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RESEARCH ARTICLE

Red and processed meat consumption and esophageal cancer risk: a systematic review and meta-analysis

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Abstract

Background The associations between red and processed meat consumption and esophageal cancer risk remain inconclusive. We performed a systematic review and meta-analysis to analyze these associations.

Methods We searched PubMed and EMBASE to identify studies published between the databases' dates of inception and May 2019.

Results We ultimately selected 33 eligible studies for analysis. We found that the summary relative risks for the associations between meat consumption and esophageal cancer risk were positive for the case–control studies ($P < 0.05$), but negative for the cohort studies included in the analysis ($P > 0.05$). Subtype analysis indicated that red and processed meat consumption was not associated with the risks of esophageal adenocarcinoma ($P > 0.05$) and esophageal squamous cell carcinoma ($P > 0.05$) in the cohort studies.

Conclusions We found case–control but not cohort studies to associate consumption of red and processed meat with the risk of esophageal cancer. Further large prospective studies are needed to validate these findings.

Keywords Esophageal cancer · Meat · Meta-analysis

Introduction

Esophageal cancer (EC) is one of the most fatal malignancies. GLOBOCAN 2018 has reported 572,034 new cases and 508,585 deaths of EC occurring worldwide [1]. Eastern Asia is one of the regions with a high rate of EC related mortality [2]. Given the increasing incidence of EC and the high mortality rate associated with the disease, novel strategies for preventing EC are urgently needed. An increasing number of studies have recently focused on the dietary factors associated with the risk of EC. For example, several studies reported that drinking beverages at high temperatures and low fruit and vegetable are risk factors for EC [3–5]. Additionally, fish consumption has been reported to be associated with a decreased the risk of EC [6]. The consumption of red and processed meat also has been shown to be associated with many chronic diseases [7–9]. However, the associations between red and processed meat consumption and the risk of EC remain unclear. Some studies have shown that meat consumption is positively associated with EC [10, 11], while other studies have found no evidence of an association between the two phenomena [12, 13].

Thus, given the large burden imposed by EC worldwide and the controversial evidence regarding the risk factors that may be associated with the disease, we conducted a systematic review and meta-analysis with the following objectives: (1) to provide an update regarding the relationship between red and processed meat consumption and the risk of EC using a larger body of evidence and the results of a quantitative analysis of the eligible data pertaining to the relationship that were published up to May 2019; and (2) to evaluate the dose–response associations between red and processed meat consumption and EC risk.

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Methods

Selection criteria

The selection criteria were as follows: (1) studies including patients whose diseases were diagnosed by endoscopy with biopsy; (2) studies including patients whose histological features were not consistent with those normally identified by the gold standard diagnostic test, i.e., endoscopy with biopsy; (3) narrative reviews, systematic reviews and meta-analyses; letters; commentaries; case reports; editorials; and studies in which only the abstract was obtained, were excluded from the analysis; (4) studies regarding the consumption of meats that did not specifically cite red or processed meat were excluded from the analysis, as were studies including patients with Barrett's esophagus, gastrointestinal stromal tumors, precancerous lesions and other digestive tract tumors; (5) we limited the language of the studies included in the analysis to English and included only studies involving humans in the analysis.

Search strategy

We searched PubMed and EMBASE for studies on the relationship between red and processed meat consumption and EC risk published between the databases' dates of inception and May 2019. The search terms included: "meat/meats", "beef", "pork", "lamb", "mutton", "bacon", "ham", "sausage", "hot dogs", "diet/dietary", "lifestyle/lifestyles" and "food/foods" in combination with "gastrointestinal/aerodigestive/digestive/alimentary/esophageal/oesophageal/esophagus/oesophagus". The reference lists of the included studies were also searched manually to identify additional relevant literature. The two sets of keywords were combined individually, and the eligibility of each study was judged independently by two authors (Zhanwei Zhao and Fei Wang).

Study quality

Study quality was assessed using the Newcastle–Ottawa Scale (NOS) [14]. The NOS assesses study quality based on three factors: the ability of case–control or cohort studies to ascertain the exposure or outcomes of interest, respectively; the selection of the study populations and the comparability of the populations. Two researchers (Zhanwei Zhao and Fei Wang) independently assessed the quality of the studies, and disagreements regarding quality were resolved by reaching a consensus with the assistance of a third researcher (Chaojun Zhang). The NOS ranges from 0 to 9 stars, and studies receiving scores of seven or more stars are considered high-quality studies.

Data extraction

A data extraction sheet was generated for each study and included information pertaining to the first author, year of publication, country, study type, study population, study period, method of dietary assessment, dietary exposures measured, dietary exposure categories, adjusted relative risks (RRs) and 95% confidence intervals (CIs) (highest to lowest), adjusted variables and NOS score.

