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

Yuni Choi, Sujin Song, Yoonju Song, Jung Eun Lee

Yuni Choi, Jung Eun Lee, Department of Food and Nutrition, Sookmyung Women’s University, Seoul 140-742, South Korea
Sujin Song, Department of Food and Nutrition, Seoul National University, Seoul 151-742, South Korea
Yoonju Song, School of Human Ecology, Catholic University of Korea, Bucheon, Gyeonggi Do 420-743, South Korea

Author contributions: Choi Y and Lee JE designed the study; Choi Y drafted the manuscript and conducted data analysis; Choi Y, Song S and Lee JE contributed to the selection of studies and data extraction, and the interpretation of the results; all authors critically reviewed the manuscript and gave final approval of the version to be published.

Supported by The Sookmyung Women’s University Research Grant (2012)

Correspondence to: Dr. Jung Eun Lee, Department of Food and Nutrition, Sookmyung Women’s University, 52 Hyochangwon-gil, Youngsan-gu, Seoul 140-742, South Korea. junglee@sm.ac.kr
Phone: +82-2-20775560 Fax: +82-2-7109479
Received: September 19, 2012 Revised: November 19, 2012
Accepted: December 5, 2012
Published online: February 21, 2013

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.

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

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 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. 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, 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% CIs for the highest or 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. 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, we combined the study-specific multivariate RRs and 95% CIs, comparing the highest and the lowest categories of red and processed meat intake.

We assessed the statistical heterogeneity among the studies by using $I^2$ and $Q$ statistics, where significance was reached at $P < 0.1$. Publication bias was evaluated by using the Egger asymmetry test, 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, which is less prone to selection or recall bias than case-control studies. We did not include one study (Yu et al.), that presented binary categories of exposure for a dose-response analysis. For two studies, 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.
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 involving 2324 cases and 1149981 participants and 18 case-control studies involving 5165 cases and 26350 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. 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 studies (P = 0.15, I² = 35.3%), but there was a heterogeneity among the case-control studies (P < 0.01, I² = 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, I² = 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 of 4 cohort studies, showing the combined RRs of 1.05 (95%CI: 0.91-1.21; P for heterogeneity = 0.42, I² = 2.2%) 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, which included 1162 cases and 1137288 participants and 15 case-control studies, which included 3851 cases and 10064 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.
Table 1  Characteristics of the studies included in the meta analysis

