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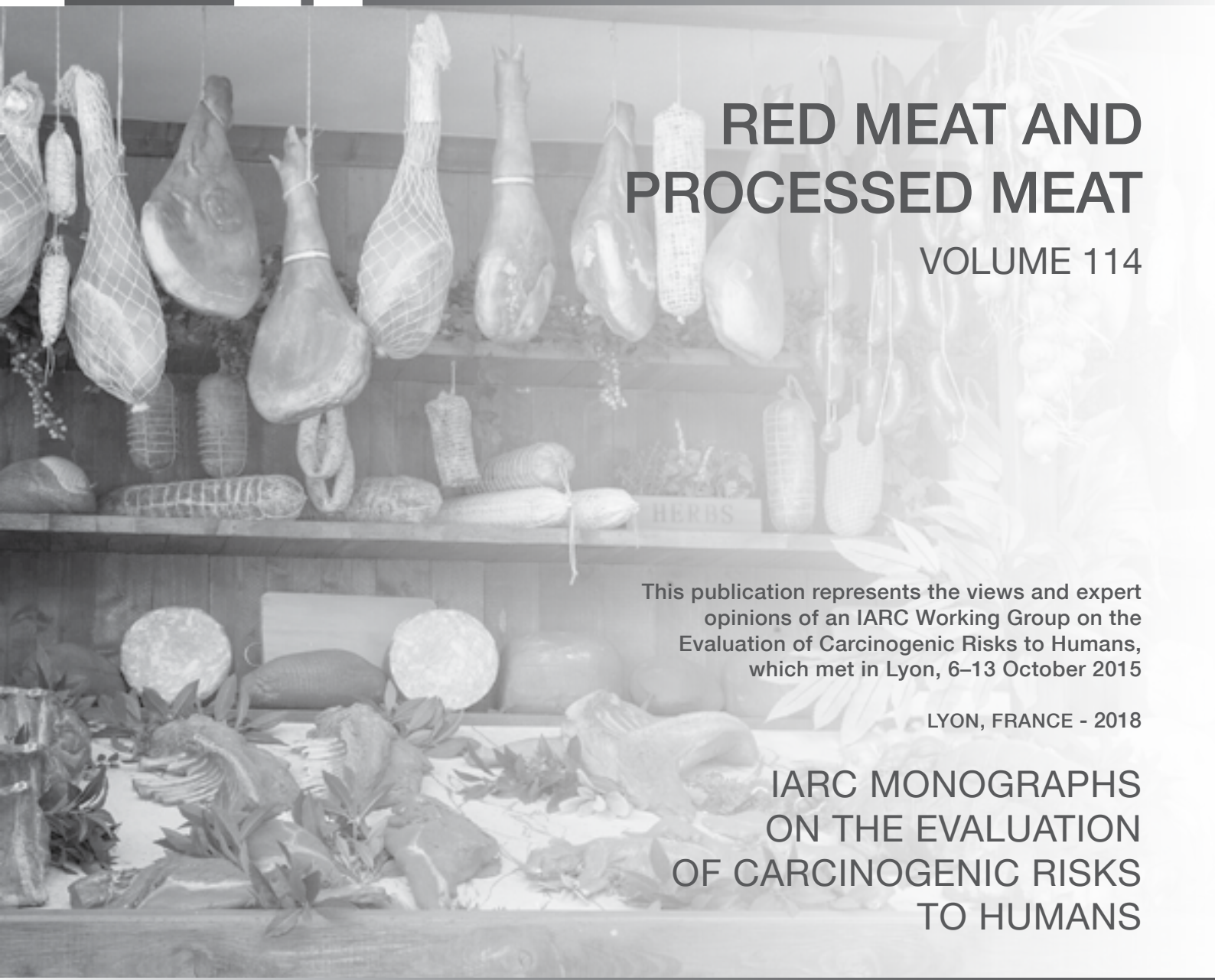

RED MEAT AND PROCESSED MEAT

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2.6 Cancer of the breast

2.6.1 Cohort studies

More details of the cohort studies can be found in Table 2.6.1 and Table 2.6.2 (web only; available at: http://publications.iarc.fr/564).

Intake of red and processed meat was evaluated in relation to cancer of the breast in cohort studies conducted in the USA, Canada, the Netherlands, the United Kingdom, Sweden, Denmark, and France, as well as in the EPIC study, which included multiple European countries, and in a cohort consortium of eight studies in North America and Europe. Important potential confounders for breast cancer included age, alcohol intake, reproductive factors (such as age at menarche, parity, age at first birth, use of oral contraceptives, age at menopause), use of postmenopausal hormones among postmenopausal women, family history of breast cancer, obesity, and energy intake. Studies that did not adjust for these covariates are noted. Recent publications with more reliable exposure assessment, more adequate adjustment for potential confounders, and longer follow-up time were included in the evaluation.

Studies were considered uninformative and not included in the evaluation if they assessed meat intake without specifying the types of meats included (e.g. Mills et al., 1988; van den Brandt et al., 1990; Vatten et al., 1990; Knekt et al., 1994; Gaard et al., 1995). In addition, studies that evaluated breast cancer in relation to dietary patterns, rather than the consumption of red or processed meat (e.g. Männistö et al., 2005; Cottet et al., 2009; Butler et al., 2010; Couto et al., 2013), or had a low number of cases (Byrne et al., 1996) were excluded from further review.

Mills et al., (1989) evaluated individual red meat items, "beef index", and breast cancer in a low-risk cohort of 20 341 Californian, Seventh-Day Adventist women aged 25–99 years. The beef index was the sum of intake from individual red meat items, including beef hamburger, beef steak, and other beef/veal. During a mean follow-up of 6 years (1976–1982), 215 primary breast cancer cases were histologically verified. The relative risk for the top (≥ 1 time/week) versus the bottom (never) category of the beef index was 1.05 (95% CI, 0.75–1.47). Intake of red meat (i.e. beef hamburger, beef steak, and other beef/veal) was not associated with breast cancer. [Alcohol and caloric intake were not adjusted for in statistical analyses. This study was part of the Pooling Project of Prospective Studies by Missmer et al., (2002). A smaller number of cases were included in the pooling project (160 cases).]

Toniolo et al. (1994) conducted a nested case–control study of 180 breast cancer cases and 829 controls from the first 6 years of follow-up (median follow-up time, 22.2 months) in the New York University Women's Health Study (NYUWHS) cohort. The study originally included 14 291 women aged 35–65 years enrolled between 1985 and 1991. Diet was assessed with a 71–food item, validated Block FFQ. The relative risk for the top versus the bottom quintile of meat intake was 1.87 (95% CI, 1.09–3.21; P_{trend} = 0.01). [The Working Group noted the relatively small sample size. In addition, the study did not specify red meat. Meat included beef, veal, lamb, or pork preparations or processed luncheon meats (ham, cold cuts, turkey rolls), that is, unprocessed and processed red meat and processed white meat. Alcohol intake was not adjusted for. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). A larger number of cases were included in the pooling project (385 cases).]

The Iowa Women's Health Study (IWHS) cohort included 41 836 postmenopausal (age, 55–69 years) women. Five nested case–control studies of the cohort were included (Zheng et al., 1998; Zheng et al., 1999; Deitz et al., 2000; Zheng et al., 2001; Zheng et al., 2002). These studies are described in more detail below.

Zheng et al. (1998) conducted a nested case–control study of 273 cases and 657 controls nested within the IWHS. All eligible subjects were asked to complete a self-administered FFQ on meat intake habits during the reference year. The questionnaire included questions on usual intake and preparation of 15 meats. A doneness score was also calculated to describe the eating preferences of the participants based on their responses to colour photographs. The study found a positive dose–response relationship between doneness of red and processed meat and breast cancer risk. The odds ratios for very well-done meat versus rare or medium-done meat were 1.54 (95% CI, 0.96–2.47) for hamburger, 2.21 (95% CI, 1.30–3.77) for beef steak, and 1.64 (95% CI, 0.92–2.93) for bacon. Women who consumed these three meats consistently very well done had an odds ratio of 4.62 (95% CI, 1.36–15.70; P_{trend} = 0.001) compared with women who consumed the meats rare or medium done. In addition, compared with women in the lowest tertile of intake of these three types of meats with a doneness level of rare/medium, those who were in the top tertile of intake with a doneness level of consistently very well done had an odds ratio of 3.01 (95% CI, 1.47–6.17). [The Working Group noted that there was a statistically significant positive association between intake of red meat and risk of breast cancer (P_{trend} = 0.02), with a 78% elevated risk observed for the highest versus the lowest tertile of intake group; however, red meat included processed meat. Reproductive factors and alcohol intake were not adjusted for in statistical analyses. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). A much larger number of cases were included in the pooling project (1130 cases).]

