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ORIGINAL ARTICLE

Meat Consumption Is Associated with Esophageal Cancer Risk in a Meat- and Cancer-Histological-Type Dependent Manner

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Abstract
Background We conducted a systematic review and meta-analysis of meat intake and esophageal cancer risk, with subgroup analyses based on meat type and histological type of cancer.
Aims The purpose of this study was to investigate the association between meat intake and risk of esophageal cancer.
Methods We searched MEDLINE, EMBASE and Cochrane Library (April 2013) for cohort and case–control studies that assessed meat intake and esophageal cancer risk. Random-effect or fixed-effect models were used to pool relative risks (RRs) from individual studies with heterogeneity and publication bias analyses carried out. Seven cohort and 28 case–control studies were included.
Results The summary RRs for esophageal cancer for the highest versus lowest consumption categories were 1.19 (95 % confidence interval [CI] 0.98–1.46) for total meat, 1.55 (95 % CI 1.22–1.96) for red meat, 1.33 (95 % CI 1.04–1.69) for processed meat, 0.72 (95 % CI 0.60–0.86) for white meat, 0.83 (95 % CI 0.72–0.96) for poultry, and 0.95 (95 % CI 0.76–1.19) for fish. When striated by histological subtype, positive associations were seen among esophageal squamous cell carcinoma and red meat, white meat and poultry, and esophageal adenocarcinoma with total meat and processed meat.
Conclusions Meat consumption is associated with esophageal cancer risk, which depends on meat type and histological type of esophageal cancer. High intake of red meat and low intake of poultry are associated with an increased risk of esophageal squamous cell carcinoma. High meat intake, especially processed meat, is likely to

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increase esophageal adenocarcinoma risk. And fish consumption may not be associated with incidence of esophageal cancer.

Keywords Meat · Fish · Esophageal cancer · Esophageal squamous cell carcinoma · Esophageal adenocarcinoma · Meta-analysis

Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer-related mortality and the eighth most frequently diagnosed cancer worldwide, with an estimate of more than 450,000 people and rapidly increasing incidence [43]. There are two major histological types of EC: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the predominant histological type of EC globally, especially the so-called Asian belt (Turkey, northeastern Iran, Kazakhstan, and northern and central China) has a very high incidence of ESCC, where it accounts for about 90 % of the total EC cases [27]. However, the incidence of EAC has dramatically increased in Australia, the United Kingdom, the United States, and some western European countries, and now exceeds that of ESCC [35]. Risk factors for ESCC are most known as tobacco smoking and alcohol drinking. Symptomatic gastro-esophageal reflux disease (GORD), as well as white race, male gender, obesity and tobacco smoking are consistently identified as established risk factors for EAC [32].

Epidemiological studies and meta-analysis have shown that diet, such as meat consumption, is associated with increased risk of colorectal cancer, pancreatic cancer and bladder cancer [33, 52, 58]. And higher consumption of white meat may reduce the risk of lung cancer and ovarian cancer [31, 60]. As for meat (including total meat, red meat, processed meat, white meat, poultry and fish) consumption and EC risk, divergent results have been reported in epidemiological studies. To our knowledge, there has been few published meta-analysis concerning a specific kind of meat intake and EC risk [6, 22, 45], and few comprehensive quantitative assessment of the association between meat consumption and EC risk was performed. Thus, we carried out a comprehensive meta-analysis to assess this association from epidemiological observational studies.

Materials and Methods

Data Source and Searches

Two independent investigators (Hong-Cheng Zhu and Xi Yang) conducted a computerized literature search in MEDLINE (PubMed, http://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (www.embase.com/), and the Cochrane Library (http://www.thecochranelibrary.com/) from their inception to April 13, 2013. The search strategy included terms of outcome (esophageal cancer, oesophageal cancer, esophageal neoplasms, esophageal squamous cell carcinoma, and esophageal adenocarcinoma) and exposure (meat, red meat, processed meat, white meat, poultry, fish, beef, pork, lamb, and goat). Further, we carried out a broader search on diet or foods and scanned the cited references of retrieved articles to identify any additional relevant studies. No language restriction was applied.

Study Selection Criteria

Red and processed meat was defined according to Word Cancer Research Fund/American Institute for Cancer Research in our meta-analysis [55]. Our inclusion criteria were: (1) a case–control or cohort design, (2) the association between meat (including total meat, red meat, processed meat, white meat, poultry and fish) and EC risk was evaluated, and (3) odds ratio (OR), relative risk (RR) or hazard ratio (HR) estimates with 95 % confidence interval (CI) were available. If data was duplicated in more than one study, the larger size or complete studies were included in this analysis. Studies were excluded if they reported on several cancer sites combined, for example, upper aerodigestive tract cancers or cancers of oral cavity, pharynx and esophagus combined. Non-peer-reviewed articles, ecologic assessments, correlation studies, experimental animal studies and mechanistic studies were excluded.

