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Research Article

Meat Consumption and Risk of Developing Esophageal Cancer: A Meta-analysis

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Abstract

Background: Meat has been linked as a risk factor for several cancers. Red meat and processed meat specifically have been suggested as risk factors for esophageal cancer, but this has not been established. We performed a meta-analysis to summarize available evidence from case-control and cohort studies on this topic.

Methods: A systematic search of MEDLINE, PubMed, EMBASE was completed up until November, 2013. Studies were included that reported confirmed histological diagnosis of cancer, odds ratios (OR) or relative risks (RR) and confidence intervals (CI). Pooled ORs and 95% CIs were calculated for the effect of different meats on the development of esophageal cancer using a random effects model. Studies were assessed for heterogeneity and publication bias.

Results: 29 studies were included in this analysis, involving 1,208,768 individuals with a total of 8,620 cases and 44,574 controls. High consumption rates were associated with development of cancer for red meat (OR 1.59; 95% CI 1.31-1.93), processed meat (OR 1.75; 95% CI 1.28-2.38), barbecued meat (OR 1.54; 95% CI 1.25–1.91) and overall (OR 1.26; 95% CI 1.11-1.43). Low and medium consumption rates were also significant for red and barbecued meat. High and medium consumption of white meat was significantly protective. High consumption of fish was also found to be protective (OR 0.73; 95% CI 0.55-0.95).

Conclusions: Findings of this meta-analysis demonstrated red meat, processed meat and barbecued meat are likely to increase the risk of esophageal cancer in a dose dependent relationship. Fish and white meat were shown to have a protective effect.

Keywords:Diet; Esophageal Neoplasms; Meat; Red Meat; Esophageal Cancer; Meta-analysis

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Introduction

Esophageal cancer is a prevalent condition, now recognized as the eighth most common cancer and the sixth most common cause of death from cancer worldwide with 481,000 new cases diagnosed and 406,000 deaths in 2008[1]. In 2012, the National Cancer Institute at the National Institutes of Health estimated that there were 17,460 new cases in the United States and 15,070 deaths attributable to esophageal cancer[2]. The two neoplasms accounting for most esophageal cancers are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) with EAC usually manifesting in the distal third of the esophagus.

Traditionally ESCC was more common than EAC, but in the past 30 years the incidence of EAC has increased dramatically. Between 1976 and 1978 the annual average age-adjusted rate of EAC in white men was 0.8 per 100,000 and by 1988-1990 this rate increased by over 300% to 2.5 per 100,000 in the same population[3]. It has since been estimated that there is a 20.6% average annual increase in the incidence of EAC for the United States and an even higher incidence rates for Australia, Great Britain and the Netherlands[4]. Both ESCC and EAC provide significant burdens to one's health as they have the potential to grow rapidly. At the time of diagnosis more than 50 percent of patients have either inoperable tumors or visible metastases radiographically[5].

The risk factors for ESCC and EAC differ substantially. Established risk factors for ESCC include: tobacco use, alcohol use, poverty, caustic injury to the esophagus, non-epidermolyticpalpoplantarkeratoderma (tylosis), Plummer-Vinson syndrome, a history of head and neck cancer, a history of breast cancer treated with radiotherapy, achalasia and frequent consumption of extremely hot beverages [5]. Identified risk factors for EAC include: tobacco use, Barrett's esophagus, weekly reflux symptoms, and obesity[5]. As obesity has been established as a risk factor for EAC and obesity in Western societies has been on the rise, investigations have looked into the correlation between diet and the risk of cancers. In relation to diet, there are many factors that can be considered, such as dairy products, bread, grains and cereal, breaded and fried foods, meat, fruits, vegetables and more. In this study only meat will be considered. Moreover, with meat and cancer in general, it has been found that overall, meat-free diets appear to be at least modestly cancer protective with a 10-12% reduction in risk[6].