Deitz et al. (2000) used a subset of the nested case–control study data from the IWHS (174 cases, 387 controls) with DNA samples, and evaluated doneness score and red meat [which included processed meat] intake and breast cancer by *NAT2* polymorphism. Polymorphisms in the *NAT2* gene may result in a rapid, intermediate, and slow acetylation phenotype. The study found that a higher intake of red meat was suggestively positively associated with breast cancer among women with the *NAT2* rapid/intermediate type (OR, 1.7; 95% CI, 0.9–3.4; for the highest vs lowest tertile of intake), but not associated with breast cancer among those with the *NAT2* slow type (OR, 0.9; 95% CI, 0.5–1.7; for the same comparison). However, the *P* value for interaction by *NAT2* genotype was not significant (*P* = 0.91). For the association between doneness score and breast cancer, there was a borderline significant interaction by *NAT2* genotype (*P* = 0.06). Compared with women who reported consuming hamburger, beef steak, and bacon rare/medium (doneness score, 3/4), those who reported consuming these meats very well done (doneness score, 9) had odds ratios of 3.9 (95% CI, 0.8–18.9; P_{trend} = 0.22) for the *NAT2* slow genotype and 7.6 (95% CI, 1.1–50.4; P_{trend} = 0.003) for the *NAT2* rapid/intermediate type. [The Working Group noted that the sample size was much more limited than the original study by Zheng et al. (1999) because a large number of the subjects had buccal cell samples instead of blood samples, and *NAT2* amplification was successful only in 9% (79/878) of buccal cell DNA samples. Sample size was too small to evaluate the interaction with genetic polymorphisms. Only age was adjusted for. Red meat included processed meat.]

A similar study using a subset of the nested case–control study data from the IWHS was conducted to evaluate the association between doneness of red meat and breast cancer risk stratified by *SULT1A1* polymorphism (Zheng et al., 2001). The study included 156 cases and 332 controls, with blood samples. The association between doneness of red meat [which included processed meat] and breast cancer appeared to differ by the polymorphism, although the *P* value for interaction was not significant (*P* = 0.40). Compared with participants consuming rare/medium-

done red meat, those who consistently consumed well-done red meat had relative risks of 3.6 (95% CI, 1.4–9.3; P_{trend} = 0.01) for the *SULT1A1* Arg/Arg genotype, 1.8 (95% CI, 0.9–3.8; P_{trend} = 0.10) for the Arg/His genotype, and 1.0 (95% CI, 0.3–3.7; P_{trend} = 0.98) for the His/His genotype. [The Working Group noted that the sample size was too small to evaluate the interaction with genetic polymorphisms, and most of the categories had fewer than 20 cases. Age, waist:hip ratio, and number of live births were adjusted for. Red meat included processed meat.]

Zheng et al. (2002) also evaluated a similar interaction between meat doneness level and breast cancer risk by *GSTM1* and *GSTT1* polymorphisms in a nested case–control study in the IWHS (202 cases, 481 controls; with blood samples and genotyping for *GSTM1*). The association between doneness of red meat and breast cancer did not vary by *GSTT1* genotype. However, there was a significant interaction by *GSTM1* genotype ($P_{interaction}$ = 0.04). Compared with women who consumed rare/medium-done meat and had the *GSTM1* genotype, those who consistently consumed well- or very well-done meat and had the *GSTM1* null genotype had a relative risk of 2.5 (95% CI, 1.3–4.5). [The Working Group noted that the sample size was too small to evaluate the interaction with genetic polymorphisms. Age, waist: hip ratio, number of live births, and family history were adjusted for. Red meat included processed meat.]

Voorrips et al. (2002) evaluated red meat and processed meat intake and breast cancer in the Netherlands Cohort Study on Diet and Cancer (NLCS), among a cohort of 62 573 women aged 55–69 years. Diet was assessed with a validated FFQ with 150 food items. Red meat, which was presented as "fresh meat", included beef and pork, and did not include processed meat. Subjects were classified into quintiles or categories of consumption (g/day), based on the distribution in the control group of 1598 women. During a mean follow-up of 6 years, 941 breast cancer cases were documented. The relative risk for the top (median, 145 g/day) versus the bottom (median, 45 g/day) quintile of red meat intake was 0.98 (95% CI, 0.73–1.33) for breast cancer. The relative risk for the top (median, 13 g/day) versus the bottom (median, 0 g/day) category of processed meat intake was 0.93 (95% CI, 0.67–1.29) for breast cancer. Intake of beef and pork was also not associated with breast cancer. [The Working Group noted that assessment and adjustment of information on postmenopausal hormone use was not mentioned. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). Almost the same number of cases was included in the pooling project (937 cases).]

Missmer et al. (2002) conducted a pooled analysis of eight prospective cohort studies (Adventist Health Study (AHS); Canadian National Breast Screening Study (CNBSS); IWHS; NLCS; New York State Cohort, (NYSC); New-York University Women's Health Study (NYUWHS); Nurses' Health Study (NHS); and Sweden Mammography Cohort (SMC)) from North America and western Europe, which used validated FFQs. A total of 7379 breast cancer cases diagnosed during up to 15 years of follow-up were included. Pooled multivariate-adjusted relative risks for an increase of 100 g/day in red meat intake were 0.98 (95% CI, 0.93–1.04) in all women, 0.97 (95% CI, 0.79–1.20) in premenopausal women, and 0.97 (95% CI, 0.91–1.03) in postmenopausal women. None of the red meat items, including ground beef, organ products or processed meats, bacon products, sausage products, and hot dogs, were associated with breast cancer risk. [The Working Group noted that red meat included both fresh and processed red meat, blood pudding, liver, and kidney.]

Holmes et al. (2003) evaluated red meat and processed meat intake and breast cancer among 88 647 women included in the NHS. Diet was assessed using a 61–food item FFQ at baseline and a 116–food item FFQ since 1984. Both FFQs were validated. FFQs were sent to the women

multiple times during follow-up. Red meats included hamburger, beef/pork/lamb as a main dish, beef/pork/lamb in sandwiches or mixed dishes, hot dogs, bacon, and other processed meats. Between 1980 and 1998, 4107 cases of invasive breast cancer were identified. There was no association between intake of red meat or processed meat and breast cancer. The relative risk for the top (≥ 1.32 servings/day) versus the bottom (≤ 0.55 servings/day) quintile of red meat intake was 0.94 (95% CI, 0.84–1.05). The relative risk for the top (≥ 0.46 servings/day) versus the bottom (≤ 0.10 servings/day) quintile of processed meat intake was 0.94 (95% CI, 0.85–1.05). The associations were similar by menopausal status. [The study was limited by the definition of red meat, which included processed meat. Fung et al. (2005) evaluated the same cohort, with a shorter follow-up period (1984–2000) and a smaller number of cases (3026 cases), and was not considered. Similarly, Wu et al. (2010) evaluated the consumption of mutagens from meats cooked at a high temperature in an NHS subcohort, with a shorter follow-up period (1996–2006) and fewer cases (2317 cases), and was not considered. The NHS was part of the Pooling Project of Prospective Studies by Missmer et al. 2002. A smaller number of cases were included in the pooling project (2661 cases).]

van der Hel et al. (2004) evaluated red meat and processed meat intake in relation to breast cancer in a nested case–control study of 229 cases (average age, 48 years) and 264 controls, with blood samples, nested within a Dutch prospective study. Controls were frequency-matched by age, town, and menopausal status. Meat consumption was recorded at baseline with the use of a validated, self-administered FFQ. Red meat intake in grams per day was calculated by adding up intakes of beef and pork. There was no association between red meat or processed meat intake and breast cancer risk. Compared with women who had a red meat intake of < 30 g/day, women who were in the high-intake category of ≥ 45 g/day had an odds ratio of 1.32 (95% CI, 0.84–2.08). Compared with women with a processed meat intake of < 20 g/day, those who were in the high-intake category of ≥ 35 g/day had an odds ratio of 1.08 (95% CI, 0.60–1.70). When polymorphisms related to metabolism of HAAs, including *NAT1, NAT2, GSTM1, GSTT1*, were evaluated, there was a positive association with *GSTM1* null genotype. When the association with red meat intake was stratified by *GSTM1* polymorphism, no interaction was observed. [The Working Group noted that the sample size was too limited to evaluate the interaction with genetic polymorphisms. Family history of breast cancer and postmenopausal hormone use were not adjusted for in the multivariate analysis.]

