smokers were examined separately. For red meat, the odds ratios with increasing tertiles were 1.1 (95% CI, 0.7–2.0) for the second tertile and 2.4 (95% CI, 1.4–4.0) for the third tertile for red meat (P_{trend} = 0.001), and 1.5 (95% CI, 0.9–2.6) and 2.5 (95% CI, 1.5–4.2) for processed meat (P = 0.001). [The Working Group noted that adjustment for smoking was accurate and detailed.]

Concerning hospital-based studies, Aune et al. (2009) from Uruguay reported associations with the highest compared with the lowest quartile of intake of red meat (OR, 2.17; 95% CI, 1.52–3.10) and processed meat (OR, 1.7; 95% CI, 1.28–2.25). They also looked at beef and lamb separately, and associations were similar. Twin papers from Uruguay were published by De Stefani et al. (2009) and Deneo-Pellegrini et al. (2015). The first differed because exposure assessment was broader with estimation of exposure to mutagens, and the second was restricted to squamous cell carcinoma in men. In addition to finding results that were very similar to Aune et al. (2009), De Stefani et al. (2009) reported results for exposure to PhIP, assessed through a database compiled from the literature (Jakszyn et al., 2004). In increasing tertiles of exposure, the odds ratios for PhIP were 1.12 (95% CI, 0.80–1.56), 1.48 (95% CI, 1.05–2.07), and 2.16 (95% CI, 1.48–3.15). Deneo-Pellegrini et al. (2015) reported on squamous cell lung cancer, and the odds ratios were 1.82 (95% CI, 1.13–2.91) and 1.09 (95% CI, 0.73–1.64) for the highest versus the lowest tertiles of intake of red meat and processed meat, respectively.

Lim et al. (2011) published the results of a hospital-based study in Singapore (399 cases, 815 controls) with high response rates (81% cases, 85% controls), but only 18 meat-related items were included in the FFQ. There was no significant association with total meat, pork, or processed meat intake. However, there was a significant association with high-bacon consumption (OR, 1.51; 95% CI, 1.06–2.16).

2.7.3 Meta-analyses

Two meta-analyses of the association between lung cancer and consumption of red or processed meat were identified. Yang et al. (2012) included 23 case–control and 11 cohort studies identified via MEDLINE, Embase, and the Web of Science through 2011. The meta-relative risk for the highest compared with the lowest category of intake was significantly greater than unity for red meat (RR, 1.34; 95% CI, 1.18–1.52), but not for processed meat intake (RR, 1.06; 95% CI, 0.90–1.25). The association with red meat was observed in never-smokers (RR, 1.66; 95% CI, 1.31–2.11), and was robust in sensitivity analyses that took into account the study type and quality. In general, results for processed meat were weak or inconsistent. All estimates (including those for red meat) showed high heterogeneity, with highly significant P values ($P < 0.001$) and high I^2 levels. There was no evidence of publication bias.

The second meta-analysis was an extension of the previous one, and aimed to explore the dose–response relationships in more detail (Xue et al., 2014). Dose–response data were available from 11 studies for red meat and 11 studies for processed meat. The meta-relative risks were 1.35 (95% CI, 1.25–1.46) for red meat (per 120 g increment) and 1.20 (95% CI, 1.11–1.29) for processed meat (per 50 g increment). In general, estimates varied considerably by study design. In cohort studies, the relative risks for red meat and processed meat were 1.21 (95% CI, 1.14–1.28; $P_{heterogeneity}$ = 0.7) and 1.09 (95% CI, 0.99–1.19; $P_{heterogeneity}$ = 0.1), respectively, with higher estimates in case–control studies. In case–control studies and other subgroup analyses by region and sex, P values for heterogeneity were highly significant.

References

Alavanja MC, Field RW, Sinha R, Brus CP, Shavers VL, Fisher EL et al. (2001). Lung cancer risk and red meat consumption among Iowa women. *Lung Cancer*, 34(1):37–46. doi:10.1016/S0169-5002(01)00227-6 PMID:11557111

Aune D, De Stefani E, Ronco A, Boffetta P, Deneo-Pellegrini H, Acosta G et al. (2009). Meat consumption and cancer risk: a case-control study in Uruguay. *Asian Pac J Cancer Prev*, 10(3):429–36. PMID:19640186

Balder HF, Goldbohm RA, van den Brandt PA (2005). Dietary patterns associated with male lung cancer risk in the Netherlands Cohort Study. *Cancer Epidemiol Biomarkers Prev*, 14(2):483–90. doi:10.1158/1055-9965.EPI-04-0353 PMID:15734976

Brennan P, Fortes C, Butler J, Agudo A, Benhamou S, Darby S et al. (2000). A multicenter case-control study of diet and lung cancer among non-smokers. *Cancer Causes Control*, 11(1):49–58. doi:10.1023/A:1008909519435 PMID:10680729

Breslow RA, Graubard BI, Sinha R, Subar AF (2000). Diet and lung cancer mortality: a 1987 National Health Interview Survey cohort study. *Cancer Causes Control*, 11(5):419–31. doi:10.1023/A:1008996208313 PMID:10877335

Butler LM, Montague JA, Koh WP, Wang R, Yu MC, Yuan JM (2013). Fried meat intake is a risk factor for lung adenocarcinoma in a prospective cohort of Chinese men and women in Singapore. *Carcinogenesis*, 34(8):1794–9. doi:10.1093/carcin/bgt113 PMID:23568952

Chiu YL, Wang XR, Qiu H, Yu IT (2010). Risk factors for lung cancer: a case-control study in Hong Kong women. *Cancer Causes Control*, 21(5):777–85. doi:10.1007/s10552-010-9506-9 PMID:20084541

De Stefani E, Boffetta P, Deneo-Pellegrini H, Ronco AL, Aune D, Acosta G et al. (2009). Meat intake, meat mutagens and risk of lung cancer in Uruguayan men. *Cancer Causes Control*, 20(9):1635–43. doi:10.1007/s10552-009-9411-2 PMID:19685149

Deneo-Pellegrini H, Ronco AL, De Stefani E (2015). Meat consumption and risk of squamous cell carcinoma of the lung: a case-control study in Uruguayan men. *Nutr Cancer*, 67(1):82–8. doi:10.1080/01635581.2015.970290 PMID:25411912

Dosil-Díaz O, Ruano-Ravina A, Gestal-Otero JJ, Barros-Dios JM (2007). Meat and fish consumption and risk of lung cancer: A case-control study in Galicia, Spain. *Cancer Lett*, 252(1):115–22. doi:10.1016/j.canlet.2006.12.008 PMID:17240050

Ganesh B, Sushama S, Monika S, Suvarna P (2011). A case-control study of risk factors for lung cancer in Mumbai, India. *Asian Pac J Cancer Prev*, 12(2):357–62. PMID:21545194

Gnagnarella P, Maisonneuve P, Bellomi M, Rampinelli C, Bertolotti R, Spaggiari L et al. (2013). Red meat, Mediterranean diet and lung cancer risk among heavy smokers in the COSMOS screening study. *Ann Oncol*, 24(10):2606–11. doi:10.1093/annonc/mdt302 PMID:23956193

Goodman MT, Hankin JH, Wilkens LR, Kolonel LN (1992). High-fat foods and the risk of lung cancer. *Epidemiology*, 3(4):288–99. doi:10.1097/00001648-199207000-00004 PMID:1637893

Hu J, Mao Y, Dryer D, White K; Canadian Cancer Registries Epidemiology Research Group(2002). Risk factors for lung cancer among Canadian women who have never smoked. *Cancer Detect Prev*, 26(2):129–38. doi:10.1016/S0361-090X(02)00038-7 PMID:12102147

Jakszyn P, Agudo A, Ibáñez R, García-Closas R, Pera G, Amiano P et al. (2004). Development of a food database of nitrosamines, heterocyclic amines, and polycyclic aromatic hydrocarbons. *J Nutr*, 134(8):2011–4. doi:10.1093/jn/134.8.2011 PMID:15284391

Knekt P, Steineck G, Järvinen R, Hakulinen T, Aromaa A (1994). Intake of fried meat and risk of cancer: a follow-up study in Finland. *Int J Cancer*, 59(6):756–60. doi:10.1002/ijc.2910590608 PMID:7989114

Kubík A, Zatloukal P, Tomásek L, Kríz J, Petruzelka L, Plesko I (2001). Diet and the risk of lung cancer among women. A hospital-based case-control study. *Neoplasma*, 48(4):262–6. PMID:11712676

Kubík A, Zatloukal P, Tomásek L, Pauk N, Petruzelka L, Plesko I (2004). Lung cancer risk among nonsmoking women in relation to diet and physical activity. *Neoplasma*, 51(2):136–43. PMID:15190423

Lam TK, Cross AJ, Consonni D, Randi G, Bagnardi V, Bertazzi PA et al. (2009). Intakes of red meat, processed meat, and meat mutagens increase lung cancer risk. *Cancer Res*, 69(3):932–9. doi:10.1158/0008-5472.CAN-08-3162 PMID:19141639

Lim WY, Chuah KL, Eng P, Leong SS, Lim E, Lim TK et al. (2011). Meat consumption and risk of lung cancer among never-smoking women. *Nutr Cancer*, 63(6):850–9. doi:10.1080/01635581.2011.589961 PMID:21774592

Linseisen J, Rohrmann S, Bueno-de-Mesquita B, Büchner FL, Boshuizen HC, Agudo A et al. (2011). Consumption of meat and fish and risk of lung cancer: results from the European Prospective Investigation into Cancer and Nutrition. *Cancer Causes Control*, 22(6):909–18. doi:10.1007/s10552-011-9764-1 PMID:21479828

Luqman M, Javed MM, Daud S, Raheem N, Ahmad J, Khan AU (2014). Risk factors for lung cancer in the Pakistani population. *Asian Pac J Cancer Prev*, 15(7):3035–9. doi:10.7314/APJCP.2014.15.7.3035 PMID:24815443

Phukan RK, Saikia BJ, Borah PK, Zomawia E, Sekhon GS, Mahanta J (2014). Role of household exposure, dietary habits and glutathione S-Transferases M1, T1 polymorphisms in susceptibility to lung cancer among women in Mizoram India. *Asian Pac J Cancer*

Prev, 15(7):3253–60. doi:10.7314/APJCP.2014.15.7.3253 PMID:24815479

Sankaranarayanan R, Varghese C, Duffy SW, Padmakumary G, Day NE, Nair MK (1994). A case-control study of diet and lung cancer in Kerala, south India. *Int J Cancer*, 58(5):644–9. doi:10.1002/ijc.2910580505 PMID:8077047

Shen M, Chapman RS, He X, Liu LZ, Lai H, Chen W et al. (2008). Dietary factors, food contamination and lung cancer risk in Xuanwei, China. *Lung Cancer*, 61(3):275–82. doi:10.1016/j.lungcan.2007.12.024 PMID:18304686

Sinha R, Kulldorff M, Curtin J, Brown CC, Alavanja MC, Swanson CA (1998). Fried, well-done red meat and risk of lung cancer in women (United States). *Cancer Causes Control*, 9(6):621–30. doi:10.1023/A:1008805525525 PMID:10189048

Suzuki I, Hamada GS, Zamboni MM, Cordeiro PB, Watanabe S, Tsugane S (1994). Risk factors for lung cancer in Rio de Janeiro, Brazil: a case-control study. *Lung Cancer*, 11(3-4):179–90. doi:10.1016/0169-5002(94)90538-X PMID:7812696

Swanson CA, Mao BL, Li JY, Lubin JH, Yao SX, Wang JZ et al. (1992). Dietary determinants of lung-cancer risk: results from a case-control study in Yunnan Province, China. *Int J Cancer*, 50(6):876–80. doi:10.1002/ijc.2910500609 PMID:1555887

Tasevska N, Sinha R, Kipnis V, Subar AF, Leitzmann MF, Hollenbeck AR et al. (2009). A prospective study of meat, cooking methods, meat mutagens, heme iron, and lung cancer risks. *Am J Clin Nutr*, 89(6):1884–94. doi:10.3945/ajcn.2008.27272 PMID:19369370

Tasevska N, Cross AJ, Dodd KW, Ziegler RG, Caporaso NE, Sinha R (2011). No effect of meat, meat cooking preferences, meat mutagens or heme iron on lung cancer risk in the prostate, lung, colorectal and ovarian cancer screening trial. *Int J Cancer*, 128(2):402–11. doi:10.1002/ijc.25327 PMID:20232386

Xue XJ, Gao Q, Qiao JH, Zhang J, Xu CP, Liu J (2014). Red and processed meat consumption and the risk of lung cancer: a dose-response meta-analysis of 33 published studies. *Int J Clin Exp Med*, 7(6):1542–53. PMID:25035778

Yang WS, Wong MY, Vogtmann E, Tang RQ, Xie L, Yang YS et al. (2012). Meat consumption and risk of lung cancer: evidence from observational studies. *Ann Oncol*, 23(12):3163–70. doi:10.1093/annonc/mds207 PMID:22855553

Zatloukal P, Kubík A, Pauk N, Tomásek L, Petruzelka L (2003). Adenocarcinoma of the lung among women: risk associated with smoking, prior lung disease, diet and menstrual and pregnancy history. *Lung Cancer*, 41(3):283–93. doi:10.1016/S0169-5002(03)00234-4 PMID:12928119

2.8 Cancer of the oesophagus

The Working Group focused their review on studies that clearly defined red meat or processed meat (see Section 1 and Section 2). Studies were excluded if: (1) risk estimates were presented for total meat (red and processed meat combined) intake; (2) the type of meat was not defined or included white meat; (3) fewer than 100 cases were reported, due to the limited statistical power, as a large database of high-quality studies were available; (4) a more recent report from the same study was available; (5) risk estimates, adjusted for important confounders, were not available (crude estimates were not considered to be informative); (6) dietary patterns were the focus; (7) outcome was assessed using mortality data; and (8) the analysis and results were reported for cancers of the upper aerodigestive tract as a group.

Important covariates for the association between red meat and cancer of the oesophagus include age, tobacco smoking, alcohol drinking (squamous cell carcinoma), BMI (adenocarcinoma), and energy intake.

2.8.1 Cohort studies

(a) Red meat

See Table 2.8.1 (web only; available at: http://publications.iarc.fr/564)

Conflicting results were reported in the three cohort studies that reported on the association between red meat consumption and oesophageal cancer reviewed by the Working Group. No association was observed between consumption of red meat and oesophageal cancer among women enrolled in the NLCS (Keszei et al., 2012), or among participants in the EPIC study (Jakszyn et al., 2013). Increased risks were observed among the NIH-AARP study cohort (Cross et al., 2011) and among men enrolled in the NLCS (Keszei et al., 2012). The NIH-AARP study also reported positive associations between haem iron intake and risk of oesophageal adenocarcinoma (EAC). [The Working Group noted that, in the EPIC study, processed meat was not included in the definition of red meat, but the sample size was limited (137 cases), and the analyses did not adjust for alcohol. A strength of the NLCS was that a detailed questionnaire with 150 items was used; however, the sample size was limited (107 oesophageal squamous cell carcinomas, ESCCs; 145 EACs). The Working Group also noted that, although the NIH-AARP study cohort was large with a large number of cases (215 ESCCs, 630 EACs), and the study investigated the intake of meat-cooking by-products and haem iron intake, the interpretation of results was hampered because processed meat was included in the definition of red meat.]

(b) Processed meat

See Table 2.8.2 (web only; available at: http://publications.iarc.fr/564)

The Working Group reviewed three studies that investigated the association between consumption of processed meat and oesophageal cancer. One report from Cross et al. (2007) was updated and, therefore, not included. Studies based on mortality data were excluded (e.g. Iso et al., 2007). The Working Group noted when important risk factors for oesophageal cancer, such as tobacco and alcohol consumption, were not adjusted for in the analyses.

In the NIH-AARP study cohort, Cross et al. (2011) reported hazard ratios for the highest versus the lowest quintile of processed meat intake, adjusted for important confounders, of 1.32 (95% CI, 0.83–2.10; P_{trend} = 0.085; 60 exposed cases) for ESCC and 1.08 (95% CI, 0.81–1.43; P_{trend} = 0.262; 181 exposed cases) for EAC. [The Working Group noted that this was a large study with a large number of cases, especially for EAC.]

In the NLCS, Keszei et al. (2012) reported adjusted relative risks for oesophageal cancer for the highest compared with the lowest category of processed meat intake of 3.47 (95% CI, 1.21–9.94; P_{trend} = 0.04; 16 exposed cases) for ESCC and

0.94 (95% CI, 0.46–1.89; P_{trend} = 0.84; 24 exposed cases) for EAC in men. Corresponding relative risks in women were below one. [The Working Group noted that a detailed questionnaire with 150 items was used. The sample size was limited.]

Within the EPIC cohort, Jakszyn et al. (2013) reported a positive association between consumption of processed meat and EAC, after adjusting for important confounders (highest vs lowest tertile HR, 2.27; 95% CI, 1.33–3.89; P_{trend} = 0.004; 62 exposed cases). [The Working Group noted that this was a large study with a large number of cases, especially for EAC. Processed meat did not include white meat. Alcohol was not adjusted for.]

2.8.2 Case–control studies

(a) Red meat

See Table 2.8.3 (web only; available at: http://publications.iarc.fr/564)

The Working Group reviewed 20 case–control studies, both hospital-based and population-based, that investigated the association between oesophageal cancer and consumption of red meat. The studies were conducted in North America, South America, Europe, Asia, and Africa (Yu et al., 1988; Rogers et al., 1993; Castelletto et al., 1994; Brown et al., 1995, 1998; Rolón et al., 1995; Bosetti et al., 2000; Levi et al., 2000; Chen et al., 2002; Xibib et al., 2003; Wang et al., 2007; Wu et al., 2007; Navarro Silvera et al., 2008; Sapkota et al., 2008; Gao et al., 2011; O'Doherty et al., 2011; Wu et al., 2011; Ward et al., 2012; Di Maso et al., 2013; De Stefani et al., 2014a; Matejcic et al., 2015). All but seven studies were population-based. Two studies reported risk estimates less than or equal to one (Rogers et al., 1993; Sapkota et al., 2008), while most of the studies reported an increased risk of oesophageal cancer was associated with red meat intake, after adjusting for important confounding factors (Yu et al., 1988; Castelletto et al., 1994; Brown et al., 1995, 1998; Rolón et al., 1995; Bosetti et al., 2000; Levi et al., 2000; Chen et al., 2002; Xibib et al., 2003; Wang et al., 2007; Wu et al., 2007; Navarro Silvera et al., 2008; Gao et al., 2011; Wu et al., 2011; O'Doherty et al., 2011; Ward et al., 2012; Di Maso et al., 2013; De Stefani et al., 2014a; Matejcic et al., 2015).

