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Consumption of red and processed meat and esophageal cancer risk: Meta-analysis

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Abstract

To summarize the evidence about the association between red and processed meat intake and the risk of esophageal cancer, we systematically searched the PubMed and EMBASE databases up to May 2012, with a restriction to English publications, and the references of the retrieved articles. We combined the study-specific relative risks (RRs) and 95%CI, comparing the highest with the lowest categories of consumption by using a random-effects model. A total of 4 cohort studies and 23 case-control studies were included in the meta-analysis. The combined RRs (95%CI) of the cohort studies comparing the highest and lowest categories were 1.26 (1.00-1.59) for red meat and 1.25 (0.83-1.86) for processed meat. For the case-control studies, the combined RRs (95%CI) comparing the highest and lowest categories were 1.44 (1.16-1.80)

for red meat and 1.36 (1.07-1.74) for processed meat. Findings from this meta-analysis suggest that a higher consumption of red meat was associated with a greater risk of esophageal cancer.

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Key words: Cohort study; Case-control study; Meta-analysis; Red meat; Processed meat; Esophageal cancer

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INTRODUCTION

The incidence rate of esophageal cancer ranked eighth worldwide, accounting for 3.8% of all new cancers, and its mortality rate ranked sixth, accounting for 5.4% of all cancer deaths in 2008^[1]. The most predominant histological types of esophageal cancer are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), representing distinct characteristics in patterns of cancer development and risk factors^[2].

Given that mutagenic compounds such as heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and N-nitroso compounds (NOCs) generated from red and processed meats were associated with cancer development^[3], concerns about a high incidence of esophageal cancer related to a high consumption of red and processed meats have been increasing. In 2007, a consensus report of experts assembled by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR)^[4] concluded through review of studies published up to 2004 that there were suggestive but inconclusive associations between red and processed meat consumption

and esophageal cancer risk. The WCRF/AICR expert report also indicated that the lack of consistent results may be because of insufficient data, especially from prospective cohort studies. Another review of studies published up to 2005^[5] suggested a possible increased risk of esophageal cancer with processed meat (9 case-control studies) and combined white and red meat (2 cohort and 18 case-control studies); however, this study concluded that more prospective data involving a larger number of cases would be needed to determine the association between meat consumption and the risk of esophageal cancer.

Since the completion of the two reviews, the results of the large prospective studies as well as new or updated case-control studies that examined association between red and processed meats and esophageal cancer risk have been published, but no meta-analysis of the prospective cohort studies has been reported. We, therefore, performed a meta-analysis of large prospective cohort and case-control studies to summarize the association between red and processed meat intake and the risk of esophageal cancer. We also quantified the dose-response relationships in the analysis of the cohort studies.

SEARCH STRATEGY

Two authors (Choi Y, Song S) independently performed a systematic search of published articles using the PubMed and EMBASE databases up to May 2012^[6]. We used the following search terms: “oesophageal or esophageal or esophagus or oesophagus” and “cancer or neoplasm or carcinoma” and “cohort or prospective or case-control” and “food or diet or meat”. We also reviewed the reference lists from the retrieved articles and those from previous review studies to identify additional relevant studies that may not have been identified by our database searches.

INCLUSION CRITERIA

Studies were included in our meta-analysis if they met the following criteria: (1) either a cohort or case-control design was used; (2) relative risk (RR) estimates and the 95%CI were provided for the association between red and/or processed meat intake and esophageal cancer; (3) the outcomes of interest were either the overall incidence of esophageal cancer or the two main histological subtypes, ESCC or EAC; and (4) the study was published in English. We included studies that reported the associations of esophageal cancer with exposures identified as “red meat” or “processed meat” and individual food items within the two groups. Studies generally included beef, pork, minced meat, lamb, veal, and offal (*e.g.*, liver, kidney) for unprocessed red meat and sausage, ham, bacon, salami, luncheon meat, or frankfurters, and any types of meat that were processed by smoking, curing, salting, or the addition of preservatives for processed meat. We excluded studies providing no apparent classification of meat or studies reporting a combination of red and white meat (*e.g.*, poultry). If data were duplicated in more than 1 study, the latest studies were included.

DATA EXTRACTION

We independently extracted the following data from each study, according to the meta-analysis of observational studies in epidemiology guidelines^[6], and any discrepancies were resolved by discussion: the first author's last name, the publication year, the country where the study was conducted, the study period, the age range of the subjects, the number of cases and controls or the cohort size, the measures and comparison levels of the exposures, the multivariate adjusted RRs with corresponding 95%CI for the highest vs lowest categories of red or processed meat intake, and the variables that were adjusted for in the analysis. For each study, we used the most fully adjusted RRs in the multivariate model. Any disagreements were resolved through consensus. The same two authors assessed the quality of the studies based on the Newcastle-Ottawa Scale, which ranged from 1 to 9 stars^[7]. The average score for each study was used in the analysis.