Kabat et al., (2007) evaluated red meat and haem iron intake and breast cancer in the CNBSS, a randomized controlled trial of screening for breast cancer involving women aged 40–59 years. Diet was assessed with a validated FFQ with 86 food items. During a mean follow-up of 16.4 years, 2491 breast cancer cases (1171 premenopausal cases, 993 postmenopausal cases) were included. The relative risk for the top (≥ 40.30 g/day) versus the bottom (< 14.25 g/day) quintile of red meat intake was 0.98 (95% CI, 0.86–1.12) for breast cancer. The relative risk for the top (> 2.95 mg/day) versus the bottom (< 1.58 mg/day) quintile of haem iron intake was 1.03 (95% CI, 0.90–1.18) for breast cancer. The results were similar by menopausal status. [The Working Group noted that red meat was not defined. Although this study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002), which evaluated red meat intake, only 419 breast cancer cases, with a shorter follow-up period (5 years), were included in the pooling project.]

Taylor et al. (2007) evaluated red meat and processed meat intake and breast cancer in the United Kingdom Women's Cohort Study (UKWCS) in 678 cases (283 premenopausal cases, 395 postmenopausal cases). Diet was assessed

between 1995 and 1998 using a 217-item, postal FFQ developed from that of the EPIC study. Red meat consisted of beef, pork, lamb, and other red meats included in mixed dishes, such as meat lasagne, moussaka, ravioli, and filled pasta with sauce. Processed meat consisted of bacon, ham, corned beef, spam, luncheon meats, sausages, pies, pasties, sausage rolls, liver pâté, salami, and meat pizza. Higher intakes of both red meat and processed meat were associated with an elevated risk of breast cancer. Compared with non-consumers, those who were in the high-intake category had a hazard ratio of 1.41 (95% CI, 1.11–1.81) for red meat (> 57 g/day) and 1.39 (95% CI, 1.09–1.78) for processed meat (> 20 g/day). When the association was evaluated by menopausal status, the hazard ratios for the highest versus the lowest quartile of intake were 1.32 (95% CI, 0.93–1.88; 61 cases) among premenopausal women and 1.56 (95% CI, 1.09–2.23; 106 cases) among postmenopausal women for red meat. [The Working Group noted that family history of breast cancer and alcohol intake were not adjusted for.]

Egeberg et al. (2008) conducted a nested case–control study among 24 697 postmenopausal women included in the Diet, Cancer and Health cohort study (1993–2000) in Denmark. The study included 378 breast cancer cases and 378 matched controls. Meat consumption was estimated from a 192-item, validated FFQ, completed at baseline, covering the participants' habitual diet during the preceding 12 months. Intake of red meat in grams per day was calculated by adding up intakes of beef, veal, pork, lamb, and offal. [Intake of processed meat included processed fish, and was not reviewed.] Compared with women whose red meat intake was < 50 g/day, those who consumed > 80 g/day had a relative risk of 1.65 (95% CI, 1.09–2.50; $P_{trend} = 0.03$). The associations were also stratified by *NAT1* and *NAT2* polymorphisms. There was no significant interaction by *NAT1* polymorphism, but there was a significant interaction by *NAT2* polymorphism for red meat intake ($P_{interaction} = 0.04$). The relative risks per 25 g/day increase in red meat intake were 1.37 (95% CI, 1.07–1.76) for the *NAT2* intermediate/fast acetylator phenotype and 1.00 (95% CI, 0.85–1.18) for the *NAT2* slow acetylator phenotype. [The Working Group noted that sample size was limited in some of the stratified analyses by *NAT* polymorphisms. Caloric intake and family history of breast cancer were not adjusted for in the multivariate analysis.]

Kabat et al. (2009) evaluated the association between red meat intake and meat preparation in relation to breast cancer among postmenopausal women only in the NIH-AARP study. Diet was assessed with the NCI Diet History Questionnaire (DHQ), a self-administered, validated FFQ with 124 food items. [Red meat included many types of processed meats, and data are not reported here.] Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs, and low-fat hot dogs made from poultry. During a follow-up of 8 years, 3818 breast cancer cases were documented. Processed meat was not associated with breast cancer risk. The relative risk for the top (> 12.5 g/1000 kcal) versus the bottom (≤ 2.2 g/1000 kcal) quintile of processed meat intake was 1.0 (95% CI, 0.90–1.12) for breast cancer. Cooking methods (grilled or barbecued meat, pan-fried meat, oven-broiled meat, sautéed meat, baked meat, or microwaved meat) and meat doneness levels (rare/medium-done cooked meat or well/very well-done cooked meat) were not associated with breast cancer risk. [The Working Group noted that an earlier publication of the NIH-AARP cohort that had a shorter follow-up and inferior adjustment for potential confounders of breast cancer (Cross et al., 2007) was not considered. Evaluation of cooking methods and doneness levels included poultry.]

Larsson et al. (2009) evaluated red meat intake and breast cancer in the SMC, which was established in 1987–1990 in central Sweden. Diet was assessed with a 67– and 96–food item FFQ at baseline and in 1997, respectively. During a mean follow-up of 17.4 years, 2952 breast cancer cases were ascertained. For overall breast cancer, the relative risks for the top (≥ 98 g/day) versus the bottom (< 46 g/day) quintile of intake were 0.98 (95% CI, 0.86–1.12) for red meat, 1.08 (95% CI, 0.96–1.22) for processed meat, 1.10 (95% CI, 0.90–1.34) for estrogen receptor (ER)+/progesterone receptor (PR)+ tumours, 0.86 (95% CI, 0.60–1.23) for ER+/PR– tumours, and 1.12 (95% CI, 0.70–1.79) for ER–/PR– tumours. [The Working Group noted that red meat included all fresh and minced pork, beef, and veal. Processed meats included ham, bacon, sausages, salami, processed meat cuts, liver pâté, and blood sausages. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). However, a much smaller number of cases were included in the pooling project (1320 cases).]

Ferrucci et al., (2009) evaluated red meat and processed meat intake and cooking methods and doneness levels, and breast cancer risk in the Prostate, Lung, Colorectal and Ovarian (PLCO) trial, a multicentre, randomized controlled trial in women aged 55–74 years who were recruited in 1993–2001. Diet was assessed with by the NCI Diet history Questionnaire (DHQ), a self-administered, validated FFQ with 124 food items. During a mean follow-up of 5.5 years, 1205 breast cancer cases were documented. [Red meat included processed meat, and data are not reported here.] Processed meat included bacon, cold cuts, hams, hot dogs, and sausage. The hazard ratio for the top (> 11.6 g/1000 kcal; median, 16.9 g/1000 kcal) versus the bottom (≤ 2.4 g/1000 kcal; median, 1.4 g/1000 kcal) quintile of processed meat intake was 1.12 (95% CI, 0.92–1.36; P_{trend} = 0.22). Intake of steak, hamburger, sausage, bacon, and pork chops was not associated with breast cancer. The hazard ratios for the top versus the bottom quintile were 1.03 (95% CI, 0.84–1.27) for pan-fried meat, 1.10 (95% CI, 0.90–1.34) for grilled meat, 1.09 (95% CI, 0.90–1.32) for well/very well-done meat, and 1.20 (95% CI, 0.99–1.45) for grilled/pan-fried well/very well-done meat. [The Working Group noted that red meat included processed meat.]

Pala et al. (2009) evaluated the association between red meat and processed meat and breast cancer in the EPIC study. Information on diet was collected from 319 826 women aged 20–70 years in 1992–2003. Diet was assessed by using country-specific (Italy and Sweden centre-specific) validated FFQs designed to capture habitual consumption of food over the preceding year. Red meat consisted of fresh, minced, and frozen beef, veal, pork, and lamb. Processed meats were mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, or heating, and included ham, bacon, sausages, blood sausages, liver pâté, salami, mortadella, tinned meat, and others. A total of 7119 invasive breast cancer cases were documented during a median of 8.8 years of follow-up. A higher intake of processed meat, but not red meat, was associated with a modest elevated risk of breast cancer. The hazard ratio for the highest (median, 84.6 g/day) compared with the lowest (median, 1.4 g/day) quintile of red meat consumption was 1.06 (95% CI, 0.98–1.14; P_{trend} = 0.19). The hazard ratio for the highest (median, 56.5 g/day) compared with the lowest (median, 1.7 g/day) quintile of processed meat consumption was 1.10 (95% CI, 1.00–1.20; P_{trend} = 0.07). The positive association was limited to postmenopausal breast cancer (3673 postmenopausal cases vs 1699 premenopausal cases). The corresponding hazard ratios were 1.13 (95% CI, 1.00–1.28; P_{trend} = 0.06) for postmenopausal women and 0.99 (95% CI, 0.82–1.19; P_{trend} = 0.72) for premenopausal women. [The Working Group noted that family history of breast cancer was not adjusted for.]

