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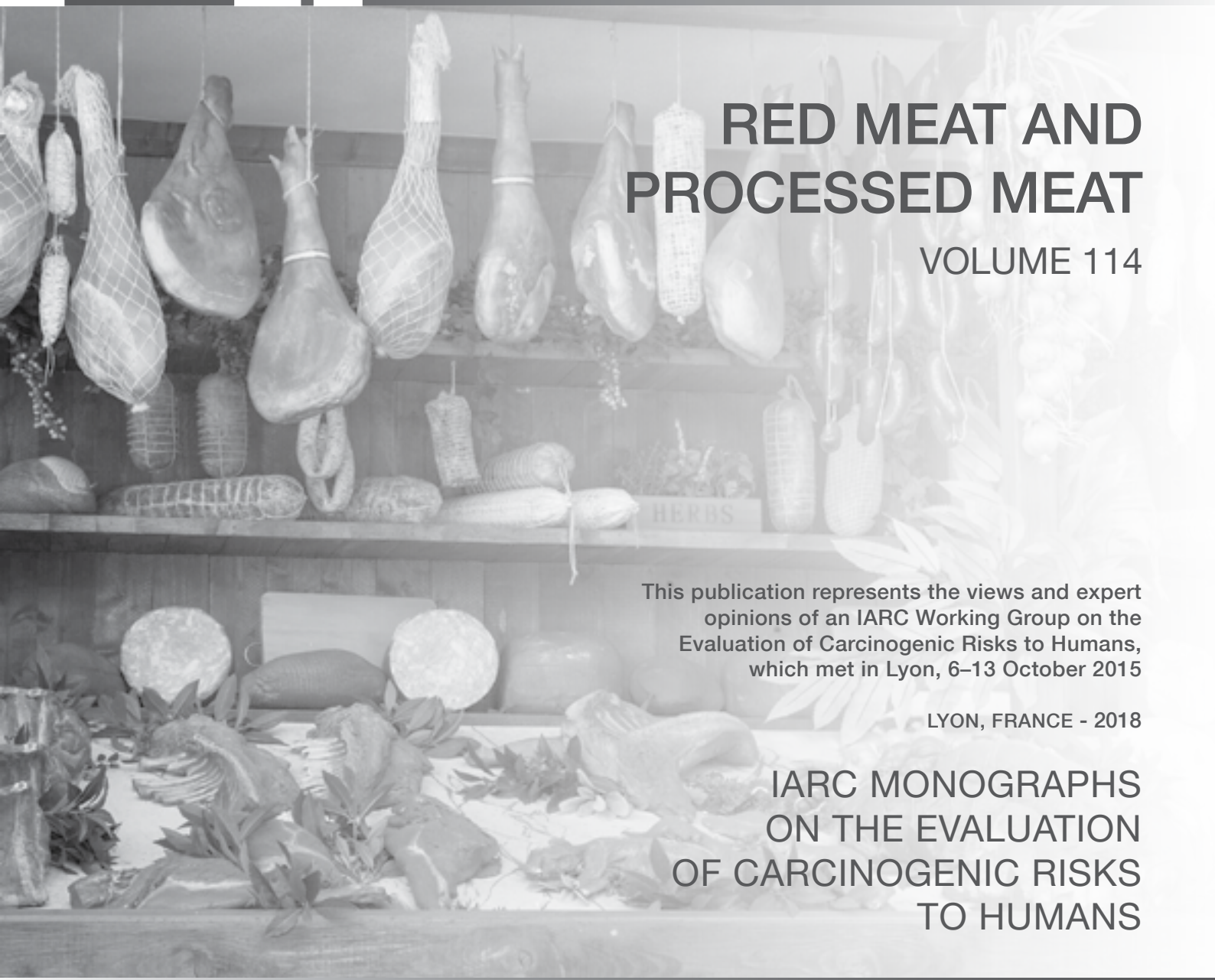

RED MEAT AND PROCESSED MEAT

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2.7 Cancer of the lung

The quality of the available studies on the association between cancer of the lung and consumption of red and processed meat was evaluated based on sample size, quality of reporting of the type of meat, inclusion of relevant confounders, study design issues (e.g. population- vs hospital-based design, response rates), and exposure assessment, including validation of dietary questionnaires. Adequate control for potential confounding by energy intake and smoking (including details on smoking history, given the strength of the association with cancer of the lung) was considered as key in the evaluation of the association between cancer of the lung and red and processed meat consumption. Studies that did not distinguish clearly between red and white meat were excluded from review, unless otherwise noted. Additional criteria are listed below for case–control studies.