| Ref. | Study period | Sex | No. of cases | No. cohorts or controls | Dietary assessment | Exposed and comparison level | Adjusted RR (95%CI) | Study quality | Adjustments for confounders |
|------|--------------|-----|--------------|-------------------------|-------------------|-----------------------------|---------------------|---------------|----------------------------|
| Keszei et al[11] | 1986-2002 | M | ESCC: 107 | 120 852 | FFQ 150 items | Red meat | ESCC | 2.66 (0.94-7.48) | 9 | Age, smoking (including years and numbers per day), total energy, BMI, alcohol drinking, vegetable, fruit, education, non-occupational PA |
| | | F | EAC: 145 | | | | Q5 vs Q1 | 0.87 (0.42-1.79) | | |
| | | M | | | | T3 vs T1 | 0.57 (0.28-1.19) | | |
| | | F | | | | EAC | 1.09 (0.44-2.75) | | |
| | | M | | | | Q5 vs Q1 | 3.47 (1.21-9.94) | | |
| | | F | | | | T3 vs T1 | 0.63 (0.28-1.44) | | |
| | | M | | | | Q5 vs Q1 | 0.94 (0.46-1.89) | | |
| | | F | | | | T3 vs T1 | 0.58 (0.22-1.50) | | |
| Cross et al[12] | 1995-2006 | C | ESCC: 215 | 494 979 | FFQ 124 items | Red meat (Q5 vs Q1) | ESCC | 1.79 (1.07-3.01) | 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 |
| | | EAC: 630 | | | | EAC | 1.15 (0.84-1.57) | | |
| | | M | | | | Red meat (Q5 vs Q1) | ESCC | 1.32 (0.83-2.10) | | |
| | | F | | | | EAC | 1.08 (0.81-1.43) | | |
| | | M | | | | Red meat (T3 vs T1) | Processed meat (Q5 vs Q1) | 1.67 (0.75-3.72) | | |
| | | F | | | | EAC | 3.54 (1.57-7.99) | | |
| González et al[13] | 1992-1998 | C | EAC: 65 | 521 457 | FFQ 88-266 items | Red meat (T3 vs T1) | Processed meat (T3 vs T1) | 1.67 (1.07-3.01) | 7 | Age, sex |
| | | | | | | Red meat (T3 vs T1) | Processed meat (T3 vs T1) | 1.15 (0.84-1.57) | | |
| Yu et al[14] | 1974-1989 | C | All: 1162 | 12 693 | Questionnaire 15 items | Pork (never vs regular/occasional) | | 1.37 (1.11-1.68) | 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 |
| Ward et al[15] | 1988-1993 | C | EAC: 124 | 449 | Questionnaire 100 items | Red meat (> 157.2 g/d vs ≤ 73.8 g/d) | Processed meat (> 52.3 g/d vs ≤ 16.1 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 |
| De Stefani et al[16] | 1996-2004 | C | ESCC: 234 | 2020 | FFQ 64 items | Red meat (T3 vs T1) | Processed 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 |
| Gao et al[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 et al[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 et al[19] | N/A | C | ESCC: 47 | 96 | FFQ 168 items | Red meat (T3 vs T1) | Processed meat (T3 vs T1) | 2.47 (0.76-7.96) | 6 | Age, sex, education, tobacco smoking, symptomatic gastroesophageal reflux, BMI, total energy |
| O’Doherty et al[20] | 2002-2005 | C | EAC: 221 | 256 | FFQ 101 items | Red meat (Q4 vs Q1) | Processed 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), *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drug use 5 yr before, interview date, gastroesophageal reflux symptoms, location, types of meat intake were mutually adjusted |

**Choi Y et al. Meat and esophageal cancer**
| Study | Year to Year | Country | Study | Questionnaire | Food Group | Frequency of Intake | Odds Ratio (95% CI) |
|-------|--------------|---------|-------|---------------|-------------|---------------------|-------------------|
| Sapkota et al. | 1999-2003 | C | ESCC: 187 | Questionnaire | Red meat | (> 1/wk vs < 1/wk) | 0.62 (0.19-2.09) |
| Navarro et al. | 1993-1995 | C | EAC: 282 | FFQ | Red meat | (high vs low) | 3.02 (1.65-5.52) |
| Wang et al. | 2004-2006 | M | ESCC: 355 | Questionnaire | Pork | (often vs none/seldom) | 2.06 (1.42-2.99) |
| Wu et al. | 1992-1997 | C | EAC: 206 | Questionnaire | Red meat | (Q4 vs Q1) | 1.91 (1.16-3.16) |
| Chen et al. | 1988-1993 | C | EAC: 124 | Questionnaire | Red meat | (Q4 vs Q1) | 1.29 (0.8-2.2) |
| Takezaki et al. | 1988-1997 | M | All: 284 | Questionnaire | Beef | (Q3 vs Q1) | 1.7 (0.9-3.0) |
| Bosetti et al. | 1992-1997 | C | ESCC: 304 | FFQ | Red meat | (Q3 vs Q1) | 1.7 (0.71-3.9) |
| Rolón et al. | 1988-1991 | C | All: 131 | FFQ | Red meat | (highest vs lowest) | 1.4 (0.61-3.2) |
| Castelletto et al. | 1986-1989 | C | ESCC: 131 | FFQ | Beef | (daily vs < daily) | 0.6 (0.3-0.9) |
| Tavani et al. | 1984-1992 | C | All: 46 | FFQ | Ham (Q3 vs Q1) | 1.4 (0.6-3.3) |
| Rogers et al. | 1983-1987 | C | All: 127 | FFQ | Liver (Q2 vs Q1) | 1.1 (0.5-2.3) |
| Yu et al. | 1975-1981 | C | Beef: 267 | Questionnaire | Beef | (> 1/wk vs < 1/wk) | 1.0 (0.6-1.7) |
| Chen et al. | 1996-2005 | M | ESCC: 320 | Questionnaire | Cured meat | (> 1/wk vs < 1/wk) | 0.8 (0.4-1.4) |
| Yang et al. | 2003-2004 | C | All: 185 | Questionnaire | Processed meat | (> 1 meal/wk) | 0.66 (0.31-1.41) |
| Levi et al. | 1992-2002 | C | All: 138 | FFQ | Processed meat | (> 3 meals/wk) | 4.48 (2.05-9.79) |
| Li et al. | 1997-2000 | C | All: 1248 | Questionnaire | Sowbelly | (daily vs < 1/wk) | 2.28 (1.6-3.3) |