Investigations looking at the role of obesity and diet have been well established for other types of cancer, for example, there is an association between red meat and colorectal cancer (CRC). It was found within the European Prospective Investigation into Cancer and Nutrition (EPIC), a prospective study following 478,040 people, that the absolute risk of development of CC within 10 years, for a study subject aged 50 years, was 1.71% for the highest category of red and processed meat intake. This led them to conclude that high consumption of red and processed meat was positively associated with CRC[7]. A systematic review following a meta-analytical approach has also been completed and demonstrated that a daily increase of 100 g of all meat or red meat is associated with a 12-17% increased risk of CRC[8].

The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) have reported that there is limited evidence from case-control studies, some of poor quality, which suggest that red meat is a cause of esophageal cancer[9]. There have been large cohort and

case-control studies but no meta-analysis or systematic review has been completed to evaluate this evidence specifically or to evaluate the risk of meat consumption on the development of EAC and ESCC although there have been large cohort and case control studies completed. The aim of this meta-analysis was to evaluate the current evidence and assess the relationship between meat consumption and the development of EAC and ESCC.

Methods

Study Protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[10]. A systematic search of the databases MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), PubMed (from 1950, and Current Contents Connect (from 1980) through to November, 2013, to identify relevant articles was completed. The search used the terms 'Meat' OR 'Neoplasms' OR 'Red Meat' OR 'Diet' OR 'Esophageal Neoplasms' OR 'Esophageal Cancer' OR 'Cooking Methods' OR 'Barbecue' OR 'Poultry' OR 'Chicken' OR 'Processed' which were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed.

Study Selection

We included studies that met the following inclusion criteria: (1) ESCC, EAC or EC (esophageal cancer) was recognized on endoscopy and confirmed histologically; (2) the risk point estimate was reported as an odds ratio (OR), relative risk (RR) or the data was presented such that an OR could be calculated; (4) the 95% confidence interval (CI) was reported, or the data was presented such that the CI could be calculated; (5) an internal comparison was used when calculating the risk estimate; (6) the total sample size of the study exceeded 200 patients. We excluded studies that did not meet the inclusion criteria.

Data Extraction

The data extraction was performed using a standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, temporal direction, population type, country, continent, case-control matching, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, CIs or data used to calculate CIs, types of meats, type of cancer, amount of meat consumed and whether diagnosis of EAC, ESCC or EC was histologically confirmed. Quality of the studies was not assessed and authors were not contacted for missing data. Adjusted ratios were extracted in preference to non-adjusted ratios, however, where ratios were not providedunadjusted ORs and CIs were calculated. Where more than one adjusted ratio was reported, we chose the ratio with the highest number of adjusted variables (Table 1). Where multiple risk estimates were available in the same study, for example due to the use of different comparator groups, they were included as separate risk estimates.

Table 1 Adjusted variables for case-control and cohort studies of meat consumption and esophageal cancer.