Loh et al. (2010) evaluated the association between red and processed meat intake and breast cancer stratified by *MGMT* Ile143Val polymorphism in the EPIC-Norfolk study in 276 cases and 1498 controls. There was no significant interaction with the polymorphism. [The Working Group noted that the sample size was too small to evaluate the interaction with genetic polymorphisms.]

Lee et al. (2013) conducted a nested case–control study within the NHS to evaluate the interaction between red meat intake and *NAT2* acetylator genotype and cytochrome P450 1A2–164 A/C (*CYP1A2*) polymorphism. The study included 579 cases and 981 matched controls. There was no interaction between *NAT2* acetylator genotype or *CYP1A2* polymorphism and red meat intake in relation to breast cancer. [The Working Group noted that the study was limited by the definition of red meat, which included processed meat. Holmes et al. (2003) evaluated red meat intake in the same cohort.]

Genkinger et al. (2013) evaluated breast cancer among African American women from the Black Women's Health Study (BWHS). The study included a total of 1268 cases, among 52 062 women, identified during 12 years of follow-up. Diet during the past year was estimated from a 68-item, modified Block FFQ completed at baseline in 1995. In 2001, a modified version of the 1995 FFQ, which asked about 85 food items, was administered to collect updated dietary information. The 1995 FFQ ascertained the intake of 13 meat items; the 2001 FFQ asked about 15 meat items. Intakes of red meat or processed meat were not associated with breast cancer. Compared with women with a red meat intake of < 100 g/week, those who consumed ≥ 400 g/week had a relative risk of 1.02 (95% CI, 0.83–1.24; P_{trend} = 0.83). Compared with women with a processed meat intake of < 100 g/week, those who consumed ≥ 200 g/week had a relative risk of 0.99 (95% CI, 0.82–1.20; P_{trend} = 0.96). The associations were similar by menopausal status. [The Working Group noted that information on the definitions of red meat and processed meat, and validation of the FFQs was not provided.]

The study by Pouchieu et al. (2014) was based on the SU.VI.MAX, a randomized, double-blind, placebo-controlled trial of a combination of low-dose antioxidants (ascorbic acid, vitamin E, β-carotene, selenium, and zinc), conducted from 1994 to 2002. The study included 190 cases, among 4684 women aged 35–60 years at baseline, identified during a median of 11.3 years of follow-up (1994–2007). Participants completed a dietary record every 2 months, in which they declared all foods and beverages consumed during periods of 24 hours. These dietary records were randomly distributed between week and weekend days, and over seasons to take into account intra-individual variability. Dietary records from the first 2 years of follow-up were used in the study. Portion sizes were assessed using a validated picture booklet, and the amounts consumed from composite dishes were estimated using French recipes validated by food and nutrition professionals. Red meat consisted of fresh, minced, and frozen beef, veal, pork, and lamb. Processed meats were mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, or heating, and included ham, bacon, sausages, blood sausages, liver pâté, salami, mortadella, tinned meat, and others. There was no association between baseline intake of either red meat or processed meat and breast cancer in the whole population. The relative risks for the top versus the bottom quartile of intake were 1.19 (95% CI, 0.79–1.80; P_{trend} = 0.3) for red meat (< 24.9 vs > 63.7 g/day) and 1.45 (95% CI, 0.92–2.27; P_{trend} = 0.03) for processed meat (< 16.4 vs > 43.5 g/day). However, processed meat intake was positively associated with breast cancer risk in the placebo group, but not in the treatment group. The relative risks for the highest compared with the lowest quartile of processed meat consumption were 2.46 (95% CI, 1.28–4.72; P_{trend} = 0.001) in the placebo group and 0.86

(95% CI, 0.45–1.63; P_{trend} = 0.7) in the antioxidant-supplemented group ($P_{interaction}$ = 0.06). [The Working Group took note of the relatively small number of cases. No information was provided on the number of cases in each red meat intake category. Adjustment of lipid intake would be an overadjustment. Some reproductive factors were not adjusted for.]

Farvid et al. (2014) also evaluated early-adulthood total red meat intake and breast cancer in the NHS II. The study included 2830 cases, among 88 803 premenopausal women aged 26–45 years, identified during 20 years of follow-up. Diet was assessed by validated FFQ, with approximately 130 food items. The study found that a higher total red meat (i.e red meat and processed read meat) intake was associated with an elevated risk of breast cancer. The relative risk for the top (median, 1.50 servings/day) versus the bottom (median, 0.14 servings/day) quintile of intake was 1.22 (95% CI, 1.06–1.40; P_{trend} = 0.01). The association was similar by menopausal status, but not statistically significant. [The Working Group noted that the study was limited by the definition of red meat, which included processed meat. Earlier studies of the cohort by Cho et al. (2003) and Cho et al. (2006) were not evaluated.]

Farvid et al. (2015) also evaluated the association between adolescent total red meat intake and breast cancer risk in the NHS II. A subcohort of 44 231 women aged 33–52 years, who filled in a special 124-item FFQ about diet during high school, were followed up for 13 years, and 1132 breast cancer cases were documented. Total red meat intake included unprocessed red meat (hamburger, beef, lamb, pork, and meatloaf) and processed red meat items (hot dog, bacon, and other processed meats such as sausage, salami, and bologna). There was a positive association between adolescent total red meat intake and premenopausal breast cancer. The relative risk for the top (median, 2.43 servings/day) versus the bottom (median, 0.7 servings/day) quintile of total red meat intake was 1.43 (95% CI, 1.05–1.94; P_{trend} = 0.007). The positive association was similar, but significant only for processed meat (RR, 1.29; 95% CI, 0.98–1.70; P_{trend} = 0.02) when intakes of red meat and processed meat were evaluated separately. The association with premenopausal breast cancer was stronger among those with ER+/PR+ breast cancer than among those with ER–/PR– breast cancer; the relative risks per 1 serving/day of total red meat were 1.23 (95% CI, 1.06–1.44) for ER+/PR+ breast cancer and 1.18 (95% CI, 0.87–1.60) for ER–/PR– breast cancer. Haem iron intake was not associated with breast cancer risk. [The Working Group noted that the relative risks for breast cancer by quintile of processed meat and red meat intake in premenopausal, postmenopausal, and all women were reported in tables. A limitation was that the adolescent dietary intake was reported when women were 33–52 years of age. An earlier study by Linos et al. (2008) was not evaluated.]

2.6.2 Case–control studies

Case–control studies on the association between breast cancer and consumption of red meat (see Table 2.6.3, web only) or processed meat (see Table 2.6.4, web only) have been conducted in North America, Latin America, Europe, North Africa, and Asia (these tables are available online at: http://publications.iarc.fr/564). These studies are organized according to the definition of red meat or processed meat, and within these categories, by publication year and study design. Important potential confounders for breast cancer include age, alcohol intake, reproductive factors, use of postmenopausal hormones among postmenopausal women, family history of breast cancer, obesity, and energy intake. Studies that did not adjust for these covariates are noted. In addition, studies with low participation rates (< 50%) in cases or controls, or with large differences in the participation rates of cases and controls are noted because this may have led to selection bias.

Studies that met several exclusion criteria were considered to be uninformative for this evaluation and were not considered further. Studies that evaluated meat intake without providing data specifically for red meat or processed meat were excluded (e.g. Hirayama, 1978; Kinlen, 1982; Talamini et al., 1984; Kato et al., 1992; Malik et al., 1993; Holmberg et al., 1994; Trichopoulou et al., 1995; Núñez et al., 1996; Potischman et al., 1998; Han et al., 2004; Lee et al., 2004; Ko et al., 2013; Bessaoud et al., 2008; Dos Santos Silva et al., 2002; La Vecchia et al., 1987). Similarly, studies that evaluated breast cancer in relation to dietary patterns instead of evaluating red or processed meat were excluded (e.g. Cui et al., 2007; Wu et al., 2009; Cade et al., 2010; Cho et al., 2010; Ronco et al., 2010; Buck et al., 2011; Zhang et al., 2011; Bessaoud et al., 2012; Jordan et al., 2013; Mourouti et al., 2014; Pou et al., 2014). Other reasons for exclusion were small sample size (about < 100 breast cancer cases) (e.g. Phillips, 1975; Kikuchi et al., 1990; Ingram et al., 1991; Morales Suárez-Varela et al., 1998; Delfino et al., 2000; Lima et al., 2008; Di Pietro et al., 2007; Landa et al., 1994), and the availability of updated or more complete data from the same population (Lee et al., 1991; Levi et al., 1993; Ronco et al., 1996; Favero et al., 1998).