STATISTICAL ANALYSIS

We conducted separate meta-analyses for case-control and cohort studies, using results that compared red and processed meat intake as well as those that assessed each type individually. We also performed a meta-analysis combining both case-control and cohort studies. Using a random-effects model that considered both within and between study variation^[8], we combined the study-specific multivariate RRs and 95%CI, comparing the highest and the lowest categories of red and processed meat intake.

We assessed the statistical heterogeneity among the studies by using Q and I^2 statistics^[9], where significance was reached at $P < 0.1$. Publication bias was evaluated by using the Egger asymmetry test^[10], with significant level at $P < 0.05$. We investigated the potential sources of heterogeneity among the studies by conducting subgroup and meta-regression analyses for histological subtype (ESCC and EAC), sex (males, females, and both sexes), study location (Asia, Europe, North America, and South America), study quality, and confounders adjusted for in the analysis [alcohol, smoking, body mass index (BMI), and fruit and/or vegetable]. We also conducted the sensitivity analysis for case-control and cohort studies separately, omitting each study individually to evaluate whether the results could have been affected substantially by any one study.

In a sensitivity analysis, we estimated a dose-response for combined RRs for 100 g/d increments of red or processed meats for 3 cohort studies^[11-13], which are less prone to selection or recall bias than case-control studies. We did not include one study (Yu *et al.*^[14]), that presented binary categories of exposure for a dose-response analysis. For two studies^[11,13], the estimates were rescaled into 100 g/d increments. All statistical analyses were performed with Stata software, version 11 (Stata Corp., College Station, TX, United States). $P < 0.05$ considered statistically significant.

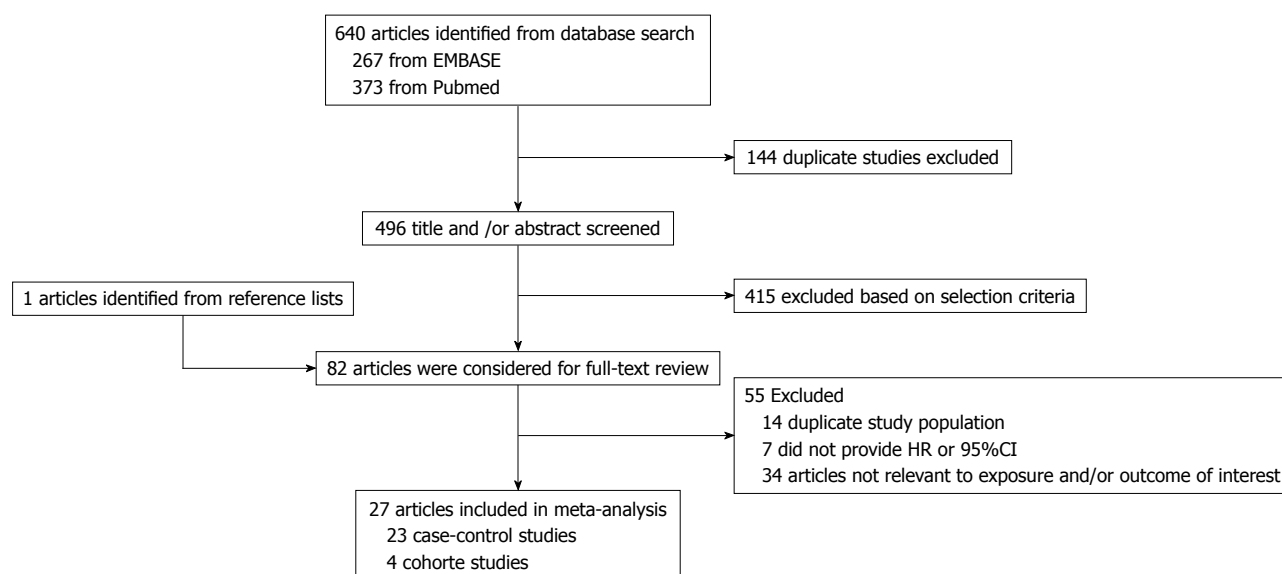


Figure 1 Selection of studies included in meta-analysis.

LITERATURE SEARCH

The preliminary literature search yielded 640 articles. Of these, 81 articles and 1 additional article identified from the reference lists were considered for further review (Figure 1). After the full-text review, 7 articles that did not provide RRs or 95%CI, 14 articles that used duplicated study populations, and 34 articles that were unrelated to exposure or outcomes of interest were excluded. A total of 27 articles were included in the meta-analysis; 22 articles (4 cohort and 18 case-control studies) that reported findings on red meat and 18 articles (3 cohorts and 15 case-controls) that reported findings on processed meat were included in the meta-analysis.