Data Abstraction and Quality Assessment

We summarized RRs for all ECs as well as ESCC and EAC separately when the results were presented according to histological subtypes. We assumed that the majority of cases from non-Western countries were ESCC, when the results were reported for all ECs [26]. Two independent researchers (Hong-Cheng Zhu and Xi Yang) extracted the following data from each study that met the criteria for inclusion: the first author's name, year of publication, geographic regions, journal, number of cases, outcome, cohort size, cohort name and duration of follow-up (cohort studies), number and type of control subjects (case–control studies), type of cancer, type of meat, consumption categories, adjusted ORs, RRs, or HRs with 95 % CI, and adjusted variables. When several risk estimates were presented for men and women, ESCC and EAC, or a single kind of meat, the detailed information was extracted. From each study, we extracted the risk estimates that reflected the greatest degree of control for potential confounders. The study quality was assessed on the basis of the

Newcastle-Ottawa Quality Assessment Scale with an energy-adjusted residual or nutrient-density model added as an item for modification of the scoring system [59]. A study with ≥7 awarded stars was defined as a high-quality study in the 10-star system.

Statistical Analysis

Statistical analyses were based on comparison of the highest intake category with the lowest intake category (which may include people who do not eat meat). The highest and lowest intake category was extracted from the highest and lowest exposure in each article. The study-specific most adjusted association estimates were used as the common measure of association across studies and the ORs were considered to be equivalent to RRs or HRs because EC is a rare outcome in humans. For studies that provided RRs separately of different gender or histological subtypes, combined RRs and CIs were pooled in overall analysis.

We performed the meta-analyses of meat (including total meat, red meat, processed meat, white meat, poultry and fish) consumption with total EC, as well as ESCC and EAC respectively, due to the discrepancy in the etiology and clinicopathological profiles between ESCC and EAC. Subgroup analysis was conducted by study quality, study design (cohort studies and case–control studies), control source (population–based and hospital-based), geographic region (Asia, Europe, the United States, South America, and Australia), and study adjustments (body mass index [BMI], smoking, alcohol drinking, and total energy intake).

To assess heterogeneity among studies, we used the Cochran Q and I^2 statistics. The null hypothesis that the studies are homogeneous was rejected if the P value for heterogeneity was <0.0.05 or the I^2 was ≥50 %. When substantial heterogeneity was detected, the summary estimate based on the random effects model was reported. Otherwise, the summary estimate based on the fixed effects model was reported [10].

Publication bias was evaluated by using funnel plots and the further Begg's-adjusted rank correlation test and Egger's regression test and a visual inspection of the funnel plot [2, 14]. A two-tailed P value <0.05 was considered to be significant. All statistical analyses were performed using STATA, version 11.0 (STATA, StataCorp, College Station, Texas, USA).

Results

Literature Search and Study Characteristics

The search generated 244 citations, of which 45 articles were considered potential value and full text was retrieved for detailed evaluation, and 20 of which were excluded due to various reasons, such as the same population, no available ORs or RRs, etc. An additional ten articles were included from the reference review (Fig. 1). The 35 articles included consisted of 24 for total meat, 15 for red meat, 15 for processed meat, four for white meat, 12 for poultry, and 25 for fish. Twenty seven are considered ESCC and ten are EAC. Subjects with EC are from Asia [7, 15, 18, 19, 21, 28, 30, 39, 41, 42, 48, 51, 57], Europe [3, 16, 20, 29, 34, 36, 37] (O'Doherty et al. [40, 46, 49]), the United States [4, 5, 8, 9, 38, 54, 56], South America [11–13, 44], and Australia [25]. The total numbers of subjects in this meta-analysis include 4,379 cases and 1,897,574 participants form seven prospective cohort studies and 8,934 cases and 21,504 controls from 28 case–control studies. The outcome was in incidence in most of the studies, while mortality was presented in two [30, 41]. One Indian case–control study reported ORs using population and hospital controls [39], so both of the available data was extracted. Most studies used food frequency questionnaires for the assessment of meat consumption and adjusted for age, sex, education, residence, smoking, alcohol drinking, BMI, total energy and a variety of other nutrients intake. The characteristics of the articles are presented in Supplementary Table 3 (cohort studies) and Supplementary Table 4 (case–control studies).