(b) Processed meat

See Table 2.8.4 (web only; available at: http://publications.iarc.fr/564)

About 15 case–control studies that investigated the association between consumption of processed meat and oesophageal cancer, conducted in different areas of the world (the USA, South America, Europe, and Asia), were included in the evaluation by the Working Group (Yu et al., 1988; Brown et al., 1995, 1998; De Stefani et al., 2014b; Bosetti et al., 2000; Takezaki et al., 2001; Hung et al., 2004; Levi et al., 2004; Yang et al., 2005; Wu et al., 2007; Navarro Silvera et al., 2008; Sapkota et al., 2008; Chen et al., 2009; O'Doherty et al., 2011; Song et al., 2012; Ward et al., 2012; Lin et al., 2015). The quality of the studies was considered, based on the reporting of the type of meat; study design issues (e.g. population-based vs hospital-based design); sample size; exposure assessment, including validation of dietary questionnaires; and inclusion of relevant confounders. Important covariates for oesophageal cancer include age, tobacco smoking, alcohol drinking, BMI (adenocarcinoma), and energy intake. Nine studies were population-based (Yu et al., 1988; Brown et al., 1995, 1998; Takezaki et al., 2001; Wu et al., 2007; Navarro Silvera et al., 2008 ; O'Doherty et al., 2011 ; Song et al., 2012; Ward et al., 2012; Lin et al., 2015), two of which adjusted for *Helicobacter pylori* (Wu et al., 2007; O'Doherty et al., 2011.

2.8.3 Meta-analyses

Among the five meta-analyses on red and processed meat published recently (Choi et al., 2013; Huang et al., 2013; Qu et al., 2013; Salehi

et al., 2013; Zhu et al., 2014), Qu et al. (2013) considered ESCC, whereas Huang et al. (2013) considered EAC only. Choi et al. (2013) considered both types, but studies without information on the histological type were not included. Salehi et al. (2013) considered all oesophageal cancers, but studies reporting only one type of red meat, such as beef, pork etc., were included in the meta-analyses by Qu et al. (2013) and Choi et al. (2013). The results of the two most recent and comprehensive meta-analyses are summarized below. [The Working Group did not place emphasis on the results of the meta-analyses due to their significant limitations.]

Zhu et al. (2014) was the most recent and comprehensive meta-analysis. The meta-analysis included all types of oesophageal cancers: ESCC and EAC, and total oesophageal cancers. The meta-analysis included three cohort studies and 12 case–control studies; however, two reports, one for EAC (Brown et al., 1995) and the other for ESCC (Brown et al., 1998), on a population-based case–control study conducted in the USA were not included. The summary relative risks of oesophageal cancer for the highest compared with the lowest categories were 1.55 (95% CI, 1.22–1.96; $P_{heterogeneity} < 0.001$; $I^2 = 63.6\%$) for red meat and 1.33 (95% CI, 1.04–1.69; $P_{heterogeneity} < 0.001$; $I^2 = 61.5\%$) for processed meat. A statistically significant association was also observed for case–control studies (OR, 1.78 and 1.39, respectively), but not for cohort studies (RR, 1.22 and 1.25, respectively). When stratified by histological type, an association was observed between ESCC and red meat, and EAC and processed meat; the summary estimates were calculated as OR, 1.86 (95% CI, 1.31–2.66) and 1.23 (95% CI, 1.01–1.50), respectively. [The Working Group noted that this review included all types of oesophageal cancers. The interpretation of this analysis was limited by the fact that two reports were missing, and papers reporting on only one type of red meat, such as beef or pork, were not included.]

Qu et al. (2013) presented a comprehensive meta-analysis that considered study design, and further analysed dose–response and linearity. A total of two cohort studies and 19 case–control studies with 6499 oesophageal cancer cases were included in the meta-analysis. The summary relative risks of oesophageal cancer for the highest compared with the lowest categories were 1.57 (95% CI, 1.26–1.95; $P_{heterogeneity} = 0.003$) for red meat intake and 1.55 (95% CI, 1.22–1.97; $P_{heterogeneity} = 0.029$) for processed meat intake. These results were consistent with those of the dose–response analyses. Stratified analysis by histological type, study design, number of cases (< 200 vs ≥ 200), and adjustment of covariates did not reveal any differences, although the summary relative risks in the population-based case–control studies and the European studies were not statistically significant. [This review did not include studies reporting on EAC; however, studies reporting on only one item of red meat were included.]

References

Bosetti C, La Vecchia C, Talamini R, Simonato L, Zambon P, Negri E et al. (2000). Food groups and risk of squamous cell esophageal cancer in northern Italy. *Int J Cancer*, 87(2):289–94. doi:10.1002/1097-0215(20000715)87:2<289::AID-IJC22>3.0.CO;2-9 PMID:10861489

Brown LM, Swanson CA, Gridley G, Swanson GM, Schoenberg JB, Greenberg RS et al. (1995). Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst*, 87(2):104–9. doi:10.1093/jnci/87.2.104 PMID:7707381

Brown LM, Swanson CA, Gridley G, Swanson GM, Silverman DT, Greenberg RS et al. (1998). Dietary factors and the risk of squamous cell esophageal cancer among black and white men in the United States. *Cancer Causes Control*, 9(5):467–74. doi:10.1023/A:1008861806923 PMID:9934713

Castelletto R, Castellsague X, Muñoz N, Iscovich J, Chopita N, Jmelnitsky A (1994). Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. *Cancer Epidemiol Biomarkers Prev*, 3(7):557–64. PMID:7827585

Chen H, Ward MH, Graubard BI, Heineman EF, Markin RM, Potischman NA et al. (2002). Dietary patterns and adenocarcinoma of the esophagus and distal stomach. *Am J Clin Nutr*, 75(1):137–44. doi:10.1093/ajcn/75.1.137 PMID:11756071

Chen YK, Lee CH, Wu IC, Liu JS, Wu DC, Lee JM et al. (2009). Food intake and the occurrence of squamous cell carcinoma in different sections of the esophagus in Taiwanese men. *Nutrition*, 25(7-8):753–61. doi:10.1016/j.nut.2009.02.002 PMID:19394796

Choi Y, Song S, Song Y, Lee JE (2013). Consumption of red and processed meat and esophageal cancer risk: meta-analysis. *World J Gastroenterol*, 19(7):1020–9. doi:10.3748/wjg.v19.i7.1020 PMID:23467465

Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R (2007). A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med*, 4(12):e325 doi:10.1371/journal.pmed.0040325 PMID:18076279

Cross AJ, Freedman ND, Ren J, Ward MH, Hollenbeck AR, Schatzkin A et al. (2011). Meat consumption and risk of esophageal and gastric cancer in a large prospective study. *Am J Gastroenterol*, 106(3):432–42. doi:10.1038/ajg.2010.415 PMID:20978481

De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Correa P, Mendilaharsu M et al. (2014a). Diet patterns and risk of squamous cell oesophageal carcinoma: a case-control study in Uruguay. *Asian Pac J Cancer Prev*, 15(6):2765–9. doi:10.7314/APJCP.2014.15.6.2765 PMID:24761898

De Stefani E, Boffetta P, Ronco AL, Deneo-Pellegrini H, Correa P, Acosta G et al. (2014b). Processed meat consumption and squamous cell carcinoma of the oesophagus in a large case-control study in Uruguay. *Asian Pac J Cancer Prev*, 15(14):5829–33. doi:10.7314/APJCP.2014.15.14.5829 PMID:25081709

Di Maso M, Talamini R, Bosetti C, Montella M, Zucchetto A, Libra M et al. (2013). Red meat and cancer risk in a network of case-control studies focusing on cooking practices. *Ann Oncol*, 24(12):3107–12. doi:10.1093/annonc/mdt392 PMID:24121119

Gao Y, Hu N, Han XY, Ding T, Giffen C, Goldstein AM et al. (2011). Risk factors for esophageal and gastric cancers in Shanxi Province, China: a case-control study. *Cancer Epidemiol*, 35(6):e91–9. doi:10.1016/j.canep.2011.06.006 PMID:21846596

Huang W, Han Y, Xu J, Zhu W, Li Z (2013). Red and processed meat intake and risk of esophageal adenocarcinoma: a meta-analysis of observational studies. *Cancer Causes Control*, 24(1):193–201. doi:10.1007/s10552-012-0105-9 PMID:23179661

Hung HC, Huang MC, Lee JM, Wu DC, Hsu HK, Wu MT (2004). Association between diet and esophageal cancer in Taiwan. *J Gastroenterol Hepatol*, 19(6):632–7. doi:10.1111/j.1440-1746.2004.03346.x PMID:15151616

Iso H, Kubota Y; Japan Collaborative Cohort Study for Evaluation of Cancer (2007). Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev*, 8:Suppl: 35–80. PMID:18260705

Jakszyn P, Luján-Barroso L, Agudo A, Bueno-de-Mesquita HB, Molina E, Sánchez MJ et al. (2013). Meat and heme iron intake and esophageal adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition study. *Int J Cancer*, 133(11):2744–50. PMID:23728954

Keszei AP, Schouten LJ, Goldbohm RA, van den Brandt PA (2012). Red and processed meat consumption and the risk of esophageal and gastric cancer subtypes in The Netherlands Cohort Study. *Ann Oncol*, 23(9):2319–26. doi:10.1093/annonc/mdr615 PMID:22351741

Levi F, Pasche C, Lucchini F, Bosetti C, Franceschi S, Monnier P et al. (2000). Food groups and oesophageal cancer risk in Vaud, Switzerland. *Eur J Cancer Prev*, 9(4):257–63. doi:10.1097/00008469-200008000-00005 PMID:10958328

Levi F, Pasche C, Lucchini F, Bosetti C, La Vecchia C (2004). Processed meat and the risk of selected digestive tract and laryngeal neoplasms in Switzerland. *Ann Oncol*, 15(2):346–9. doi:10.1093/annonc/mdh060 PMID:14760132

Lin S, Wang X, Huang C, Liu X, Zhao J, Yu IT et al. (2015). Consumption of salted meat and its interactions with alcohol drinking and tobacco smoking on esophageal squamous-cell carcinoma. *Int J Cancer*, 137(3):582–9. doi:10.1002/ijc.29406 PMID:25544988

Matejcic M, Vogelsang M, Wang Y, Iqbal Parker M (2015). NAT1 and NAT2 genetic polymorphisms and environmental exposure as risk factors for oesophageal squamous cell carcinoma: a case-control study. *BMC Cancer*, 15(1):150. doi:10.1186/s12885-015-1105-4 PMID:25886288

Navarro Silvera SA, Mayne ST, Risch H, Gammon MD, Vaughan TL, Chow WH et al. (2008). Food group intake and risk of subtypes of esophageal and gastric cancer. *Int J Cancer*, 123(4):852–60. doi:10.1002/ijc.23544 PMID:18537156

O'Doherty MG, Cantwell MM, Murray LJ, Anderson LA, Abnet CC; FINBAR Study Group (2011). Dietary fat and meat intakes and risk of reflux esophagitis, Barrett's esophagus and esophageal adenocarcinoma. *Int J Cancer*, 129(6):1493–502. doi:10.1002/ijc.26108 PMID:21455992

Qu X, Ben Q, Jiang Y (2013). Consumption of red and processed meat and risk for esophageal squamous cell carcinoma based on a meta-analysis. *Ann Epidemiol*, 23(12):762–770.e1. doi:10.1016/j.annepidem.2013.09.003 PMID:24176821

Rogers MA, Thomas DB, Davis S, Vaughan TL, Nevissi AE (1993). A case-control study of element levels and cancer

of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev*, 2(4):305–12. PMID:8348053

Rolón PA, Castellsagué X, Benz M, Muñoz N (1995). Hot and cold mate drinking and esophageal cancer in Paraguay. *Cancer Epidemiol Biomarkers Prev*, 4(6):595–605. PMID:8547825

Salehi M, Moradi-Lakeh M, Salehi MH, Nojomi M, Kolahdooz F (2013). Meat, fish, and esophageal cancer risk: a systematic review and dose-response meta-analysis. *Nutr Rev*, 71(5):257–67. doi:10.1111/nure.12028 PMID:23590703

Sapkota A, Hsu CC, Zaridze D, Shangina O, Szeszenia-Dabrowska N, Mates D et al. (2008). Dietary risk factors for squamous cell carcinoma of the upper aerodigestive tract in central and eastern Europe. *Cancer Causes Control*, 19(10):1161–70. doi:10.1007/s10552-008-9183-0 PMID:18512121

Song Q, Wang X, Yu IT, Huang C, Zhou X, Li J et al. (2012). Processed food consumption and risk of esophageal squamous cell carcinoma: A case-control study in a high risk area. *Cancer Sci*, 103(11):2007–11. doi:10.1111/j.1349-7006.2012.02387.x PMID:22827896

Takezaki T, Gao CM, Wu JZ, Ding JH, Liu YT, Zhang Y et al. (2001). Dietary protective and risk factors for esophageal and stomach cancers in a low-epidemic area for stomach cancer in Jiangsu Province, China: comparison with those in a high-epidemic area. *Jpn J Cancer Res*, 92(11):1157–65. doi:10.1111/j.1349-7006.2001.tb02135.x PMID:11714439

Wang JM, Xu B, Rao JY, Shen HB, Xue HC, Jiang QW (2007). Diet habits, alcohol drinking, tobacco smoking, green tea drinking, and the risk of esophageal squamous cell carcinoma in the Chinese population. *Eur J Gastroenterol Hepatol*, 19(2):171–6. doi:10.1097/MEG.0b013e32800ff77a PMID:17273005

Ward MH, Cross AJ, Abnet CC, Sinha R, Markin RS, Weisenburger DD (2012). Heme iron from meat and risk of adenocarcinoma of the esophagus and stomach. *Eur J Cancer Prev*, 21(2):134–8. doi:10.1097/CEJ.0b013e32834c9b6c PMID:22044848

Wu AH, Tseng CC, Hankin J, Bernstein L (2007). Fiber intake and risk of adenocarcinomas of the esophagus and stomach. *Cancer Causes Control*, 18(7):713–22. doi:10.1007/s10552-007-9014-8 PMID:17562192

Wu M, Zhang ZF, Kampman E, Zhou JY, Han RQ, Yang J et al. (2011). Does family history of cancer modify the effects of lifestyle risk factors on esophageal cancer? A population-based case-control study in China. *Int J Cancer*, 128(9):2147–57. doi:10.1002/ijc.25532 PMID:20602339

Xibib S, Meilan H, Moller H, Evans HS, Dixin D, Wenjie D et al. (2003). Risk factors for oesophageal cancer in Linzhou, China: a case-control study. *Asian Pac J Cancer Prev*, 4(2):119–24. PMID:12875624

Yang CX, Wang HY, Wang ZM, Du HZ, Tao DM, Mu XY et al. (2005). Risk factors for esophageal cancer: a case-control study in South-western China. *Asian Pac J Cancer Prev*, 6(1):48–53. PMID:15780032

Yu MC, Garabrant DH, Peters JM, Mack TM (1988). Tobacco, alcohol, diet, occupation, and carcinoma of the esophagus. *Cancer Res*, 48(13):3843–8. PMID:3378219

Zhu HC, Yang X, Xu LP, Zhao LJ, Tao GZ, Zhang C et al. (2014). Meat consumption is associated with esophageal cancer risk in a meat- and cancer-histological-type dependent manner. *Dig Dis Sci*, 59(3):664–73. doi:10.1007/s10620-013-2928-y PMID:24395380

2.9 Other cancers

The Working Group focused their review on studies that clearly defined red meat or processed meat (see Section 1). Studies were excluded if: (1) risk estimates were presented for total meat (red and processed meat combined) intake; (2) the type of meat was not defined; (3) fewer than 100 cases were reported, due to the limited statistical power; (4) a more recent report from the same study was available; (5) risk estimates, adjusted for important confounders, were not available (crude estimates were not considered to be informative); (6) dietary patterns were the focus; and (7) outcomes were assessed using mortality data.

The tables for this section are available online at: http://publications.iarc.fr/564.

2.9.1 Non-Hodgkin lymphoma

For studies on non-Hodgkin lymphoma, apart from the criteria previously mentioned for all cancers, the studies were also evaluated carefully in regard to the main confounders, including age, sex, and energy intake. Some studies additionally adjusted for occupational exposures (if available) or excluded participants with HIV infection, namely in case–control studies. The Working Group noted when studies did not meet the criteria.

(a) Cohort studies

Five cohort studies reported on red meat consumption and risk of non-Hodgkin lymphoma, and four of these studies reported on processed meat consumption separately. Data on red meat and processed meat intake combined were not reported here.

(i) Red meat

See Table 2.9.1 (web only; available at: http://publications.iarc.fr/564)

The IWHS was a prospective cohort study that included 35 156 women aged 55–69 years at baseline in 1986 and who were followed up for 7 years (Chiu et al., 1996). A total of 104 incident cases of non-Hodgkin lymphoma were identified during the course of follow-up that also had usable dietary data. A 126-item, validated SQFFQ was used to estimate, among others, red meat and processed meat intake. [In this study, the red meat group included bacon, hot dogs, processed meat, liver, beef stew, hamburger, and beef as a main dish, which corresponded to red meat and processed meat combined. In addition, pork and lamb were not explicitly specified.] None of the separate meat components of the red meat group were significantly associated with non-Hodgkin lymphoma, except for the consumption of hamburger. The fully adjusted relative risk for the highest tertile (> 4 servings/month of hamburger) compared with the lowest tertile (< 4 servings/month of hamburger) of consumption amounted to 2.35 (95% CI, 1.23–4.48; $P_{trend} = 0.02$).

In 1992, after the cases had already been identified, an additional questionnaire, returned by 79% of the participants (64% of incident cases), was used to collect information about doneness levels of red meat, and specified beef, pork, and lamb as examples of red meat. The results for doneness of red meat revealed an inverse association with consumption of well-done red meat versus rare to medium–rare (RR, 0.47; 95% CI, 0.22–0.99; $P_{trend} = 0.09$). [The Working Group concluded that the inverse association with well-done red meat needed to be interpreted with caution because of potential information bias, since the information was collected later during follow-up, when cases had already occurred, and there were very few cases in the reference category ($n = 11$).]

The association between red and processed meat and risk of non-Hodgkin lymphoma ($n = 199$) in 88 410 women after 14 years of follow-up was investigated in the NHS (Zhang et al., 1999). Consumption of beef, pork, or lamb as a main dish was significantly associated with

an increased risk of non-Hodgkin lymphoma. The adjusted relative risk for the highest compared with the lowest quintile of intake was 2.2 (95% CI, 1.1–4.4; P_{trend} = 0.002). Analyses according to cooking methods showed a significant association between consumption of broiled beef, pork, or lamb as a main dish and non-Hodgkin lymphoma (consumption of 2–4 times/week vs < 1 time/month RR, 1.8; 95% CI, 1.0–3.3), although the *P* value for trend was not significant (*P* = 0.09). There was an elevated, but non-significant, association with barbecued beef, pork, or lamb consumed ≥ 1 time/week compared with barbecued beef, pork, or lamb consumed < 1 time/month (RR, 1.5; 95% CI, 0.9–2.4; P_{trend} = 0.13). [The Working Group noted that this was a large study that showed an association with consumption of red meat.]