RED MEAT INTAKE

We identified 4 cohort studies^[11-14] involving 2324 cases and 1 149 981 participants and 18 case-control studies^[15-32] involving 5165 cases and 26 350 control subjects (Table 1). Two of the 22 studies reported results for both ESCC and EAC, 16 studies reported the results for either EAC or ESCC, and 6 reported results for overall esophageal cancer without the histological subtypes. Six studies were conducted in Asia, 6 in Europe, 7 in United States, and 3 in South America. The studies used either a food frequency questionnaire (FFQ) or a structured questionnaire form to measure red meat intake. Fifteen studies provided RR estimates that were adjusted for alcohol intake, 16 for smoking habit, 12 for BMI, and 7 for fruit and/or vegetable intake. Eight studies were given a score of 7 stars or above, representing a high quality of studies^[7]. The combined RRs (95%CI) comparing the highest and lowest categories of red meat intake were 1.26 (1.00-1.59) for the 4 cohort studies and 1.44 (1.16-1.80) for the 18 case-control studies (Figure 2A). There was no evidence of heterogeneity among the cohort stud-

ies ($P = 0.15$, $I^2 = 35.3\%$), but there was a heterogeneity among the case-control studies ($P < 0.01$, $I^2 = 72.8\%$). Combining the two types of study design resulted in an overall combined RR of 1.38 (95%CI: 1.17-1.64; P for heterogeneity: $P < 0.01$, $I^2 = 67.1\%$). Excluding a single study did not substantially influence the combined estimates of the cohort or case-control studies. There was no statistical evidence of publication bias according to the Egger asymmetry test ($P = 0.79$ for cohort studies and $P = 0.34$ for case-control studies). Dose-response associations were examined in 3^[11-13] of 4 cohort studies, showing the combined RRs of 1.05 (95%CI: 0.91-1.21; P for heterogeneity = 0.42, $I^2 = 0.2\%$) for every 100 g/d increment of red meat intake. The associations did not vary significantly by histological subtypes, study location, sex, and study quality (Table 2). In addition, the associations did not differ by adjusted confounding factors including alcohol, smoking, BMI, and fruit and vegetable intakes (data not shown).

PROCESSED MEAT INTAKE

We conducted a meta-analysis of 3 cohort studies^[11-13], which included 1162 cases and 1 137 288 participants and 15 case-control studies^[15,16,19-21,24,25,27,30,32-37], which included 3851 cases and 10 064 controls (Table 1). Two of the 18 studies examined both ESCC and EAC as the primary endpoints, 13 studies reported the results for either EAC or ESCC and 5 did not differentiate between histological subtypes. Five studies were conducted in Asia, 7 in Europe, 5 in United States, and 1 in South America. The studies used either a FFQ or a structured questionnaire form to measure processed meat intake. Fourteen studies provided RR estimates that were adjusted for alcohol intake, 15 for smoking habit, 10 for BMI, and 8 for fruit and/or vegetable intake. Six studies were given a score of 7 or greater, indicating a high methodological quality^[7].

Table 1 Characteristics of the studies included in the meta analysis

Ref.	Study period	Sex	No. of cases	No. cohorts or controls	Dietary assessment	Exposure and comparison level	Adjusted RR (95%CI)	Study quality ¹	Adjustment for confounders
Cohort studies									
Keszei <i>et al</i> ^[11]	1986-2002	M	ESCC: 107	120 852	FFQ 150 items	Red meat		9	Age, smoking (including years and numbers per day), total energy, BMI, alcohol drinking, vegetable, fruit, education, non-occupational PA
		F	EAC: 145			ESCC			
		M				Q5 vs Q1	2.66 (0.94-7.48)		
		F				T3 vs T1	0.87 (0.42-1.79)		
						EAC			
		M				Q5 vs Q1	0.57 (0.28-1.19)		
		F				T3 vs T1	1.09 (0.44-2.75)		
						Processed meat			
Cross <i>et al</i> ^[12]	1995-2006	C	ESCC: 215	494 979	FFQ 124 items	Red meat		9	Age, sex, BMI, education, ethnicity, smoking, alcohol drinking, PA at work, vigorous PA, daily intakes of fruit, vegetable, saturated fat, energy
			EAC: 630			(Q5 vs Q1)			
						ESCC	1.79 (1.07-3.01)		
						EAC	1.15 (0.84-1.57)		
						Processed meat			
						(Q5 vs Q1)			
						ESCC	1.32 (0.83-2.10)		
						EAC	1.08 (0.81-1.43)		
González <i>et al</i> ^[13]	1992-1998	C	EAC: 65	521 457	FFQ 88-266 items	Red meat	1.67 (0.75-3.72)	8	Sex, height, weight, education, smoking, smoking intensity, work and leisure PA, intakes of alcohol, energy, vegetable, citrus fruit, non-citrus fruit, types of meat intake were mutually adjusted
						Processed meat (T3 vs T1)	3.54 (1.57-7.99)		
Yu <i>et al</i> ^[14]	1974-1989	C	All: 1162	12 693	Questionnaire 15 items	Pork (never vs regular/occasional)	1.37 (1.11-1.68)	7	Age, sex
Case-control studies									
Ward <i>et al</i> ^[15]	1988-1993	C	EAC: 124	449	Questionnaire 100 items	Red meat (> 157.2 g/d vs ≤ 73.8 g/d)	2.85 (1.00-8.16)	5	Age, sex, race, vital status, year of birth, sex, No. of cigarettes per day, BMI, intakes of retinoic acid, folate, riboflavin, zinc, carbohydrate, protein, total energy.
						Processed meat (> 52.3 g/d vs ≤ 16.1 g/d)	1.40 (0.62-3.15)		
De Stefani <i>et al</i> ^[16]	1996-2004	C	ESCC: 234	2020	FFQ 64 items	Red meat (T3 vs T1)	4.97 (2.98-8.29)	7	Age, sex, residence, education, BMI, smoking, drinking, mate temperature, total energy, total intakes of vegetable and fruit, scored pattern
						Processed meat (T3 vs T1)	0.76 (0.51-1.13)		
Gao <i>et al</i> ^[17]	1997-2005	C	ESCC: 600	1514	Questionnaire 35 items	Red meat (> weekly vs monthly/seldom/never)	1.37 (1.03-1.82)	5	Age, sex, geographic region
Wu <i>et al</i> ^[18]	2003-2007	C	All: 1495	3819	FFQ	Red meat (Q4 vs Q1)	1.13 (0.94-1.36)	7	Age, sex, education, previous income, BMI, pack-years smoking, weekly ethanol intake, study area
Hajizadeh <i>et al</i> ^[19]	N/A	C	ESCC: 47	96	FFQ 168 items	Red meat (T3 vs T1)	2.47 (0.76-7.96)	6	Age, sex, education, tobacco smoking, symptomatic gastroesophageal reflux, BMI, total energy
						Processed meat (T3 vs T1)	1.10 (0.36-2.47)		
O'Doherty <i>et al</i> ^[20]	2002-2005	C	EAC: 221	256	FFQ 101 items	Red meat (Q4 vs Q1)	3.15 (1.38-7.20)	7	Age, sex, smoking, BMI 5 yr before interview date, education, job type, Intakes of energy, fruit, vegetable, alcohol (g/d), <i>Helicobacter pylori</i> infection, nonsteroidal anti-inflammatory drug use 5 yr before, interview date, gastroesophageal reflux symptoms, location, types of meat intake were mutually adjusted
						Processed meat (Q4 vs Q1)	1.41 (0.67-2.95)		

