2.8 Cancer of the oesophagus

The Working Group focused their review on studies that clearly defined red meat or processed meat (see Section 1 and Section 2). Studies were excluded if: (1) risk estimates were presented for total meat (red and processed meat combined) intake; (2) the type of meat was not defined or included white meat; (3) fewer than 100 cases were reported, due to the limited statistical power, as a large database of high-quality studies were available; (4) a more recent report from the same study was available; (5) risk estimates, adjusted for important confounders, were not available (crude estimates were not considered to be informative); (6) dietary patterns were the focus; (7) outcome was assessed using mortality data; and (8) the analysis and results were reported for cancers of the upper aerodigestive tract as a group.

Important covariates for the association between red meat and cancer of the oesophagus include age, tobacco smoking, alcohol drinking (squamous cell carcinoma), BMI (adenocarcinoma), and energy intake.

2.8.1 Cohort studies

(a) Red meat

See Table 2.8.1 (web only; available at: http://monographs.iarc.fr/ENG/Monographs/vol114/index.php)

Conflicting results were reported in the three cohort studies that reported on the association between red meat consumption and oesophageal cancer reviewed by the Working Group. No association was observed between consumption of red meat and oesophageal cancer among women enrolled in the NLCS (Keszei et al., 2012), or among participants in the EPIC study (Jakszyn et al., 2013). Increased risks were observed among the NIH-AARP study cohort (Cross et al., 2011) and among men enrolled in the NLCS (Keszei et al., 2012). The NIH-AARP study also reported positive associations between haem iron intake and risk of oesophageal adenocarcinoma (EAC). [The Working Group noted that, in the EPIC study, processed meat was not included in the definition of red meat, but the sample size was limited (137 cases), and the analyses did not adjust for alcohol. A strength of the NLCS was that a detailed questionnaire with 150 items was used; however, the sample size was limited (107 oesophageal squamous cell carcinomas, ESCCs; 145 EACs). The Working Group also noted that, although the NIH-AARP study cohort was large with a large number of cases (215 ESCCs, 630 EACs), and the study investigated the intake of meat-cooking by-products and haem iron intake, the interpretation of results was hampered because processed meat was included in the definition of red meat.]

(b) Processed meat

See Table 2.8.2 (web only; available at: http://monographs.iarc.fr/ENG/Monographs/vol114/index.php)

The Working Group reviewed three studies that investigated the association between consumption of processed meat and oesophageal cancer. One report from Cross et al. (2007) was updated and, therefore, not included. Studies based on mortality data were excluded (e.g. Iso et al., 2007). The Working Group noted when important risk factors for oesophageal cancer, such as tobacco and alcohol consumption, were not adjusted for in the analyses.

In the NIH-AARP study cohort, Cross et al. (2011) reported hazard ratios for the highest versus the lowest quintile of processed meat intake, adjusted for important confounders, of 1.32 (95% CI, 0.83–2.10; P_{trend} = 0.085; 60 exposed cases) for ESCC and 1.08 (95% CI, 0.81–1.43; P_{trend} = 0.262; 181 exposed cases) for EAC. [The Working Group noted that this was a large study with a large number of cases, especially for EAC.]

In the NLCS, Keszei et al. (2012) reported adjusted relative risks for oesophageal cancer for the highest compared with the lowest category of

processed meat intake of 3.47 (95% CI, 1.21–9.94; P_{trend} = 0.04; 16 exposed cases) for ESCC and 0.94 (95% CI, 0.46–1.89; P_{trend} = 0.84; 24 exposed cases) for EAC in men. Corresponding relative risks in women were below one. [The Working Group noted that a detailed questionnaire with 150 items was used. The sample size was limited.]

Within the EPIC cohort, Jakszyn et al. (2013) reported a positive association between consumption of processed meat and EAC, after adjusting for important confounders (highest vs lowest tertile HR, 2.27; 95% CI, 1.33–3.89; P_{trend} = 0.004; 62 exposed cases). [The Working Group noted that this was a large study with a large number of cases, especially for EAC. Processed meat did not include white meat. Alcohol was not adjusted for.]

2.8.2 Case–control studies

(a) Red meat

See Table 2.8.3 (web only; available at: http://monographs.iarc.fr/ENG/Monographs/vol114/index.php)

The Working Group reviewed 20 case–control studies, both hospital-based and population-based, that investigated the association between oesophageal cancer and consumption of red meat. The studies were conducted in North America, South America, Europe, Asia, and Africa (Yu et al., 1988; Rogers et al., 1993; Castelletto et al., 1994; Brown et al., 1995, 1998; Rolón et al., 1995; Bosetti et al., 2000; Levi et al., 2000; Chen et al., 2002; Xibib et al., 2003; Wang et al., 2007; Wu et al., 2007; Navarro Silvera et al., 2008; Sapkota et al., 2008; Gao et al., 2011; O'Doherty et al., 2011; Wu et al., 2011; Ward et al., 2012; Di Maso et al., 2013; De Stefani et al., 2014a; Matejcic et al., 2015). All but seven studies were population-based. Two studies reported risk estimates less than or equal to one (Rogers et al., 1993; Sapkota et al., 2008), while most of the studies reported an increased risk of oesophageal cancer was associated with red meat intake, after adjusting for important confounding factors (Yu et al., 1988; Castelletto et al., 1994; Brown et al., 1995, 1998; Rolón et al., 1995; Bosetti et al., 2000; Levi et al., 2000; Chen et al., 2002; Xibib et al., 2003; Wang et al., 2007; Wu et al., 2007; Navarro Silvera et al., 2008; Gao et al., 2011; Wu et al., 2011; O'Doherty et al., 2011; Ward et al., 2012; Di Maso et al., 2013; De Stefani et al., 2014a; Matejcic et al., 2015).