Statistical analysis

The data were collected and analyzed using SPSS 17.0 (Chicago, IL, USA). RevMan5.3 (The Cochrane Collaboration, Oxford, UK) and STATA version 12.1 (STATA Corporation, College Station, TX, USA) software were used for the data synthesis and analysis.

Random-effects models were used to pool the summary relative risks/odds ratios (RRs/ORs) and 95% CIs. The median or mean level of meat intake for each category was assigned to each corresponding RR for each study. When the corresponding data were not reported, the midpoint of the upper and lower boundaries of each category was designated the average intake value. When the highest category was open-ended, we assumed the open-ended interval to be the same as the adjacent interval. If the lowest category was open-ended, we assumed the lowest boundary to be 0.

Heterogeneity between studies was detected using Q (a $P < 0.1$ represented statistically significant heterogeneity) and I^2 statistics ($I^2 < 50\%$ was indicative of low heterogeneity, and $I^2 > 50\%$ was indicative of substantial heterogeneity) [15]. Subgroup analyses, in which the studies were assessed according to their geographic areas, sample sizes, publication years, quality scores, questionnaires and adjustments (smoking, alcohol, BMI, energy intake, physical activity and dietary fiber intake), were conducted to identify the sources of the heterogeneity between studies. Meta-regression analyses were conducted to determine if geographic area, sample size, publication year and quality score were significant sources of between-study heterogeneity ($P < 0.1$ was indicative of a significant source of heterogeneity).

Publication bias was assessed using funnel plots, Begg's test and Egger's test ($P < 0.1$ was indicative of significant publication bias) [16]. Sensitivity analyses were conducted to investigate the influence of a specific study on the pooled risk estimate by removing one study in each turn.

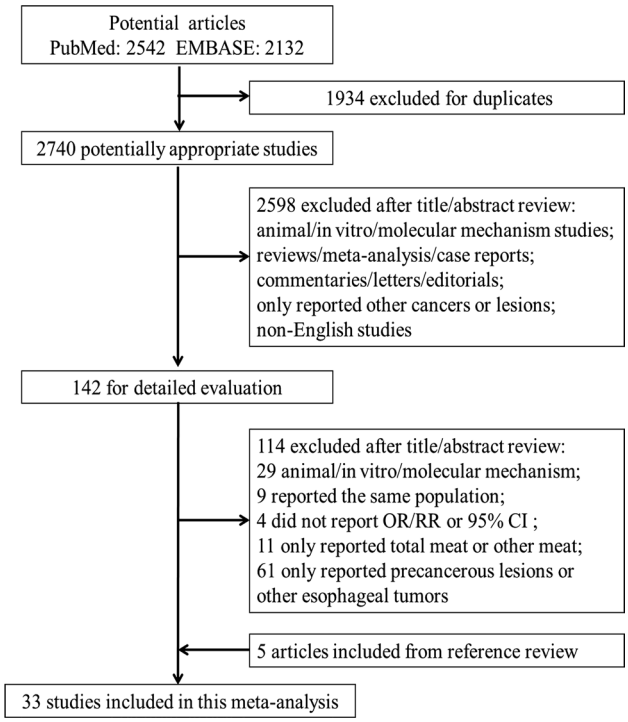

Fig. 1 Flowchart of the process for the identification of relevant studies

Results

Literature selection, study characteristics and quality scores

Thirty-three studies met the criteria for inclusion in the analysis and provided 56 separate estimates (red meat = 28, processed meat = 24) of the associations between red and processed meat consumption and EC risk (Fig. 1). The analysis included 1,156,150 participants and 11,449 cases. The quality scores ranged from 5 to 9 (Table 1).

Red meat

High vs low consumption

Twenty-two case–control studies with 28 estimates were included in the analysis and the pooled RR for the relationship between red meat consumption and EC was 1.44 (1.20–1.72). Three cohort studies with six estimates were included in the analysis, and the pooled RR for the relationship between red meat consumption and EC was 1.10 (0.80–1.53) (Fig. 2a). Subtype analyses of case–control studies demonstrated that (Fig. 2b) red meat consumption was associated with esophageal squamous cell carcinoma (ESCC) (RR = 1.74, 95% CI = 1.12–2.69), while analysis of cohort studies yielded negative results (RR = 1.43, 95% CI = 0.48–4.23). Subtype analysis of case–control studies yielded positive results (RR = 1.66, 95% CI = 1.22–2.46), while analysis of cohort studies yielded negative results (RR = 0.87, 95% CI = 0.60–1.28) regarding the relationship between red meat consumption and esophageal adenocarcinoma (EAC) (Fig. 2c).

Heterogeneity

We noted high heterogeneity ($P < 0.01$, $I^2 = 68\%$) between the case–control studies, but did not observe significant heterogeneity ($P = 0.10$, $I^2 = 46\%$) between the cohort studies.