The association between red and processed meat intake and risk of chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) was investigated in a pooled analysis of two prospective cohort studies: the NIH-AARP study and the PLCO trial. The analysis was restricted to Caucasians, and excluded outliers of energy intake (top and bottom 1%) and BMI (< 18.5 or > 50 kg/m^2). Among 525 982 participants from both cohorts, 1129 incident CLL/SLL cases were identified after 11.2 years of follow-up. Red meat consumption (age-, sex-, and BMI-adjusted HR, 0.90; 95% CI, 0.76–1.08) was not associated with risk of CLL/SLL for the highest compared with the lowest quartile of intake (Tsai et al., 2010). [The Working Group noted that this was a large study. There was no adjustment for energy intake, but BMI was adjusted for.]

In the EPIC study (Rohrmann et al., 2011), 410 411 participants were followed up for a median of 8.5 years, resulting in the identification of 1267 non-Hodgkin lymphoma cases classified according to the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) and reclassified according to the Third Edition (ICD-O-3). Diet was assessed over the previous 12 months with validated questionnaires that covered meals or food groups, and individual average portions or standard portions. Red meat included beef, pork, and mutton/lamb. Red meat consumption was neither associated with non-Hodgkin lymphoma nor with any of the subtypes (the latter results were not shown). The multivariate-adjusted hazard ratio for the highest quintile of red meat consumption (≥ 80 g/day) compared with the lowest quintile (< 20 g/day) was 1.01 (95% CI, 0.82–1.26; P_{trend} = 0.55). [The Working Group noted that this was an important study because it was large and had a wide range of intake.]

The NIH-AARP study was a large prospective cohort study conducted in six different states and two metropolitan areas in the USA (Daniel et al., 2012a). The cohort included 492 186 individuals aged 50–71 years who were followed up for a mean of 9 years, resulting in the identification of 3611 incident cases of non-Hodgkin lymphoma (ICD-O-3). Usual dietary intake over the past year was assessed using a 124-item, validated FFQ. Red meat consumption was not associated with non-Hodgkin lymphoma or with any of the subtypes. The adjusted relative risk was 0.93 (95% CI, 0.83–1.05; P_{trend} = 0.27) for the highest quintile of red meat consumption (median, 48.1 g/1000 kcal) compared with the lowest quintile of red meat consumption (median, 6.8 g/1000 kcal). Doneness of meat was estimated for a subcohort, and extra analyses with these exposures did not reveal any association between doneness of meat and risk of non-Hodgkin lymphoma. Estimates of meat-cooking mutagens (from CHARRED) and meat-related compounds (i.e. haem iron and nitrate and nitrite) were also assessed, and none were found to be associated with non-Hodgkin lymphoma. [The Working Group concluded that this was a very informative study because of the large power, the well-described and seemingly comprehensive definition of the outcome and the exposures, and the ability to distinguish

between subtypes, sex, and other potential effect modifiers.]

(ii) Processed meat

See Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

In the IWHS, previously described (Chiu et al., 1996), processed meat was not defined further. Processed meat consumption was not associated with risk of non-Hodgkin lymphoma. The age- and energy-adjusted relative risk for the highest tertile (> 6 servings/month) of consumption of processed meat compared with the lowest tertile (< 4 servings/month) of consumption of processed meat was 1.11 (95% CI, 0.68–1.79; P_{trend} = 0.67). [The Working Group noted that it was difficult to draw conclusions based on the comparison of > 6 to < 4 servings/month; however, this could have been a typing error in the publication. The lack of definition of the processed meat group was a potential limitation of this study. In addition, the range of intake was very narrow, and the intake was low overall. Therefore, the results on processed meat consumption from this study should be regarded cautiously.]

In the pooled-analysis study described above, processed meat consumption (HR, 0.88; CI, 0.74–1.05) was not associated with risk of CLL/SLL, when comparing the highest with the lowest quartile of intake (Tsai et al., 2010).

In the EPIC study, previously described (Rohrmann et al., 2011), processed meat included all meat products, including ham, bacon, different types of sausages, canned/smoked/dried meat, pâté, hamburger, and meatballs. Processed meat consumption was not associated with non-Hodgkin lymphoma, yet a significant positive association with B-cell chronic lymphocytic leukaemia (BCLL) was observed. The multivariate-adjusted hazard ratio for the highest quintile (≥ 80 g/day) compared with the lowest quintile (< 20 g/day) of processed meat consumption was 1.06 (95% CI, 0.82–1.37; P_{trend} = 0.82) for non-Hodgkin lymphoma. A significant positive association was only observed for BCLL (HR for highest vs lowest quintile of intake, 2.19; 95% CI, 1.27–3.77; P_{trend} = 0.01). The results for the other subgroups were not reported because of the small number of exposed cases or non-significant associations. [The association observed for the BCLL subgroup may have been a chance finding amidst the many associations that were tested in this study. The Working Group concluded that this was an important study because it was large with a wide range of intake.]

In the NIH-AARP study, previously described (Daniel et al., 2012a). Processed meat consumption was not associated with non-Hodgkin lymphoma or with any of the subtypes (results for the latter not provided in this summary). The multivariate-adjusted relative risk of non-Hodgkin lymphoma for the highest quintile of processed meat consumption (median, 23.6 g/1000 kcal) compared with the lowest quintile of processed meat consumption (median, 2.2 g/1000 kcal) was 0.99 (95% CI, 0.89–1.11; P_{trend} = 0.45). The adjusted relative risk was 1.07 (95% CI, 0.95–1.20; P_{trend} = 0.91) for the highest quintile of red processed meat consumption (median, 19.9 g/1000 kcal) compared with the lowest quintile of red processed meat consumption (median, 1.4 g/1000 kcal). [The Working Group concluded that this was a very informative study because of the large power, the well-described and seemingly comprehensive definition of the outcome and the exposures, and the ability to distinguish between subtypes, sex, and other potential effect modifiers.]

(b) Case–control studies

Four population-based case–control studies and four hospital-based case–control studies reported on the association between red meat consumption and/or processed meat consumption and non-Hodgkin lymphoma.

(i) Red meat

See Table 2.9.3 (web only; available at: http://publications.iarc.fr/564)

Cross et al. (2006) conducted a population-based case–control study in four areas of the USA covered by NCI-sponsored SEER registries. A total of 458 (87% response rate) newly diagnosed, histologically confirmed non-Hodgkin lymphoma patients without HIV infection and 383 (90% response rate) controls matched by age (5 years), centre, ethnicity, and sex participated. There was no significant association between red meat intake and risk of non-Hodgkin lymphoma. Red meat consumption was assessed using a 117-item, self-administered FFQ (which was based on the 1995 revision of the Block questionnaire) covering usual diet over the past 12 months. [The definition of red meat was not specifically mentioned, but since the different cooking methods and doneness levels specified the following meats, they were potentially included in the red meat definition: hamburger, steak, pork chops, bacon, and sausage; therefore, red meat may have partially included some processed meats.] Based on cooking levels and doneness levels of the meats, several HAA intakes were estimated, but are not reported in this *Monograph*. The multivariate-adjusted odds ratio for the highest quartile compared with the lowest quartile of red meat intake was 1.10 (95% CI, 0.67–1.81; P_{trend} = 0.87). There was also no association with red meat intake according to different cooking methods (i.e. red meat with known cooking methods, either barbecued, pan-fried, or broiled) and doneness levels of red meat (rare, rare/medium, medium, or well-done red meat). [The Working Group noted that this study had very high response rates for cases and controls.]

A population-based case–control study was carried out in Canada (1994–1997). The study included a large group of histologically confirmed cases of cancer, among which 1666 were non-Hodgkin lymphomas, and 5039 were controls (Hu et al., 2008). A short version of the Block FFQ was used. The FFQ contained 69 items and ascertained usual dietary intake 2 years earlier. Red meat intake included intake from beef, pork, or lamb as a main dish; beef, pork, or lamb as a mixed dish (stew or casserole, pasta dish); and hamburger. Red meat intake was not associated with risk of non-Hodgkin lymphoma. The multivariate-adjusted odds ratio for the highest quartile of intake (≥ 5.1 servings/week) compared with the lowest quartile of intake (≤ 2 servings/week) of red meat was 1.1 (95% CI, 0.9–1.3; P_{trend} = 0.60). [The main strength of this study was that it was a large case–control study, but no details were provided on the number of cases per exposure category.] An earlier report of the previous study (Purdue et al., 2004), based on nearly the same data, reported essentially the same results (not presented in the table).

In a population-based case–control study in the USA (1999–2002), among 336 newly diagnosed, histologically confirmed non-Hodgkin lymphoma patients and 460 controls, red meat intake was significantly associated with non-Hodgkin lymphoma (Aschebrook-Kilfoy et al., 2012). A validated, 117-item FFQ (a modified Block questionnaire, HHHQ) was used. Red meat consisted of beef (hamburger/cheeseburger patties, roast beef/sandwiches, beef stew/pot pie, steak, tacos/burritos), pork (pork chops, roast), and liver. Additional analyses were conducted for meat-related carcinogens, estimated with the CHARRED database. The multivariate-adjusted odds ratio, additionally adjusted for white and processed meat intake, was 1.5 (95% CI, 1.1–2.2; P_{trend} = 0.01) for the highest tertile (≥ 61.8 g/1000 kcal) compared with the lowest tertile (< 41.2 g/1000 kcal) of intake. The associations were most pronounced for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, and the association with DLBCL was especially evident with hamburger patties. [The Working Group noted that, although no associations

were observed for other disease subgroups, there were too few cases in these subgroups to draw conclusions.]

A hospital-based case–control study was conducted in north-eastern and southern Italy (1999–2002). The study included 190 incident, histologically confirmed non-Hodgkin lymphoma patients (excluding HIV-infected patients) and 484 controls (Talamini et al., 2006a). The cases were between 18 and 84 years of age, and were admitted to the major reference hospitals of the areas for surveillance. The controls were of the same age range and were admitted for a wide spectrum of acute conditions to the same network of hospitals. A validated, 63-item FFQ that covered the 2 years before diagnosis or hospital admission was used to estimate exposure. Red meat consumption was calculated from weekly serving sizes of beef, veal, pork, liver, pasta/rice with meat sauce, and lasagne/cannelloni. Red meat consumption was not associated with non-Hodgkin lymphoma. The multivariate-adjusted odds ratio for non-Hodgkin lymphoma was 0.93 (95% CI, 0.56–1.55; P_{trend} = 0.65) for the highest (> 3.25 servings/week) compared with the lowest (≤ 1.6 servings/week) quartile of red meat intake. An earlier hospital-based case–control study was also conducted in northern Italy (1983–1996) among 200 histologically confirmed non-Hodgkin lymphoma patients (< 5% non-response rate for cases and controls) [no mention of exclusion of HIV-infected individuals] (Tavani et al., 2000). The control group comprised 7990 patients younger than 75 years admitted to the same network of hospitals as the cancer cases for a wide spectrum of acute non-neoplastic conditions. Red meat was defined as beef, veal, and pork. Lamb, horse, goat, and offal were not included in the questionnaire. Canned meat and preserved meat were excluded. The information was collected through a 40-item FFQ that was not validated, but it did show a correlation of 0.61 for reproducibility of meat intake. It was estimated that a portion of red meat in Italy was between 100 and 150 g. There was also no evidence from this study of an association between red meat intake and non-Hodgkin lymphoma. The multivariate-adjusted odds ratio for the highest (≥ 7 portions/week) compared with the lowest tertile (≤ 3 portions/week) of intake of red meat was 1.2 (95% CI, 0.8–1.7). The adjusted odds ratio associated with an increase in intake of red meat of 1 average portion/day was 1.2 (95% CI, 0.9–1.7). [The Working Group noted that adjustment for energy intake was possible only for gastrointestinal cancers in this study.]

A hospital-based case–control study was conducted in Uruguay between 1996 and 2004. The study included 369 non-Hodgkin lymphoma cases and 3606 controls (De Stefani et al., 2013). All incident and microscopically confirmed non-Hodgkin lymphoma cases that occurred in the Cancer Institute of Uruguay were considered eligible for the study and were defined according to the WHO guidelines (Feller & Diebold, 2004). Controls were identified through the same institute. All interviews were conducted shortly after admittance, and an FFQ was used to assess exposure [validity not specified]. Red meat was defined as beef or lamb, and reported as servings per year. Red meat consumption was not associated with non-Hodgkin lymphoma. The odds ratio for the highest compared with the lowest tertile of red meat consumption was 1.25 (95% CI, 0.92–1.69; P_{trend} = 0.14). [The Working Group noted that there was no mention of exclusion of patients with HIV. It was also unclear what time period the FFQ referred to, and there was no mention of its validity. In addition, the unit of measurement for the exposure (i.e. servings/year) was unusual. The definition of red meat did not include pork.]

An earlier hospital-based case–control study was conducted in Uruguay (1988–1995). The study included 160 incident cases of non-Hodgkin lymphoma (92% response rate) [no mention of exclusion of HIV-infected

individuals] and 163 hospital-based controls matched by age (in 10-year age groups), sex, and residence and urban/rural status (De Stefani et al., 1998). Dietary intake was assessed through a food frequency form used by interviewers. [There was no mention of the period of intake that was covered.] Red meat was defined as beef and lamb. In this study, a significant association between red meat intake and non-Hodgkin lymphoma was reported for men, but the association was not significant for women. The odds ratio for non-Hodgkin lymphoma for the highest tertile (≥ 12.7 servings/week) compared with the lowest tertile (≤ 7.7 servings/week) of red meat intake was 2.53 (95% CI, 1.01–6.34; P_{trend} = 0.04) for men and 2.45 (95% CI, 0.88–6.82; P_{trend} = 0.08) for women (≥ 9.3 vs ≤ 6.0 servings/week, respectively). [The Working Group noted that results on specific types of red meats and cooking methods were provided, but only for certain subgroups, not all (only beef, and only barbecued and salted meat). Therefore, these risk estimates are not displayed further, neither in the text nor in the table, to avoid reporting bias.]

A hospital-based case–control study was conducted in India (1997–1999) in 390 men with microscopically confirmed non-Hodgkin lymphoma and 1383 controls with no evidence of disease (microscopically confirmed cancer-free) selected from the comprehensive cancer centre (Balasubramaniam et al., 2013). Red meat was defined as mutton, liver, pork, brain, etc. and based on interviews using a structured questionnaire on food items and frequency per week, covering a period of 1 year before the interview. Red meat consumption was strongly associated with non-Hodgkin lymphoma. The adjusted odds ratio for red meat consumption compared with no red meat consumption [dichotomous variable] was 7.3 (95% CI, 2.2–24.6). [The Working Group noted that the number of exposed cases was not provided for subgroups of red meat consumers. In addition, it is unknown whether the odds ratio was also adjusted for age and energy intake. It is also unclear whether only newly diagnosed non-Hodgkin lymphoma patients were included or whether patients living with the diagnosis for some time already were included. There was also no mention of whether HIV-infected cases were excluded. Although this was a study in India with a large number of vegetarians, only a dichotomous variable of red meat intake was provided (yes/no), and it is plausible that there was some residual confounding.]

(ii) Processed meat

See Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

In the population-based case–control study in the USA conducted by Cross et al. (2006), described earlier in the red meat subsection, processed meat included bacon, sausage, ham, hot dogs, liver, and luncheon meats. There was no significant association between processed meat intake and risk of non-Hodgkin lymphoma. The adjusted odds ratio for the highest quartile compared with the lowest quartile of processed meat intake was 1.18 (95% CI, 0.74–1.89; P_{trend} = 0.94).

In the population-based case–control study that was conducted in Canada (1994–1997), previously described in Section 2.9.1(b)(i) (Hu et al., 2008), processed meat intake included hot dogs, smoked meat, or corned beef; bacon and sausage. Processed meat consumption was not associated with non-Hodgkin lymphoma. The odds ratio for the highest quartile (≥ 5.42 servings/week) compared with the lowest quartile (≤ 0.94 servings/week) of intake of processed meat was 1.2 (95% CI, 0.9–1.4; P_{trend} = 0.15). The analysis was adjusted for age (10-year age group), province, education, BMI, sex, alcohol use, pack-years of smoking, total vegetable and fruit intake, and total energy intake. [The main strength of this study was that it was a large case–control study, but little detail was provided on the number of cases per exposure category.] An earlier publication on almost the same data as those in this

case–control study reported a positive association with processed beef/pork/lamb, defined as hot dogs, luncheon meats (salami, bologna; 1 piece or slice), smoked meat or corned beef (1 piece or slice), and bacon (1 slice), which could have been defined as processed red meat (Purdue et al., 2004). The Working Group decided to evaluate only the most recent publication as the results were contradictory.

In the population-based case–control study that was conducted in eastern Nebraska, USA (1999–2002), described in Section 2.9.1(b)(i) (Aschebrook-Kilfoy et al., 2012), processed meat intake was not associated with non-Hodgkin lymphoma. The multivariate-adjusted odds ratio was 1.3 (95% CI, 0.9–1.9; P_{trend} = 0.2) for the highest tertile of intake (≥ 13.1 g/1000 kcal) compared with the lowest tertile of intake (< 6.2 g/1000 kcal). An earlier population-based case–control study was conducted, in part by the same group, in eastern Nebraska, USA. The study included 385 histologically confirmed non-Hodgkin lymphoma cases diagnosed between 1983 and 1986 and 1432 controls (Ward et al., 1994). Controls were frequency-matched by ethnicity, sex, vital status, and age (5-year age groups). Interviews were conducted with the cases (60%) and controls (56%) themselves, and for the remaining, with the next of kin (when cases had died). Interviews included questions about the frequency of consumption of 30 food items, including meat. Processed meat was defined as bacon/sausage and processed ham/hot dogs. Processed meat intake was not associated with non-Hodgkin lymphoma. For men, the age-adjusted odds ratio was 0.6 (95% CI, 0.4–1.1) for those who consumed processed meat > 6 times/week compared with those who consumed processed meat < 2 times/week. For women, the age-adjusted odds ratio was 1.2 (95% CI, 0.7–2.1) for those who consumed processed meat > 4 times/week compared with those who consumed processed meat < 2 times/week. The odds ratio did not change materially after additional adjustment for non-Hodgkin lymphoma risk factors in this study (i.e. ever-use of herbicides; ever-use of the herbicide 2,4-dichlorophenoxyacetic acid; use of organophosphate insecticides; family history of lymphatic or haematopoietic cancer; ever-use of permanent hair dye, women only; and type of respondent, subject/next of kin). [The Working Group concluded that a limitation of this study was that a relatively large part of the population was not directly interviewed, but the lifestyle information was obtained through interviews with the next of kin (40% of cases, 44% of controls). Finally, the multivariate adjustment did not include energy intake.]