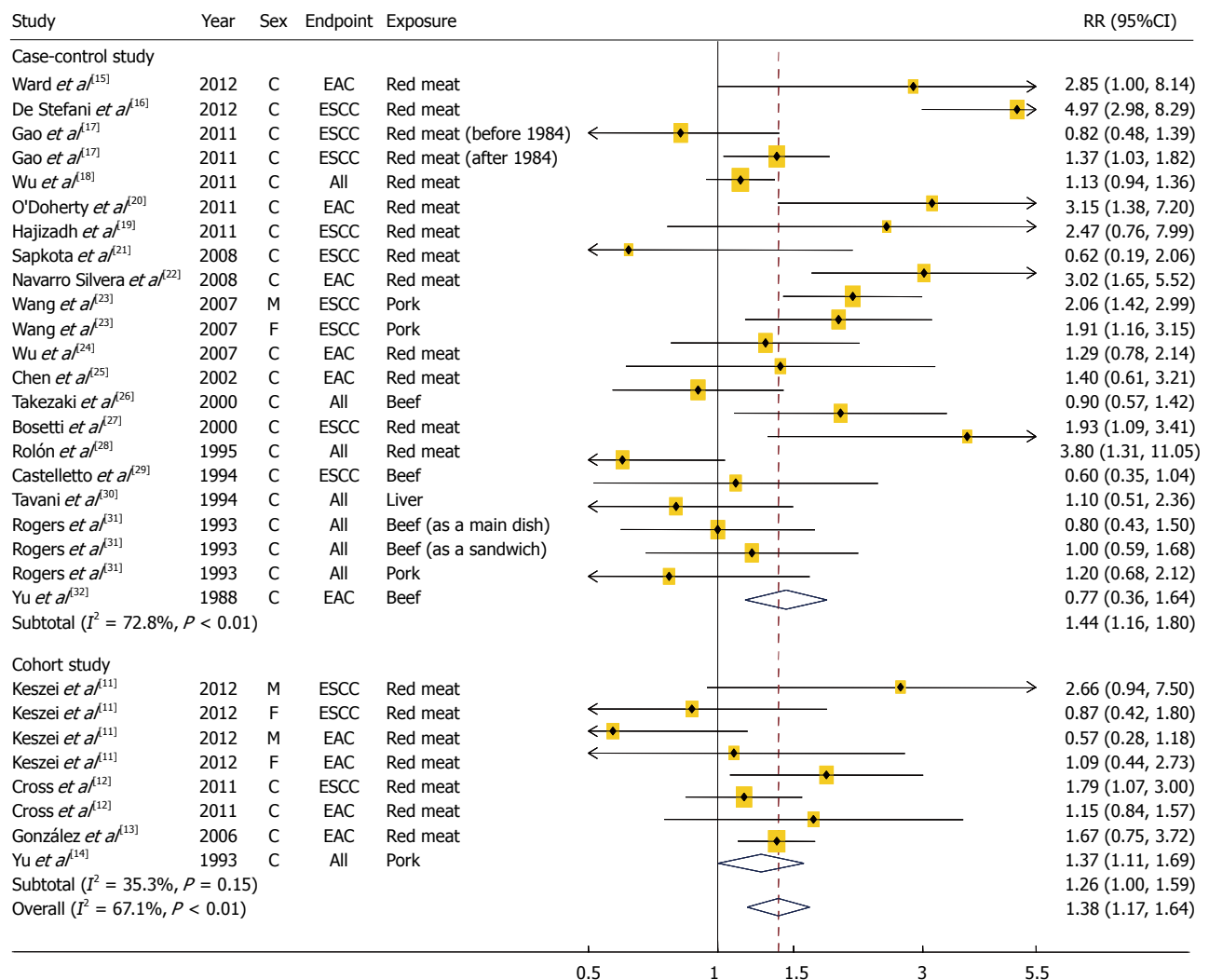
Sapkota <i>et al</i> ^[21]	1999-2003	C	ESCC: 187	1110	Questionnaire 23 items	Red meat ($\geq 1/\text{wk}$ vs $< 1/\text{mo}$) Processed meat (≥ 1 time/wk vs < 1 time/mo)	0.62 (0.19-2.09) 1.12 (0.52-2.41)	6	Age, sex, country, tobacco pack-year, education, BMI, frequency of alcohol consumption, vegetable, fruit consumption
Navarro Silvera <i>et al</i> ^[22]	1993-1995	C	EAC: 282	687	FFQ 104 items	Red meat (high vs low)	3.02 (1.65-5.52)	7	Age, sex, study site, race, proxy status, income, education, BMI, No. of smoking cigarettes per day, intakes of beer, wine, liquor, and energy
Wang <i>et al</i> ^[23]	2004-2006	M	ESCC: 355	408	Questionnaire	Pork (often vs none/seldom)	2.06 (1.42-2.99) 1.91 (1.16-3.16)	5	Age, sex, marital status, education
Wu <i>et al</i> ^[24]	1992-1997	C	EAC: 206	1308	Questionnaire 124 items	Red meat (Q4 vs Q1) Processed meat (Q4 vs Q1)	1.29 (0.8-2.2) 1.23 (0.7-2.1)	5	Age, sex, race, birthplace, education, smoking, BMI, reflux, use of vitamins, total energy
Chen <i>et al</i> ^[25]	1988-1993	C	EAC: 124	449	Questionnaire 54 items	Red meat (Q4 vs Q1) Processed meat (Q4 vs Q1)	1.4 (0.61-3.2) 1.7 (0.71-3.9)	7	Age, sex, energy intake, respondent type, BMI, alcohol drinking, smoking, education, family history, vitamin supplement use, age squared for EAC
Takezaki <i>et al</i> ^[26]	1988-1997	M	All: 284	11 888	Questionnaire	Beef ($\geq 3/\text{wk}$ vs $\leq 3/\text{mo}$)	0.9 (0.6-1.5)	5	Age, year and season of visit, smoking, drinking
Bosetti <i>et al</i> ^[27]	1992-1997	C	ESCC:304	743	FFQ 78 items	Red meat (Q5 vs Q1) Processed meat (Q5 vs Q1)	1.93 (1.09-3.41) 1.39 (0.85-2.26)	5	Age, sex, area of residence, education, tobacco smoking, alcohol drinking, non-alcohol energy
Rolón <i>et al</i> ^[28]	1988-1991	C	All: 131	379	FFQ	Red meat (highest vs lowest)	3.8 (1.3-11.0)	5	Age, sex, alcohol, smoking, design variable of the study, hospital group, intakes of red meats, fats, fish, milk