Publication bias

As only three cohort studies were included in the analysis, tests for publication or small study bias were not conducted. Sensitivity analysis of the included cohort studies showed that the changes in the recalculated RRs were not significant, as the RRs ranged from 1.46 (0.57–3.73) when Yu 1993 (12.8%) was excluded from the analysis to 1.28 (0.99–1.65) when Keszei 2012 (3.3%) was excluded from the analysis.

Dose–response analysis

Two cohort studies were included in the analysis, and the pooled RR for a 100 g/day increase in red meat consumption was 1.16 (0.81–1.67) and was without heterogeneity ($P = 0.57$, $I^2 = 0\%$). These results demonstrated that red meat consumption was non-significantly positively associated with the risk of EC. Non-linear dose–response analysis was not conducted because of the small number of studies included in the analysis.

Processed meat

High vs low consumption

Nineteen case–control studies were included in the analysis and the pooled RR for the relationship between processed meat consumption and EC was 1.50 (1.22–1.85). Three cohort studies with six estimates were included in the analysis, and the pooled RR for the relationship between processed meat consumption and EC was 1.21 (0.78–1.88) (Fig. 3a). Subtype analysis of case–control studies indicated that processed meat consumption was positively associated with ESCC (RR = 1.54, 95% CI = 1.09–2.16) and that significant between-study heterogeneity was present ($P < 0.01$, $I^2 = 67\%$); however, analysis of two large cohort studies indicated that processed meat consumption was negatively associated with ESCC (RR = 1.34, 95% CI = 0.61–2.91) (Fig. 3b). Subtype analyses of the three cohort studies (RR = 1.15, 95% CI = 0.81–1.63) and four case–control

Table 1 Baseline characteristics of included studies for red and processed meat consumption and esophageal cancer risk

First author, year, country	Study type	Case/control (cohort, *n*)	Study period	Method of dietary assessment	Type of dietary exposure	Dietary exposure categories	Adjusted RRs/ORs (95% CI) (highest to lowest)	Adjusted variables	NOS score
Yu 1988 USA[17]	cc	275/275	1975–1981	FFQ-111	Beef Smoked meat	Tertile	1.30 (0.60–2.70) 1.70 (0.90–3.00)	Age, smoking, alcohol	6
Rogers 1993 USA[18]	cc	127/466	1983–1987	FFQ-125	Beef as a main dish Beef as a sandwich Pork	≥1/week vs < 1/week	0.80 (0.40–1.40) 1.00 (0.60–1.70) 1.20 (0.80–2.50)	Age, gender, cigarettes, alcohol, energy intake, β-carotene intake, ascorbic acid intake	6
Tavani 1994 Italy[19]	cc	46/230	1984–1992	FFQ-14	Liver Ham	Tertile	1.10 (0.50–2.30) 1.40 (0.60–3.30)	Age, sex, education, alcohol intake	5
Castelletto 1994 Argentina[20]	cc	131/262	1986–1989	FFQ-10	Beef	≥1 vs < 1 daily	0.60 (0.30–0.90)	Age, sex, hospital, education, smoking, alcohol, barbecued meat, vegetables	5
Rolon 1995 Paraguay[21]	cc	131/381	1988–1991	FFQ-50	Red meat	Quartile	3.80 (1.30–11.0)	Age, sex, alcohol, smoking, design variable of the study, hospital group, fats, fish, milk	6
Bosetti 2000 Italy[22]	cc	304/743	1992–1997	FFQ-78	Red meat Processed meat	Quintile	1.93 (1.09–3.41) 1.39 (0.85–2.26)	Age, sex, area of residence, education, tobacco smoking, alcohol, and non-alcohol energy	7
Takezaki 2000 Japan[23]	cc	284/11936	1988–1997	Questionnaire	Beef	≥3/week vs ≤ 3/month	0.90 (0.60–1.50)	Age, year and season of visit, smoking, drinking	6
Takezaki 2001 China[24]	cc	199/333a	1990–1992	FFQ-152	Salted meat	Tertile	0.93 (0.38–2.29)	Age, sex, smoking	6
Chen 2002 USA[25]	cc	124/449	1988–1993	HHHQ-NS	Red meat Processed meat	Quintile	1.40 (0.61–3.20) 1.70 (0.71–3.90)	Age, sex, energy intake, respondent type, BMI, alcohol, tobacco, education, family history, and vitamin	7
Li 2003 China[26]	cc	1248/1248	1997–2000	FFQ-12	Sowbelly	Daily vs < 1/week	2.28 (1.50–3.30)	Age, sex, income, residence, occupation, alcohol, tobacco	6
Levi 2004 Switzerland [27]	cc	138/1271	1992–2002	FFQ-79	Processed meat	Quartile	4.48 (2.05–9.79)	Education, smoking, drinking, energy intake, fruit and vegetable	7