In the hospital-based case–control study in Uruguay between 1996 and 2004 including 369 non-Hodgkin lymphoma cases and 3606 controls, previously described in Section 2.9.1(b)(i), consumption of processed meat was defined as servings per year of bacon, sausage, blood pudding, mortadella, salami, saucisson, hot dog, and ham (De Stefani et al., 2013). The odds ratio for the highest compared with the lowest tertile of processed meat consumption was 0.95 (95% CI, 0.72–1.25; P_{trend} = 0.86). There was a positive association between salted meat (which was part of processed meat) intake and non-Hodgkin lymphoma. The odds ratio for the highest tertile versus the lowest tertile of salted meat intake was 2.29 (95% CI, 1.62–3.22; P_{trend} < 0.0001). [A limitation was that it was unclear which time period the FFQ referred to, and there was no mention of its validity. In addition, the unit of measurement for the exposure (i.e. servings/year) was strange.] An earlier hospital-based case–control study was also conducted by this group in Uruguay (1988–1995) and described previously. Processed meat included salami, saucisson, ham, and mortadella (De Stefani et al., 1998). There was no significant dose–response association between processed meat consumption and non-Hodgkin lymphoma for either men or women. The odds ratios for the highest versus the lowest tertile of processed meat intake were 1.03 (95% CI,

0.43–2.42; P_{trend} = 0.92) for men and 1.90 (95% CI, 0.66–5.45; P_{trend} = 0.09) for women. There was a positive association between non-Hodgkin lymphoma and salted meat intake among men, but not among women. The odds ratio for the highest (≥ 1.1 servings/week) versus the lowest (never) tertile of salted meat intake among men was 4.96 (95% CI, 1.39–17.7; P_{trend} = 0.01).

A hospital-based case–control study was conducted in the USA (2002–2008) in 603 pathologically confirmed, incident cases of non-Hodgkin lymphoma (excluding those with HIV infection) and 1007 frequency-matched controls (matched by 5-year age group, sex, and geographical location of residence) (Charbonneau et al., 2013). A 103–food item, validated, self-administered FFQ (based on the 1995 revised Block questionnaire) was used. The definition of processed meat included hot dogs, ham, bologna, and lunchmeats. The multivariate-adjusted odds ratio for the highest compared with the lowest quartile of consumption (> 6 vs ≤ 0.9 servings/month, respectively) was 1.37 (95% CI, 1.02–1.83; P_{trend} = 0.03). Although the associations between processed meat consumption and follicular lymphoma, CLL/SLL, and DLBCL were all in the same direction and of the same magnitude as the association with non-Hodgkin lymphoma overall, none reached statistical significance.

(c) Meta-analyses

A recent meta-analysis of all cohort and case–control studies reporting on the relationship between red meat and/or processed meat consumption and non-Hodgkin lymphoma was conducted by Fallahzadeh et al. (2014). Although significant positive summary estimates were provided for both red meat consumption and processed meat consumption, and some disease subgroups, caution is warranted when interpreting these results. First, not all studies were included; six case–control studies were missing (Ward et al., 1994; De Stefani et al., 1998; Tavani et al., 2000; Hu et al., 2008, 2011; Balasubramaniam et al., 2013; Charbonneau et al., 2013), and one cohort study was missing (Chiu et al., 1996). In addition, one cohort study that was included was not eligible because there was no mention of red and processed meat consumption specifically (Erber et al., 2009), as the paper dealt with dietary patterns. The exposure categories were not comparable across studies. Therefore, this meta-analysis was not used to evaluate the evidence in regard to non-Hodgkin lymphoma.

2.9.2 Cancer of the liver (hepatocellular carcinoma)

(a) Cohort studies

(i) Red meat

See Table 2.9.1 (web only; available at: http://publications.iarc.fr/564)

Two informative prospective cohort studies reported on red and/or processed meat consumption and risk of cancer of the liver (hepatocellular carcinoma).

In the EPIC study, a large prospective cohort study in 10 European countries, red meat consumption was investigated in association with hepatocellular carcinoma (Fedirko et al., 2013). The cohort included 477 206 participants who were followed up for a mean of 11.4 years, resulting in the identification of 191 hepatocellular carcinoma cases, classified according to ICD-10. Diet was assessed over the previous 12 months with validated questionnaires on meals or food groups, and individual average portions or standard portions. Red meat included all fresh, minced, and frozen beef, veal, pork, mutton, lamb, horse, and goat. Red meat consumption was not associated with risk of hepatocellular carcinoma. The multivariate-adjusted hazard ratio for the highest quartile (> 63.4 g/day) compared with the lowest quartile (0–16.6 g/day) of red meat consumption was 1.25 (95% CI, 0.68–2.27; P_{trend} = 0.950). Additional adjustment

for hepatitis B and C infection was made possible through a nested case–control study, which also did not show an association between red meat and risk of hepatocellular carcinoma. [The Working Group noted that this was an important study because it was large with a wide range of intake.]

(ii) Processed meat

See Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

In the NIH-AARP study, previously described, processed meat consumption was also investigated in relation to risk of liver cancer incidence (Cross et al., 2007). Processed meat was defined as bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs, and low-fat hot dogs made from poultry. Processed meat consumption was not associated with risk of liver cancer incidence. The multivariate-adjusted relative risk of liver cancer for the highest quintile of processed meat consumption (median, 22.6 g/1000 kcal) compared with the lowest quintile of processed meat consumption (median, 1.6 g/1000 kcal) was 1.09 (95% CI, 0.77–1.53; P_{trend} = 0.82) (Freedman et al., 2010). [The Working Group noted that hepatitis B and C virus infection status was not likely to be an important confounder in these analyses.]

In the EPIC study, previously described, processed meat included mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, and heating (Fedirko et al., 2013). Processed meat included ham, bacon, sausages, salami, bologna, and corned beef, for example. Processed meat consumption was not associated with hepato-energy-cellular carcinoma. The multivariable energy-adjusted hazard ratio for the highest quartile (> 44.4 g/day) compared with the lowest quartile (0–11.4 g/day) of processed meat consumption was 0.90 (95% CI, 0.52–1.55; P_{trend} = 0.414). Additional adjustment for hepatitis B and C infection was made possible through a nested case–control study, which did not show an association between processed meat and hepatocellular carcinoma risk. [The Working Group noted that this was an important study because it was large with a wide range of intake.]

(b) Case–control studies

(i) Red meat

See Table 2.9.3 (web only; available at: http://publications.iarc.fr/564)

A hospital-based case–control study conducted in Italy (1999–2002) reported on the association between red meat consumption and hepatocellular carcinoma (Talamini et al., 2006b). The study included 185 incident cases and 412 controls. The controls were from the same hospitals and were matched to cases by age, sex, and study centre. An interview-based, validated FFQ covering the 2 years before diagnosis or hospital admission, and including 63 foods, food groups, or recipes was used. Red meat consumption was calculated from weekly serving sizes of beef, veal, pork, liver, pasta/rice with meat sauce, and lasagne/cannelloni. Red meat consumption was not significantly associated with risk of hepatocellular carcinoma. The multivariate-adjusted odds ratio for the highest (> 3.00 servings/week) compared with the lowest (< 1.50 servings/week) energy-adjusted quartile of red meat intake was 2.07 (95% CI, 0.88–4.82), and there was no linear trend (P_{trend} = 0.23). Adjustment included energy intake and the hepatitis virus. An earlier hospital-based case–control study was conducted in northern Italy (1983–1996) among 428 patients with histologically confirmed liver cancer (> 95% response rate) (Tavani et al., 2000). The control group comprised 7990 patients younger than 75 years admitted to the same network of hospitals as the cancer cases for a wide spectrum of acute non-neoplastic conditions. Red meat was defined as beef, veal, and pork. Lamb, horse, goat, and offal were not included in the questionnaire.

The associations were adjusted for age, year of recruitment, sex, education, smoking habits, and alcohol, fat, and fruit and vegetable intakes. There was no evidence of an association between red meat intake and liver cancer. The adjusted odds ratio for the highest tertile (≥ 7 times/week) compared with the lowest tertile (≤ 3 times/week) of intake was 0.8 (95% CI, 0.6–1.1). The adjusted odds ratio associated with an increase in intake of 1 average serving/day of red meat was 0.9 (95% CI, 0.7–1.1).

(ii) Processed meat

See Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

A hospital-based case–control study was conducted in Italy between 1999 and 2002 (Talamini et al., 2006b). The study included 185 incident cases. Of the cases, 78.2% were histologically or cytologically confirmed, and the remaining were diagnosed based on ultrasound, tomography, and elevated α-fetoprotein levels. The 412 controls were from the same hospitals, but excluded those in which hospital admission was related to alcohol and tobacco use or hepatitis viruses, or excluded those hospitalized for chronic diseases that might have led to substantial lifestyle modifications. The controls were matched to cases by age, sex, and study centre. An interview-based, validated FFQ covering the 2 years before diagnosis or hospital admission, and including 63 foods, food groups, or recipes was used. The processed meat and pork food group included pork, beef, veal, prosciutto, ham, salami, and sausages. Processed meat and pork consumption was not associated with hepatocellular carcinoma. The adjusted odds ratio for the highest (> 3.00 servings/week) compared with the lowest (< 1.25 servings/week) energy-adjusted quartile of processed/pork meat intake was 0.83 (95% CI, 0.40–1.70; P_{trend} = 0.86). Adjustment included energy intake and the hepatitis virus.

(c) Meta-analyses

A systematic literature review and meta-analysis published in 2014 (Luo et al., 2014) concluded that red meat consumption and processed meat consumption were not associated with hepatocellular carcinoma. [The studies were not restricted to those that were able to account for hepatitis B or C infection or to those that were able to adjust for potential confounders, such as alcohol consumption.] For red meat consumption, separate analyses by study type showed a null association for case–control studies (pooled RR, 0.97; 95% CI, 0.71–1.32; for the highest compared with the lowest pooled exposure groups) and a significant positive association for cohort studies (pooled RR, 1.43; 95% CI, 1.08–1.90; for the highest compared with the lowest pooled exposure groups). The more recent studies also tended to show a positive association compared with the older studies. A difference between study types was not reported for processed meat consumption, probably due to the small number of studies. [The Working Group noted that the comparison groups of meat consumption that were pooled across the studies varied substantially, which made it difficult to draw definite conclusions.]

2.9.3 Cancers of the gallbladder and biliary tract

(a) Cohort studies

No cohort studies were available to the Working Group.

(b) Case–control studies

See Table 2.9.3 (web only; available at: http://publications.iarc.fr/564)

One case–control study that investigated the association between red meat consumption and cancer of the gallbladder was found eligible by the Working Group. No studies looking into the consumption of processed meat in relation to cancer of the gallbladder were identified.

A hospital-based case–control study was conducted in northern Italy (1983–1996) among 60 patients with histologically confirmed gallbladder cancer (< 5% non-response) (Tavani et al., 2000). The control group comprised 7990 patients younger than 75 years admitted to the same network of hospitals as the cancer cases for a wide spectrum of acute non-neoplastic conditions. Dietary information was collected through a 40-item FFQ that was not validated, but showed a correlation of 0.61 for reproducibility of meat intake. Red meat was defined as beef, veal, and pork. Lamb, horse, goat, and offal were not included in the questionnaire. It was estimated that a serving of red meat in Italy was between 100 and 150 g. The associations were adjusted for age, year of recruitment, sex, education, smoking habits, and alcohol, fat, and fruit and vegetable intakes [BMI was not adjusted for]. There was no evidence of an association between red meat intake and gallbladder cancer. The adjusted odds ratio for the highest tertile (≥ 7 times/week) compared with the lowest tertile (≤ 3 times/week) of intake was 0.7 (95% CI, 0.3–1.4). The adjusted odds ratio associated with an increase in intake of 1 average serving/day of red meat was 0.6 (95% CI, 0.3–1.2).

2.9.4 Cancer of the testis

(a) Cohort studies

No cohort studies were available to the Working Group.

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

One case–control study that investigated the association between consumption of red meat and processed meat and cancer of the testis was found eligible by the Working Group.

A population-based case–control study was conducted in Canada (1994–1997) among 686 histologically confirmed cases and 5039 controls (Hu et al., 2008). The odds ratio for testicular cancer for the highest quartile of intake (≥ 6.1 servings/week) compared with the lowest quartile of intake (≤ 2 servings/week) of red meat was 1.1 (95% CI, 0.8–1.6; P_{trend} = 0.87). The analysis was adjusted for age (10-year age group), province, education, BMI, sex, alcohol use, pack-years of smoking, total vegetable and fruit intake, and total energy intake. The results for processed meat were based on the same numbers as those reported in two papers by Hu et al. (2008, 2011). Processed meat intake included intake from hot dogs, smoked meat, or corned beef; bacon and sausage. Processed meat consumption was significantly associated with an increased risk of testicular cancer. The multivariate-adjusted odds ratio for the highest quartile of intake (≥ 6.95 servings/week) compared with the lowest quartile of intake (≤ 1.41 servings/week) of processed meat was 1.5 (95% CI, 1.2–2.2; P_{trend} = 0.01). [The Working Group concluded that the main strength of this study was that it was a large case–control study, but little detail was provided on the number of cases per exposure category.]

2.9.5 Cancer of the kidney

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

There were three publications on red meat and processed meat consumption and risk of cancer of the kidney (renal cell carcinoma, RCC) based on prospectively collected large data sets: results from a pooled study of 13 prospective cohorts (Lee et al., 2008), results from the NIH-AARP study (Daniel et al., 2012b), and results from the EPIC study, which included 10 cohorts (Rohrmann et al., 2015). The studied populations were from North America, Europe, and Australia. The cohort study of Seventh-Day Adventists in California, USA, by Fraser et al. (1990) had only 14 RCC cases, and was not considered in this review. Only one study analysed

separately histological subtypes of RCC: clear cell and papillary RCC (Daniel et al., 2012b). All three publications from the prospective studies, based on 691–1814 incident cases of RCC, were informative.

A pooled analysis of 13 prospective studies (Lee et al., 2008) included 530 469 women and 244 483 men from the USA and Canada (nine cohorts), Europe (three cohorts), and Australia (one cohort) who were followed up for 7–20 years. The study was based on 1478 incident cases of RCC (709 in women, 769 in men). All cohorts used validated FFQs, and harmonized exposure and outcome data. Consumption of red meat (beef, pork, lamb, liver, and veal) was not associated with risk of RCC (P_{trend} = 0.93), and there was no heterogeneity between studies (between studies $P_{heterogeneity}$ = 0.75). However, there was a suggestion of heterogeneity of results observed for women and men (between studies $P_{heterogeneity}$ due to sex = 0.06); the relative risks for 80 g/day versus 20–60 g/day were 1.20 (95% CI, 0.93–1.55) for women and 0.88 (95% CI, 0.72–1.07) for men. Processed meat (sausage, bacon, hot dog, ham, and luncheon meat) was not associated with the risk (P_{trend} = 0.31), and there was no heterogeneity of results observed (between studies Pheterogeneity = 0.96; between studies $P_{heterogeneity}$ due to sex = 0.40). [The Working Group noted that all 13 cohorts used validated FFQs. The models were adjusted for age, total energy intake, BMI, pack-years of smoking, history of hypertension, fruit and vegetable intake, alcohol, and reproductive factors in women. The potential interaction with sex for red meat should be noted.]

The largest prospective study of RCC was based on the NIH-AARP study (Daniel et al., 2012b). The study included 176 179 men and 125 983 women who filled in a validated, 124-item FFQ and a second questionnaire (risk factor questionnaire) that included a validated meat-cooking (pan-fried, grilled or barbecued, oven-broiled, sautéed, baked, or microwaved) module at baseline (1995–1996). Over 9 years (mean) of follow-up, 1814 cases of RCC were diagnosed (including 498 clear cell and 115 papillary adenocarcinomas). There was no association between red meat (P_{trend} = 0.99) or processed red meat (P_{trend} = 0.16) and total RCC. A significant association was observed between red meat and an increased risk of papillary RCC (Q5 vs Q1 HR, 1.79; 95% CI, 0.94–3.42; P_{trend} = 0.008) and between processed meat and clear cell RCC (P_{trend} = 0.04). Haem iron intake was associated with a tendency towards an increased risk of RCC (HR, 1.15; 95% CI, 0.94–1.40; P_{trend} = 0.03; for quintile 5 vs quintile 1) and a 2.4-fold risk of papillary RCC (P_{trend} = 0.003). [Of note, the previously described study by Daniel et al. (2012b) with 1814 RCC cases was an extended update of the published report on RCC in the NIH-AARP cohort by Cross et al. (2007), which was based on 1363 cases diagnosed during up to 8.2 years of follow-up. Models were adjusted for age, education, BMI, total energy intake, smoking status, physical activity, family history of cancer, ethnicity, marital status, fruit and vegetable intake, and alcohol intake. Red and processed red meat were mutually adjusted, and adjusted for poultry and fish intake. Results were not modified by sex.]

Rohrmann et al. (2015) presented results from the EPIC cohorts, which included 335 014 women and 142 217 men from 10 European countries who were recruited between 1992 and 2000, and followed up to December 2008. Among the women and men, 691 incident RCC cases were identified. Meat consumption was assessed at baseline using validated, country-specific FFQs. In women, a high intake of red meat, which included beef, pork, mutton/lamb, horse, goat, and processed red meat, which included ham, bacon, sausages, and a small part of minced meat that had been bought as a ready-to-eat-product, had a significantly increased risk of RCC. The hazard ratios per 50 g/day of intake were 1.36 (95% CI, 1.14–1.62) for red meat and 1.78 (95% CI,

1.05–3.03) for processed red meat. No association was observed in men. After multivariate adjustment, a statistically significant interaction was observed between red meat consumption and sex ($P_{interaction}$ = 0.002), and a weaker interaction was observed for processed meat ($P_{interaction}$ = 0.06). Furthermore, for processed meat, the association with RCC incidence was prominent in premenopausal women and was lacking in postmenopausal women ($P_{interaction}$ = 0.02). [The Working Group noted that all 10 cohorts used validated FFQs. The models were adjusted for age, centre, education, BMI, total energy intake, smoking status and duration, history of hypertension, fruit intake, vegetable intake, and alcohol intake. The potential interaction with sex for red meat should be noted.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

Four population-based case–control studies (one in the USA, one in Canada, one in Europe, and one in Australia) and four hospital-based case–control studies (one in central Europe, one in Italy, and two in Uruguay) of RCC were eligible based on the criteria defined in the introduction of Section 2.9.

(i) Population-based

Wolk et al. (1996) reported results of a multicentre, population-based case–control study performed in Australia, Denmark, Sweden, and the USA. The study included 1185 incident, histologically confirmed RCC cases (698 men, 487 women) and 1526 controls frequency-matched to cases by sex and age (response rates were not reported). No association was observed with red meat or processed meat consumption; for both, the P_{trends} were not significant. However, a statistically significant association was observed with fried meat (OR, 1.44; 95% CI, 1.15–1.79; for fried/sautéed vs baked/roasted) and degree of "doneness" (for well done/charred/burnt vs rare + medium–rare OR, 1.24; 95% CI, 0.99–1.59; P_{trend} = 0.05). [The Working Group noted that specific definitions of red meat and processed meat were not presented. The limits/median values of intake amounts/frequencies were also not reported.]