Castelletto <i>et al</i> ^[29]	1986-1989	C	ESCC: 131	261	FFQ 10 food groups	Beef (\geq daily vs $<$ daily)	0.6 (0.3-0.9)	6	Age, sex, design variable, hospital, education, No. of cigarettes smoking per day, intakes of alcohol, barbecued meat, potatoes, raw vegetables, cooked vegetables
Tavani <i>et al</i> ^[30]	1984-1992	C	All: 46	230	FFQ 14 items	Ham (Q3 vs Q1) Liver (Q2 vs Q1)	1.4 (0.6-3.3) 1.1 (0.5-2.3)	5.5	Age, sex, education, total alcohol intake
Rogers <i>et al</i> ^[31]	1983-1987	C	All: 127	466	FFQ 125 items	Beef ($\geq 1/\text{wk}$ vs $< 1/\text{wk}$) As a main dish As a sandwich Pork ($\geq 1/\text{wk}$ vs $< 1/\text{wk}$)	0.8 (0.4-1.4) 1.0 (0.6-1.7) 1.2 (0.8-2.5)	5	Age, sex, pack-years of cigarette, drink-years of alcohol, energy intake, beta-carotene intake, ascorbic acid intake
Yu <i>et al</i> ^[32]	1975-1981	C	Beef: 267 Fried bacon or ham: 265 Barbecued or smoked meat: 268	Beef: 267 Fried bacon or ham: 265 Barbecued or smoked meat: 268	Questionnaire 10 food groups	Beef ($\geq 5/\text{wk}$ vs $\leq 1/\text{wk}$) Fried bacon or ham ($\leq 1/\text{wk}$ vs $\geq 5/\text{wk}$) Barbecued or smoked meat ($\geq 2/\text{wk}$ vs $\leq 1/\text{wk}$)	1.3 (0.6-2.7) 2.0 (1.1-3.5) 1.7 (0.9-3.0)	5	Age, sex, race
Chen <i>et al</i> ^[33]	1996-2005	M	ESCC: 320	709	Questionnaire 6 items	Cured meat ($\geq 1/\text{wk}$ vs $< 1/\text{wk}$)	0.8 (0.4-1.4)	5	Age, educational level, ethnicity, source of hospital, smoking, alcohol drinking, areca nut chewing
Yang <i>et al</i> ^[34]	2003-2004	C	All: 185	185	Questionnaire 9 Items	Processed meat (> 3 meals/wk vs < 1 meal/wk)	0.66 (0.31-1.41)	5.5	Family history of esophageal cancer, occupation, smoking, drinking, eating hot food, eating speed, intakes of vegetables, fruit, pickled vegetables, fresh meat, egg, tea, water supply
Levi <i>et al</i> ^[35]	1992-2002	C	All:138	660	FFQ 79 items	Processed meat (> 3.2 freq/wk vs < 0.8 freq/wk)	4.48 (2.05-9.79)	6	Age, sex, education, smoking, intakes of alcohol, energy, fruit and vegetable intake
Li <i>et al</i> ^[36]	1997-2000	C	All:1248	1248	Questionnaire 12 items	Sowbelly (daily vs $< 1/\text{wk}$)	2.28 (1.6-3.3)	5	Age, sex, income, residence, occupation, alcohol, tobacco