Table 1 (continued)

First author, year, country	Study type	Case/control (cohort, *n*)	Study period	Method of dietary assessment	Type of dietary exposure	Dietary exposure categories	Adjusted RRs/ORs (95% CI) (highest to lowest)	Adjusted variables	NOS score
Hung 2004 China[28]	cc	284/480	1996–2002	FFQ-NS	Cured meat	≥1 vs < 1 per week	1.40 (0.70–2.80)	Age, educational, ethnicity, hospital, smoking, alcohol and areca nut chewing	7
Yang 2005 China[29]	cc	185/185	2003–2004	FFQ-NS	Processed meat	Tertile	0.89 (0.52–1.50)	Family history of EC and occupation	5
Wu 2007 USA[30]	cc	206/1308	1992–1997	FFQ-124	Red meat Processed meat	Quartile	1.29 (0.80–2.20) 1.23 (0.70–2.10)	Age, sex, race, birthplace, education, smoking, BMI, GR, use of vitamins, total calories, *H. pylori*	8
Wang 2007 China[31]	cc	355/408	2004–2006	Questionnaire	Sauce-stewed pork	Often vs none/seldom	M 2.06 (1.42–2.99) F 1.91 (1.16–3.16)	Age, sex, marital status, education	6
Sapkota 2008 France[32]	cc	187/1228	1999–2003	FFQ-23	Unprocessed red meat Ham/salami/sausage	Tertile	0.62 (0.19–2.09) 1.12 (0.52–2.41)	Age, country, gender, smoking, education, BMI, alcohol, vegetable and fruit	6
Chen 2009 China[33]	cc	320/709	1996–2005	FFQ-6	Cured meat	≥1 vs < 1 per week	0.80 (0.40–1.40)	Age, education, ethnicity source of hospital, smoking, alcohol drinking, and areca nut chewing	7
Aune 2009 Uruguay[34]	cc	234/2032	1996–2004	FFQ-64	Red meat	Tertile	3.36 (1.97–5.72)	Age, sex, residence, education, income, interviewer, smoking, alcohol, dairy foods, grains, fatty foods, fruits and vegetables, fish, poultry, mate, BMI, energy intake	7

Table 1 (continued)

First author, year, country	Study type	Case/control (cohort, *n*)	Study period	Method of dietary assessment	Type of dietary exposure	Dietary exposure categories	Adjusted RRs/ORs (95% CI) (highest to lowest)	Adjusted variables	NOS score
Wu 2011 China[35]	cc	1254/3483	2003–2007	FFQ-NS	Red meat	Quartile	1.15 (1.00–1.32)	Age, gender, education level, previous income, BMI, smoking, ethanol intake, number of siblings and study area, family history of cancer in first-degree relatives	8
Gao 2011 China[36]	cc	166/403	1997–2005	FFQ-NS	Red meat Salted meat	Tertile	1.37 (1.00–1.82) 1.20 (0.98–1.46)	Age, gender, geographic region	6
Hajizadeh 2011 Iran[37]	cc	47/96	2010 (6 months)	FFQ-168	Red meat Processed meat	Tertile	2.47 (0.76-7.96) 1.10 (0.36–2.47)	GR and BMI	5
O'Doherty 2011 UK[38]	cc	224/256	2002–2005	FFQ-101	Fresh red meat Processed meat	Quartile	3.15 (1.38–7.20) 1.41 (0.67–2.95)	Age, sex, smoking, BMI, job type, location, education, energy intake, fruit and vegetable, alcohol, *H. pylori*, NSAID use, GR	8
De Stefani 2012 Uruguay[39]	cc	234/2020	1996–2004	FFQ-64	Red meat	Tertile	4.97 (2.98–8.29)	Age, gender, residence, education, BMI, smoking, drinking, mate temperature, total energy, total vegetable and fruits intake, and all scored patterns	7
Song 2012 China[40]	cc	254/254	2008–2010	FFQ-NS	Salted meat	Tertile	2.57 (1.02–6.43)	Age, smoking and alcohol, the other two processed foods, fruit and vegetable, family history and income	7
Ward 2012 USA[13]	cc	124/449	1992–1994	HHHQ-NS	Unprocessed red meat Processed meat	Quartile	1.92 (0.73–5.06) 1.40 (0.62–3.15)	Year of birth, gender, cigarettes, education, vitamin C, fiber, carbohydrate, total calories	7

Table 1 (continued)