(a) Red meat and/or processed meat

(i) Population-based studies

Lubin et al. (1981) conducted a study in Canada with 577 cases and 826 controls. The study evaluated intake of beef and pork. Women who consumed beef daily had a relative risk of 1.53 (95% CI, 1.1–2.1) compared with women who consumed beef < 3 times/week in the age-adjusted analysis. Similarly, compared with women who consumed pork ≤ 1 day/month, those who consumed it ≥ 1 time/week had a relative risk of 2.16 (95% CI, 1.6–2.9) in the age-adjusted analysis. [The Working Group noted that the response rate was much lower among controls. The FFQ was not validated. Only age was adjusted for in statistical analyses.]

Hislop et al. (1986) evaluated intake of beef and pork and breast cancer in British Columbia, Canada. A total of 846 cases (74% participation rate) and 862 controls (79% participation rate) were included. Eligible cases included women younger than 70 years who were registered in the British Columbia Cancer Registry during 1980–1982. A pool of controls, frequency-matched on age, was created from the neighbours or acquaintances of the cases. Diet was assessed with a mailed, self-administered questionnaire for four different age periods. Compared with a beef intake of less than once daily, those who consumed beef daily had an odds ratio of 1.47 (95% CI, 1.12–1.92). Compared with a pork intake of less than once weekly, those who consumed pork weekly had an odds ratio of 1.13 (95% CI, 0.92–1.39). [The Working Group noted that diet was not assessed with a validated and standardized assessment tool. Odds ratios were adjusted for age only. The evaluation of intake was dichotomous only.]

Toniolo et al. (1989) evaluated intake of cured meat [i.e. processed meat] and offal and breast cancer in Italy. A total of 250 cases (91% participation rate) and 499 controls (86% participation rate) were included. Women younger than 75 years who resided in the province of Vercelli were included. Cases were women with microscopically confirmed invasive breast cancer who were free of local or distant metastases, except in the regional lymph nodes. Controls were female residents who were frequency-matched to the cases within 10-year age strata in an approximately 2:1 ratio. Diet was assessed with a dietary history method. The relative risk for the top versus the bottom intake of cured meat [i.e. processed meat] was 1.3. [The Working Group noted that diet was assessed with a validated assessment tool. Odds ratios were adjusted for age and caloric intake only, and 95% confidence intervals were not provided.]

Matos et al. (1991) conducted a population-based study in Argentina that included 196 cases recruited in 1979–1981 and 205 controls selected from friends and sanguineous family members of the cases. The study evaluated beef consumption based on cooking methods (barbecued, deep-fried, baked, boiled, stewed). None of the associations were significant. [The Working Group noted that the study had a modest sample size, and did not report the response rate among controls. The FFQ was not validated. Only age, age at first birth, and years of schooling were adjusted for in the statistical analysis. The consumption of beef was adjusted for other meat items, and the way of cooking for the other ways of cooking.]

Ambrosone et al. (1998) conducted a population-based case–control study of diet and breast cancer in New York, USA, with 740 cases and 810 controls. Controls younger than 65 years were randomly selected from the New York State Motor Vehicle Registry, and those 65 years and over were identified from Health Care Financing Administration lists. Of the premenopausal women contacted, 66% of eligible cases and 62% of eligible controls participated, and of the postmenopausal women contacted, 54% of cases and 44% of controls participated. An FFQ with the usual portion sizes of over 300 foods was administered to assess usual intake 2 years before the interview. Processed meat included ham, hot dogs, sausages, bacon, and cold cuts. The study found that intake of beef or pork was not associated with breast cancer risk in either premenopausal or postmenopausal women. Processed meat intake was non-significantly associated with premenopausal breast cancer; intake of > 48 g/day compared with < 14 g/day was associated with an odds ratio of 1.4 (95% CI, 0.9–2.3; $P_{trend} = 0.09$). [The Working Group noted the low response rate, especially among controls, which might have led to selection bias. There was no description of validation of the FFQ. Caloric intake was not adjusted for.]

Hermann et al. (2002) evaluated diet and breast cancer among women up to 50 years of age [thus, probably almost all of them were premenopausal women] in Germany (355 cases, 838 controls). Cases were women with a diagnosis of incident in situ or invasive breast cancer (35% participation rate). Controls were matched by exact age and study region, and were selected from a random list of residents provided by the population registries (37% participation rate). Diet was assessed with a 176-item FFQ similar to the FFQ used in the German part of the EPIC study, which was validated in other populations. The study found that the highest quartile of intake of red meat (≥ 65 g/day) was associated with an increased risk of breast cancer of up to 85% (OR, 1.85; 95% CI, 1.23–2.78; $P_{trend} = 0.016$) compared with the lowest quartile of intake (1–21 g/day). The odds ratios for the highest intake categories (≥ 33 g/day for beef, ≥ 39 g/day for pork, and ≥ 73 g/day for processed meat) were 1.58 (95% CI, 1.06–2.36; $P_{trend} = 0.04$), 1.47 (95% CI, 0.98–2.21; $P_{trend} = 0.07$), and 1.29 (95% CI, 0.86–1.95; $P_{trend} = 0.17$) for beef, pork, and processed meat, respectively. [The Working Group noted the modest sample size, and the median time between diagnosis of breast cancer and FFQ administration was 209 days for the cases, which led to a low response rate. This study overlapped with Brandt et al. (2004).]

Using essentially the same data set, Brandt et al. (2004) evaluated the association with breast cancer risk, stratified by the allelic length of the epidermal growth factor receptor (*EGFR*) gene CA simple sequence repeat. The sample size was further reduced to 311 cases and 689 controls, after excluding those with no genetic data. The positive association between red meat intake and breast cancer appeared to be limited to those with the long/long allele of *EGFR* (OR for red meat intake of ≥ 65 vs < 22 g/day, 10.68; 95% CI, 1.57–72.58; $P_{trend} = 0.03$) and those with the short/short allele of *EGFR* (OR for the same comparison, 1.86; 95% CI, 1.06–3.27; $P_{trend} = 0.02$), but

was not shown among those with the short/long allele of *EGFR*. Processed meat was not evaluated. [The Working Group noted that the sample size for the evaluation of the long/long allele of *EGFR* was limited, with six cases in the reference category. Caloric intake was not adjusted for. The data set was also used in (Hermann et al., 2002).]

Steck et al. (2007) evaluated the lifetime intakes of grilled or barbecued and smoked meats [i.e. processed meats] among 1508 cases and 1556 controls in a population-based case–control study in Long Island, New York, USA. Cases (82% eligible) were identified through the pathology/cytology records of 33 institutions, and lived in Nassau County and Suffolk County. Controls (63% eligible) were identified using random digit dialling and Centers for Medicare & Medicaid Services rosters. Meat intake was assessed as part of an in-home questionnaire administered by a trained interviewer. The consumption patterns of four categories of grilled/barbecued and smoked meats over each decade of life since the teenage years were examined. The participants also completed a Block FFQ, which included approximately 100 food items, that assessed diet in the previous year. The associations were evaluated by menopausal status. In postmenopausal women, compared with those who consumed grilled/barbecued red meat (beef, pork, and lamb) ≤ 630 times over their lifetime, those who consumed grilled/barbecued red meat ≥ 2163 times over their lifetime had an odds ratio of 1.32 (95% CI, 1.01–1.72; $P_{trend} = 0.10$). Compared with those who consumed smoked ham, pork, and lamb [i.e. processed meat] ≤ 810 times over their lifetime, those who consumed smoked ham, pork, and lamb ≥ 2278 times over their lifetime had an odds ratio of 1.30 (95% CI, 0.99–1.69; $P_{trend} = 0.22$). However, there was no association among premenopausal women, probably because the sample size was much smaller among premenopausal women. [The Working Group noted that the much lower response rate in controls was a limitation that might have led to selection bias. In addition, although energy intake was adjusted for, only a limited number of breast cancer risk factors were adjusted for.]