¹Study quality was assessed using the Newcastle-Ottawa Scale (range: 1-9 stars). RR: Relative risk; M: Male; F: Female; C: Combined males and females; ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; FFQ: Food frequency questionnaire; BMI: Body mass index; PA: Physical activity; N/A: Not available.

Table 2 Combined relative risks and 95%CI for esophageal cancer associated with red meat or processed meat by other factors in both cohort and case-control studies

Factors	Red meat			Processed meat		
	Studies Ref. (n)	RR (95%CI)	P for heterogeneity	Studies Ref. (n)	RR (95%CI)	P for heterogeneity
Histological subtypes						
EAC	9 [11-13,15,20,22,24,25,32]	1.42 (1.02-1.98)	0.19	8 [11-13,15,20,24,25,32]	1.38 (1.07-1.78)	0.3
ESCC	9 [11,12,16,17,19,21,23,27,29]	1.55 (1.10-2.17)		7 [11,12,16,19,21,27,33]	1.08 (0.80-1.44)	
Study location						
Asia	6 [14,17,18,19,23,26]	1.33 (1.09-1.62)	0.67	5 [19,33,34,36,37]	1.09 (0.61-1.95)	0.65
Europe	6 [11,13,20,21,27,30]	1.33 (0.86-2.07)		7 [11,13,20,21,27,30,35]	1.49 (0.99-2.23)	
United States	7 [12,15,22,24,25,31,32]	1.32 (1.03-1.70)		5 [12,15,21,25,32]	1.30 (1.08-1.57)	
South America	3 [16,28,29]	2.20 (0.48-10.04)		1 [16]	0.76 (0.51-1.13)	
Sex						
Male	3 [11,23,26]	1.26 (0.66-2.41)	0.88	2 [11,33]	1.24 (0.58-2.65)	0.14
Female	2 [11,23]	1.31 (0.78-2.21)		1 [11]	0.61 (0.33-1.13)	
Both	19 [12-22,24,25,27-32]	1.42 (1.17-1.71)		16 [12,13,15,16,19-21,24,25,27,30,32,34-37]	1.43 (1.15-1.77)	
Study quality ¹						
≥ 7	8 [11-14,16,18,20,22]	1.60 (1.20-2.13)	0.23	6 [11-13,16,20,25]	1.20 (0.88-1.62)	0.42
< 7	14 [15,17,19,21,23-32]	1.25 (1.02-1.54)		12 [15,19,21,24,27,30,32-37]	1.43 (1.11-1.86)	

¹Study quality was assessed using the Newcastle-Ottawa Scale (range, 1-9 stars); RR: Relative risk; ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma.