First author, year, country	Study type	Case/control (cohort, *n*)	Study period	Method of dietary assessment	Type of dietary exposure	Dietary exposure categories	Adjusted RRs/ORs (95% CI) (highest to lowest)	Adjusted variables	NOS score
Di Maso 2013 Italy[41]	cc	505/1259	1991–2009	FFQ-NS	Red meat	Tertile	2.01 (1.43–2.84)	Age, sex, education, BMI, smoking, alcohol, vegetable and fruit intake	8
De Stefani 2014 Uruguay[42]	cc	876/1492	1990-2005	FFQ-NS	Salted meat	Quartile	3.82 (2.74–5.33)	Age, sex, residence, education, smoking, drinking, mate consumption, total energy, total vegetable and fruit, red meat and other cured meats consumption	7
Golozar 2015 Iran[43]	cc	236/576	2003-2007	FFQ-115	Red meat Processed meat	Quartile	2.82 (1.21–6.57) 3.34 (1.32–8.45)	Ethnicity, education, wealth, opium use, tobacco smoking, family history, BMI, tea temperature, vegetable intake, DMFT categories, and eating discomfort frequency	8
Rosato 2018 Italy[44]	cc	695/2582	1985-2007	FFQ-78	Processed meat	Tertile	1.51 (1.18–1.91)	Sex, age, study center, year of interview, education, tobacco smoking, alcohol, BMI, vegetable consumption, fruit consumption, and total energy intake	8
Yu 1993 China[45]	co	1162/12,693	1974-1989	FFQ-NS	Pork	Regular or occasional vs never	1.37 (1.11–1.68)	Age and sex	7
Corss 2011 USA[46]	co	505/494,979	1995-1996	FFQ-124	Processed meat	Quintile	1.32 (0.83–2.10)	Age, sex, BMI, education, ethnicity, smoking, alcohol, physical activity, fruit and vegetables, saturated fat, and calories	9

Table 1 (continued)

First author, year, country	Study type	Case/control (cohort, *n*)	Study period	Method of dietary assessment	Type of dietary exposure	Dietary exposure categories	Adjusted RRs/ORs (95% CI) (highest to lowest)	Adjusted variables	NOS score
Keszei 2012 Netherlands[47]	co	252/120,852	1986-2002	FFQ-150	Red meat Processed meat	Quintile	2.66 (0.94–7.48) 3.47 (1.21–9.94)	Age, smoking, energy intake, BMI, non-occupational physical activity, alcohol, vegetable and fruit, education	9
Jakszyn 2013 Europe[48]	co	137/481,419	1998-2009	FFQ-NS	Unprocessed red meat Processed meat	Tertile	1.00 (0.60–1.66) 2.27 (1.33–3.89)	Sex, smoking, BMI, total energy, fruits and vegetables, education	7

EC esophageal cancer, *cc* case–control, *co* cohort, *RRs/ORs* relative risks/odds ratios, 95% *CI* 95% confidence intervals, *M* male, *F* female, *FFQ* food frequency questionnaire, *HHHQ* health habits and history questionnaire, *NS* not specified, *BMI* body mass index, *GR* gastroesophageal reflux, *NSAID* nonsteroidal anti-inflammatory drug, *DMFT* decayed, missed, and/or filled teeth

studies (RR = 1.138 95% CI = 0.96–1.97) demonstrated that processed meat consumption was not associated with EAC (Fig. 3c).

Heterogeneity

Significant heterogeneity ($P < 0.01$, $I^2 = 55\%$) was present between the case–control studies and ($P = 0.04$, $I^2 = 69\%$) between the cohort studies.

Publication bias

Due to the inclusion of only three cohort studies in the analysis, tests for publication or small study bias were not conducted. Sensitivity analysis of the included cohort studies showed that the changes in recalculated RRs were not significant, as the RRs ranged from 1.11 (0.89-1.37) when Jakszyn 2013 (6.0%) was excluded from the analysis to 1.54 (0.79-3.01) when Keszei 2012 (7.1%) was excluded from the analysis.

Dose–response analysis

Three cohort studies were included in the analysis, and the pooled RR for a 50 g/day increase in processed meat consumption was 1.41 (1.10-1.82). No between-study heterogeneity ($P = 0.42$, $I^2 = 0\%$) was present. However, sensitivity analysis demonstrated significant changes in the recalculated RRs, which ranged from 1.22 (0.86–1.71) when Jakszyn 2013 (45.1%) was excluded from the analysis to 1.47 (1.10–1.96) when Keszei 2012 (13.7%) was excluded from the analysis. Non-linear dose–response analysis was not conducted because of the small number of studies included in the analysis.