2.7.1 Cohort studies

See Table 2.7.1 and Table 2.7.2 (web only; available at: http://publications.iarc.fr/564)

Six cohort studies were considered informative with respect to the association between cancer of the lung and meat intake. Unlike for other cancer sites, such as the colorectum, there were fewer studies available for the review of cancer of the lung. Therefore, the Working Group included most studies of lung cancer and red or processed meat, with exceptions as noted. The Working Group included one study investigating mortality; given the short survival of lung cancer patients, mortality is a reasonable surrogate for incidence. Balder et al. (2005) was excluded because it referred to a mixed category of "pork, processed meat, and potatoes". The study by Knekt et al. (1994) was excluded because it only reported results for fried meat (did not specify if red or white).

Breslow et al. (2000) studied 20 195 individuals with dietary data from the 1987 National Health Interview Survey, who were then linked to the National Death Index. Baseline diet was assessed with a 59-item FFQ. Food groups, including total meat/poultry/fish, red meats, and processed meats, were analysed after adjustment for age, sex, BMI, smoking, and other variables, but not total energy. There were 158 deaths from lung cancer. Red meat intake was associated with lung cancer mortality. The relative risk was 1.6 (95% CI, 1.0–2.6; P_{trend} = 0.014) for the highest (6.6 servings/week) versus the lowest (0–2.3 servings/week) quartile. No association was found with processed meat (P_{trend} = 0.721). [The Working Group noted that this was a small study based on mortality, with a limited FFQ and no adjustment for total energy.]

Tasevska et al. (2009) studied 278 380 men and 189 596 women from the National Institutes of Health-AARP Diet and Health (NHI-AARP) study. Diet was assessed with a 124-item FFQ. Meat-cooking modalities were investigated, and the CHARRED database was used to estimate the intake of HAAs, benzo[*a*]pyrene (BaP), and haem iron. A high intake of red meat was associated with an increased risk of lung cancer in both men (HR, 1.22; 95% CI, 1.09–1.38; P_{trend} = 0.005) and women (HR, 1.13; 95% CI, 0.97–1.32; P_{trend} = 0.05) for the highest compared with the lowest category of intake. A high intake of processed meat increased the risk only in men (HR, 1.23; 95% CI, 1.10–1.37; P_{trend} = 0.003). In an analysis stratified by smoking status, never-smoking men and women had increased risks with red meat consumption that were not statistically significant. The hazard ratios for the 90th versus the 10th percentile were 1.19 (95% CI, 0.69–2.06; P_{trend} = 0.52) in men and 1.21 (95% CI, 0.76–1.94; P = 0.44) in women for red meat. The relative risk for the highest versus the lowest tertile of intake of well/very well-done meat was 1.20 (95% CI, 1.07–1.35; P_{trend} = 0.002), and for intake of MeIQx, it was 1.20 (95% CI, 1.04–1.38;

P_{trend} = 0.04) in men. Haem iron intake for the highest compared with the lowest quintile was associated with an increased risk of lung carcinoma in both men (HR, 1.25; 95% CI, 1.07–1.45; P_{trend} = 0.02) and women (HR, 1.18; 95% CI, 0.99–1.42; P_{trend} = 0.002).

Linseisen et al. (2011) used the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, with 1822 incident lung cancers, exposure assessment based on a validated FFQ and 24-hour recall, and statistical analyses including adjustment for several smoking variables. With a continuous model, they found a statistically non-significant increase in risk of lung cancer. The relative risks were 1.06 (95% CI, 0.89–1.27) per 50 g increment of red meat and 1.13 (95% CI, 0.95–1.34) for the same amount of processed meat. Some subcohorts included health-conscious or vegetarian subjects [very large size].

Tasevska et al. (2011) used the Prostate, Lung, Colorectal and Ovarian (PLCO) cohort in which lung cancer screening was offered. There were 454 lung cancer cases in men and 328 in women. No information was given on response rates and losses to follow-up. No association was found with red meat or processed meat intake in men in multivariable modelling. Women showed slightly elevated relative risks with increasing quintiles of red meat intake (from ≤ 14.6 to > 42.5 g/1000 kcal): 1.33 (95% CI, 0.91–1.94), 1.60 (95% CI, 1.10–2.33), 1.24 (95% CI, 0.84–1.85), 1.30 (95% CI, 0.87–1.95), with no dose–response (P_{trend} = 0.65; adjusted for total energy intake and several other confounders, including smoking). [The Working Group noted that the study included both screened and non-screened arms, and the authors reported that associations were similar. There was accurate adjustment for smoking variables.]