Yuan et al. (1998) performed a population-based case–control study between 1986 and 1994 in a non-Asian population in Los Angeles, USA. The study included 1204 histologically confirmed RCC cases (70% diagnosed) and 1204 neighbourhood controls matched by sex, age (≤ 5 years), and ethnicity (69% first-eligible residents, and 19% second-eligible and 12% third-eligible controls). No association with processed meat (fried bacon/ham, salami/pastrami/corned beef, bologna, hot dogs/Polish sausage, and other luncheon meats) was observed (P_{trend} = 0.57). [The Working Group noted that a specific definition of processed meat was presented. There was a large number of cases and an acceptable response rate. The model was adjusted for BMI and smoking, but not for energy intake.]

Hu et al. (2008) studied 1345 RCC cases (727 men, 618 women) diagnosed between 1994 and 1997 in eight provinces in Canada. RCC was one of 19 cancer types studied (56.3% response rate for all ascertained cancers and 69.7% response rate for all contacted cancers), and 5039 controls (62.1% response rate and 66.8% response rate, respectively) were randomly selected within the age and sex groups of the population. A self-administered, 69-item FFQ was used (modified version of the validated Block questionnaire), and diet 2 years before the study was assessed. Among the 1345 renal cell cancer patients, the mean (SD) intake of red meat was 4.7 (4.8) servings/week, and the mean (SD) intake of processed meat was 4.7 (7.7) servings/week. Red meat (beef, pork, or lamb as a main dish or as a mixed dish, and hamburger) was not associated with an increased risk of RCC (P_{trend} = 0.21). Processed meat (hot dogs, smoked meat, corned beef; bacon and sausage) was associated with a statistically

significant increased risk of RCC (Q4 vs Q1 OR, 1.3; 1.1–1.6; P_{trend} = 0.02). [The Working Group noted that specific definitions of red meat and processed red meat were presented. The response rate was relatively low, and there was a large number of cases. Models were adjusted for energy intake, BMI, smoking, alcohol, fruit and vegetables, and other variables.]

Grieb et al. (2009) studied 335 RCC cases (69% response rate) and 337 population-based controls (42% response rate). Controls were frequency-matched to cases by sex, age (≤ 5 years), and ethnicity. A validated, 70-item Block FFQ was used. Consumption of red meat (beef steaks, pot roasts, and ground meat) was associated with a significantly increased risk of RCC among all subjects (OR, 4.43; 95% CI, 2.02–9.75; P_{trend} < 0.001) for ≥ 5 times/week versus < 1 time/week and among women (OR, 3.04; 95% CI, 1.60–5.79; P_{trend} < 0.001) for ≥ 3 times/week versus < 1 time/week. A significant RCC risk was also observed among women who consumed bacon and breakfast sausages (i.e. processed meat) ≥ 3 times/week versus < 1 time/week (OR, 1.87; 95% CI, 0.88–3.96; P_{trend} = 0.03). [The Working Group noted that a specific definition of red meat was presented. The number of cases was limited, and there was a low response rate among controls. The model was adjusted for BMI and smoking, but not for energy intake.]

(ii) Hospital-based

A multicentre study (Hsu et al., 2007) was performed in eastern and central European countries (in the Russian Federation, Romania, Poland, and the Czech Republic). The study included 1065 incident RCC cases (622 men, 443 women; 90–98.6% response rates across study centres) and 1509 hospital-based controls (90.3–96.1% response rates). Controls were hospitalized for conditions unrelated to smoking or genitourinary disorders, and were frequency-matched by age. A 23-item FFQ was used. A high consumption of red meat (beef, pork, lamb) was associated with an increased risk (OR, 2.01; 95% CI, 1.02–3.99; P_{trend} < 0.01), but consumption of processed meat (ham, salami, sausages) was not associated with an increased risk (OR, 1.03; 95% CI, 0.71–1.51). [The Working Group noted that specific definitions of red meat and processed meat were presented. A short FFQ with 23 food items was validated during the pilot stage, and response rates were high in cases and controls. Models were adjusted for age, BMI, smoking, alcohol, vegetables, and other variables, but not for energy intake.]

Bravi et al. (2007) reported results from a case–control study in northern, central, and southern Italy that was performed in 1992–2004. The study included 767 incident, histologically confirmed RCC cases (494 men, 273 women; > 95% response rate) and 1534 controls (matched 1:2). Controls were admitted to the same hospitals for acute non-neoplastic conditions not related to long-term diet modifications. An interviewer-administered FFQ included 78 foods and beverages. Red meat consumption was not associated with an increased risk (P_{trend} = 0.17). Processed meat was associated with a decreased risk (OR, 0.64; 95% CI, 0.45–0.90; P_{trend} = 0.006). [Specific definitions of red meat and processed meat were not presented. The 78-item FFQ was validated, and there were high response rates in cases and controls. Models were adjusted for period of interview, years of education, age, BMI, smoking, alcohol, family history of kidney cancer, and energy intake.] The study by Tavani et al. (2000), which was performed earlier (1983–1996) in the same study area of northern Italy, and included 190 kidney cancer cases and 7990 controls, did not demonstrate any association between consumption of red meat and risk of kidney cancer (P_{trend} = 0.55).

Aune et al. (2009) reported the results of a multisite cancer case–control study performed in 1996–2004 in Uruguay. The study included 114 RCC cases (94.5% response rate for all cancer sites) and 2032 hospital controls (96% response

rate). A high intake of red meat was associated with RCC risk. For T3 (≥ 250 g/day; 18 cases) versus T1 (< 150 g/day; 53 cases), the odds ratio was 2.72 (95% CI, 1.22–6.07; P_{trend} = 0.06). There was no association with processed meat (P_{trend} = 0.52).

Data from essentially the same study (114 RCC cases, 2532 controls) were analysed separately for men and women by De Stefani et al. (2012). There was a suggestion of an increased risk with processed meat intake among women (for T3 vs T1 OR, 2.15; 95% CI, 0.90–5.13; P_{trend} = 0.07), but not among men (P_{trend} = 0.51). Mean consumption of processed meat was 25.3 g/day in men and 33.9 g/day in women. [The Working Group noted that specific definitions of red meat and processed meat were not presented. The FFQ was not validated. There was a high response rate, but a limited number of cases. The model was adjusted for BMI, smoking, fruit and vegetables, other dietary factors, and energy intake.]

(c) Meta-analyses

The results from a meta-analysis by Alexander & Cushing (2009) of total red meat (not considered here) and processed meat consumption and RCC risk were based on 16 prospective studies (three individual cohorts and one pooled analysis of 13 cohorts) and seven case–control studies. Meta-analysis of processed meat consumption based on the cohorts (n = 3) showed a statistically significant increased risk of RCC with high intake ($RR_{summary}$ for high vs low intake, 1.19; 95% CI, 1.03–1.37; $P_{heterogeneity}$ = 0.984). The summary relative risk of seven case–control studies did not show an increased risk with processed meat consumption (highest vs lowest category $RR_{summary}$, 1.01; 95% CI, 0.83–1.23; $P_{heterogeneity}$= 0.028).

The results from two large cohorts (NIH-AARP and EPIC) (Daniel et al., 2012b; Rohrmann et al., 2015) were published after the meta-analysis. [The Working Group noted that some studies suggested that a positive association may be present in women only and may be confined to papillary adenocarcinoma only. Meat-cooking methods may also be associated with an increased RCC risk. However, these hypotheses were tested in very few/single studies, and the evidence was very limited.]

2.9.6 Cancer of the bladder

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

Five cohort studies were published on incidence of cancer of the bladder in relation to red meat and processed meat consumption. Two were performed in Europe (one in Sweden and the other was the EPIC study in 10 European countries), two were performed in the USA, and one was performed in Japan. One study was based on long-term diet and took into account changes in food consumption over time, and four studies had only baseline dietary information available. All studies presented results for red meat and processed meat separately.

The most informative four cohorts were published by Michaud et al. (2006), based on long-term diet; Larsson et al. (2009), based on 485–1001 incident cases; Ferrucci et al. (2010); and Jakszyn et al. (2011). The study by Nagano et al. (2000) included only 114 incident cases, and red meat was not specified.

The study by Michaud et al. (2006), which included data from the Health Professionals Follow-up Study (HPFS) (47 422 men) and the Nurses' Health Study (NHS) (88 471 women), was based on long-term diet (repeated validated FFQs over time). During up to 22 years of follow-up of the two American cohorts, 808 incident bladder cancer cases (504 in men, 304 in women) were confirmed, including in situ cancers. No associations were observed between risk of bladder cancer and red meat (beef, pork, lamb) as a main dish (P_{trend} = 0.35) and as a mixed dish (P_{trend} = 0.52).

There were no associations with consumption of processed meat, including sausage, salami, bologna, etc. (P_{trend} = 0.81); hot dogs (P_{trend} = 0.47); or hamburger (P_{trend} = 0.17). However, there was a statistically significant association with bacon intake of ≥ 5 servings/week versus no consumption (RR, 2.10; 95% CI, 1.24–3.55; P_{trend} = 0.006), which was confined to never-smokers only (men and women). [The Working Group noted that the analyses were based on long-term consumption and adjusted for age, energy intake, pack-years of smoking, geographical region, and total fluid intake. Stratified analyses of bacon (only) by smoking status were performed.]

Another cohort study (Ferrucci et al., 2010), based on the NIH-AARP study of 300 933 American men and women who filled in a validated, 124-item FFQ, included 854 bladder cancer cases diagnosed during 7 years of follow-up. There was no increased risk with processed meat (bacon, sausage, luncheon meats, ham, and hot dogs) (P_{trend} = 0.55). There was no evidence of effect modification for the meat exposures by smoking (data were not reported). [The Working Group noted that red meat was not analysed separately. Analyses were adjusted for age, energy intake, fruit, vegetables, beverages, and detailed smoking status. Stratified analyses by smoking status were performed.]

The two cohort studies in Europe – one was in Sweden and was based on the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men, which included 485 bladder cancer cases diagnosed during 9.4 years of follow-up of 82 002 men and women (Larsson et al., 2009), and the other was the EPIC study in 10 European countries (Jakszyn et al., 2011), which included 1001 cases diagnosed during 8.7 years of follow-up of 481 419 participants – did not support the hypothesis that red meat or processed meat consumption is associated with an increased risk of bladder cancer. [The Working Group noted that, in the Swedish cohort, red meat (beef, pork, veal; hamburger and meatballs; liver and kidney) and processed meat (ham, salami, sausage, and cold cuts) were clearly defined. In the two cohorts, risk estimates were adjusted for age, sex, education, energy intake, and detailed history of smoking status. The EPIC study additionally adjusted for the study centre. In the EPIC study, red meat included fresh and processed meat.]

Nagano et al. (2000) did not observe an association between consumption of red meat (not specified) and processed meat (ham/sausage) and bladder cancer incidence. Study subjects who filled in a 22-item FFQ were members of the Life Span Study (LSS) cohort, which included 38 540 atomic bomb survivors, among whom 114 bladder cancers were diagnosed during up to 14 years of follow-up. [The Working Group noted that the study was performed in a general population. The definition of red meat was not specified, and the study was limited by low statistical power.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

The Working Group identified 11 case–control studies that investigated the association between red and processed meat consumption and bladder cancer; eight of the studies were in men and women, and three of the studies were in men only. Men and women were studied in three population-based studies (two from the USA, one from Canada) and five hospital-based studies (two from Europe, one from the USA, one from China, one from Japan); three of the hospital-based studies (two from Spain, one from Uruguay) were in men only. Nine of the eleven studies presented results for both red meat and processed meat separately.

(i) Population-based

Hu et al. (2008) studied 1029 bladder cancer cases (56.3% response rate for ascertained and 69.7% response rate for contacted) and

5039 controls (62.1% response rate and 66.8% response rate, respectively). The controls were randomly selected within the age and sex groups of the population in eight Canadian provinces. A self-administered, 69-item FFQ was used (a modified version of the validated Block questionnaire), and diet 2 years before the study was assessed. Red meat (beef, pork, or lamb as a main dish or as a mixed dish, and hamburger) and processed meat (hot dogs, smoked meat, corned beef; bacon and sausage) were both associated with a statistically significant increased risk of bladder cancer. For Q4 versus Q1, the odds ratios were 1.3 (95% CI, 1.0–1.7; P_{trend} = 0.04) and 1.6 (95% CI, 1.2–2.1; P_{trend} < 0.0002), respectively. The mean (SD) intake of red meat was 4.7 (3.6) servings/week, and the mean (SD) intake of processed meat was 4.9 (6.5) servings/week. No difference was observed by smoking status. [The Working Group noted that specific definitions of red meat and processed meat were presented, but the response rate was relatively low. Analyses were adjusted for energy intake, BMI, smoking, alcohol, fruit and vegetables, and other variables. Analyses by smoking status were performed.]

Wu et al. (2012) presented a population-based study in three states in north-eastern USA (2001–2004). The study included 1171 cases (65% response rate) and 1418 controls (65% eligible) frequency-matched by state, sex, and age (5-year groups). Diet was assessed with a validated, self-administered, 124-item Block DHQ. Red meat (beef, veal, pork, and lamb) was not associated with an increased risk of cancer of the bladder (P_{trend} = 0.258). Processed meat (ham, bacon, sausage, hot dog, and cold cuts) was associated with a statistically significant increased risk (median for Q4 vs Q1, 13.5 vs 1.9 g/1000 kcal, OR, 1.41; 95% CI, 1.08–1.84; P_{trend} = 0.024). No difference by smoking status was observed. No association with meat-cooking methods was observed. [The Working Group noted that specific definitions of red and processed red meat were presented, but the response rate was relatively low. Analyses were adjusted for energy intake, BMI, smoking, and other variables. Stratified analyses by smoking status were performed.]

Catsburg et al. (2014) reported results from the population-based Los Angeles Bladder Cancer Study (1987–1996). The study included non-Asian individuals, and 1660 cases (80% response rate) and 1586 controls (95% response rate) matched by age (5-year), sex, and ethnicity. Assessment of usual adult dietary habits covered the consumption of 40 food groups 2 years before the in-person interview. Processed meat consumption (fried bacon, ham, salami, pastrami, corned beef, bologna, hot dogs, Polish sausage, and other lunchmeats, including red or white processed meats) was not associated with risk of bladder cancer (P_{trend} = 0.846). However, there was a statistically significant positive association observed with intake of salami/pastrami/corned beef (for weekly vs < 2 times/year OR, 1.95; 95% CI, 1.10–3.46; P_{trend} = 0.006) and liver (for 4–11 times/year vs never OR, 1.76; 95% CI, 1.09–2.85; P_{trend} = 0.016), particularly among non-smokers. Haem iron intake was also associated with an increased risk of bladder cancer among never-smokers only. For Q5 (≥ 5.2 mg/day) versus Q1 (≤ 1.0 mg/day), the odds ratio was 1.97 (95% CI, 1.16–3.33; P_{trend} = 0.010). Results from this study suggested that consumption of meat with a high amine and haem content, such as salami and liver, may be associated with an increased risk of bladder cancer. [The Working Group noted that the definition of processed meat was clearly specified. This was a large study with a high response rate. It was a strength that analyses were stratified by smoking status, and were adjusted for BMI, and other variables. Adjustment was made for total servings of food per day rather than energy intake. Red meat included corned beef (i.e. processed meat).]

(ii) Hospital-based

Riboli et al. (1991) conducted a multicentre study in Spain (1983–1986) that included 432 male cases (71.9% response rate) and 792 controls (hospital-based, 70.5% response rate; population-based, 65.7% response rate) matched by sex, age (5-year groups), and area of residence. No statistically significant association was observed with red meat (beef, pork, lamb) (Q4 vs Q1 OR, 0.67; 95% CI, 0.46–0.96; P_{trend} = 0.06) and processed meat (Q4 vs Q1 OR, 1.20; 95% CI, 0.82–1.75; P_{trend} = 0.22). [The Working Group noted that processed (cured) meat was not specified. The study used a validated, French questionnaire that was modified/adapted to Spanish food habits. The response rate was acceptable, and models were adjusted for smoking and energy intake. There was no stratification by smoking.]

The study by Tavani et al. (2000) was performed in 1983–1996 in northern Italy, and included 431 bladder cancer cases and 7990 controls (non-neoplastic patients from the same hospitals). The response rate was > 95% for both cases and controls. Red meat (beef, veal, pork) was marginally associated with bladder cancer (per 1 serving/day OR, 1.3; 95% CI, 1.0–1.6; $P_{trend} \leq 0.01$). [The Working Group noted the high response rate. The model was not adjusted for total energy intake, but was adjusted for smoking, and fat, alcohol, and fruit and vegetable intakes. It was not stratified by smoking.]

García-Closas et al. (2007) conducted a study that included 912 cases (63% eligible) and 873 hospital controls (69% response rate) from five different areas in Spain (1998–2001). A validated, 127-item FFQ was used. Neither red meat (beef, veal, lamb, pork) nor processed meat was associated with risk of bladder cancer (P_{trend} = 0.09 and 0.66, respectively). Meat-cooking method, doneness level, or HAA intake were not significantly associated with risk. [The Working Group noted that a definition of red meat was presented, but processed meat was not defined. The FFQ was validated, but dietary data collection was performed by different ways: 49% of the FFQs were administered with the help of a relative, 34% were self-administered, and 17% were administered by the interviewer. Of the FFQs, 39% were completed while in the hospital, and 61% were completed at home a few days after discharge. The response rate was not high. It was adjusted for smoking and fruit and vegetables, but not for energy. There was no stratification by smoking.]

Lin et al. (2012) recruited 884 newly diagnosed and histologically confirmed bladder cancer patients from the University of Texas MD Anderson Cancer Center and Baylor College of Medicine (92% response rate) in the USA, and 878 healthy clinic-based controls when they arrived for annual physical examinations (76.7% response rate). Controls were frequency-matched by age (5-year groups), sex, and ethnicity. The study was performed from 1999 to 2009. A validated, 135-item FFQ including questions on meat-cooking methods was administered by research interviewers to assess diet during the year before the interview. Consumption of red meat (beef, veal, lamb, pork, and game) was associated with a statistically significant increased risk (OR, 1.95; 95% CI, 1.41–2.68) for the highest versus the lowest quartile (P_{trend} < 0.001). In analyses stratified by smoking, a higher risk was observed among heavy smokers (for Q4 vs Q1 OR, 2.22; 95% CI, 1.34–3.68), but there was no statistically significant interaction. No association was observed with processed meat (hot dogs or franks, sausage, or chorizo) intake. In a subset of 177 cases and 306 controls with available data on estimates of dietary intake of HAAs, the odds ratio was 3.32 (95% CI, 1.37–8.01) for Q4 (≥ 239 ng/day) versus Q1 (≤ 52 ng/day) of total HAAs (P_{trend} = 0.003). [The Working Group noted that specific definitions of red meat and processed meat were presented. The study included around 900 cases, and the response rate was high. Analyses were adjusted for energy intake, smoking, and

ethnicity. Stratified analyses of red meat by smoking status were performed.]