Discussion

Three previous systematic reviews evaluated the associations between red and processed meat consumption and esophageal cancer risk, namely, the studies by Salehi et al. [49], Qu et al. [50] and Choi et al. [51]. However, some issues were not adequately addressed by these analyses, which reported different results. First, because case–control studies may provide information regarding exposures that was obtained after patient cancer diagnose, the results of the studies may be affected by inaccurate dietary intake measurements and recall bias. Cohort studies are less prone to bias than case–control studies. Thus, performing separate estimates according to study design is important and necessary for evaluating the associations between meat consumption and esophageal cancer risk. Second, two subtypes of esophageal cancer exist, namely, esophageal squamous cell carcinoma

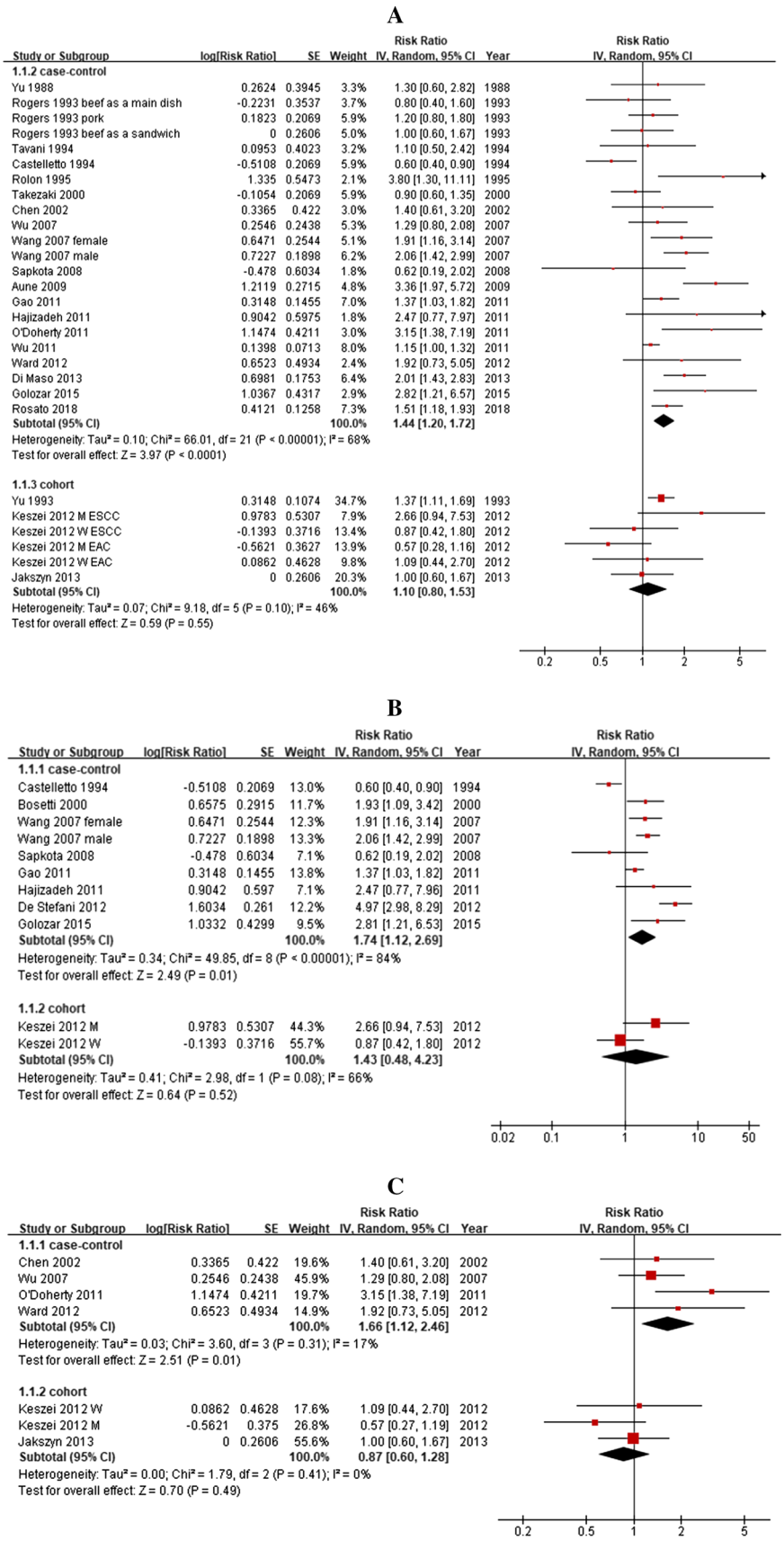

Fig. 2 Forest plots of red meat consumption (highest vs lowest) and esophageal cancer risk. **a** Esophageal cancer; **b** esophageal squamous cell carcinoma; **c** esophageal adenocarcinoma. *M* men, *W* women