Gnagnarella et al. (2013) invited asymptomatic volunteers aged 50 years or older who were current smokers or recent quitters, and had smoked at least 20 pack-years, to undergo annual screening with computed tomography. They assessed participants' diet at baseline using a self-administered FFQ that included 188 food items and beverages. During a mean screening period of 5.7 years, 178 of 4336 participants were diagnosed with lung cancer. In the multivariable analysis, red meat consumption was associated with an increased risk of lung cancer [HR for quartile 4 vs quartile 1, 1.73; 95% CI, 1.15–2.61; P_{trend} = 0.003]. [The Working Group noted that this was a relatively small study of heavy smokers.]

Butler et al. (2013) published a study based on data from a prospective cohort study among Chinese in Singapore that included 1004 lung cancer cases. A 165-item FFQ was used. The relative risk for fried meat was 1.13 (95% CI, 0.98–1.31) for the second tertile and 1.09 (95% CI, 0.94–1.27) for the third tertile of intake, but it was not specified whether fried meat was red or white. The corresponding relative risks for adenocarcinomas were 1.31 (95% CI, 1.03–1.68) and 1.36 (95% CI, 1.06–1.74). Risk estimates for fried pork consumption separately showed no clear association. [The Working Group concluded that a limitation was that the fried meat definition included both white and red meat. The strengths were that the study used a validated FFQ, had a large sample size, and adequately controlled for smoking, with 70% of the cohort being non-smokers.]

2.7.2 Case–control studies

See Table 2.7.3 and Table 2.7.4 (web only; available at: http://publications.iarc.fr/564)

The Working Group identified 21 case–control studies on the association between lung cancer and red and processed meat consumption from the USA, Uruguay, Europe, China, and China, Hong Kong Special Administrative Region, India, Canada, Singapore, Pakistan, and Brazil. When there were multiple publications from the same study, only the most recent one was included. Most of these studies were not

originally designed to assess meat consumption, and most of the available papers reported positive associations. The potential for reporting bias (i.e. reporting only statistically significant associations among the many associations that were investigated), therefore, needed to be considered in the evaluation of these findings.

The Working Group subsequently excluded eight case–control studies (most hospital-based) because the type of meat (red or white) was not specified (Suzuki et al., 1994; Phukan et al., 2014), the methods of control selection were unclear (Kubík et al., 2001; Shen et al., 2008; Chiu et al., 2010), the response rates were not given (Dosil-Díaz et al., 2007), or the information on adjustment for confounders was inadequate (Ganesh et al., 2011; Luqman et al., 2014). Brennan et al. (2000) was included, in spite of the lack of distinction between white and red meat, because it was one of the few studies to report estimates for non-smokers only.

Goodman et al. (1992) conducted a population-based study in Hawaii, USA, among 326 cases of histologically confirmed lung cancer and 865 controls. Exposure assessment was good, with an FFQ with 130 items. Results were inconsistent, with an increased risk for sausages, luncheon meat, and bacon in men (weaker and not statistically significant in women) and lack of association for red meat. A strong interaction was found with smoking, with odds ratios rising up to 11.8 (95% CI, 2.3–61.6) for smokers with > 70 pack-years of cigarettes consuming more than the median intake of sausages (men only for squamous cell carcinoma). There was also a statistically significant association with estimated nitrosamine intake. [The Working Group noted that the method of selection of controls changed during the conduction of the study. Strong odds ratios were based on the subgroup analysis.]

The study by Swanson et al. (1992) from China was based on a case–control design nested within an occupational population (a mining company) and a population-based study in a city. The response rate was very high. The accuracy of cancer ascertainment was uncertain, although the authors stated that it was based on pathological examinations. No association with meat intake (almost exclusively pork) was found. [The Working Group noted that there was a very small number of non-smoking cases.]

Sankaranarayanan et al. (1994) conducted a hospital-based study in India, based on 387 cases. Controls were relatives of patients or bystanders. Forty-five items were included in the dietary questionnaire. Strong but statistically unstable associations were reported for beef, with no dose–response. [The Working Group noted that the number of meat eaters in this study was small.]