The study-specific quality scores are summarized in Supplementary Table 1 and Supplementary Table 2, according to the 10-point scoring system. The quality score ranged from 3 to 10 on the scale. The median score of cohort and case–control studies were 9 and 7, respectively. High-quality studies (score ≥ 7) consisted of all the seven cohort studies and 18 case–control studies.

Total Meat and Esophageal Cancer

Among the 24 studies of 8,765 cases on total meat intake and total EC, six provide statically significant positive association. In our meta-analysis, we found a 19 % increment of the association between high total meat consumption and EC risk, while the result was not statically significant (RR = 1.19, 95 % CI = 0.98–1.46) (Fig. 2). Statistically significant heterogeneity was detected (I^2 = 73.3 %, $P < 0.001$). Publication bias was indicated from Egger's test ($P = 0.009$) but not Begg's test ($P = 0.107$). In subgroup analyses, positive association was found among population-based studies (RR = 1.54, 95 % CI = 1.13–2.10), and studies that adjusted for BMI (RR = 1.50, 95 % CI = 1.15–1.97) and energy intake (RR = 1.47, 95 % CI = 1.06–2.05). When striated by histological subtype, we found no positive association between high intake of total meat and ESCC risk among the 18 studies. But a strong association of 96 % increment

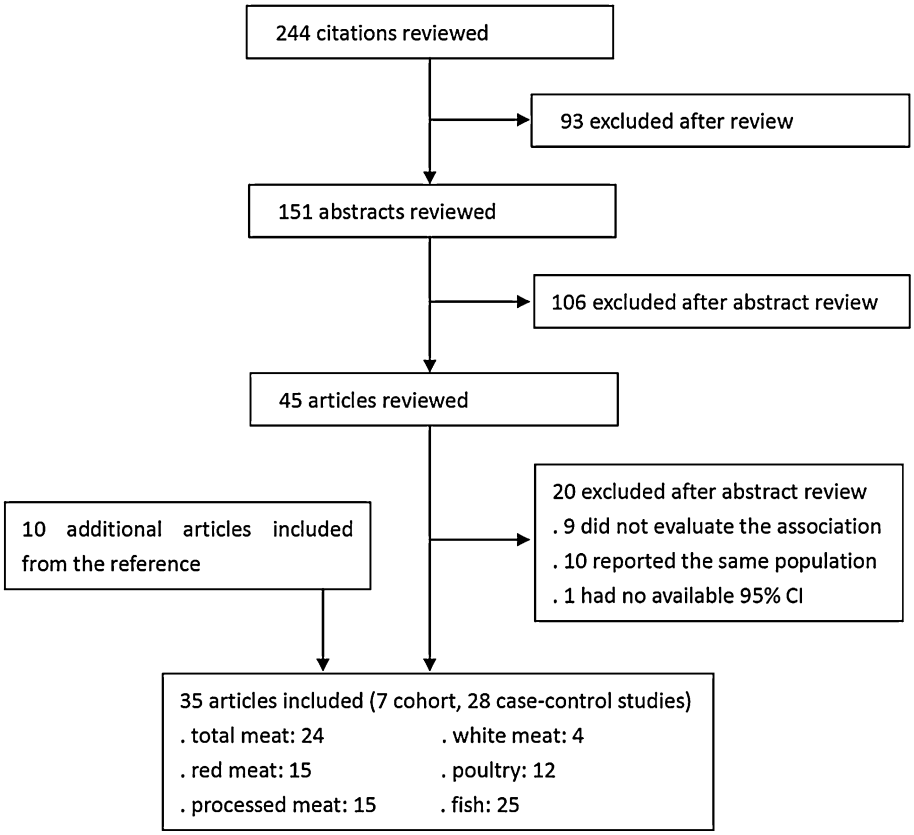

Fig. 1 Reference searched and selection of studies in the meat-analysis

was observed among high intake of total meat and EAC among the six studies, with statistically significant heterogeneity ($I^2 = 62.9$ %, $P = 0.019$) and no publication bias (Egger's test, $P = 0.743$; Begg's test, $P = 0.851$). Subgroup analyses of high-quality studies (RR = 1.96, 95 % CI = 1.26–3.03), population-based case–control studies (RR = 1.99, 95 % CI = 1.18–3.36), and studies that adjusted for BMI (RR = 1.57, 95 % CI = 1.17–2.11), smoking (RR = 1.65, 95 % CI = 1.23-2.22), alcohol (RR = 1.41, 95 % CI = 1.01–1.96), and energy intake (RR = 1.96, 95 % CI = 1.26–3.03) confirmed the positive association (Supplementary Table 5).