*Study 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 |
|--------------------------|----------|----------------|
| RR (95%CI)               | P for    | RR (95%CI)     | P for    |
|                          | heterogeneity | heterogeneity   |
|                          | (n)       |                | (n)       |
| Histological subtypes    |          |                |          |
| EAC                      | 9 [11-13,15,20,22,24,25,32] | 1.42 (1.02-1.98) | 0.19 |
| ESCC                     | 9 [11,12,16,17,19,21,23,27,29] | 1.55 (1.10-2.17) | 0.19 |
| Study location           |          |                |          |
| Asia                     | 6 [14,17,18,19,23,26] | 1.33 (1.09-1.62) | 0.67 |
| Europe                   | 6 [11,13,20,21,27,30] | 1.23 (0.86-2.07) | 0.67 |
| United States            | 7 [12,15,22,24,25,31,32] | 1.32 (1.03-1.70) | 0.67 |
| South America            | 3 [16,28,29] | 2.20 (0.48-10.04) | 0.76 |
| Sex                      |          |                |          |
| Male                     | 3 [11,23,26] | 1.26 (0.66-2.41) | 0.88 |
| Female                   | 2 [11,23] | 1.31 (0.78-2.21) | 0.88 |
| Both                     | 19 [12-22,24,25,27-32] | 1.42 (1.17-1.71) | 0.88 |
| Study quality¹           |          |                |          |
| ≥ 7                      | 8 [11-14,16,18,20,22] | 1.60 (1.20-2.13) | 0.23 |
| < 7                      | 14 [15,17,19,21,23,32] | 1.25 (1.02-1.54) | 0.23 |

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

Study Year Sex Endpoint Exposure RR (95%CI)

Case-control study

Ward et al[12] 2012 C EAC Red meat 2.85 (1.00, 8.14)
De Stefani et al[22] 2012 C ESCC Red meat 4.97 (2.98, 8.29)
Gao et al[23] 2011 C ESCC Red meat (before 1984) 0.82 (0.48, 1.39)
Gao et al[24] 2011 C ESCC Red meat (after 1984) 1.37 (1.03, 1.82)
Wu et al[25] 2011 C All Red meat 1.13 (0.94, 1.36)
O’Doherty et al[26] 2011 C EAC Red meat 3.15 (1.38, 7.20)
Hjalte et al[26] 2011 C ESCC Red meat 2.47 (0.76, 7.99)
Sapkota et al[27] 2008 C ESCC Red meat 0.62 (0.19, 2.06)
Navarro Silveira et al[28] 2008 C EAC Red meat 3.02 (1.65, 5.52)
Wang et al[29] 2007 M ESCC Pork 2.06 (1.42, 2.99)
Wang et al[29] 2007 F ESCC Pork 1.91 (1.16, 3.15)
Wu et al[30] 2007 C EAC Red meat 1.29 (0.78, 2.14)
Chen et al[31] 2002 C EAC Red meat 1.40 (0.61, 2.31)
Takahashi et al[30] 2000 C All Beef 0.90 (0.57, 1.42)
Bosetti et al[33] 2000 C ESCC Red meat 1.93 (1.09, 3.41)
Roló et al[30] 1995 C All Red meat 3.80 (1.31, 11.05)
Castelletto et al[34] 1994 C ESCC Beef 0.60 (0.35, 1.04)
Tavani et al[35] 1994 C All Liver 1.10 (0.51, 2.36)
Rogers et al[36] 1993 C All Beef (as a main dish) 0.80 (0.43, 1.50)
Rogers et al[36] 1993 C All Beef (as a sandwich) 1.00 (0.59, 1.68)
Rogers et al[36] 1993 C All Pork 1.20 (0.68, 2.12)
Yu et al[37] 1988 C EAC Beef 0.77 (0.36, 1.64)
Subtotal (I² = 72.8%, P < 0.01) 1.44 (1.16, 1.80)