A

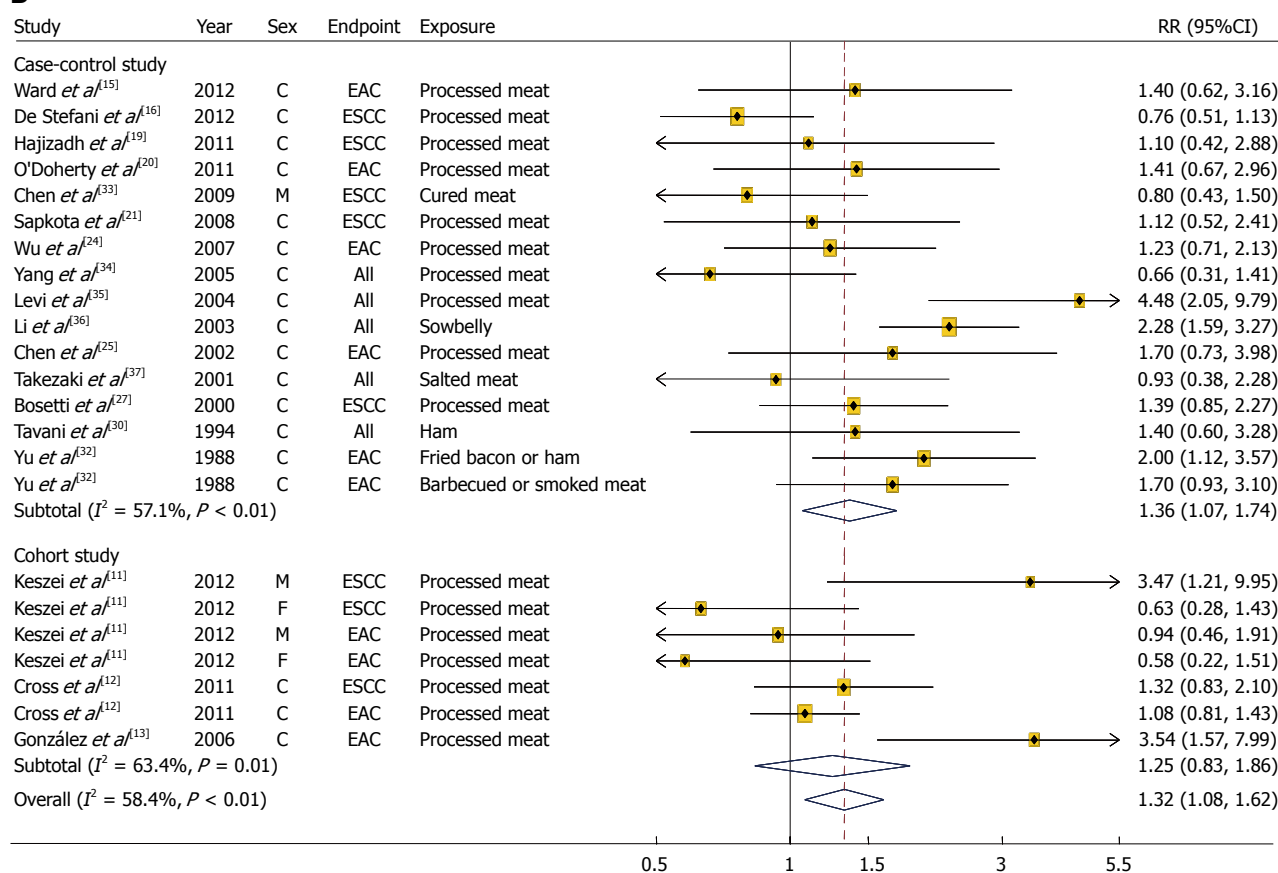
B

Figure 2 The combined relative risks and 95%CI of esophageal cancer risk for the highest vs lowest categories of red meat (A) and processed meat (B). M: Male; F: Female; C: Combined males and females; ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma.

In a meta-analysis of the 15 case-control studies, we found that the highest categories of processed meat intake were associated with a 36% increase in esophageal cancer risk when compared with the lowest categories (95%CI: 1.07-1.74; Figure 2B); however, we found a non-significant, positive association when we examined only the cohort studies (RR: 1.25; 95%CI: 0.83-1.86). When we examined whether an individual study was the source of heterogeneity among either the cohort or case-control studies, there were heterogeneities between the case-control studies ($P < 0.01$, $I^2 = 57.1\%$) and the cohort studies ($P = 0.01$, $I^2 = 63.4\%$). When the results from the cohort and case-control studies were combined, the overall combined RR comparing the highest and the lowest category of processed meat was 1.32 (95%CI: 1.08-1.62; P for heterogeneity: $P < 0.01$, $I^2 = 58.4\%$). The heterogeneity observed between the prospective studies of processed meat intake and esophageal cancer risk was no longer significant ($P = 0.12$) after excluding a study by González *et al.*^[13]. However, excluding any one case-control study from the analysis did not influence the heterogeneity findings observed among case-control studies.

No publication bias was found for either the cohort or case-control studies ($P = 0.65$ for the cohort studies and $P = 0.80$ for the case-control studies). In a dose-response meta-analysis of 3 cohort studies, we found

that each 100 g/d increase in processed meat intake was positively, but not significantly, associated with esophageal cancer risk (RR: 1.37; 95%CI: 0.88-2.13). There was no evidence of heterogeneity ($P = 0.17$, $I^2 = 33.5\%$).