(b) Processed meat

See Table 2.8.4 (web only; available at: http://monographs.iarc.fr/ENG/Monographs/vol114/index.php)

About 15 case–control studies that investigated the association between consumption of processed meat and oesophageal cancer, conducted in different areas of the world (the USA, South America, Europe, and Asia), were included in the evaluation by the Working Group (Yu et al., 1988; Brown et al., 1995, 1998; De Stefani et al., 2014b; Bosetti et al., 2000; Takezaki et al., 2001; Hung et al., 2004; Levi et al., 2004; Yang et al., 2005; Wu et al., 2007; Navarro Silvera et al., 2008; Sapkota et al., 2008; Chen et al., 2009; O'Doherty et al., 2011; Song et al., 2012; Ward et al., 2012; Lin et al., 2015). The quality of the studies was considered, based on the reporting of the type of meat; study design issues (e.g. population-based vs hospital-based design); sample size; exposure assessment, including validation of dietary questionnaires; and inclusion of relevant confounders. Important covariates for oesophageal cancer include age, tobacco smoking, alcohol drinking, BMI (adenocarcinoma), and energy intake. Nine studies were population-based (Yu et al., 1988; Brown et al., 1995, 1998; Takezaki et al., 2001; Wu et al., 2007; Navarro Silvera et al., 2008 ; O'Doherty et al., 2011 ; Song et al., 2012; Ward et al., 2012; Lin et al., 2015), two of which adjusted for *Helicobacter pylori* (Wu et al., 2007; O'Doherty et al., 2011.

2.8.3 Meta-analyses

Among the five meta-analyses on red and processed meat published recently (Choi et al., 2013; Huang et al., 2013; Qu et al., 2013; Salehi et al., 2013; Zhu et al., 2014), Qu et al. (2013) considered ESCC, whereas Huang et al. (2013) considered EAC only. Choi et al. (2013) considered both types, but studies without information on the histological type were not included. Salehi et al. (2013) considered all oesophageal cancers, but studies reporting only one type of red meat, such as beef, pork etc., were included in the meta-analyses by Qu et al. (2013) and Choi et al. (2013). The results of the two most recent and comprehensive meta-analyses are summarized below. [The Working Group did not place emphasis on the results of the meta-analyses due to their significant limitations.]

Zhu et al. (2014) was the most recent and comprehensive meta-analysis. The meta-analysis included all types of oesophageal cancers: ESCC and EAC, and total oesophageal cancers. The meta-analysis included three cohort studies and 12 case–control studies; however, two reports, one for EAC (Brown et al., 1995) and the other for ESCC (Brown et al., 1998), on a population-based case–control study conducted in the USA were not included. The summary relative risks of oesophageal cancer for the highest compared with the lowest categories were 1.55 (95% CI, 1.22–1.96; $P_{\text{heterogeneity}} < 0.001$; $I^2 = 63.6\%$) for red meat and 1.33 (95% CI, 1.04–1.69; $P_{\text{heterogeneity}} < 0.001$; $I^2 = 61.5\%$) for processed meat. A statistically significant association was also observed for case–control studies (OR, 1.78 and 1.39, respectively), but not for cohort studies (RR, 1.22 and 1.25, respectively). When stratified by histological type, an association was observed between ESCC and red meat, and EAC and processed meat; the summary estimates were calculated as OR, 1.86 (95% CI, 1.31–2.66) and 1.23 (95% CI, 1.01–1.50), respectively. [The Working Group noted that this review included all types of oesophageal cancers. The interpretation of this analysis was limited by the fact that two reports were missing, and papers reporting on only one type of red meat, such as beef or pork, were not included.]

Qu et al. (2013) presented a comprehensive meta-analysis that considered study design, and further analysed dose–response and linearity. A total of two cohort studies and 19 case–control studies with 6499 oesophageal cancer cases were included in the meta-analysis. The summary relative risks of oesophageal cancer for the highest compared with the lowest categories were 1.57 (95% CI, 1.26–1.95; $P_{\text{heterogeneity}} = 0.003$) for red meat intake and 1.55 (95% CI, 1.22–1.97; $P_{\text{heterogeneity}} = 0.029$) for processed meat intake. These results were consistent with those of the dose–response analyses. Stratified analysis by histological type, study design, number of cases (< 200 vs ≥ 200), and adjustment of covariates did not reveal any differences, although the summary relative risks in the population-based case–control studies and the European studies were not statistically significant. [This review did not include studies reporting on EAC; however, studies reporting on only one item of red meat were included.]

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