Fu et al. (2011) used the Nashville Breast Health Study (the USA). The study included 2386 (62% response rate) newly diagnosed primary breast cancer (invasive ductal or ductal carcinoma in situ) cases between the ages of 25 and 75 years. The majority of the participants were residents of the Nashville metropolitan area. The study included 1703 controls (71% response rate), which had virtually identical criteria to the cases. Of the controls, 87% were identified by random digit dialling households, and the remaining controls were mostly identified among women who received a screening mammography with a normal finding. Interviewer-administered telephone interviews were used to obtained information on usual intake frequency, portion size, cooking method, and doneness of 11 meats in the previous year before the interviews (for controls) or cancer diagnosis (for cases). All participants who completed questions on food doneness had a photograph booklet in front of them during the telephone interview. Red meat included hamburgers, cheeseburgers, beef patties, beef steaks, pork chops, ham steaks, and ribs (short ribs or spare ribs). Processed meat included bacon, sausage, and hot dogs/frankfurters. Compared with those in the lowest quartile of intake, those in the highest quartile of intake had odds ratios of 1.7 (95% CI, 1.3–2.4; $P_{trend} < 0.001$) for red meat and 1.7 (95% CI, 1.2–2.3; $P_{trend} < 0.001$) for well-done red meat among postmenopausal women. Corresponding odds ratios were 1.3 (95% CI, 0.9–2.0; $P_{trend} = 0.031$) for red meat and 1.5 (95% CI, 1.1–2.2; $P_{trend} = 0.017$) for well-done red meat among premenopausal women. The results for individual processed meat items, but not for total processed meats, were presented. Compared with those in the lowest quartile of intake, those in the highest quartile of intake had odds ratios of 1.2 (95% CI, 1.0–1.4; $P_{trend} = 0.006$) for bacon, 1.0 (95% CI, 0.7–1.3; $P_{trend} = 0.612$) for sausage,

and 1.0 (95% CI, 0.8–1.3; P_{trend} = 0.633) for hot dogs/frankfurters. [The Working Group noted that the FFQ was not validated and that red meat included some processed meat (e.g. ham).]

Chandran et al. (2013), in the USA, evaluated ethnic disparities with red and processed meat intake and breast cancer in African Americans (803 cases, 889 controls) and Caucasians (755 cases, 701 controls). Controls were identified by random digit dialling of residential telephone and cell phone numbers. Diet was assessed with an FFQ with approximately 125 food items, which was validated in other USA populations. Processed meat included lunchmeats, as well as bacon, sausages, bratwursts, chorizo, salami, and hot dogs. For Caucasian women, the odds ratios for the top versus the bottom quartile of intake were 1.48 (95% CI, 1.07–2.04; P_{trend} = 0.07) for processed meat (> 15.19 vs ≤ 2.35 g/1000 kcal per day) and 1.40 (95% CI, 1.01–1.94; P_{trend} = 0.29) for red meat (> 24.70 vs ≤ 4.14 g/1000 kcal per day). For African American women, the odds ratios for the top versus the bottom quartile of intake were 1.21 (95% CI, 0.89–1.64; P_{trend} = 0.18) for processed meat (> 15.19 vs ≤ 2.35 g/1000 kcal per day) and 0.84 (95% CI, 0.61–1.14; P_{trend} = 0.28) for red meat (> 24.70 vs ≤ 4.14 g/1000 kcal per day). The results supported an association between red meat or processed meat consumption and increased breast cancer risk in Caucasian women. However, in African American women, only processed meat consumption was positively associated with breast cancer. [The Working Group concluded that the strengths of the study included the large sample of African American women, and evaluation by menopausal status and hormone receptor status. In addition, an extensive list of covariates was adjusted for. Limitations included the much lower response rate in controls, which may have led to selection bias and limited statistical power in some subgroup analyses. In addition, alcohol intake was not adjusted for in statistical analyses.]

Mourouti et al. (2015) evaluated red meat and processed meat in 250 cases and 250 controls from Greece. Breast cancer patients that visited the pathology–oncology clinics of five major general hospitals in Athens, Greece, were recruited as cases (average age, 56 years). Controls were selected from the same catchment area, and had a participation rate of 88%. Diet was assessed with a validated SQFFQ with 86 questions. Red meat included beef, lamb, veal, and pork. Processed meat included cured and smoked meats, ham, bacon, sausages, and salami. The study found a positive association with processed meat intake, but not with red meat intake. Compared with non-consumers, women who consumed processed meat 1–2 times/week and women who consumed processed meat ≥ 6 times/week had odds ratios of 2.65 (95% CI, 1.36–5.14) and 2.81 (95% CI, 1.13–6.96), respectively ($P < 0.05$). Compared with women who consumed red meat ≤ 1 time/week, those who consumed red meat 8–10 times/week had an odds ratio of 0.99 (95% CI, 0.31–3.12). [The Working Group noted that the study had a modest sample size, but did not adjust for caloric intake, alcohol intake, and reproductive factors.]

(ii) Hospital-based studies

Richardson et al. (1991) conducted a hospital-based case–control study in southern France that included 409 cases and 515 controls. Cases were women between 28 and 66 years of age with histologically confirmed primary carcinoma of the breast. Controls were women of the same age group who were admitted for the first time to a nearby hospital or hospitalized for general surgery in a large clinic. Among the 932 people interviewed, all cases joined, but eight controls refused to join the study. A dietary history questionnaire of similar design to the one described in Block (1982) with 55 food items was used to assess diet. The study found a non-significant positive association between processed pork meat intake and breast cancer (OR, 1.4;

95% CI, 0.9–2.0; intake of > 87.5 vs ≤ 25 g/week). [The Working Group noted that no description was provided whether the dietary history questionnaire was validated. Information on caloric intake was not available for adjustment in statistical analyses.]

Franceschi et al. (1995) conducted a hospital-based case–control study in Italy in 1991–1994. The study included 2569 cases and 2588 controls. Cases were women with first histologically confirmed cancer of the breast, diagnosed no later than 1 year before the interview, and with no previous diagnoses of cancer at other sites. Controls were patients with no history of cancer admitted to major teaching and general hospitals in the same catchment area of the cases for acute non-neoplastic, non-gynaecological conditions, unrelated to hormonal or digestive tract diseases, or to long-term modifications of diet. Diet was measured with a 79–food item, validated FFQ. Red meat included steak, roast beef, lean ground beef, boiled beef, beef or veal stew, wiener schnitzel, liver, and pasta with meat sauce and with meat filling. Pork and processed meats included pork chop, prosciutto, ham, salami, and sausages. Compared with those in the lowest quintile of red meat intake (≤ 2.0 servings/week), participants in the highest quintile of red meat intake (> 5.3 servings/week) had an odds ratio of 1.09 (95% CI, 0.90–1.31). Compared with those in the lowest quintile of pork and processed meat intake (≤ 1.0 servings/week), participants in the highest quintile of pork and processed meat intake (> 4.5 servings/week) had an odds ratio of 1.09 (95% CI, 0.89–1.33). The participation rate of cases and controls was > 95%. In addition, a limited number of breast cancer risk factors (age and parity) were adjusted for. This study was included in a later analysis of case–control studies conducted in Italy and Switzerland (Di Maso et al. 2013). [The Working Group noted that, in this study, pork (i.e. red meat) was included in processed meat, and red meat did not include pork.]

Tavani et al. (2000) conducted a large hospital-based study of red meat intake and multiple cancer sites in Italy that included 3412 breast cancer cases. Controls (n = 7990) were selected among those who were admitted to the same network of hospitals as the cases. Controls with a wide spectrum of acute non-neoplastic conditions were accrued. A structured questionnaire asked about the frequency of intake of approximately 40 foods and total red meat consumption per week. Red meat included beef, veal, and pork, and excluded canned and preserved meat. Compared with those who consumed ≤ 3 portions/week of red meat, women who consumed > 6 portions/week of red meat had an odds ratio of 1.2 (95% CI, 1.1–1.4). [The Working Group noted that the participation rate of cases and controls was > 95%. The questionnaire asking about food intake was not validated. Processed meat was not evaluated separately. Caloric intake was not adjusted for in statistical analyses.]

Di Maso et al. (2013) evaluated data with information on cooking practices from a network of case–control studies conducted in Italy and Switzerland between 1991 and 2009. Multiple cancer sites were evaluated in relation to red meat intake and intake by cooking method (roasting/grilling, boiling/stewing, frying/pan-frying). For breast cancer analysis, 3034 cases and 11 656 controls were included. Trained personnel administered a structured questionnaire to cases and controls during hospitalization. Subjects' usual diet in the 2 years before diagnosis (or hospital admission for controls) was investigated using an FFQ that included specific food items on weekly consumption of red meat according to different cooking methods (i.e. boiling/stewing, roasting/grilling, or frying/pan-frying). Serving size was defined as an average serving in the Italian diet. Red meat included beef, veal, pork, horse meat, and half of the first course, including meat sauce (e.g. lasagne, pasta/rice with bologna sauce), and did not include processed meat. The

FFQ was tested for validity. Compared with those who consumed < 60 g/day of red meat, those who consumed ≥ 90 g/day of red meat had an odds ratio of 1.18 (95% CI, 1.04–1.33; P_{trend} < 0.01). The odds ratios per 50 g/day increase in red meat intake were 1.14 (95% CI, 1.02–1.28) for pre- and perimenopausal women and 1.10 (95% CI, 1.01–1.19) for postmenopausal women ($P_{interaction}$ = 0.55). Among the cooking methods, roasting/grilling conferred the highest risk (OR, 1.20; 95% CI, 1.08–1.34) for an increase of 50 g/day of red meat. [The Working Group noted that the study included Franceschi et al. (1995), previously reported in this section.]