Another case–control study of men was performed in Uruguay in 1996–2004 (Ronco et al., 2014). The 225 cases (97.8% response rate) and 1510 hospital controls (97.1% response rate) were interviewed face to face, and reported on their frequency of consumption of 64 food items. Red meat (beef, lamb) intake was not associated with an increased risk (P_{trend} = 0.33). Consumption of processed meat (bacon, sausage, mortadella, salami, saucisson, hot dog, ham, salted meat) was associated with an increased risk (OR, 1.55; 95% CI, 1.07–2.24) for tertile 3 versus tertile 1 (amounts were not specified) (P_{trend} = 0.018). [The Working Group noted that clear definitions of red meat and processed meat were presented. The FFQ was not validated, and there was a high response rate. The analysis was adjusted for energy intake, BMI, smoking, alcohol, fruit and vegetables, and other variables. It was not stratified by smoking.]

Small studies of men and women, one in Serbia including 130 cases and 130 hospital controls (Radosavljević et al., 2005), and one in Japan including 124 cases and 620 hospital controls (Wakai et al., 2004), were given less weight by the Working Group in the evaluation of the total evidence due to the small number of cases.

(c) Meta-analysis

The meta-analysis of red meat consumption in relation to bladder cancer risk by Li et al. (2014) included five cohorts and nine case–control studies. The summary results of the five cohort studies (4814 bladder cancer cases, 1 494 283 total population) did not show a significant association ($RR_{summary}$ for high vs low intake, 1.08; 95% CI, 0.97–1.20; $P_{heterogeneity}$ = 0.236) between red meat consumption and bladder cancer risk. The summary results of the nine case–control studies (4270 bladder cancer cases, 26 025 controls) for the highest compared with the lowest category of red meat consumption showed a $RR_{summary}$ of 1.23 (95% CI, 0.91–1.67; $P_{heterogeneity}$ < 0.0001).

The meta-analysis of processed meat consumption in relation to risk of bladder cancer was based on five cohorts and six case–control studies (Li et al., 2014). The summary results of the five cohort studies (3927 bladder cancer cases, 1 051 404 total population) did not show a significant association ($RR_{summary}$ for high vs low intake, 1.08; 95% CI, 0.96–1.20; $P_{heterogeneity}$ = 0.553). The summary results of the six case–control studies (3635 bladder cancer cases, 17 151 controls) for the highest compared with the lowest category of processed meat consumption showed a statistically significant increased risk ($RR_{summary}$, 1.46; 95% CI, 1.10–1.95; $P_{heterogeneity}$ = 0.002).

Overall, no significant association was observed in the summary risk estimates of the cohort studies for red meat or processed meat, and no heterogeneity was observed between the cohorts. In contrast, the summary risk estimates based on the case–control studies were higher (statistically significant $RR_{summary}$ for processed meat), and highly significant heterogeneity of results was observed between the case–control studies, both for red meat and processed meat.

Of note, a summary of studies from North and South America (three cohorts and four case–control studies), both on red meat and processed meat, showed a statistically significant increased risk of bladder cancer with high versus low consumption. The summary relative risks were 1.25 (95% CI, 1.02–1.54) and 1.33 (95% CI, 1.06–1.67), respectively (for both, between studies $P_{heterogeneity}$ = 0.001). No published meta-analyses stratified by smoking status were available.

2.9.7 Cancer of the ovary

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

Seven cohort studies addressed the incidence of cancer of the ovary in relation to red meat and/or processed meat intake. The studies were performed in the USA (four studies) and Europe (three studies), and were published between 1999 and 2011.

There were two cohorts with repeated dietary assessments: the NHS (Bertone et al., 2002) and the SMC (Larsson & Wolk, 2005). The cohorts included 15–17 years of follow-up and around 300 ovarian cases each. Three other cohorts, two from Europe (EPIC study) (Schulz et al., 2007; Gilsing et al., 2011) and one from the USA (Cross et al., 2007), including 340–581 cases with 8–16 years of follow-up, had only baseline information about diet. Results from the other two cohorts were not informative because they lacked specific information about red meat consumption (Kushi et al., 1999) or had a low number of cases (only 71 in Seventh-Day Adventist women) (Kiani et al., 2006).

The study by Bertone et al. (2002) was conducted in the USA between 1980 and 1996, with repeated dietary assessments (1980, 1984, 1986, and 1990), and included 301 incident cases of invasive epithelial ovarian cancer among 80 258 women. Consumption of red meat as a main dish (beef, pork, lamb) was not statistically significantly associated with an increased risk of ovarian cancer. The relative risk for consumption ≥ 2 times/week versus 1–3 times/month was 1.30 (95% CI, 0.93–1.82; P_{trend} = 0.16). [The Working Group noted that red meat was defined, and processed red meat was not studied. Long-term diet was assessed. Models were adjusted for age, reproductive factors, smoking status, and tubal ligation. There was adjustment for energy intake, but no adjustment for other types of meats.]

Larsson & Wolk (2005) used data from the SMC, which included follow-up from 1987 to 2004, and dietary assessments in 1987 and 1997. During an average follow-up of 14.7 years, invasive epithelial ovarian cancer was diagnosed in 288 of 61 057 women. Red meat as a main dish (beef, pork) was not associated with an increased risk of this cancer (P_{trend} = 0.27). None of the individual red meat or processed meat items were associated with ovarian cancer (all P_{trends} > 0.24). [The Working Group noted that the definition of red meat that was presented may have included processed meat. Models were adjusted for age, energy intake, BMI, education, reproductive factors, and intake of fruit, vegetables, and dairy products. They were not adjusted for other types of meats.]

Schulz et al. (2007) analysed data from the EPIC study (325 731 women from 10 European countries), which included follow-up to 2004, and baseline dietary assessment between 1992 and 2000. Primary invasive ovarian cancers were diagnosed in 581 participants. No association was observed with red meat (P_{trend} = 0.89) or with processed meat (P_{trend} = 0.23). [The Working Group noted that definitions of red meat and processed meat were not presented. Models were adjusted for age, BMI, energy intake, reproductive factors, smoking, education, and unilateral ovariectomy; there was no mutual adjustment for type of meat.]

In a study by Cross et al. (2007), an American cohort (NIH-AARP) established in 1995–1996 including 199 312 women who were followed up through 2003, 552 ovarian cancers were diagnosed. The findings were not significant for consumption of processed meat, which included bacon, cold cuts (red and white meat), ham, hamburger, hot dogs (regular and from poultry), sausages (red and white meat), luncheon meats (red and white) (P_{trend} = 0.30), as reported at baseline.

Gilsing et al. (2011) used data from the Netherlands Cohort Study (NLCS), which included 62 573 postmenopausal women at baseline in 1986, among whom 340 were diagnosed with ovarian cancer during 16.3 years of follow-up. No association was observed between consumption of red meat, including beef, pork, minced meat, and liver (P_{trend} = 0.85), or

processed meat (P_{trend} = 0.74) and risk of ovarian cancer. [The Working Group noted that red meat items were specified, but not processed meat. The model adjusted for age, energy intake, and reproductive factors.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

The Working Group identified seven case–control studies suitable for inclusion. The studies were from Australia, Canada, the USA, Italy, and China. Four of the studies were population-based. Only two of the seven studies, both population-based, presented results for red meat and processed meat separately.

(i) Population-based

Shu et al. (1989) reported results from a population-based case–control study (1984–1986) from Shanghai. The study included 172 histologically confirmed epithelial ovarian cancer cases (75.1% response rate) and 172 randomly selected population controls matched within 5-year age groups (100% response rate). Information on usual adult consumption of 63 common foods was collected through face-to-face interviews by trained interviewers. No association was observed with consumption of red meat (pork, spare ribs, pigs' feet, salted pork, pork liver, beef, and lamb), adjusted for education (P_{trend} = 0.19). [The Working Group noted that processed red meat was not studied separately, and salted pork was included in the red meat category. The model (conditional logistic regression) was adjusted only for education, and not for energy intake.]

McCann et al. (2003) conducted a population-based case–control study of diet and ovarian cancer in western New York. The study involved 124 primary, histologically confirmed ovarian cancer cases and 696 controls frequency-matched by age and county of residence. Diet in the 12-month period 2 years before the study was assessed with a detailed FFQ by in-person interview. Red meat intake (not specified if processed meat was included) was not statistically significantly associated with risk of ovarian cancer. [The Working Group noted that a specific definition of red meat was not presented. The response rate was not specified. There was a small number of cases. The model was adjusted for several variables and for energy intake.]

Pan et al. (2004) reported results from a population-based case–control study performed in seven of 10 provinces in Canada. The 442 incident, histologically confirmed cases were diagnosed between 1994 and 1997, and participated in the study (68.6% eligible). The frequency-matched control selection varied by province, depending on the availability of different provincial registries. Random samples stratified by age were selected (2135 controls represented 65% of contacted women). A self-administered, 69-item FFQ was used (a modified version based on the validated Block and NHS FFQs), and diet 2 years before the study was assessed. No association was observed with red meat (beef, pork, or lamb as a main dish or as a mixed dish; stew or casserole, pasta dish; and hamburger) (P_{trend} = 0.10) or processed meat (hot dogs, smoked meat, or corned beef; bacon and sausage) (P_{trend} = 0.82). Of note, these data (442 cases) were reanalysed by Hu et al. (2008) with the same results (P_{trend} = 0.83 and 0.72, respectively). [The Working Group noted that the definitions of red meat and processed meat were presented by Hu et al. (2008). The model was adjusted for BMI, smoking, other variables, and energy intake.]

Kolahdooz et al. (2010) analysed data from two combined population-based case–control studies in Australia. The analyses included 2049 cases and 2191 controls. Response rates in the first study (Survey of Women's Health, SWH, 1990–1993) were 90% among eligible cases and 73% among controls. Response rates in the second study (Australian Ovarian Cancer Study, AOCS, 2002–2005) were 85% and 47%, respectively. Controls in both studies were randomly

selected from the electoral roll, and matched by state of residence and 5-year age group. Dietary information was collected using validated instruments, via face-to-face interviews in SWH and self-administered in AOCS. No association was observed between consumption of red meat (beef, lamb, pork as a main dish or as a mixed dish) and risk of ovarian cancer (≥ 7 servings/week vs < 3 servings/week OR, 1.07; 0.80–1.42; P_{trend} = 0.5). Women with the highest consumption of processed meat (≥ 4 vs < 1 serving/week) had an increased risk (OR, 1.18; 95% CI, 1.15–1.21; P_{trend} = 0.03). Liver consumption was also associated with an increased risk (for ≥ 1 vs < 1 serving/month OR, 1.48; 95% CI, 1.20–1.81; P_{trend} = 0.002). [The Working Group noted that a specific definition was presented for red meat, but not for processed meat. The FFQ was validated. There was a low response rate among controls in the AOCS study. The model was adjusted for several factors (age, oral contraceptives, education, parity) and for energy intake.]

(ii) Hospital-based

Tavani et al. (2000) reported results from a multisite cancer case–control study performed in northern Italy in 1983–1996. The study included 971 cases of ovarian cancer (> 95% response rate) and 4470 hospital-based controls (> 95% response rate). The women were asked to fill in a 40-item FFQ. Consumption of red meat (beef, veal, pork) was associated with a significantly increased risk (OR, 1.3; 95% CI, 1.1–1.5 per increment of 1 portion/day; $P_{trend} \leq 0.01$). Processed meat was not studied. The model was adjusted for age, education, smoking, and alcohol, fat, fruit, and vegetable intakes. [The Working Group noted that a specific definition of red meat was presented. The 40-item FFQ was not validated. There was a high response rate among cases and controls. The model was not adjusted for energy intake.]

The study by Zhang et al. (2002), performed in China in 1999–2000, included 254 histologically confirmed ovarian cancer cases and 652 controls (mainly hospital visitors and non-neoplastic outpatients). The response rate was high (> 95%), and a 120-item FFQ was used. No linear association was observed with "fresh meat" consumption. The odds ratios were 1.78 (95% CI, 1.00–3.20) for the second quartile (7.50–13.20 vs ≤ 7.45 kg/year), 1.98 (95% CI, 1.10–3.60) for the third quartile, and 1.98 (95% CI, 1.00–3.80) for the fourth quartile (≥ 22.75 vs ≤ 7.45 kg/year). The model was adjusted for energy intake. [The Working Group noted that "fresh meat" was not specified, but was probably red meat because poultry was analysed separately. There was a high response rate.]

Di Maso et al. (2013) published a large hospital-based study performed in 1991–2009 in Italy and Switzerland (1031 ovarian cancer cases, 2411 non-neoplastic hospital controls). Response rates were similar among cases and controls (85–98%). A validated FFQ was used. A statistically significant positive association with consumption of red meat (beef, veal, pork, horse meat, and mixed red meat dishes) was observed (per increase of 50 g/day OR, 1.29; 95% CI, 1.16–1.43; $P_{trend} < 0.01$). When analysed by menopausal status, this was restricted to postmenopausal women. Cooking practices influenced the observed associations. The odds ratios were 1.33 (95% CI, 1.12–1.57) for an increase of 50 g/day of roasted/grilled red meat, 1.48 (95% CI, 1.19–1.84) for an increase of 50 g/day of boiled/stewed red meat, and 1.96 (95% CI, 1.34–2.87) for an increase of 50 g/day of fried/pan-fried meat. However, the test for heterogeneity between the observed risks for different cooking methods was not significant (P = 0.18). The model was adjusted for several factors, including age, education, BMI, smoking, alcohol, and vegetable and fruit intake. [The Working Group noted that a specific definition of red meat was presented. The FFQ was validated. There was a high response rate. The model was not adjusted for energy intake.]

(c) Meta-analyses

Results from a dose–response meta-analysis that quantitatively summarized eight prospective cohorts (Wallin et al., 2011) and included together 2349 incident ovarian cancer cases did not show a statistically significant association between red meat or processed meat and risk of ovarian cancer. For an intake increment of 4 servings/week, the summary relative risks of ovarian cancer were 1.07 (95% CI, 0.97–1.19) for red meat (100 g/serving) and 1.07 (95% CI, 0.97–1.17) for processed meat (30 g/serving). No heterogeneity between the studies was observed in red meat ($P_{heterogeneity}$ = 0.972) or processed meat ($P_{heterogeneity}$ = 0.647) analyses. Results from this dose–response meta-analysis suggested that consumption of red and processed meat was not associated with risk of ovarian cancer.

2.9.8 Cancer of the endometrium

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

Five prospective cohort studies on incidence of cancer of the endometrium in relation to red meat and processed meat consumption were published in 1995–2013. Two were performed in the USA, two were performed in Canada, and one was performed in Sweden. Four studies presented results for red meat and processed meat separately, and one presented results for red meat only and for haem iron. One of the studies used information on long-term diet.

Only two cohort studies were informative. The studies included 720 incident endometrial cancer cases (long-term diet) (Genkinger et al., 2012) and 1486 incident endometrial cancer cases (Arem et al., 2013). Two other studies did not specify the definition of red meat (Zheng et al., 1995; Kabat et al., 2008), and one had limited statistical power (van Lonkhuijzen et al., 2011); these studies are only described in the tables.

Genkinger et al. (2012) reported results from the Swedish prospective cohort (SMC), which included 60 895 women who filled in a validated, 67-item FFQ at baseline in 1987–1990, and 39 227 of them also filled in a 96-item FFQ in 1997. During 21 years of follow-up, 720 women developed endometrial cancer. Red meat (hamburgers, meatballs, beef, pork, and veal) and processed meat (sausage, hot dogs, bacon, ham, salami, lunchmeat, and blood pudding/sausage) were not significantly associated with an increased risk (P_{trend} = 0.11 and 0.12, respectively). Liver consumption was associated with an increased risk (HR, 1.29; 95% CI, 1.06–1.56; for intake of ≥ 100 vs < 100 g/week). Haem iron intake based on updated long-term consumption was associated with an increased risk (HR, 1.24; 95% CI, 1.01–1.53; for highest vs lowest quartile; P_{trend} = 0.03). [The Working Group noted that exposure was well defined. In addition, there was long-term dietary assessment with a validated FFQ, and a relatively large number of incident cases. Models were adjusted for age, energy intake, BMI, parity, and education.]

The largest prospective study of endometrial cancer was based on the NIH-AARP study (Arem et al., 2013). The study included 111 356 women who filled in a validated, 124-item FFQ, and 67% of them also filled in a second questionnaire (risk factor questionnaire) that included a validated meat-cooking (pan-fried, grilled or barbecued, oven-broiled, sautéed, baked, or microwaved) module at baseline in 1995–1996. During a mean follow-up of 9.3 years, 1486 cases of endometrial cancer were diagnosed. Consumption of red meat (beef, pork, hamburger, steak, and liver) and processed meat (bacon, cold cuts, ham, hot dogs, and sausage) was not associated with risk of endometrial cancer (P_{trend} = 0.45 and 0.70, respectively). No association with cooking-related mutagens was observed. [The Working Group noted that this study had the largest number of cases, with detailed questions on cooking methods and well-defined exposure.

The model adjusted for age, energy intake, BMI, and smoking status, and mutually adjusted for other meat intake.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

The Working Group identified five eligible population-based case–control studies from the USA, China, Canada, and Sweden, and two hospital-based studies from Italy.

(i) Population-based

Goodman et al. (1997) performed a case–control study in Hawaii in 1985–1993. The study included 332 histologically confirmed cases of endometrial cancer (66% response rate) and 511 population-based controls matched by age and ethnicity (73% response rate). A 250-item dietary history interview was used. Red meat consumption was associated with a significantly increased risk (for Q4 vs Q1 OR, 2.0; 95% CI, 1.1–3.7; P_{trend} = 0.03), but no association was observed with processed meat (P_{trend} = 0.38). Beef intake, analysed separately, was associated with an increased risk (for Q4 vs Q1 OR, 1.8; 95% CI not reported; P_{trend} = 0.04) but pork was not associated with an increased risk (P_{trend} = 0.53). The model was adjusted for BMI, other factors, and energy intake. [The Working Group noted that a specific definition of red meat or processed meat was not presented. The 250-item dietary history was validated. The response rate among cases was not high.]

McCann et al. (2000) performed a study of endometrial cancer in western New York that included 232 cases (51% response rate) and 639 population-based controls (51% response rate). Diet was assessed with a 172-item FFQ by trained nurse interviewers. No association was observed with consumption of red meat (P_{trend} = 0.96) or processed meat (P_{trend} = 0.64). [The Working Group noted that specific definitions of red meat and processed meat were not presented. The 172-item FFQ was not validated. There was a low response rate and a rather limited number of cases. The model was adjusted for BMI, smoking, and other factors, and mutually adjusted for other foods. It was not adjusted for energy intake.]