Red Meat, Processed Meat, and Esophageal Cancer

Our analysis of 15 articles found a 55 % and a 33 % increment of red (RR = 1.55, 95 % CI = 1.22–1.96) and processed (RR = 1.33, 95 % CI = 1.04–1.69) meat intake and EC risk (Figs. 3, 4). Statistically significant heterogeneity (red meat, $I^2 = 63.6$ %, $P < 0.001$; processed meat, $I^2 = 61.5$ %, $P < 0.001$) but no publication bias (red meat: Egger's test, $P = 0.326$ and Begg's test, $P = 0.132$; processed meat: Egger's test, $P = 0.159$ and Begg's test, $P = 0.345$) was detected. The positive association was observed across most subgroup analyses, including high-quality studies (red meat: RR = 1.52, 95 % CI = 1.15–2.02; processed meat: RR = 1.35, 95 % CI = 1.03–1.78), case–control studies (red meat: RR = 1.78, 95 % CI = 1.30–2.44; processed meat: RR = 1.29, 95 % CI = 1.00–1.93), Asia, the United States, and most of the adjustments. When striated by histological subtype, a strong association of 86 % increment was found between high red meat consumption and ESCC risk (RR = 1.86, 95 % CI = 1.31–2.66) with no publication bias (Egger's test, $P = 0.415$; Begg's test, $P = 0.621$), as well as a 23 % increment between high processed meat intake and EAC risk (RR = 1.23, 95 % CI = 1.01–1.50) with no publication bias (Egger's test, $P = 0.289$; Begg's test, $P = 0.186$). In subgroup analyses, increased positive association was also seen in high-quality studies (RR = 1.93, 95 % CI = 1.23–3.03), cohort studies (RR = 1.54, 95 % CI = 1.04–2.27), case–control studies (RR = 2.01, 95 % CI = 1.28–3.16), Asia, Europe, the United States, and studies adjusted for smoking, alcohol, and energy for ESCC and red meat. Increased positive association was observed in population-based case–control studies for red (RR = 1.42, 95 % CI = 1.02–1.98) and processed (RR = 1.45, 95 % CI = 1.04–2.03) meat intake and EAC risk. And in the four US studies, a 28 % increment was seen among red meat intake and EAC risk (RR = 1.28, 95 % CI = 1.01–1.62) (Supplementary Table 5).