(b) Red meat and processed meat combined or not clearly defined

(i) Population-based studies

Ewertz and Gill (1990) evaluated intake of individual red meat items and breast cancer in Denmark. A total of 1474 cases (88% participation rate) and 1322 age-matched controls (79% participation rate) were included. Cases were recruited from the Danish Cancer Registry and the nationwide clinical trial of the Danish Breast Cancer Cooperative Group (DBCG). Controls were an age-stratified random sample of the general female population, selected from the central population register. Diet was assessed with an FFQ with 21 food items. Intake of lean pork, medium-fat pork, fatty pork, and liver was evaluated. The relative risk for the top versus the bottom quartile of intake of medium-fat pork was 1.34 (95% CI, 1.05–1.71). No other items were significantly related to breast cancer. [The Working Group noted that diet was assessed 1 year after the diagnosis among cases. Information on validation of the FFQ was not provided. Odds ratios were adjusted for age at diagnosis and place of residence only.]

Goodman et al. (1992) evaluated bacon, sausage, liver and pork, and other meats, including spam, luncheon meats, beef, and lamb, but not red meat or processed meat intake in 272 postmenopausal breast cancer cases and 296 controls in Hawaii, USA. The study selected 43 different food items that largely contribute to the intake of fat and animal protein in Japanese and Caucasian women. A dose–response relation with breast cancer risk and sausage intake was suggested (P_{trend} < 0.01). The odds ratio for high (> 60 g/week) versus low (none) sausage intake was 1.7 (95% CI, 1.2–2.4). [The Working Group noted the modest sample size. In addition, there was no separate evaluation of red meat or processed meat. Caloric intake was not adjusted for. Age, ethnicity, age at first birth, and age at menopause were adjusted for, but other breast cancer risk factors were not adjusted for.]

Witte et al. (1997) conducted a family-matched case–control study including cases from a multicentre genetic epidemiology study of breast cancer conducted in the USA and Canada in 1989. Survivors of bilateral premenopausal breast cancer with at least one sister who was alive in 1989 were included, and one or more of the sisters served as controls. A total of 140 cases and 222 unaffected sisters of the cases were included. Cases and controls were mailed a 61-item SQFFQ to assess diet a median time of > 13 years after diagnosis. Red meat was not positively associated with breast cancer risk (OR, 0.6; 95% CI, 0.3–1.3) for the highest versus the lowest quartile (14.1 vs 4.5 servings/week) of intake. [The Working Group noted that the sample size was small. Red meat was not defined.]

Männistö et al. (1999) evaluated intake of beef and pork [i.e. red meat] and breast cancer in Finland. The subjects were participants in the Kuopio Breast Cancer Study who lived in the catchment area of the Kuopio University Hospital in 1990–1995. A total of 310 cases aged 25–75 years (81% participation rate), and 454 controls (72% participation rate) from the Finnish National Population Register and 506 controls (92% participation rate) who were referred to the same examinations as the cases

and subsequently found healthy were included. Diet was assessed with a validated FFQ with 110 food items. Among premenopausal women, the odds ratios for the top versus the bottom quintile (> 77 vs < 37 g/day) of intake of beef and pork [red meat] were 0.6 (95% CI, 0.3–1.4) versus population controls and 0.5 (95% CI, 0.3–1.2) versus referral controls. Among postmenopausal women (top vs bottom quintile, > 68 vs < 29 g/day), the corresponding odds ratios were 0.9 (95% CI, 0.5–1.7) and 1.0 (95% CI, 0.5–2.0). [The Working Group noted that caloric intake was not adjusted for in statistical analyses.]

Shannon et al. (2003) conducted a population-based case–control study of diet and postmenopausal breast cancer in western Washington, USA, with 441 cases and 370 controls. Diet was assessed by FFQ with 95 food items. The study found that red meat was, but processed meat was not, associated with an elevated breast cancer risk. The odds ratio for the top quartile (> 0.82 servings/day) compared with the bottom quartile (≤ 0.29 servings/day) of intake was 2.03 (95% CI, 1.28–3.22; $P_{trend} = 0.002$) for red meat intake. [The Working Group noted that red meat and processed meat were not defined. The response rate was low, especially among controls (50%). In addition, the FFQ might not have been validated because there was no description of validation.]

Shannon et al. (2005) evaluated intake of red meat and processed meat and breast cancer in China. The study was nested within a randomized trial of breast self-examination. A total of 378 cases (85% participation rate) and 1070 age- and menstrual status–matched controls (64–82% participation rate) were included. Diet was assessed with an interviewer-administered FFQ with 115 food items. Red meat included beef, pork, pork chops, spare ribs, pig trotters, ham, pork liver, beef, other red meats, organ meat (except liver), and lamb or mutton. The odds ratio for the top (≥ 6.1 servings/week) versus the bottom (≤ 3.0 servings/week) quartile of red meat intake was 1.24 (95% CI, 0.77–1.99). The odds ratio for the top (≥ 2 servings/month) versus the bottom (≤ 0.5 servings/month) quartile of cured meat intake was 1.2 (95% CI, 0.82–1.74). Red meat or cured meat [i.e. processed meat] intake was not associated with breast cancer risk. [The Working Group noted that, although the study was based on a prospective clinical trial study, there was no follow-up of participants after dietary assessment, which was based on the status of the cases and controls, and for cases, was conducted before biopsy, and thus, was considered as a case–control study. The statistical analysis was adjusted for age, total energy intake, and breastfeeding only. Red meat included ham, which is a processed meat.]

Mignone et al. (2009) used data from the Collaborative Breast Cancer Study (CBCS) in the USA. The study included 2686 cases and 3508 community controls. Recent incident invasive breast cancer cases were identified through their respective state cancer registries. Community controls were selected at random (within age strata) from lists of licenced drivers and Medicare beneficiaries with no history of breast cancer. Detailed questions on red meat consumption and cooking practices in the recent past (approximately 5 years before diagnosis in the cases or a comparable time referent in the controls) were collected. Women were asked to report on the degree of doneness for red meat. Compared with women who consumed red meat < 2 servings/week, those who consumed ≥ 5 servings/week had an odds ratio of 0.98 (95% CI, 0.81–1.18) in the multivariate analysis among all women. Corresponding odds ratios were 0.82 (95% CI, 0.60–1.13) among premenopausal women and 1.02 (95% CI, 0.80–1.31) among postmenopausal women. [The Working Group noted that the study did not appear to utilize the full FFQ. Red meat was not clearly defined, but presumably did not include processed meat because processed meat items were not described

as assessed. Caloric intake was not adjusted for in the multivariate analysis.]

Rabstein et al. (2010) in Germany included 1020 cases and 1047 population-based controls. Women with a histopathologically confirmed breast cancer diagnosis within 6 months before enrolment were included (88% response rate). Current residence in the study region, age not more than 80 years, and Caucasians were selected. Controls were frequency-matched to cases by year of birth in 5-year classes with the same inclusion criteria as cases. The study evaluated red meat intake and breast cancer by hormone receptor status and *NAT2* polymorphism. Regular (> 1 time/week) consumption of red meat was associated with an elevated risk of breast cancer compared with rare (< 1 time/month) consumption (OR, 1.59, 95% CI, 1.11–1.99). The positive association was similar by hormone receptor status; the corresponding odds ratios were 1.33 (95% CI, 0.95–1.87) for ER+ cases (n = 601), 1.71 (95% CI, 0.95–3.09) for ER– cases (n = 169), 1.42 (95% CI, 1.00–2.00) for PR+ cases (n = 569), and 1.43 (95% CI, 0.85–2.41) for PR– cases (n = 195). The association was also similar by *NAT2* acetylation status ($P_{interaction}$ = 0.16); the corresponding odds ratios were 1.71 (95% CI, 1.15–2.55) for slow acetylators (n = 569) and 1.73 (95% CI, 1.15–2.61) for fast acetylators (n = 439). [The Working Group concluded that the study lacked information on the dietary assessment, the validation study of the dietary assessment tool, and the definition of red meat.]