A study from Ontario, Canada (Jain et al., 2000), included 552 cases (70% response rate) and 563 controls (41% response rate) frequency-matched by age group and area of residence. In-person, in-home interviews inquired about detailed dietary history 1 year before the diagnosis/before the interview. The dietary history method inquired about 250 food items. No association with consumption of red meat (beef, pork, veal, lamb, game, meat stews, and meat soups) was observed (P_{trend} = 0.55). The model was adjusted for age, body weight, history of diabetes, education, smoking, reproductive factors, and energy intake. [The Working Group noted that a specific definition of red meat was presented. The 250-item dietary history was validated. There was a low response rate among controls.]

Xu et al. (2006) reported results from a case–control study in Shanghai. The study included 1204 endometrial cancer cases (82.8% response rate) diagnosed in 1997–2003 and 1212 population-based controls (74.4% response rate), who were interviewed in person with a 76-item FFQ. Consumption of red meat (pork, beef, mutton) was associated with an increased risk (for Q4 vs Q1 OR, 1.3; 1.0–1.8; P_{trend} = 0.02), but cooking methods or doneness of the meat was not associated with an increased risk. The same study was analysed by Kallianpur et al. (2010), and an increased risk associated with haem iron intake (P_{trend} < 0.01) was reported. The model was adjusted for age, menopausal status, diagnosis of diabetes, BMI, alcohol, physical activity, and energy intake, and was mutually adjusted for other kinds of meats. [The Working Group noted that a specific definition of red meat was presented. The FFQ was validated versus 24-hour dietary recall. There was a relatively high response rate.]

(ii) Hospital-based

Tavani et al. (2000) reported results from a multisite cancer case–control study performed in northern Italy in 1983–1996. The study included 750 cases of endometrial cancer and 4770 hospital controls (> 95% response rates for cases and controls). The women were asked to fill in a 40-item FFQ. Consumption of red meat (beef, veal, pork) was associated with a significantly increased risk (OR, 1.5; 95% CI, 1.2–1.9 per increment of 1 portion/day). Processed meat was not studied. The model was adjusted for BMI, smoking, fruit, and vegetables, but not for energy intake. [The Working Group noted that a specific definition of red meat was presented. The 40-item FFQ was not validated. There was a high response rate among cases and controls. The model was not adjusted for energy intake.]

Bravi et al. (2009) reported results from another case–control study performed in three Italian areas in 1992–2006. The study included 454 cases and 908 hospital controls (> 95% response rates for cases and controls). A validated 78-item FFQ (vs 2 × 7-day dietary records) was used during in-person interviews. Red meat consumption was associated with a significantly increased risk (OR, 2.07; 95% CI, 1.29–3.33; for an increment of 1 portion/day; $P_{trend} = 0.002$). No association was observed with processed meat consumption ($P_{trend} = 0.24$). Based on the same data, Di Maso et al. (2013) reported the risk for endometrial cancer related to an increment of 50 g/day of red meat consumption (OR, 1.30; 95% CI, 1.10–1.55), when the model was adjusted for age, education, BMI, smoking, alcohol, vegetable intake, and fruit intake, but not for energy intake.

[The Working Group noted that a definition of red meat was presented by Di Maso et al. (2013), but processed meat was not defined. A validated FFQ was used. The response rate was high. The model was adjusted for energy intake in the analyses by Bravi et al., but not in the analyses by Di Maso et al.]

(c) Meta-analyses

A meta-analysis of red meat (Bandera et al., 2007), based on seven case–control studies, showed an increased risk of endometrial cancer was associated with red meat consumption ($OR_{summary}$, 1.51; 95% CI, 1.19–1.93 per 100 g/day of red meat; $P_{heterogeneity} = 0.97$). Results from three cohorts – the NIH-AARP cohort (Arem et al., 2013), the SMC cohort (Genkinger et al., 2012), and a Canadian cohort (van Lonkhuijzen et al., 2011), published after the meta-analysis, did not show a statistically significant increased risk of endometrial cancer with consumption of red meat or processed meat.

2.9.9 Leukaemia

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

Two prospective cohort studies reported on the association between the intake of red and/or processed meat and the risk of different types of leukaemia.

The association between red and processed meat intake and risk of acute myeloid leukaemia was investigated in the NIH-AARP study (1995–2003) in a prospective cohort of 491 163 individuals (Ma et al., 2010). A total of 338 incident cases of acute myeloid leukaemia were identified during a median follow-up of 7.5 years. A 124-item, validated FFQ was used. Processed meat was defined as all types of cold cuts, bacon, ham, hot dogs, and sausages from red and white meats. Consumption of processed meat was not associated with risk of acute myeloid leukaemia. The multivariate-adjusted hazard ratio for the highest compared with the lowest quintiles of consumption was 0.84 (95% CI, 0.60–1.18; $P_{trend} = 0.64$). Different cooking methods showed no clear associations with outcome. [The Working Group noted that this was a large informative study, with comprehensive analyses

of meat variables and cooking methods. Red meat included processed meat.]

The potential associations between red meat and processed meat and leukaemia were investigated in the EPIC cohort (Saberi Hosnijeh et al., 2014). In 477 325 participants followed up for a mean of 11.34 years, 773 incident leukaemia patients (373 lymphoid leukaemia patients, 342 myeloid leukaemia patients) were identified. Neither the consumption of red meat nor processed meat was associated with risk of leukaemia. For red meat, the multivariate-adjusted, calibrated hazard ratios per 50 g/day of intake were 0.98 (95% CI, 0.79–1.22) for all leukaemia, 1.06 (95% CI, 0.76–1.49) for myeloid leukaemia, and 0.89 (95% CI, 0.65–1.22) for lymphoid leukaemia. For processed meat, the multivariate-adjusted, calibrated hazard ratio per 50 g/day of intake were 1.08 (95% CI, 0.85–1.35) for all leukaemia, 1.03 (95% CI, 0.92–1.16) for myeloid leukaemia, and 1.29 (95% CI, 0.93–1.77) for lymphoid leukaemia. Red meat and processed meat were also not associated with leukaemia subtypes (i.e. acute myeloid leukaemia, chronic myeloid leukaemia, and chronic lymphoid leukaemia). [The Working Group noted that this large study enabled the investigation of multiple leukaemia subtype outcomes. Red meat and processed meat were not defined.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

There were a few case–control studies that reported on the association between intake of red and/or processed meat and risk of different types of leukaemia, but only one was considered eligible (Liu et al., 2015). One of these studies (Yamamura et al., 2013) did not meet the criteria for inclusion [numbers for cases and controls in subgroups not provided, wide confidence intervals, and red meat definition not provided]. One case–control study (Peters et al., 1994) on processed meat intake in children and their parents and risk of childhood leukaemia was excluded because of unavailability of response rates and a limited dietary questionnaire (12 items) on usual food intake of the mother, father, and child.

A multicentre case–control study in China investigated the association between red meat consumption and risk of adult leukaemia (Liu et al., 2015). Between 2008 and 2013, 442 cases aged 15 years or older (97.8% response rate) and 442 outpatient controls were recruited. The controls were selected from a larger group that served as controls in many other case–control studies and other cancer outcomes, and were matched post hoc to cases by age group, sex, and study site; the recruitment date did not exceed that for matching to cases by more than 1 year. [The response rate of the controls was not provided.] A validated and reproducible, 103-item FFQ was administered in face-to-face interviews. Red meat consumption was derived from seven food items, including pork chops/spare ribs, pigs' feet, fresh pork (lean), fresh pork (fat and lean), pork liver, organ meats, beef, and mutton. There was no significant association between red meat consumption and risk of all leukaemias (multivariate-adjusted OR, 1.06; 95% CI, 0.91–1.22 per 50 g/day) or acute myeloid leukaemia (OR, 0.99; 95% CI, 0.77–1.28). [The Working Group noted that this study had high response rates. Although it was a hospital-based study, the setting made this study comparable to a population-based study.]

2.9.10 Cancer of the brain

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

There were no cohort studies reporting on the association between consumption of red and/or processed meat and risk of brain tumours in children. Michaud et al. (2009) analysed combined data from three USA prospective cohort studies with 335 adult glioma cases diagnosed during 24

years of follow-up. No associations were observed between red meat, processed meat, bacon, or hot dogs and risk of glioma. Another large USA cohort study with 585 adult glioma cases found no significant trends for glioma risk with consumption of red or processed meat (Dubrow et al., 2010).

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

There was an international, collaborative, pooled case–control study on maternal diet during pregnancy (including cured meat intake) and risk of childhood brain tumours in the children of the mothers (Pogoda et al., 2009). The individual case–control studies already included in this international study are, therefore, not described separately in this *Monograph* (although a follow-up publication investigating the interaction with GST variants is mentioned) (Searles Nielsen et al., 2011). There was also a joint, collaborative, pooled case–control study on adult brain tumours (Terry et al., 2009).

The international, collaborative case–control study (Pogoda et al., 2009) included nine study centres from seven countries (Sydney, Australia; Winnipeg, Canada; Paris, France; Tel Hashomer, Israel; Milan, Italy; Valencia, Spain; and Los Angeles, San Francisco, and Seattle, USA). Most of the 1218 (75% response rate based on estimates from centres for which this was available) cases were diagnosed between 1982 and 1992, and 2223 controls (71% response rate) were included. The age ranged from 0 to 19 years. Mothers were asked about their food consumption during the past year and during the index pregnancy (i.e. pregnancy with the study participant). Data collection from all nine centres was conducted via a common protocol. The dietary questionnaire focused on foods high in nitrate and/or nitrite, and on foods containing nitrosation inhibitors (i.e. vitamins C and E). Dietary consumption was estimated in average grams per day. Cured meats (a type of processed meat) included 4–10 items, depending on the centre (and thus geographical location). Cured meat consumption by the mother during pregnancy was associated with an increased risk of all brain tumours combined, but particularly astroglial tumours. The multivariable odds ratios for the top compared with the bottom quartile of consumption were 1.5 (95% CI, 1.1–2.1; P_{trend} = 0.03) for all brain tumours combined, 1.8 (95% CI, 1.2–2.6; P_{trend} = 0.01) for astroglial tumours, and 1.2 (95% CI, 0.9–1.6; P_{trend} = 0.15) for primitive neuroectodermal tumours. There was no confounding or effect modification by prenatal vitamin supplementation. [The Working Group concluded that this was an informative study because of the large size of the study, the geographical variation of the pooled studies, and the large number of food items that questioned about cured meats. However, recall bias (rumination bias) by mothers could not be excluded since diet often had to be recalled over a long period of time in the past, as the children were up to aged 19 years.]

In a follow-up study of one of the population-based case–control studies (Preston-Martin et al., 1996) included in Pogoda et al. (2009), the interaction with six GST variants was investigated (Searles Nielsen et al., 2011). A total of 202 cases of childhood brain cancer diagnosed at ≤ 10 years of age and 286 controls living in California or Washington, USA, between 1978 and 1990 were included in the study. Dietary information was obtained from mothers, on average, 5.3 years or 6.4 years after the birth of the child in cases and controls, respectively. Cured meat (processed meat) was defined as ham, bacon, hot dogs, sausage, luncheon meat, or "other cured meats" combined. Risk of childhood brain tumours rose with increasing intake of cured meat by the mother during pregnancy among children without GSTT1 (OR, 1.29; 95% CI, 1.07–1.57; for each increase in the frequency of consumption per week) or with potentially reduced GSTM3 (any –63C allele, OR, 1.14; 95%

CI, 1.03–1.26), whereas no increased risk was observed among those with GSTT1 or presumably normal GSTM3 levels ($P_{interaction}$ = 0.01 for each).

Another collaborative, pooled case–control study on cured meat consumption and adult brain tumours (Terry et al., 2009) did not show an association between cured meat consumption and risk of adult brain tumours.

2.9.11 Cancer of the breast in men

A case–control study evaluated risk factors for cancer of the breast in men, and evaluated red meat intake as one of the risk factors (Hsing et al., 1998). Consumption of red meat ≥ 7 times/week was associated with a 1.8-fold risk (95% CI, 0.6–4.9), although the trend was not significant. [The Working Group noted that the high frequency might have been due to underestimation by the authors of the effects of smoking and drinking.]

References

Alexander DD, Cushing CA (2009). Quantitative assessment of red meat or processed meat consumption and kidney cancer. *Cancer Detect Prev*, 32(5-6):340–51. doi:10.1016/j.cdp.2009.02.002 PMID:19303221

Arem H, Gunter MJ, Cross AJ, Hollenbeck AR, Sinha R (2013). A prospective investigation of fish, meat and cooking-related carcinogens with endometrial cancer incidence. *Br J Cancer*, 109(3):756–60. doi:10.1038/bjc.2013.252 PMID:23695021

Aschebrook-Kilfoy B, Ollberding NJ, Kolar C, Lawson TA, Smith SM, Weisenburger DD et al. (2012). Meat intake and risk of non-Hodgkin lymphoma. *Cancer Causes Control*, 23(10):1681–92. doi:10.1007/s10552-012-0047-2 PMID:22890783

Aune D, De Stefani E, Ronco A, Boffetta P, Deneo-Pellegrini H, Acosta G et al. (2009). Meat consumption and cancer risk: a case-control study in Uruguay. *Asian Pac J Cancer Prev*, 10(3):429–36. PMID:19640186

Balasubramaniam G, Saoba S, Sarade M, Pinjare S (2013). Case-control study of risk factors for Non-Hodgkin lymphoma in Mumbai, India. *Asian Pac J Cancer Prev*, 14(2):775–80. doi:10.7314/APJCP.2013.14.2.775 PMID:23621236

Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML (2007). Consumption of animal foods and endometrial cancer risk: a systematic literature review and meta-analysis. *Cancer Causes Control*, 18(9):967–88. doi:10.1007/s10552-007-9038-0 PMID:17638104

Bertone ER, Rosner BA, Hunter DJ, Stampfer MJ, Speizer FE, Colditz GA et al. (2002). Dietary fat intake and ovarian cancer in a cohort of US women. *Am J Epidemiol*, 156(1):22–31. doi:10.1093/aje/kwf008 PMID:12076885

Bravi F, Bosetti C, Scotti L, Talamini R, Montella M, Ramazzotti V et al. (2007). Food groups and renal cell carcinoma: a case-control study from Italy. *Int J Cancer*, 120(3):681–5. doi:10.1002/ijc.22225 PMID:17058282

Bravi F, Scotti L, Bosetti C, Zucchetto A, Talamini R, Montella M et al. (2009). Food groups and endometrial cancer risk: a case-control study from Italy. *Am J Obstet Gynecol*, 200(3):293.e1–7. doi:10.1016/j.ajog.2008.09.015 PMID:19091304

Catsburg CE, Gago-Dominguez M, Yuan JM, Castelao JE, Cortessis VK, Pike MC et al. (2014). Dietary sources of N-nitroso compounds and bladder cancer risk: findings from the Los Angeles bladder cancer study. *Int J Cancer*, 134(1):125–35. doi:10.1002/ijc.28331 PMID:23775870

Charbonneau B, O'Connor HM, Wang AH, Liebow M, Thompson CA, Fredericksen ZS et al. (2013). Trans fatty acid intake is associated with increased risk and n3 fatty acid intake with reduced risk of non-hodgkin lymphoma. *J Nutr*, 143(5):672–81. doi:10.3945/jn.112.168658 PMID:23486982

Chiu BC, Cerhan JR, Folsom AR, Sellers TA, Kushi LH, Wallace RB et al. (1996). Diet and risk of non-Hodgkin lymphoma in older women. *JAMA*, 275(17):1315–21. doi:10.1001/jama.1996.03530410029029 PMID:8614116

Cross AJ, Ward MH, Schenk M, Kulldorff M, Cozen W, Davis S et al. (2006). Meat and meat-mutagen intake and risk of non-Hodgkin lymphoma: results from a NCI-SEER case-control study. *Carcinogenesis*, 27(2):293–7. doi:10.1093/carcin/bgi212 PMID:16113054

Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R (2007). A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med*, 4(12):e325 doi:10.1371/journal.pmed.0040325 PMID:18076279

Daniel CR, Sinha R, Park Y, Graubard BI, Hollenbeck AR, Morton LM et al. (2012a). Meat intake is not associated with risk of non-Hodgkin lymphoma in a large prospective cohort of U.S. men and women. *J Nutr*, 142(6):1074–80. doi:10.3945/jn.112.158113 PMID:22535761

Daniel CR, Cross AJ, Graubard BI, Park Y, Ward MH, Rothman N et al. (2012b). Large prospective investigation of meat intake, related mutagens, and risk of renal cell carcinoma. *Am J Clin Nutr*, 95(1):155–62. doi:10.3945/ajcn.111.019364 PMID:22170360

De Stefani E, Fierro L, Barrios E, Ronco A (1998). Tobacco, alcohol, diet and risk of non-Hodgkin's lymphoma: a case-control study in Uruguay. *Leuk Res*, 22(5):445–52. doi:10.1016/S0145-2126(97)00194-X PMID:9652731

De Stefani E, Boffetta P, Ronco AL, Deneo-Pellegrini H, Correa P, Acosta G et al. (2012). Processed meat consumption and risk of cancer: a multisite case-control study in Uruguay. *Br J Cancer*, 107(9):1584–8. doi:10.1038/bjc.2012.433 PMID:23011480

De Stefani E, Ronco AL, Deneo-Pellegrini H, Boffetta P, Correa P, Barrios E et al. (2013). Meat, milk and risk of lymphoid malignancies: a case-control study in Uruguay. *Nutr Cancer*, 65(3):375–83. doi:10.1080/01635581.2013.761255 PMID:23530636

Di Maso M, Talamini R, Bosetti C, Montella M, Zucchetto A, Libra M et al. (2013). Red meat and cancer risk in a network of case-control studies focusing on cooking practices. *Ann Oncol*, 24(12):3107–12. doi:10.1093/annonc/mdt392 PMID:24121119

Dubrow R, Darefsky AS, Park Y, Mayne ST, Moore SC, Kilfoy B et al. (2010). Dietary components related to N-nitroso compound formation: a prospective study of adult glioma. *Cancer Epidemiol Biomarkers Prev*, 19(7):1709–22. doi:10.1158/1055-9965.EPI-10-0225 PMID:20570910

Erber E, Maskarinec G, Gill JK, Park SY, Kolonel LN (2009). Dietary patterns and the risk of non-Hodgkin lymphoma: the Multiethnic Cohort. *Leuk Lymphoma*, 50(8):1269–75. doi:10.1080/10428190903030841 PMID:19811330

Fallahzadeh H, Cheraghi M, Amoori N, Alaf M (2014). Red meat intake and risk of non-Hodgkin lymphoma: a meta-analysis. *Asian Pac J Cancer Prev*, 15(23):10421–5. doi:10.7314/APJCP.2014.15.23.10421 PMID:25556486