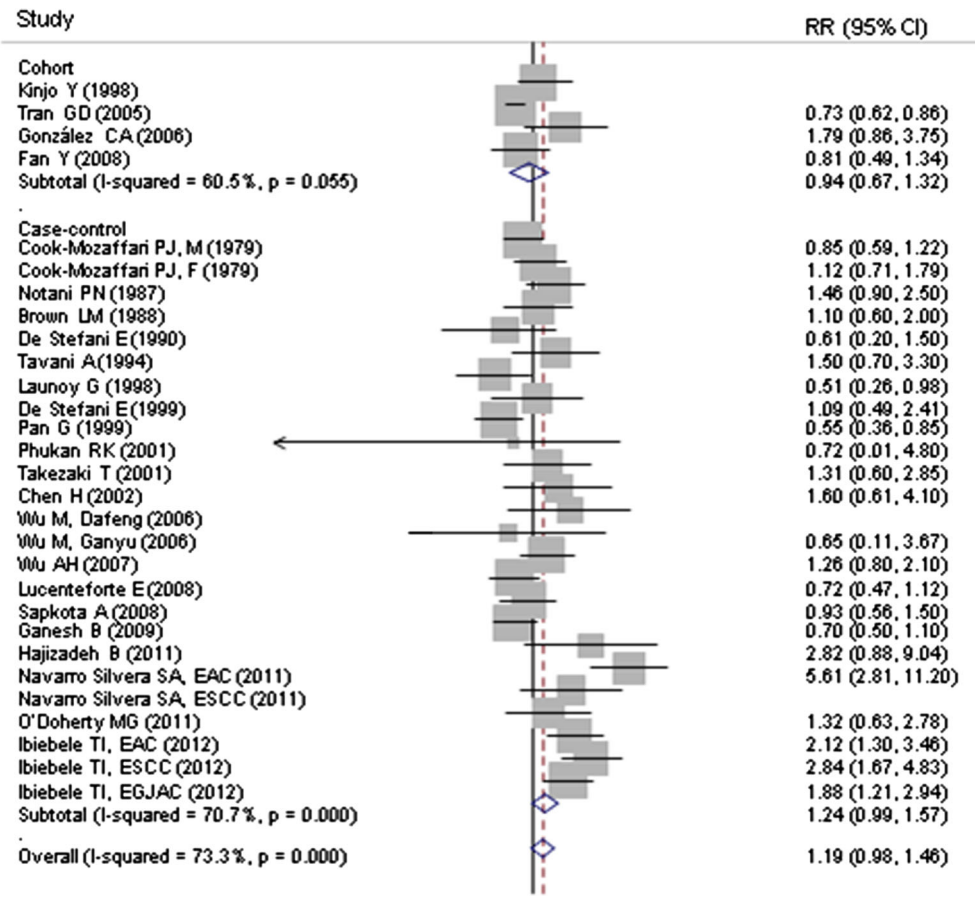

Fig. 2 Estimates (95 % CIs) of total meat intake (highest vs. lowest category) and esophageal cancer risk. *Squares* indicate study-specific relative risks (size of the square reflects the study-specific statistical weight, i.e., the inverse of the variance); *horizontal lines* indicate 95 % confidence intervals; *diamonds* indicate summary relative risk estimate with corresponding 95 % confidence intervals. *M* male, *F* female, *EAC* esophageal adenocarcinoma, *ESCC* esophageal squamous cell carcinoma, *EGJAC* esophagogastric junction adenocarcinoma. Dafeng and Ganyu are the name of two counties in China

White Meat, Poultry, Fish, and Esophageal Cancer

A high intake of poultry can weakly decrease the risk of total EC (RR = 0.83, 95 % CI = 0.72–0.96) as well as the histological type of ESCC (RR = 0.73, 95 % CI = 0.60–0.89) (Fig. 5). No statistically significant heterogeneity (EC, $I^2 = 34.5$ %, $P = 0.099$; ESCC, $I^2 = 6.9$ %, $P = 0.378$) and publication bias (EC: Egger's test $P = 0.858$, Begg's test $P = 0.956$; ESCC: Egger's test $P = 0.285$, Begg's test $P = 0.421$) was detected. The combined results were consistent with the overall results among high-quality studies (RR = 0.56, 95 % CI = 0.40–0.77), case–control studies (RR = 0.74, 95 % CI = 0.60–0.91), and all adjustments of BMI, smoking, alcohol, and energy intake for ESCC, and case–control (RR = 0.76, 95 % CI = 0.63–0.91) studies for total EC but not statistically significant in cohort studies and high-quality studies for total EC. A 53 % decrement was observed among poultry intake and ESCC risk in European populations (RR = 0.47, 95 % CI = 0.31–0.73). Intake of fish was not associated with EC risk (RR = 0.95, 95 % CI = 0.76–1.19) with heterogeneity ($I^2 = 79.2$ %, $P < 0.001$) but no publication bias (Egger's test $P = 0.416$, Begg's test $P = 0.368$), including both ESCC (RR = 1.08, 95 % CI = 0.80–1.46) and EAC (RR = 0.81, 95 % CI = 0.54–1.20). In the four studies of total white meat, positive association was observed among total EC (RR = 0.72, 95 % CI = 0.60–0.86) and ESCC (RR = 0.63, 95 % CI = 0.48–0.83) with no publication bias (EC: Egger's test $P = 0.332$, Begg's test $P = 0.624$; ESCC: Egger's test $P = 0.420$, Begg's test $P = 0.117$). And the results were consistent in case–control studies (RR = 0.58, 95 % CI = 0.42–0.80) and South American populations (RR = 0.60, 95 % CI = 0.42–0.84) (Supplementary Table 5).

Discussion

This is a comprehensive meta-analysis to report an association between meat and fish intake and esophageal cancer and its histological subtypes. Our findings indicated that high meat intake is associated with esophageal cancer risk, and this association varied by meat type and histological type of EC. High total meat intake is associated with a 96 % increment of EAC based on the six eligible studies. High red meat intake strongly increased EC risk, especially ESCC with strong evidence of high-quality studies, cohort