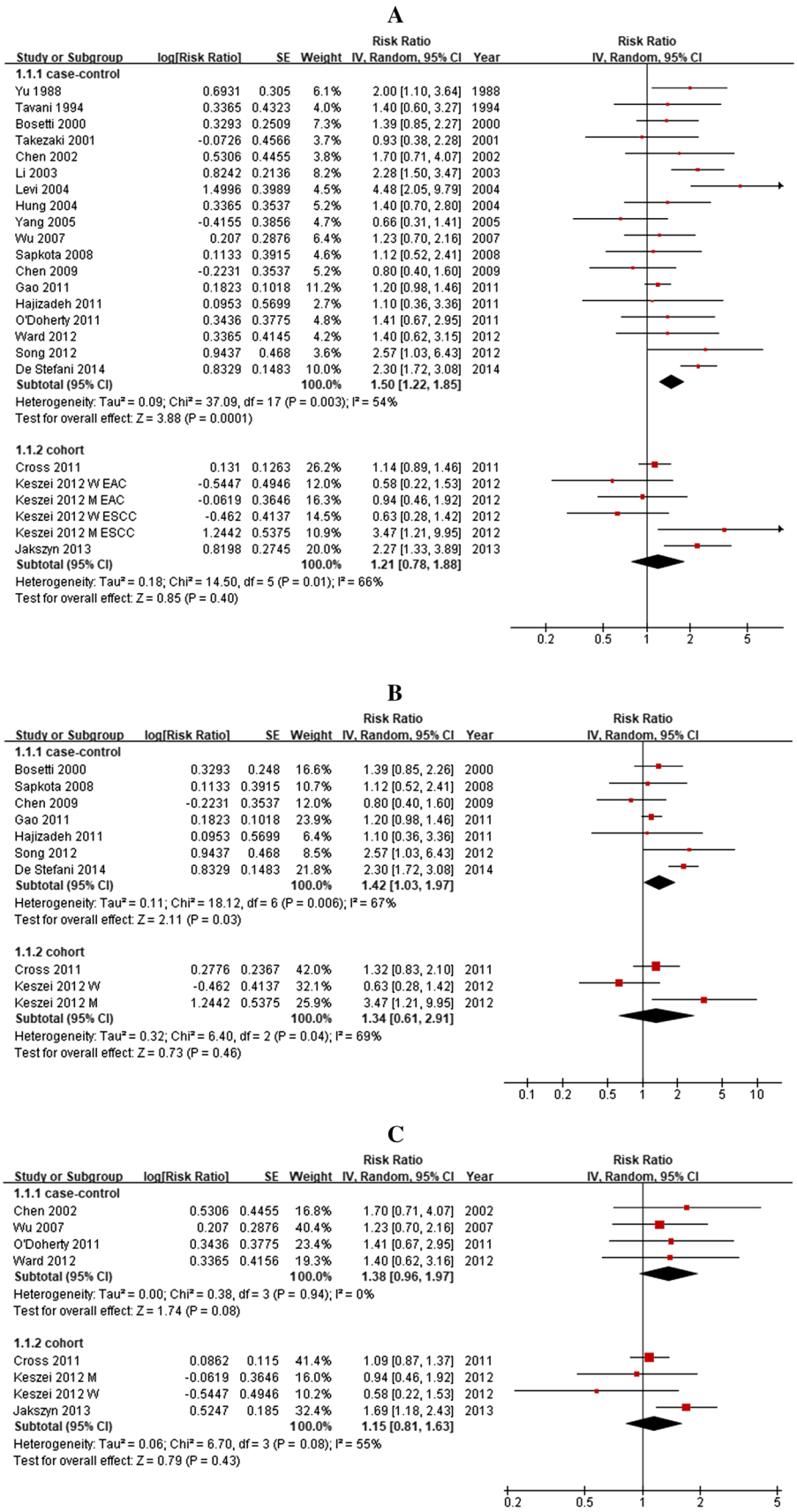

Fig. 3 Forest plots of processed-meat consumption (highest vs lowest) and esophageal cancer risk. **a** Esophageal cancer; **b** esophageal squamous cell carcinoma; **c** esophageal adenocarcinoma. *M* men, *W* women

and esophageal adenocarcinoma. Thus, performing separate estimates according to subtype is also important and necessary for evaluating the associations between meat consumption and esophageal cancer risk. As mentioned above, there were some differences between two reports with respect to their results. Salehi et al. [49] found that red meat consumption was associated with a significantly increased risk of esophageal squamous cell carcinoma but not esophageal adenocarcinoma and that processed meat consumption was associated with a significantly increased risk of esophageal adenocarcinoma but not esophageal squamous cell carcinoma. In contrast, Qu et al. [50] found that red and processed meat consumption was associated with a significantly increased risk of esophageal squamous cell carcinoma; however, that study did not obtain data regarding esophageal adenocarcinoma. Choi et al. [51] did not provide the detailed data on subtype of EC. Third, Salehi et al. [49] identified relevant studies published up to 2011, Qu et al. [50] identified relevant studies published up to 2012 and Choi et al. [51] identified relevant studies published up to 2012. Many high-quality studies regarding the relationship between red and processed meat consumption and EC risk have appeared during the recent years and an updated meta-analysis of the literature may clarify the impact of these recent studies on the understanding of the relationship between red and processed meat consumption and EC. Thus, to address the above questions, we conducted an updated systematic review and meta-analysis.