Sinha et al. (1998) reported on a population-based study from the USA that included 593 cases and 628 controls, drawn from the drivers' licences or health care financing rosters. [The selection of controls was unclear, particularly oversampling of smokers.] A 110-item Health Habits and History Questionnaire (HHHQ) with 15 items related to red meat was used to assess exposure. Information on cooking methods and doneness levels was also obtained. Only women were included. There were statistically significant increases in risk with 10 g/day increments in the consumption of all red meat, well-done red meat, and fried red meat. When comparing the 90th and 10th percentiles, lung cancer risk increased for all red meat (OR, 1.8; 95% CI, 1.2–2.7), for well-done red meat (OR, 1.5; 95% CI, 1.1–2.1), and for fried red meat (OR, 1.5; 95% CI, 1.1–2.0).

Brennan et al. (2000) conducted a multicentre, hospital-based case–control study in non-smokers (defined as having smoked < 400 cigarettes in a lifetime) in Europe with a large samples size (506 cases, 1045 controls); diseases in controls were not specified. There was no association with meat intake, except in small cell carcinomas. Odds ratios were 1.2 (95% CI, 0.3–4.5) and 1.6 (95% CI, 1.1–2.2)

in increasing tertiles (weekly/several times and weekly/daily vs never, respectively). [The Working Group noted that the study was informative because it provided data on non-smokers. However, no distinction between white and red meat was made, and no adjustment for second-hand smoke was made.]

Alavanja et al. (2001) conducted a population-based study in the USA, with 360 cases identified through the Surveillance, Epidemiology, and End Results (SEER) Program and 574 controls sampled from drivers' licences and Medicare rosters (females only). A 70-item FFQ (NCI Block questionnaire) was used. Red meat was defined as hamburger, beef burritos, beef stew, pot pie, meatloaf, beef (fat unspecified), pork (fat unspecified), ham, lunchmeats, bacon, liver, sausage, or hot dogs. [The response rate, particularly in controls, was low.] The researchers found an association with increasing levels of red meat intake. Odds ratios were 1.7 (95% CI, 0.9–3.3) for 3.5–5.5 times/week, 2.0 (95% CI, 1.4–4.0) for 5.6–7.6 times/week, 2.5 (95% CI, 1.2–5.2) for 7.7–9.8 times/week, and 3.3 (95% CI, 1.7–7.6) for > 9.8 times/week (P_{trend} = 0.005). In addition, effect modification by histological type and smoking was considered. The odds ratios for red meat consumption were similar among adenocarcinoma cases (OR, 3.0; 95% CI, 1.1–7.9) and non-adenocarcinoma cases (OR, 3.2; 95% CI, 1.3–8.3), and among lifetime non-smokers and ex-smokers (OR, 2.8; 95% CI, 1.4–5.4) and current smokers (OR, 4.9; 95% CI, 1.1–22.3). [Red meat included processed meat.]

Hu et al. (2002) published the results of a population-based study in Canada in which controls were drawn from an insurance plan or random digit dialling. Only women who never smoked were included. A 70-item FFQ based on the NCI Block questionnaire was used. Overall, 161 cases and 483 controls were included, with a 1:3 case–control ratio. Modest associations were found with red meat (OR, 0.8 for second quartile, 2–3 servings/week; OR, 1.4. for third quartile, 3.1–5 servings/week; OR, 1.4 for fourth quartile, > 5 servings/week; none statistically significant). An increase in risk for processed red meat and bacon was not statistically significant, except for smoked meat (third tertile vs first tertile OR, 2.1; 95% CI, 1.1–4.0). Never-smokers were examined separately with the following results: for red meat, in increasing quartiles of servings/week, OR were 0.8 (95% CI, 0.4–1.5), 1.4 (95% CI, 0.7–2.6), and 1.4 (95% CI, 0.7–2.8), and for smoked meat, in increasing tertiles, 1.3 (95% CI, 0.8–2.3) and 2.1 (95% CI, 1.1–4.0). [The Working Group noted that the study size was small.]

Zatloukal et al. (2003) published the results of a study in the Czech Republic using spouses, relatives, and friends of hospital patients as controls. They found an association between lung cancer and increasing tertiles of intake of red meat, but only for histologies other than adenocarcinoma. The odds ratios were 1.54 (95% CI, 0.89–2.67) for weekly consumption and 1.81 (95% CI, 1.04–3.8) for daily consumption (P_{trend} = 0.04) [subgroup analysis noted].

Kubík et al. (2004) published the results of a hospital-based study in the Czech Republic among non-smoking women only (130 cases; 1022 controls were spouses, friends, or relatives of hospital patients). [Only nine food items were included in the dietary questionnaire.] They found an association with red meat (≥ 1 time/day to ≥ 1 time/week vs ≤ 1 time/week to > 1 time/month ; OR, 2.2; 95% CI, 1.07–4.51).