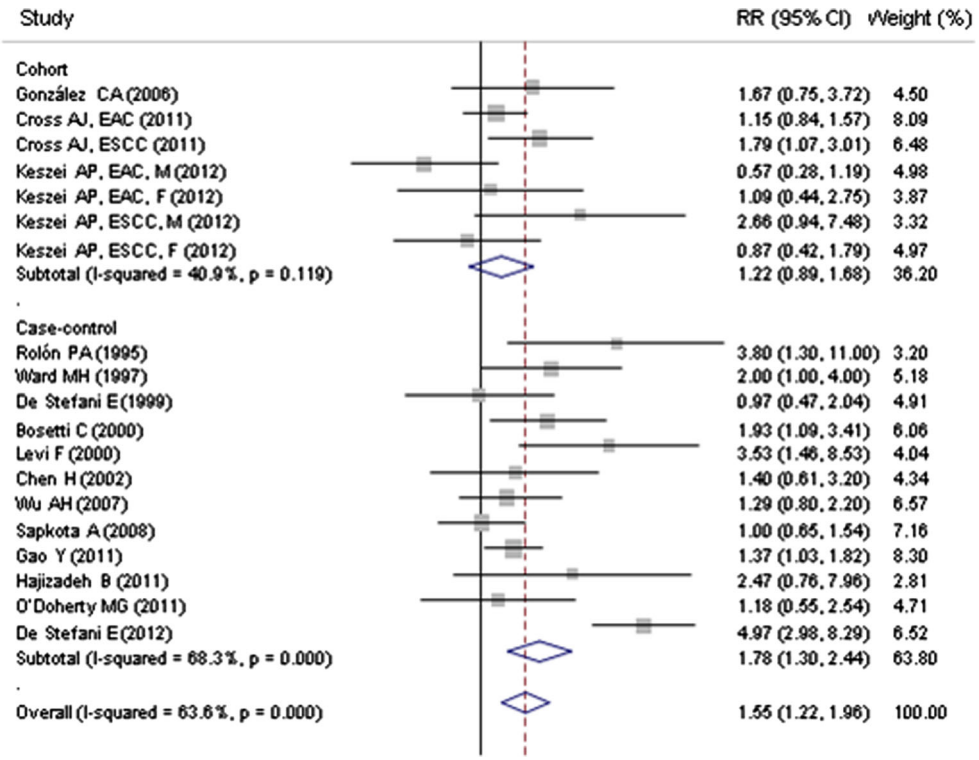

Fig. 3 Estimates (95 % CIs) of red meat intake (highest vs. lowest category) and esophageal cancer risk. *Squares* indicate study-specific relative risks (size of the square reflects the study-specific statistical weight, i.e., the inverse of the variance); *horizontal lines* indicate 95 % confidence intervals; diamonds indicate summary relative risk estimate with corresponding 95 % confidence interval. *M* male, *F* female, *EAC* esophageal adenocarcinoma, *ESCC* esophageal squamous cell carcinoma

studies, most subgroup analysis of geographic locations and adjustments. High processed meat intake is probably associated with total EC risk, while evidence is not strong enough in high-quality studies, cohort studies and its histological subtypes. Poultry intake can weakly decrease total EC and ESCC risk, with strong evidence of ESCC from high-quality studies and all adjustments. Some positive association was also seen in the four studies of total white meat intake and EC risk, consistent with the overall results of poultry. No positive findings were indicated from the 25 studies of fish, consistent with the general conclusions with a meta-analysis published in 2012, though some data differs [22].

The World Cancer Research Fund/American Institute for Cancer Research consensus report concluded that red and processed meat as risk factors for esophageal cancer was "limited suggestive increased," although there was no consideration for histologic subtype, largely because of lack of data. For total meat intake, increased positive association was seen among studies of EAC but not total EC and ESCC. Interestingly enough, a decreased association was seen among the three cohort studies of high total meat intake and ESCC risk. The controversial results may be due to bias caused by the mixture of total meat, indicating that different meat types play different roles in the incidence of cancer. For red meat intake, a 52 and 93 % increment was observed in the meta-analysis of total EC and ESCC, and evidence form high-quality studies, cohort studies and most other subgroup analyses is consistent with the overall results. However, positive association of red meat and EAC risk was seen among the four European hospital-based case–controls, which was not able to prove the role of high red meat intake on EAC incidence. For processed meat, a 33 and 23 % increment was observed for total EC and EAC, with stronger evidence from high-quality studies, population-based case–control studies, American populations and studies adjusted for smoking and alcohol drinking. Only hospital-based case–control studies confirmed the results of high processed meat intake and EAC, which still calls for more evidence of the positive association. For total white meat, decrement was seen in the summary RR of total EC as well as ESCC, with statistically significant results from case–control studies and South American populations. But only four studies of 1,385 cases were included in this analysis, which is not strong enough to prove this association. For poultry, a 17 and 27 % decrement was found for total EC and ESCC, with stronger evidence from high-quality studies, case–control studies and all adjustments of ESCC, indicating that high poultry intake may decrease ESCC risk. For fish, no statically significant association was found in the overall evidence, with decrement only seen in European studies and studies adjusted for energy, indicating that fish consumption may not be associated with EC risk.