Fedirko V, Trichopolou A, Bamia C, Duarte-Salles T, Trepo E, Aleksandrova K et al. (2013). Consumption of fish and meats and risk of hepatocellular carcinoma: the European Prospective Investigation into Cancer and Nutrition (EPIC). *Ann Oncol*, 24(8):2166–73. doi:10.1093/annonc/mdt168 PMID:23670094

Feller AC, Diebold J (2004). *Histopathology of Nodal and Extranodal Non-Hodgkin's Lymphomas, based on the WHO classification*. 3rd rev. ed. Berlin, Germany: Springer-Verlag. doi:10.1007/978-3-642-18653-0

Ferrucci LM, Sinha R, Ward MH, Graubard BI, Hollenbeck AR, Kilfoy BA et al. (2010). Meat and components of meat and the risk of bladder cancer in the NIH-AARP Diet and Health Study. *Cancer*, 116(18):4345–53. doi:10.1002/cncr.25463 PMID:20681011

Fraser GE, Phillips RL, Beeson WL (1990). Hypertension, antihypertensive medication and risk of renal carcinoma in California Seventh-Day Adventists. *Int J Epidemiol*, 19(4):832–8. doi:10.1093/ije/19.4.832 PMID:2084009

Freedman ND, Cross AJ, McGlynn KA, Abnet CC, Park Y, Hollenbeck AR et al. (2010). Association of meat and fat intake with liver disease and hepatocellular carcinoma in the NIH-AARP cohort. *J Natl Cancer Inst*, 102(17):1354–65. doi:10.1093/jnci/djq301 PMID:20729477

García-Closas R, García-Closas M, Kogevinas M, Malats N, Silverman D, Serra C et al. (2007). Food, nutrient and heterocyclic amine intake and the risk of bladder cancer. *Eur J Cancer*, 43(11):1731–40. doi:10.1016/j.ejca.2007.05.007 PMID:17596928

Genkinger JM, Friberg E, Goldbohm RA, Wolk A (2012). Long-term dietary heme iron and red meat intake in relation to endometrial cancer risk. *Am J Clin Nutr*, 96(4):848–54. doi:10.3945/ajcn.112.039537 PMID:22952183

Gilsing AM, Weijenberg MP, Goldbohm RA, van den Brandt PA, Schouten LJ (2011). Consumption of dietary fat and meat and risk of ovarian cancer in the Netherlands Cohort Study. *Am J Clin Nutr*, 93(1):118–26. doi:10.3945/ajcn.2010.29888 PMID:21068347

Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ et al. (1997). Diet, body size, physical activity, and the risk of endometrial cancer. *Cancer Res*, 57(22):5077–85. PMID:9371506

Grieb SM, Theis RP, Burr D, Benardot D, Siddiqui T, Asal NR (2009). Food groups and renal cell carcinoma: results from a case-control study. *J Am Diet Assoc*, 109(4):656–67. doi:10.1016/j.jada.2008.12.020 PMID:19328261

Hsing AW, McLaughlin JK, Cocco P, Co Chien HT, Fraumeni JF Jr (1998). Risk factors for male breast cancer (United States). *Cancer Causes Control*, 9(3):269–75. doi:10.1023/A:1008869003012 PMID:9684707

Hsu CC, Chow WH, Boffetta P, Moore L, Zaridze D, Moukeria A et al. (2007). Dietary risk factors for kidney cancer in Eastern and Central Europe. *Am J Epidemiol*, 166(1):62–70. doi:10.1093/aje/kwm043 PMID:17456477

Hu J, La Vecchia C, DesMeules M, Negri E, Mery L, Group CCRE; Canadian Cancer Registries Epidemiology Research Group (2008). Meat and fish consumption and cancer in Canada. *Nutr Cancer*, 60(3):313–24. doi:10.1080/01635580701759724 PMID:18444165

Hu J, La Vecchia C, Morrison H, Negri E, Mery L; Canadian Cancer Registries Epidemiology Research Group(2011). Salt, processed meat and the risk of cancer. *Eur J Cancer Prev*, 20(2):132–9. doi:10.1097/CEJ.0b013e3283429e32 PMID:21160428

Jain MG, Howe GR, Rohan TE (2000). Nutritional factors and endometrial cancer in Ontario, Canada. *Cancer Contr*, 7(3):288–96. doi:10.1177/107327480000700312 PMID:10832115

Jakszyn P, González CA, Luján-Barroso L, Ros MM, Bueno-de-Mesquita HB, Roswall N et al. (2011). Red meat, dietary nitrosamines, and heme iron and risk of bladder cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Cancer Epidemiol Biomarkers Prev, 20(3):555–9. doi:10.1158/1055-9965.EPI-10-0971 PMID:21239687

Kabat GC, Miller AB, Jain M, Rohan TE (2008). Dietary iron and haem iron intake and risk of endometrial cancer: a prospective cohort study. *Br J Cancer*, 98(1):194–8. doi:10.1038/sj.bjc.6604110 PMID:18059399

Kallianpur AR, Lee SA, Xu WH, Zheng W, Gao YT, Cai H et al. (2010). Dietary iron intake and risk of endometrial cancer: a population-based case-control study in Shanghai, China. *Nutr Cancer*, 62(1):40–50. doi:10.1080/01635580903191544 PMID:20043258

Kiani F, Knutsen S, Singh P, Ursin G, Fraser G (2006). Dietary risk factors for ovarian cancer: the Adventist Health Study (United States). *Cancer Causes Control*, 17(2):137–46. doi:10.1007/s10552-005-5383-z PMID:16425091

Kolahdooz F, van der Pols JC, Bain CJ, Marks GC, Hughes MC, Whiteman DC et al.; Australian Cancer Study (Ovarian Cancer) and the Australian Ovarian Cancer Study Group (2010). Meat, fish, and ovarian cancer risk: Results from 2 Australian case-control studies, a systematic review, and meta-analysis. *Am J Clin Nutr*, 91(6):1752–63. doi:10.3945/ajcn.2009.28415 PMID:20392889

Kushi LH, Mink PJ, Folsom AR, Anderson KE, Zheng W, Lazovich D et al. (1999). Prospective study of diet and ovarian cancer. *Am J Epidemiol*, 149(1):21–31. doi:10.1093/oxfordjournals.aje.a009723 PMID:9883790

Larsson SC, Wolk A (2005). No association of meat, fish, and egg consumption with ovarian cancer risk. *Cancer Epidemiol Biomarkers Prev*, 14(4):1024–5. doi:10.1158/1055-9965.EPI-04-0795 PMID:15824185

Larsson SC, Johansson JE, Andersson SO, Wolk A (2009). Meat intake and bladder cancer risk in a Swedish prospective cohort. *Cancer Causes Control*, 20(1):35–40. doi:10.1007/s10552-008-9214-x PMID:18704711

Lee JE, Spiegelman D, Hunter DJ, Albanes D, Bernstein L, van den Brandt PA et al. (2008). Fat, protein, and meat consumption and renal cell cancer risk: a pooled analysis of 13 prospective studies. *J Natl Cancer Inst*, 100(23):1695–706. doi:10.1093/jnci/djn386 PMID:19033572

Li F, An S, Hou L, Chen P, Lei C, Tan W (2014). Red and processed meat intake and risk of bladder cancer: a meta-analysis. *Int J Clin Exp Med*, 7(8):2100–10. PMID:25232394

Lin J, Forman MR, Wang J, Grossman HB, Chen M, Dinney CP et al. (2012). Intake of red meat and heterocyclic amines, metabolic pathway genes and bladder cancer risk. *Int J Cancer*, 131(8):1892–903. doi:10.1002/ijc.27437 PMID:22261697

Liu P, Holman CD, Jin J, Zhang M (2015). Diet and risk of adult leukemia: a multicenter case-control study in China. *Cancer Causes Control*, 26(8):1141–51. doi:10.1007/s10552-015-0608-2 PMID:26071869

Luo J, Yang Y, Liu J, Lu K, Tang Z, Liu P et al. (2014). Systematic review with meta-analysis: meat consumption and the risk of hepatocellular carcinoma. *Aliment Pharmacol Ther*, 39(9):913–22. doi:10.1111/apt.12678 PMID:24588342

Ma X, Park Y, Mayne ST, Wang R, Sinha R, Hollenbeck AR et al. (2010). Diet, lifestyle, and acute myeloid leukemia in the NIH-AARP cohort. *Am J Epidemiol*, 171(3):312–22. doi:10.1093/aje/kwp371 PMID:20042434

McCann SE, Freudenheim JL, Marshall JR, Brasure JR, Swanson MK, Graham S (2000). Diet in the epidemiology of endometrial cancer in western New York (United States). *Cancer Causes Control*, 11(10):965–74. doi:10.1023/A:1026551309873 PMID:11142531

McCann SE, Freudenheim JL, Marshall JR, Graham S (2003). Risk of human ovarian cancer is related to dietary intake of selected nutrients, phytochemicals and food groups. *J Nutr*, 133(6):1937–42. doi:10.1093/jn/133.6.1937 PMID:12771342

Michaud DS, Holick CN, Giovannucci E, Stampfer MJ (2006). Meat intake and bladder cancer risk in 2 prospective cohort studies. *Am J Clin Nutr*, 84(5):1177–83. doi:10.1093/ajcn/84.5.1177 PMID:17093172

Michaud DS, Holick CN, Batchelor TT, Giovannucci E, Hunter DJ (2009). Prospective study of meat intake and dietary nitrates, nitrites, and nitrosamines and risk of adult glioma. *Am J Clin Nutr*, 90(3):570–7. doi:10.3945/ajcn.2008.27199 PMID:19587083

Nagano J, Kono S, Preston DL, Moriwaki H, Sharp GB, Koyama K et al. (2000). Bladder-cancer incidence in relation to vegetable and fruit consumption: a prospective study of atomic-bomb survivors. *Int J Cancer*, 86(1):132–8. doi:10.1002/(SICI)1097-0215(20000401)86:1<132::AID-IJC21>3.0.CO;2-M PMID:10728607

Pan SY, Ugnat AM, Mao Y, Wen SW, Johnson KC; Canadian Cancer Registries Epidemiology Research Group (2004). A case-control study of diet and the risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev*, 13(9):1521–7. PMID:15342455

Peters JM, Preston-Martin S, London SJ, Bowman JD, Buckley JD, Thomas DC (1994). Processed meats and risk of childhood leukemia (California, USA). *Cancer Causes Control*, 5(2):195–202. doi:10.1007/BF01830266 PMID:8167267

Pogoda JM, Preston-Martin S, Howe G, Lubin F, Mueller BA, Holly EA et al. (2009). An international case-control study of maternal diet during pregnancy and childhood brain tumor risk: a histology-specific analysis by food group. *Ann Epidemiol*, 19(3):148–60. doi:10.1016/j.annepidem.2008.12.011 PMID:19216997

Preston-Martin S, Pogoda JM, Mueller BA, Holly EA, Lijinsky W, Davis RL (1996). Maternal consumption of cured meats and vitamins in relation to pediatric brain tumors. *Cancer Epidemiol Biomarkers Prev*, 5(8):599–605. PMID:8824361

Purdue MP, Bassani DG, Klar NS, Sloan M, Kreiger N; Canadian Cancer Registries Epidemiology Research Group (2004). Dietary factors and risk of non-Hodgkin lymphoma by histologic subtype: a case-control analysis. *Cancer Epidemiol Biomarkers Prev*, 13(10):1665–76. PMID:15466985

Radosavljević V, Janković S, Marinković J, Dokić M (2005). Diet and bladder cancer: a case-control study. *Int Urol Nephrol*, 37(2):283–9. doi:10.1007/s11255-004-4710-8 PMID:16142557

Riboli E, González CA, López-Abente G, Errezola M, Izarzugaza I, Escolar A et al. (1991). Diet and bladder cancer in Spain: a multi-centre case-control study. *Int J Cancer*, 49(2):214–9. doi:10.1002/ijc.2910490212 PMID:1879967

Rohrmann S, Linseisen J, Jakobsen MU, Overvad K, Raaschou-Nielsen O, Tjonneland A et al. (2011). Consumption of meat and dairy and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*, 128(3):623–34. doi:10.1002/ijc.25387 PMID:20473877

Rohrmann S, Linseisen J, Overvad K, Lund Würtz AM, Roswall N, Tjonneland A et al. (2015). Meat and fish consumption and the risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. *Int J Cancer*, 136(5):E423–31. doi:10.1002/ijc.29236 PMID:25258006

Ronco AL, Mendilaharsu M, Boffetta P, Deneo-Pellegrini H, De Stefani E (2014). Meat consumption, animal products, and the risk of bladder cancer: a case-control study in Uruguayan men. *Asian Pac J Cancer Prev*, 15(14):5805–9. doi:10.7314/APJCP.2014.15.14.5805 PMID:25081704

Saberi Hosnijeh F, Peeters P, Romieu I, Kelly R, Riboli E, Olsen A et al. (2014). Dietary intakes and risk of lymphoid and myeloid leukemia in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Nutr Cancer*, 66(1):14–28. doi:10.1080/01635581.2014.847471 PMID:24279598

Schulz M, Nöthlings U, Allen N, Onland-Moret NC, Agnoli C, Engeset D et al. (2007). No association of consumption of animal foods with risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev*, 16(4):852–5. doi:10.1158/1055-9965.EPI-07-0054 PMID:17416784

Searles Nielsen S, Mueller BA, Preston-Martin S, Farin FM, Holly EA, McKean-Cowdin R (2011). Childhood brain tumors and maternal cured meat consumption in pregnancy: differential effect by glutathione S-transferases. *Cancer Epidemiol Biomarkers Prev*, 20(11):2413–9. doi:10.1158/1055-9965.EPI-11-0196 PMID:21914837

Shu XO, Gao YT, Yuan JM, Ziegler RG, Brinton LA (1989). Dietary factors and epithelial ovarian cancer. *Br J Cancer*, 59(1):92–6. doi:10.1038/bjc.1989.18 PMID:2757927

Talamini R, Polesel J, Montella M, Dal Maso L, Crovatto M, Crispo A et al. (2006a). Food groups and risk of non-Hodgkin lymphoma: a multicenter, case-control study in Italy. *Int J Cancer*, 118(11):2871–6. doi:10.1002/ijc.21737 PMID:16385566

Talamini R, Polesel J, Montella M, Dal Maso L, Crispo A, Tommasi LG et al. (2006b). Food groups and risk of hepatocellular carcinoma: A multicenter case-control study in Italy. *Int J Cancer*, 119(12):2916–21. doi:10.1002/ijc.22267 PMID:16998792

Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F et al. (2000). Red meat intake and cancer risk: a study in Italy. *Int J Cancer*, 86(3):425–8. doi:10.1002/(SICI)1097-0215(20000501)86:3<425::AID-IJC19>3.0.CO;2-S PMID:10760833

Terry MB, Howe G, Pogoda JM, Zhang FF, Ahlbom A, Choi W et al. (2009). An international case-control study of adult diet and brain tumor risk: a histology-specific analysis by food group. *Ann Epidemiol*, 19(3):161–71. doi:10.1016/j.annepidem.2008.12.010 PMID:19216998

Tsai HT, Cross AJ, Graubard BI, Oken M, Schatzkin A, Caporaso NE (2010). Dietary factors and risk of chronic lymphocytic leukemia and small lymphocytic lymphoma: a pooled analysis of two prospective studies. *Cancer Epidemiol Biomarkers Prev*, 19(10):2680–4. doi:10.1158/1055-9965.EPI-10-0585 PMID:20929883

van Lonkhuijzen L, Kirsh VA, Kreiger N, Rohan TE (2011). Endometrial cancer and meat consumption: a case-cohort study. *Eur J Cancer Prev*, 20(4):334–9. doi:10.1097/CEJ.0b013e328344747c PMID:21422932

Wakai K, Hirose K, Takezaki T, Hamajima N, Ogura Y, Nakamura S et al. (2004). Foods and beverages in relation to urothelial cancer: case-control study in Japan. *Int J Urol*, 11(1):11–9. doi:10.1111/j.1442-2042.2004.00740.x PMID:14678179

Wallin A, Orsini N, Wolk A (2011). Red and processed meat consumption and risk of ovarian cancer: a dose-response meta-analysis of prospective studies. *Br J Cancer*, 104(7):1196–201. doi:10.1038/bjc.2011.49 PMID:21343939

Ward MH, Zahm SH, Weisenburger DD, Gridley G, Cantor KP, Saal RC et al. (1994). Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). *Cancer Causes Control*, 5(5):422–32. doi:10.1007/BF01694756 PMID:7999964

Wolk A, Gridley G, Niwa S, Lindblad P, McCredie M, Mellemgaard A et al. (1996). International renal cell cancer study. VII. Role of diet. *Int J Cancer*, 65(1):67–73. doi:10.1002/(SICI)1097-0215(19960103)65:1<67::AID-IJC12>3.0.CO;2-F PMID:8543399

Wu JW, Cross AJ, Baris D, Ward MH, Karagas MR, Johnson A et al. (2012). Dietary intake of meat, fruits, vegetables, and selective micronutrients and risk of bladder cancer in the New England region of the United States. *Br J Cancer*, 106(11):1891–8. doi:10.1038/bjc.2012.187 PMID:22568968

Xu WH, Dai Q, Xiang YB, Zhao GM, Zheng W, Gao YT et al. (2006). Animal food intake and cooking methods

in relation to endometrial cancer risk in Shanghai. *Br J Cancer*, 95(11):1586–92. doi:10.1038/sj.bjc.6603458 PMID:17060930

Yamamura Y, Oum R, Gbito KY, Garcia-Manero G, Strom SS (2013). Dietary intake of vegetables, fruits, and meats/beans as potential risk factors of acute myeloid leukemia: a Texas case-control study. *Nutr Cancer*, 65(8):1132–40. doi:10.1080/01635581.2013.834946 PMID:24168094

Yuan JM, Gago-Dominguez M, Castelao JE, Hankin JH, Ross RK, Yu MC (1998). Cruciferous vegetables in relation to renal cell carcinoma. *Int J Cancer*, 77(2):211–6. doi:10.1002/(SICI)1097-0215(19980717)77:2<211::AID-IJC7>3.0.CO;2-T PMID:9650554

Zhang B, Li X, Nakama H, Zhang X, Wei N, Zhang X et al. (2002). A case-control study on risk of changing food consumption for colorectal cancer. *Cancer Invest*, 20(4):458–63. doi:10.1081/CNV-120002145 PMID:12094540

Zhang S, Hunter DJ, Rosner BA, Colditz GA, Fuchs CS, Speizer FE et al. (1999). Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. *J Natl Cancer Inst*, 91(20):1751–8. doi:10.1093/jnci/91.20.1751 PMID:10528026

Zheng W, Kushi LH, Potter JD, Sellers TA, Doyle TJ, Bostick RM et al. (1995). Dietary intake of energy and animal foods and endometrial cancer incidence. The Iowa women's health study. *Am J Epidemiol*, 142(4):388–94. doi:10.1093/oxfordjournals.aje.a117646 PMID:7625403