Cohort study

Kesztei et al[11] 2012 M ESCC Red meat 2.66 (0.94, 7.50)
Kesztei et al[11] 2012 F ESCC Red meat 0.87 (0.42, 1.80)
Kesztei et al[11] 2012 M EAC Red meat 0.57 (0.28, 1.18)
Kesztei et al[11] 2012 F EAC Red meat 1.09 (0.44, 2.73)
Cross et al[12] 2011 C ESCC Red meat 1.79 (1.07, 3.00)
Cross et al[12] 2011 C EAC Red meat 1.15 (0.84, 1.57)
González et al[38] 2006 C EAC Red meat 1.67 (0.75, 3.72)
Yu et al[39] 1993 C All Pork 1.37 (1.11, 1.69)
Subtotal (I² = 35.3%, P = 0.15) 1.26 (1.00, 1.59)
Overall (I² = 67.1%, P < 0.01) 1.38 (1.17, 1.64)
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, I² = 57.1%)* and the cohort studies *(P = 0.01, I² = 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, *I²* = 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.*[38]. 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 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, I² = 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 intake compared to low intake.
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[39]. Hem 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[3,38]. The esophagus is frequently exposed to these dietary mutagenic and/or carcinogetic 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 carcinogetic 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[38] 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[49] or by a review study[50], 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.

ACKNOWLEDGMENTS

We thank Dr. Cross for data provision for our dose-response meta-analysis part.

REFERENCES

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]
2 Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. Gastroenterol Clin North Am 2009, 38: 27-57, vii [PMID: 19327566 DOI: 10.1016/j.gtc.2009.01.004]
3 Cross AJ, Sinha R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. Environ Mol Mutagen 2004;
Choi Y et al. Meat and esophageal cancer

14. You Y, Taylor PR, Li JY, Dawsey SM, Wang GQ, Guo WD, Wang W, Liu BQ, Blot WJ, Shen Q. Retrospective cohort study of risk-factors for esophageal cancer in Lixinian, People's Republic of China. Cancer Causes Control 1993; 4: 195-202 [PMID: 8318635]

15. Ward MH, Cross AJ, Abnet CC, Sinha R, Markian RS, Weisnberger DD. Heme iron from meat and risk of adenocarcinoma of the esophagus and stomach. Eur J Cancer Prev 2012; 21: 134-138 [PMID: 22034848 DOI: 10.1097/CEJ.0b013e328349b6c]

16. De Stefani E, Devere-Pellegrini H, Ronco AL, Boffetta P, Correa P, Aune D, Mendilaharsu M, Acosta G, Silva C, Landó G, Luaces ME. Red and processed meat consumption and the risk of squamous cell carcinoma of the esophagus: a case-control study in Uruguay. Nutr Cancer 2012; 64: 294-299 [PMID: 22242927 DOI: 10.1080/01635581.2012.648299]