Lam et al. (2009) published a well-designed population-based study in Italy, with high response rates (87% cases, 72% controls) and large numbers (1903 cases, 2073 controls). Exposure assessment included a 58-item FFQ, with estimation of exposure to mutagens and detailed information on cooking practices. The researchers found increased odds ratios with increasing tertiles of red meat intake, 1.3 (95% CI, 1.1–1.6) and 1.8 (95% CI, 1.5–2.2). The odds ratios with increasing tertiles of processed meat intake were 1.3 (95% CI, 1.1–1.5) and 1.7 (95%

CI, 1.4–2.1). The odds ratios for estimated intake of the mutagen PhIP were 1.1 (95% CI, 0.9–1.4) and 1.5 (95% CI, 1.2–1.8). Never-smokers were examined separately. For red meat, the odds ratios with increasing tertiles were 1.1 (95% CI, 0.7–2.0) for the second tertile and 2.4 (95% CI, 1.4–4.0) for the third tertile for red meat (P_{trend} = 0.001), and 1.5 (95% CI, 0.9–2.6) and 2.5 (95% CI, 1.5–4.2) for processed meat (P = 0.001). [The Working Group noted that adjustment for smoking was accurate and detailed.]

Concerning hospital-based studies, Aune et al. (2009) from Uruguay reported associations with the highest compared with the lowest quartile of intake of red meat (OR, 2.17; 95% CI, 1.52–3.10) and processed meat (OR, 1.7; 95% CI, 1.28–2.25). They also looked at beef and lamb separately, and associations were similar. Twin papers from Uruguay were published by De Stefani et al. (2009) and Deneo-Pellegrini et al. (2015). The first differed because exposure assessment was broader with estimation of exposure to mutagens, and the second was restricted to squamous cell carcinoma in men. In addition to finding results that were very similar to Aune et al. (2009), De Stefani et al. (2009) reported results for exposure to PhIP, assessed through a database compiled from the literature (Jakszyn et al., 2004). In increasing tertiles of exposure, the odds ratios for PhIP were 1.12 (95% CI, 0.80–1.56), 1.48 (95% CI, 1.05–2.07), and 2.16 (95% CI, 1.48–3.15). Deneo-Pellegrini et al. (2015) reported on squamous cell lung cancer, and the odds ratios were 1.82 (95% CI, 1.13–2.91) and 1.09 (95% CI, 0.73–1.64) for the highest versus the lowest tertiles of intake of red meat and processed meat, respectively.

Lim et al. (2011) published the results of a hospital-based study in Singapore (399 cases, 815 controls) with high response rates (81% cases, 85% controls), but only 18 meat-related items were included in the FFQ. There was no significant association with total meat, pork, or processed meat intake. However, there was a significant association with high-bacon consumption (OR, 1.51; 95% CI, 1.06–2.16).

2.7.3 Meta-analyses

Two meta-analyses of the association between lung cancer and consumption of red or processed meat were identified. Yang et al. (2012) included 23 case–control and 11 cohort studies identified via MEDLINE, Embase, and the Web of Science through 2011. The meta-relative risk for the highest compared with the lowest category of intake was significantly greater than unity for red meat (RR, 1.34; 95% CI, 1.18–1.52), but not for processed meat intake (RR, 1.06; 95% CI, 0.90–1.25). The association with red meat was observed in never-smokers (RR, 1.66; 95% CI, 1.31–2.11), and was robust in sensitivity analyses that took into account the study type and quality. In general, results for processed meat were weak or inconsistent. All estimates (including those for red meat) showed high heterogeneity, with highly significant P values ($P < 0.001$) and high I^2 levels. There was no evidence of publication bias.

The second meta-analysis was an extension of the previous one, and aimed to explore the dose–response relationships in more detail (Xue et al., 2014). Dose–response data were available from 11 studies for red meat and 11 studies for processed meat. The meta-relative risks were 1.35 (95% CI, 1.25–1.46) for red meat (per 120 g increment) and 1.20 (95% CI, 1.11–1.29) for processed meat (per 50 g increment). In general, estimates varied considerably by study design. In cohort studies, the relative risks for red meat and processed meat were 1.21 (95% CI, 1.14–1.28; $P_{heterogeneity}$ = 0.7) and 1.09 (95% CI, 0.99–1.19; $P_{heterogeneity}$ = 0.1), respectively, with higher estimates in case–control studies. In case–control studies and other subgroup analyses by region and sex, P values for heterogeneity were highly significant.

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