Our analysis yielded detailed evidence indicating that increased consumption of red and processed meat increased the risk of EC in the case–control studies; however, we noted no associations between meat consumption and EC risk in the cohort studies. Similarly, subtype analyses of EC showed that red or processed meat consumption was negatively associated with the risk of EAC and ESCC in the cohort studies. Taken together, our detailed findings have clarified the associations between consumption of red and processed meat and the risk of EC have thus provided us with valuable information with which updated dietary recommendations can be updated.

Several potential mechanisms may underlie the effects of red and processed meat consumption on the risk of EC. First, the positive associations observed in the case–control studies may be biologically plausible. Cooking red meat is one of the major sources of carcinogens such as polycyclic aromatic hydrocarbons, heterocyclic amines, nitrate and *N*-nitroso compounds, which are believed to play an important role in the development of EC [52]. Second, the high iron intake associated with red and processed meat consumption may also play a role in the development of EC by causing oxidative damage and facilitating the endogenous formation of carcinogenic *N*-nitroso compounds [13, 53]. Finally, bacteriological and virological studies have identified mechanisms that explain the associations between red and processed meat consumption and the risk of EC to a degree. Helicobacter pylori (*H. pylori)* may be a protective factor of EC [54] and human papillomavirus (HPV) infection may be associated with an increased risk of EC [55]. However, the results of many cohort studies and meta-analyses do not support these hypotheses. For example, a European prospective investigation regarding cancer and nutrition suggested that no association exists between increased unprocessed red meat consumption and the risk of EAC [48]. Although some prospective studies showed that red meat consumption is positively associated with gastrointestinal cancer, their definitions of red meat also included processed red meat, which may have influenced to the above associations [46, 56, 57]. Additionally, Barrett's esophagus is considered to be the strongest risk factor and only known precursor for EAC [58]. However, the results of our previous study did not support the idea that positive associations exist between high red and processed meat consumption and the risk of Barrett's esophagus [59]. Thus, additional studies are needed to verify the existence these associations.

Study strengths and limitations

Our study had several strengths. For example, we performed separate analyses according to study design and EC subtype, which provided us with more detailed data and increased the power of the meta-analysis, thereby strengthening its conclusions. Our analysis was based on a significantly large sample and a quantitative analysis of eligible data, which provided us with sufficient reliable, robust and current evidence regarding the relationship between red and processed meat consumption and the risk of EC and increased the statistical power of the analysis. We broadly and systematically searched multiple databases for all investigations of the relationship between red and processed meat consumption and the risk of EC that were published from the databases' dates of inception to May 2019 and identified all the major published studies regarding this phenomenon. Study selection and data extraction were performed independently and in duplicate by two investigators, which increased the validity of the results. Furthermore, we conducted dose–response analyses to assess these associations rather than merely performing categorical comparisons.

However, several limitations of the present meta-analysis must be taken into consideration.

First, the studies included in the analysis were observational, and residual confounding and unmeasured factors could not be excluded from the study. In particular, most of the studies included in the analysis lacked information regarding *H. pylori* infection and gastroesophageal reflux. Only two studies [12, 37] examined the role of *H.*

pylori infection in EC development. Thus, the results of the analysis should be interpreted with caution due to the presence of possible confounders, and future analyses should consider studies regarding *H. pylori* infection and gastroesophageal reflux.

Second, our analyses showed that significant heterogeneity was present among the studies and that this heterogeneity may have been related to the publication year, cases numbers, geographic region, exposure measurement methods, study quality score, meat consumption classifications, and other confounders. Heterogeneity was observed mainly in the analysis comparing the highest and the lowest levels of meat consumption and may be at least partially attributable to differences in the categories of meat consumption among the included studies. We used random-effects models to account for between-study heterogeneity. The ranges from the lowest to the highest categories varied, and the levels of red and processed meat consumption between the lowest and highest categories differed among the included studies, which may have resulted in bias and influenced the accuracy of the results.

Conclusions

The results of the meta-analysis indicate that the case–control studies but not the cohort studies associated the consumption of red and processed meat with the risk of EC. Additional large prospective studies are needed to validate these findings.

Author contributions Zhanwei Zhao, and Fei Wang wrote the main manuscript text, participated in the design of the work. Di Chen participated in the analysis of the data and prepared figures. Chaojun Zhang carried out the study design, the analysis and interpretation of the data and drafted the manuscript. All authors have reviewed the manuscript. Zhanwei Zhao, Fei Wang and Di Chen contributed equally to this work.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest for each author.

Ethical statement This work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed. Our meta-analysis did not involve human participants and animals.

Informed consent All participants provided informed consent prior to their participation.

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