There are not many studies investigating components of meat or compounds formed during cooking or processing of meat in relation to esophageal cancer [12, 54]. It has been hypothesized that mutagenic HCAs and PAHs from

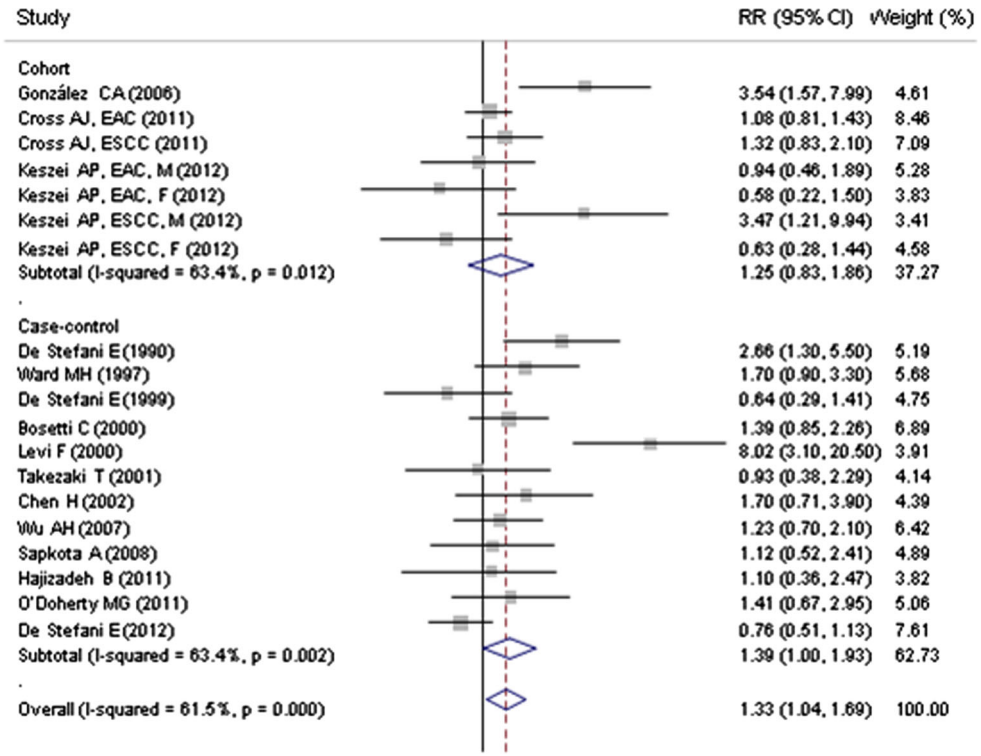

Fig. 4 Estimates (95 % CIs) of processed meat intake (highest vs. lowest category) and esophageal cancer risk. *Squares* indicate study-specific relative risks (size of the square reflects the study-specific statistical weight, i.e., the inverse of the variance); *horizontal lines* indicate 95 % confidence intervals; diamonds indicate summary relative risk estimate with corresponding 95 % confidence interval. *M* male, *F* female, *EAC* esophageal adenocarcinoma, *ESCC* esophageal squamous cell carcinoma