When stratifying the analyses by histological subtypes, study location, sex, and study quality, we found no significant differences in the associations, although the magnitude of the associations differed slightly in these subgroups (Table 2). The associations also did not vary by adjusted confounding factors including alcohol, smoking, BMI, and fruit and vegetable intakes (data not shown).

DISCUSSION

To our knowledge, this is the first systematic meta-analysis of cohort and case-control studies to summarize the evidence regarding the association between red or processed meat intake and the risk of esophageal cancer. High red meat consumption was associated with a 38% higher risk of esophageal cancer compared to low consumption in a meta-analysis of both case-control and cohort studies. A 26% higher risk of esophageal cancer was observed among those who had high red meat intake compared to those with low intake in a meta-analysis of 4 cohort studies. With regard to processed meat, we found a higher risk of esophageal cancer with high processed

meat intake compared to low intake in a meta-analysis of case-control studies, but the combined estimate of cohort studies did not reach statistical significance. Prospective cohort studies are less prone to selection or recall bias compared to case-control studies, which is critical in research of diet and cancer etiology. Therefore, a significant association in only the case-control studies and not in the meta-analysis of the 3 cohort studies could not provide adequate supportive evidence of an increased risk associated with processed meat consumption. However, the results for more prospective cohort studies need to be reported to obtain a clearer conclusion.

There are possible underlying mechanisms linking the consumption of red and processed meats and the incidence of cancer. HCAs and PAHs are chemical compounds with mutagenic potential that are formed when meat is boiled, fried, or grilled at high temperatures^[3]. Animal studies have suggested that these two mutagenic compounds may induce changes in DNA, possibly promoting carcinogenesis^[3,38]. Another class of meat-related mutagen is NOCs, the majority of which are potent carcinogens^[39] formed either endogenously or exogenously. Processed meat is typically preserved by adding nitrate or nitrite, which increases the formation of NOCs^[3]. Heme iron, largely derived from red meat sources, has been suggested to promote the endogenous formation of NOCs^[40]. There is only limited epidemiological evidence, however, to suggest that the dietary intake of nitrite or nitrosamine is positively associated with the risk of esophageal cancer^[5]. The esophagus is frequently exposed to these dietary mutagenic and/or carcinogenic compounds as stomach and colon, permitting food to pass from the esophagus into the stomach. While the specific mechanism by which meat causes esophageal cancer has not been fully elucidated, one likely reason may involve the potential for increase the susceptibility to carcinogenesis by repeated exposure of esophagus to the mutagenic and/or carcinogenic compounds, given their effects on carcinogenesis in animal models^[3,38,39].

The results from the subgroup and meta-regression analysis could not completely explain the potential sources of between-study heterogeneity because we did not observe statistically significant differences by histological subtype, study location, sex, or study quality. For red meat intake, it appeared that a single study did not substantially influence the overall combined RR, whereas, the observed heterogeneity among the prospective studies of processed meat intake and esophageal cancer risk disappeared when the study by González *et al.*^[13] was excluded. However, the observed heterogeneity among the case-control studies of processed meat intake and esophageal cancer risk was not materially altered in sensitivity analyses excluding one study at a time.

Our meta-analysis had some limitations. Although the majority of the studies adjusted for known potential confounding factors, there may be a possibility that unidentified or residual confounding factors remained that were not adjusted for in the multivariate analysis or by covariates inadequately measured. Most studies, however,

adjusted for alcohol and smoking, both of which are established risk factors for esophageal cancer. Additionally, we found an increased risk of esophageal cancer with high red meat intake in a meta-analysis of well-scored studies, which were relatively recent and adjusted for various potential confounding factors. The random measurement error of meat consumption that occurred during dietary assessment or the systematic error resulting from recall or selection bias in the case-control studies may have influenced our findings; however, we found a statistically significant association between red meat intake and esophageal cancer risk in a meta-analysis of prospective studies, which supports the hypothesis that red meat intake increases the risk of esophageal cancer.

Our meta-analysis also included several strengths. Our meta-analysis updated the recent large prospective and case-control studies with a larger number of cases that were not included in previous reviews. In particular, the inclusion of new data from large cohort studies, which were unavailable when earlier conclusions of these associations were made by the WCRF/AICR expert panel^[4] or by a review study^[5], enabled us to provide more unbiased evidence compared to the review that included only case-control studies. The findings from this meta-analysis were not subject to publication bias, indicating that the probability of publishing a study did not rely on the strength and direction of the associations.

CONCLUSION

The findings from our meta-analysis of either prospective cohort or case-control studies suggest that a high consumption of red meat may increase the risk of esophageal cancer. Although we found an increased risk in a meta-analysis of the case-control studies for processed meat intake in relation to esophageal cancer risk, the prospective cohort studies did not strongly support this evidence. There is a need for further large scale prospective studies to determine whether processed meat intake increases the risk of esophageal cancer. Moreover, further studies evaluating the effect of red or processed meat intake on individual histological subtypes of esophageal cancer are warranted.

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