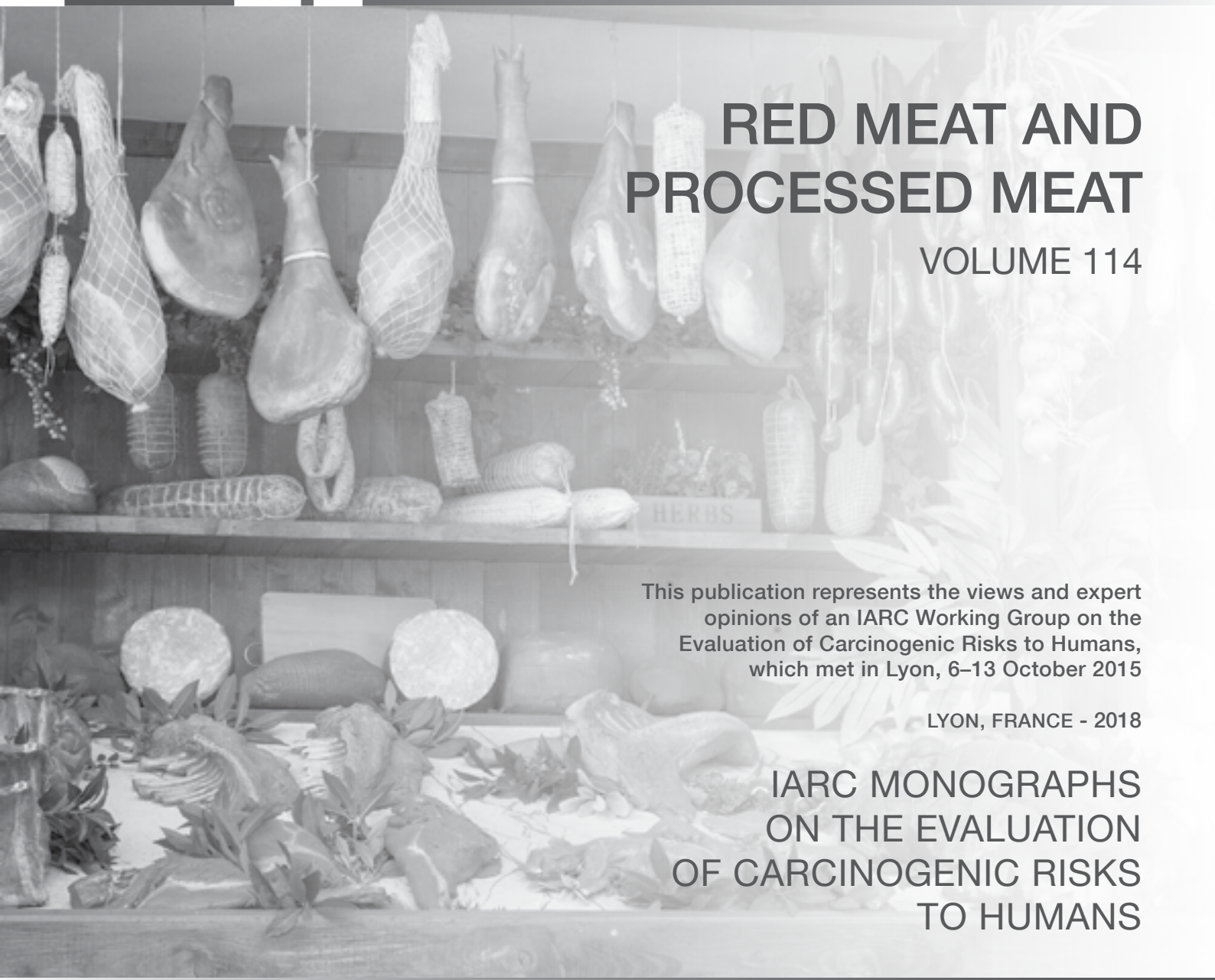
IARC MONOGRAPHS



RED MEAT AND PROCESSED MEAT

VOLUME 114

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International Agency for Research on Cancer

World Health Organization

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.]

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