The population-based Shanghai Breast Cancer Study was analysed by Dai et al. (2002), Kallianpur et al. (2008), and Bao et al. (2012). The study consisted of a phase 1 (1996–1998) and phase 2 (2002–2004). Cases were identified through the rapid case ascertainment system of the Shanghai Cancer Registry and were permanent residents of urban Shanghai (age, 25–70 years); 1602 eligible breast cancer cases were identified during phase 1, and 2388 cases were identified during phase 2 (86% participant rate). Controls were randomly selected from women in the Shanghai Resident Registry and frequency-matched to cases by age in 5-year intervals (78% participation rate). Diet was measured with a validated, 76–food item FFQ that included 19 animal foods.

Dai et al. (2002) published the association between red meat intake and breast cancer using phase 1 subjects (1459 cases, 1556 controls). Red meat included pork, beef, and lamb. Red meat intake and breast cancer risk were evaluated and stratified by the deep-frying cooking method (never, ever, well done). The positive association between red meat intake and breast cancer appeared to be stronger in those who used ever or well-done deep-frying cooking method than in those who never used this cooking method. After adjusting for total energy and other potential confounders, the odds ratios for > 87 g/day of red meat compared with < 29 g/day of red meat were 1.49 (95% CI, 1.04–2.15) for never-users of the deep-frying cooking method, 1.78 (95% CI, 1.24–2.55) for ever-users of the deep-fried cooking method, and 1.92 (95% CI, 1.30–2.83) for well-done users of the deep-frying cooking method. [The Working Group noted that no information was provided on whether red meat included processed meat. Alcohol intake was not adjusted for in statistical analyses.]

Bao et al. (2012) used subjects from phases 1 and 2 of the Shanghai Breast Cancer Study (3443 cases, 3474 controls). Red meat was positively associated with breast cancer. Compared with women who consumed ≤ 26 g/day of red meat, those who consumed ≥ 82 g/day of red meat had an odds ratio of 1.45 (95% CI, 1.22–1.72; P_{trend} < 0.0001). Corresponding odds ratios were 1.51 (1.20–1.90) for ER+/PR+, 1.55 (1.16–2.07) for ER–/PR–, 1.81 (95% CI, 1.15–2.84) for ER+/PR–, and 1.29 (95% CI, 0.81–2.03) ER–/PR+ breast cancers (for ER+/PR+ and ER–/PR– , $P_{heterogeneity}$ = 0.57). [The Working Group noted that no information was provided on whether red meat included processed meat.]

Kallianpur et al. (2008) evaluated iron intake in the phase 1 and 2 population (3452 cases, 3474 controls). After adjusting for known risk factors, including total energy intake, animal-derived (largely haem) iron intake was positively associated with breast cancer risk ($P_{trend} < 0.01$). The odds ratio for the top versus the bottom quartile of intake was 1.50 (95% CI, 1.19–1.88). The association was similar by menopausal status. [The Working Group noted that no information was provided on whether red meat included processed meat. Alcohol intake was not adjusted for in statistical analyses.]

(ii) Hospital-based studies

Lee et al. (1992) conducted a study among Singapore Chinese women, comprising 200 cases (93% response rate) and 420 hospital-based controls (94% response rate). Diet was assessed by interview using a 90–food item FFQ. Red meat intake was associated with breast cancer in premenopausal women (109 cases), but not in postmenopausal women (91 cases). The odds ratios for the highest versus the lowest tertile of red meat intake (≥ 48.6 vs < 22.0 g/day) was 2.6 (95% CI, 1.3–4.9) in premenopausal women and 1.2 (95% CI, 0.6–2.4) in postmenopausal women. [The Working Group noted that red meat intake was mostly pork, but also included beef and mutton; it was not specified whether processed meat was excluded. The study had a modest sample size. The FFQ was not validated in this population.]

De Stefani et al. (1997) conducted a hospital-based case–control study in Uruguay in 1994–1996 that included 352 breast cancer cases (96% participation) and 382 controls (98% participation). The study used an FFQ with 64 items that was not validated. The study found an increased risk of breast cancer was associated with a higher beef intake and lamb intake. The odds ratios were 3.84 (95% CI, 2.09–7.05) for beef and 2.38 (95% CI, 1.27–4.47) for lamb for the top versus the bottom quartile of intake (≥ 365 vs ≤ 154 servings/year) and for the third versus the first tertile of intake (< 12 vs > 53 servings/year), respectively. The results were not similar by menopausal status since P_{trend} was significant only among postmenopausal women. Processed meat was not associated with breast cancer risk. [The Working Group noted that this was a hospital-based study with a small sample size. The FFQ was not validated. Adjustment of fat intake in the multivariate analysis would have been an overadjustment. Red meat included processed meat, so data are not presented here.]

A hospital-based case–control study of breast cancer was conducted in Guangdong, China, with 438 cases (96% response rate) and 438 controls (98% response rate) by Zhang et al. (2009). Diet was assessed with an 81–food item, validated FFQ. Processed meat included sausage, ham, bacon, and hot dog. The odds ratio for the highest quartile of intake was 1.44 (95% CI, 0.97–2.15; $P_{trend} = 0.07$) for processed meat. [The Working Group took note of the high participation rate. Alcohol intake was not adjusted for in statistical analyses. Red meat included processed meat, so data are not given here.]

Kruk (2007), in Poland, evaluated 858 cases and 1085 controls aged 28–78 years, and evaluated the association between red meat intake and breast cancer. Cases were identified from the Szczecin Regional Cancer Registry and were diagnosed with histologically confirmed invasive cancer. Controls were frequency-matched by age (5-year age group) and place of residence. Most controls (853) were selected among patients admitted to ambulatories in the same area as the cases to control for health. The remaining 232 controls were selected from hospital patients. Diet was assessed by FFQ, which was modified from the Block (the USA) and Franceschi (Italy) FFQs to include 18 main, Polish-specific food groups. Kruk & Marchlewicz (2013) described that red meat included pork, beef, or lamb that was broiled, fried, or canned. The study presented the results by menopausal status (310

premenopausal, 548 postmenopausal cases). The positive association between red meat intake and breast cancer risk was significant in premenopausal women and was suggestive, but not significant, among postmenopausal women. The odds ratios comparing those who consumed 0 servings/week of red meat with those who consumed ≥ 5 servings/week of red meat were 2.96 (95% CI, 1.49–5.91; P_{trend} = 0.009) among premenopausal women and 1.51 (95% CI, 0.89–2.57; P_{trend} = 0.65) among postmenopausal women. [The Working Group noted that the study had low response rates among cases. The FFQ was not validated. Caloric intake was not adjusted for. Kruk & Marchlewicz used the same data set and stratified the association by physical activity level. Red meat included processed meat.]

Kruk & Marchlewicz (2013) used the same data set as Kruk (2007), and evaluated the association between red meat and processed meat intake and breast cancer stratified by lifetime physical activity. A positive association between processed meat intake and breast cancer was only significant among those with low lifetime physical activity. The odds ratio comparing those who consumed ≤ 2 servings/week of processed meat with those who consumed ≥ 7 servings/week of processed meat was 1.78 (95% CI, 1.04–3.59) among women with < 105 metabolic equivalent hours per week of physical activity. Separate results were not presented by menopausal status. [The Working Group noted that the study had low response rates among cases. The FFQ was not validated. Caloric intake was not adjusted for. It was unclear whether the reported data were the result of a true effect modification by physical activity because the statistically significant subgroup had the largest sample size, and the *P* value for interaction was not calculated. Red meat included canned red meat (i.e. processed meat), so data are not reported here.]

Ronco et al. (2012) conducted a hospital-based case–control study (253 cases, 497 controls) and evaluated multiple risk factors for premenopausal breast cancer in Uruguay. Red meat included beef, barbecue, and milanesas (a typical form of fried meat in Uruguay). The study found that a high consumption of red meat, which was based on two food items, was associated with a higher risk of breast cancer (OR, 2.2; 95% CI, 1.35–3.60). [The Working Group concluded that the limitations were that this was a hospital-based study with a relatively small sample size. In addition, the study used a limited and non-validated FFQ, had no category cut-points for red meat intake, and made no adjustment for caloric intake in statistical analyses.]

Laamiri et al. (2014) reported that both red meat and processed meat intake were strongly positively associated with breast cancer among 400 cases and 400 controls from Morocco. Cases were recruited from the National Institute of Oncology. Controls were recruited at the institute after they had undergone a mammography that showed no signs of breast cancer. Diet was measured by FFQ. The odds ratios were 4.61 [95% CI, 2.26–9.44] for red meat intake and 9.78 [95% CI, 4.73–20.24] for processed meat intake. [The Working Group concluded that the study lacked information on response rates, details of items collected in the FFQ, validation study of the dietary assessment tool, and definition of red meat and processed meat, as well as the increment unit for the odds ratios, which appeared to treat red meat and processed meat as continuous variables. The study also did not adjust for alcohol intake, caloric intake, and reproductive factors.]

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