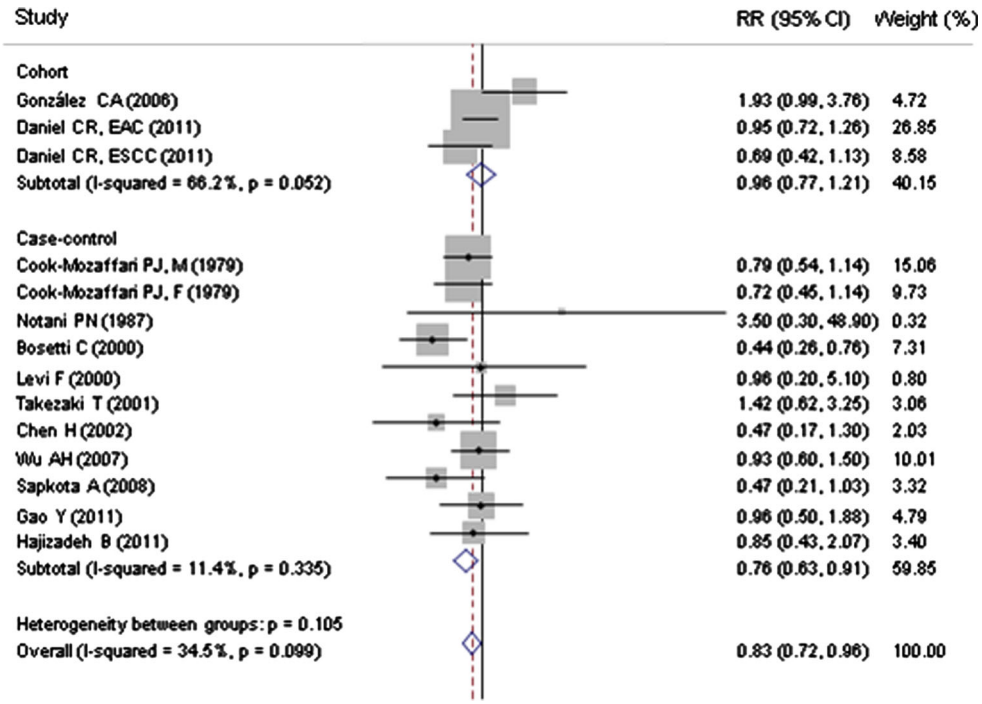

Fig. 5 Estimates (95 % CIs) of poultry intake (highest vs. lowest category) and esophageal cancer risk. *Squares* indicate study-specific relative risks (size of the square reflects the study-specific statistical weight, i.e., the inverse of the variance); *horizontal lines* indicate 95 % confidence intervals; *diamonds* indicates summary relative risk estimates with corresponding 95 % confidence interval. *M* male, *F* female, *EAC* esophageal adenocarcinoma, *ESCC* esophageal squamous cell carcinoma

cooking could contribute to EC risk [8]. However, only one epidemiological study reported MeIQx and DiMeIQx caused the highest increased risk of squamous cell carcinoma and no association for adenocarcinoma of esophagus [50]. A second possible mechanism for the adverse effect of red meat is heme iron, which contributes to endogenous formation of carcinogenic N-nitroso compounds and may act as a pro-oxidant and catalyze lipid peroxidation causing DNA damage in tissues [24]. Prospective cohort studies suggested the association of heme iron intake of squamous cell carcinoma but not adenocarcinoma of esophagus [1, 8, 53], which can further explain the results of subgroup

analysis of different histological types in our findings. In addition, high temperature during cooking meat may produce heterocyclic amines and polycyclic aromatic hydrocarbons, and high levels of saturated fat present in meat may play a role [47]. The mechanism by which poultry intake may be associated with a lower EC risk is not well understood, but may be possibly due to its lower content of heme iron compared with red meat. Another explanation is that high poultry eaters often have a healthier overall eating pattern and lifestyle [17, 60].

There have been published meta-analyses concerning red and processed meat intake and esophageal cancer risk [6, 23, 45]. Strengths of our studies include a large size (1,897,574 participants and 4,379 esophageal cancer cases from cohort studies, and 8,934 cases and 21,504 controls from case–control studies). And this is a comprehensive and high-valued meta-analysis to investigate meat and fish intake and EC risk, with sufficient data from different meat type (total meat, red meat, processed meat, white meat, poultry, and fish) and histological type of EC (ESCC and EAC). However, our meta-analysis still has several limitations. First, there was a significant heterogeneity in study results, which could partly be explained by the large size of study population, and in most analyses of individual kind of meat and EC type, evidence is statistically significantly stronger in the case–control studies than in the cohort studies. Case–control studies, especially hospital-based ones are more susceptible to bias and may lead to overestimation of the association. Second, because of a broad classification of meat in each component study our findings were likely to be influenced by the misclassification of meat, for example, the item "red/white meat" in some studies may include some processed meat while some just contain fresh meat. And some studies consider fish as a kind of meat and were included in total meat while others do not. Some studies provide results of some specific kinds of meat. Third, meat in each study may be prepared by a number of methods, and the method of cooking could be associated with cancer incidence [47]. Fourth, the intake quantity in each study varies, including grams/day, times/week, grams/1,000 kcal, quartiles, quintiles, etc. The highest and lowest intake varies across studies. The highest intake in one study may be similar to the median or lowest in another, which could cause bias to the overall results. Fifth, the association could be attributed to other factors, including BMI, smoking, alcohol drinking, total energy intake, etc., due to inability to fully adjust for various confounders. Moreover, we failed to evaluate a dose–response relation because of different methods used to report meat intake across studies. Thus, the summary results may be overestimated by the relative risk.

In summary, our analysis indicates that meat consumption is associated with EC risk, and the association depends on meat type and histological type of this carcinoma. The incidence of ESCC can be increased by high intake of red meat and decreased by poultry. High meat intake, especially processed meat, is likely to increase EAC risk. Fish intake may not be associated with EC risk. However, well-designed cohort or intervention studies and mechanism researches are needed to investigate this issue.

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Conflict of interest None.

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