17. Gao Y, Hu N, Han XY, Ding T, Giffen C, Goldstein AM, Taylor PR. Risk factors for esophageal and gastric cancers in Shanxi Province, China: a case-control study. Cancer Epidemiol Biomarkers Prev 2011; 35: e91-e99 [PMID: 21846596 DOI: 10.1094/cebp.2011.06.006]

18. Wu M, Zhang ZF, Kampman E, Zhou YJ, Han RQ, Yang J, Zhang XF, Gu XP, Liu AM, van’t Veer P, Kok FJ, Zhao JK. Does family history of cancer modify the effects of lifestyle risk factors on esophageal cancer? A population-based case-control study in China. Int J Cancer 2011; 128: 2147-2157 [PMID: 20602339 DOI: 10.1002/ijc.25532]

19. Hajizadeh B, Jessri M, Moasher SM, Rad AH, Rashidkhani B. Fruits and vegetables consumption and esophageal squamous cell carcinoma: a case-control study. Nutr Cancer 2011; 63: 707-713 [PMID: 21614725 DOI: 10.1080/01635581.2011.563028]

20. O’Doherty MG, Cantwell MM, Murray LJ, Anderson LA, Abnet CC. Dietary fat and meat intake and risk of reflux esophagitis, Barrett’s esophagus and esophageal adenocarcinoma. Int J Cancer 2011; 129: 1493-1502 [PMID: 21455992 DOI: 10.1002/ijc.26108]

21. Sapkota A, Hsu CC, Zaridze D, Shangina O, Szaszienia-Dabrowska N, Mates D, Fabianová E, Rudnai P, Janout V, Hoklava I, Brennan P, Boffetta P, Hashibe M. Dietary risk factors for squamous cell carcinoma of the upper aerodigestive tract in central and eastern Europe. Cancer Causes Control 2008; 19: 1161-1170 [PMID: 18512121 DOI: 10.1007/s10552-008-9183-0]

22. Navarro Silveira SA, Mayne ST, Risch H, Gammon MD, Vaghan TL, Chow WH, Dubrow R, Schoenberg JB, Stanford JL, West AB, Rotterdam H, Blot WJ, Fraumeni JF. Food group intake and risk of subtypes of esophageal and gastric cancer. Int J Cancer 2008; 122: 852-860 [PMID: 18537186 DOI: 10.1002/ijc.23544]

23. Wang JM, Xu B, Rao JY, Shen HB, Xue HC, Jiang QW. Diet habits, alcohol drinking, tobacco smoking, green tea drinking, and the risk of esophageal squamous cell carcinoma in the Chinese population. Eur J Gastroenterol Hepatol 2007; 19: 171-176 [PMID: 17273005 DOI: 10.1097/MEG.0b013e32803bb77a]

24. Wu AH, Tseng CC, Hankin J, Bernstein L. Fiber intake and risk of adenocarcinomas of the esophagus and stomach. Cancer Causes Control 2007; 18: 713-722 [PMID: 17562192 DOI: 10.1007/s10552-007-9148-1]

25. Chen H, Ward MH, Graubard BI, Heineman EF, Markin RM, Potischman NA, Russell RM, Weisnberger DD, Tucker KL. Dietary patterns and adenocarcinoma of the esophagus and distal stomach. Am J Clin Nutr 2002; 75: 137-144 [PMID: 11756071]

26. Takezaki T, Shinoda M, Hatouka S, Hasegawa Y, Nakamura S, Hirose K, Inoue M, Hamajima N, Kuroishi T, Matsuura S, Tajima K. Subsite-specific risk factors for hypopharyngeal and esophageal cancer (Japan). Cancer Causes Control 2000; 11: 597-608 [PMID: 10977104 DOI: 10.1023/A:100890129756]

27. Bosetti C, La Vecchia C, Talamini R, Simonato L, Zambon P, Negri E, Trichopoulou A, Lagiou P, Bardini R, Franceschi S. Food groups and risk of squamous cell esophageal cancer in northern Italy. Int J Cancer 2000; 87: 289-294 [PMID: 10861489]

28. Rolón PA, Castellsagué X, Benz M, Muñoz N. Hot and cold mate drinking and esophageal cancer in Paraguay. Cancer Epidemiol Biomarkers Prev 1995; 4: 595-605 [PMID: 8547825]

29. Castelletto R, Castellsague X, Muñoz N, Iscovitch J, Chopita N, Jnelmstisky A. Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. Cancer Epidemiol Biomarkers Prev 1994; 3: 557-564 [PMID: 7827585]

30. Tavani A, Negri E, Franceschi S, La Vecchia C. Risk factors for esophageal cancer in lifelong nonsmokers. Cancer Epidemiol Biomarkers Prev 1994; 3: 387-392 [PMID: 7920205]

31. Rogers MA, Jakszyn P, Pera G, Agudo A, Bingham S, Palma D, Ferrari P, Boeing H, del Giudice G, Plebani M, Carneiro HB, Ocke M, Peeters PH, Numans ME, Clavel-Chapelon F, Canzian F, Mayne ST, Risch H, Gammon MD, Vagh TL, Chow WH, Dubrow R, Schoenberg JB, Stanford JL, West AB, Rotterdam H, Blot WJ, Fraumeni JF. Food group intake and risk of subtypes of esophageal and gastric cancer. Int J Cancer 2008; 122: 852-860 [PMID: 18537186 DOI: 10.1002/ijc.23544]
cohol, diet, occupation, and carcinoma of the esophagus. Cancer Res 1988; 48: 3843-3848 [PMID: 3378219]

33 Chen YK, Lee CH, Wu IC, Liu JS, Wu DC, Lee JM, Goan YG, Chou SH, Huang CT, Lee CY, Hung HC, Yang JF, Wu MT. Food intake and the occurrence of squamous cell carcinoma in different sections of the esophagus in Taiwanese men. Nutrition 2009; 25: 753-761 [PMID: 19394796 DOI: 10.1016/j.nut.2009.02.002]

34 Yang CX, Wang HY, Wang ZM, Du HZ, Tao DM, Mu XY, Chen HG, Lei Y, Matsuo K, Tajima K. Risk factors for esophageal cancer: a case-control study in South-western China. Asian Pac J Cancer Prev 2005; 6: 48-53 [PMID: 15780032]

35 Levi F, Pasche C, Lucchini F, Bosetti C, La Vecchia C. Processed meat and the risk of selected digestive tract and laryngeal neoplasms in Switzerland. Ann Oncol 2004; 15: 346-349 [PMID: 14760132 DOI: 10.1093/annonc/mdh060]

36 Li K, Yu P. Food groups and risk of esophageal cancer in Chaoshan region of China: a high-risk area of esophageal cancer. Cancer Invest 2003; 21: 237-240 [PMID: 12743989 DOI: 10.1081/CNV-120016420]

37 Takezaki T, Gao CM, Wu JZ, Deng JH, Liu YT, Zhang Y, Li SP, Su P, Liu TK, Tajima K. Dietary protective and risk factors for esophageal and stomach cancers in a low-epidemic area for stomach cancer in Jiangsu Province, China: comparison with those in a high-epidemic area. Int J Cancer Res 2001; 92: 1157-1165 [PMID: 11714439 DOI: 10.1111/j.1349-7006.2001.tb02135.x]

38 Sugimura T, Wakabayashi K, Nakagama H, Nagao M. Heterocyclic amines: Mutagens/carcinogens produced during cooking of meat and fish. Cancer Sci 2004; 95: 290-299 [PMID: 15072585 DOI: 10.1111/j.1349-7006.2004.tb03205.x]

39 Mirvish SS. Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. Cancer Lett 1995; 93: 17-48 [PMID: 7600541 DOI: 10.1016/0304-3835(95)03786-V]

40 Cross AJ, Pollock JR, Bingham SA. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. Cancer Res 2003; 63: 2358-2360 [PMID: 12750250]