Study	Variables Adjusted for:
Keszei, A.P. et al[11]	Age, smoking status, years of cigarette smoking, # of cigarettes smoked per day, total energy intake, BMI, alcohol intake, vegetable intake, fruit intake, levels of education, non occupational physical activity
Ward, M.H. et al[12]	Year of birth, sex, cigarettes/day (none, <30/day, 30+/day), quartiles of BMI, continuous intake of retinoic acid, folate, riboflavin, zinc, carbohydrate, protein, total calories.
Gao, Y. et al[13]	Age, gender, geographic region
O'Doherty et al[14]	Age, sex, smoking status, body mass index, job type education, energy intake, fruit intake, vegetable intake, alcohol intake, Helicobacter pylori infection nonsteroidal anti-inflammatory drug use, gastroesophageal reflux symptoms and location
Navarro Silvera, S. A., et al[15]	Gender, age, site, race, income, education, proxy status, energy intake, and mutual adjustment for other principle components) OR and 95% CI, comparing principal components scores (quartiles, 1 Z low) and cancer risk.
Cross. A. J., et al[16]	Adjusted for age, sex, BMI, education, ethnicity, tobacco smoking, alcohol drinking, usual physical activity at work, vigorous physical activity, and the daily intake of fruit saturated fat and calories
Mulholland, H.G.[17]	Age, sex, energy intake, smoking status, BMI, education. Occupation. Alcohol, regular NSAID use, location, H pylori, energy adjusted saturated fat intake; energy-adjusted glycemic index intake and GERD
Ibiebele, T.I. et al[18]	Age, gender; cumulative history of smoking in pack years, lifetime mean alcohol intake; heartburn and acid reflux symptoms); educational status (no further education; total fruit and vegetable intake and total energy intake
Fan, Y. et al[19]	Level of education, body mass index, number of years of smoking, number of drinks consumed per day, and number of years of drinking.
Sapkota, A. et al[20]	Age, country, gender, tobacco pack-years, education, BMI, frequency of alcohol consumption, total vegetable consumption, total fruit consumption
Wu. A.H et al[21]	Age, sex, race, birthplace, education, smoking, BMI, reflux, use of vitamins, and total calories
Gonzalez C.A. et al[22]	Sex, height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, alcohol intake, energy intake, vegetable intake, citrus fruit intake, and non-citrus fruit intake. Red meat, poultry, and processed meat intakes were mutually adjusted
Hung, H. et al[23]	Age, educational levels, ethnicity, source of hospital, smoking, alcohol drinking and areca nut chewing
De Stefani, E. et al[24]	Age, sex, residence, urban/rural status, education, body mass index, tobacco smoking, alcohol drinking, mate drinking and total energy

	intake.
Chen, H. et al[25]	Age, sex, energy intake, respondent type, BMI, alcohol use, tobacco use, education, family history, vitamin supplement use for both types of cancer, and for age squared for esophageal adenocarcinoma
Bosetti, C. et al[26]	Age, sex, area of residence, education, tobacco smoking, alcohol drinking and non-alcohol energy.
Levi, F. et al[27]	Age, sex, education, smoking, alcohol and non alcohol total energy intake
De Stefani, E. et al[28]	Age, sex, residence, urban/rural status, body mass index, tobacco smoking, alcohol drinking, and total energy intake.
Brown, L.M. et al[29]	Age, area, smoking, alcohol, and food calories
Ward, M. et al[30]	Gender, year of birth and red meat intake.
Zhang, Z. et al[31]	Age, sex, race, education, total dietary intake of calories, smoking, alcohol use, and body mass index.
Tzonou, A. et al[32]	Age, sex, birthplace, schooling, height, analgesics, coffee drinking, alcohol intake, tobacco smoking and energy intake, though not mutually
Rolon, P. A., et al[33]	Lifetime consumption of alcohol, cigarette smoking and design variables age group, sex and hospital group, plus consumption of red meats, fats, fish and milk. For beef model not adjusted for red meat
Castelletto, R et al[34]	Age, sex, hospital, education, # of cigarettes/day; alcohol consumption, barbecued meat, potatoes, raw vegetables and cooked vegetables
Guo, W. et al[35]	Years of smoking and cancer history in 1st degree relative
Hu, J. et al[36]	Alcohol, smoking, income and occupation
Brown, L.M, et al[37]	Cigarettes and alcohol
Yu, M et al[38]	Education, tobacco, consumption of alcohol, bacon or ham, fresh fruits, raw vegetables, bread preference, occupational exposure to metal dust
Cook-Mozaffari, P et al[39]	Village of residence, age, sex and language group

Table 2 Characteristics of case control and cohort studies of meat consumption and esophageal cancer

Study [country]	Year	Study Designb	Study Population	Years of Study	Agec (years)	Total Size	Case	Control	Type of Meat/Cancer Type
Keszei, A.P. et al[11] [a]	2012	Co	Population	1986-2003	Mean Men 61.2 Mean Women 61.3	120,852	252		R, Pr, ESCC, EAC
Ward, M.H. et al[12] [b]	2012	CC	Population	1992-1994	EAC > 21	573	124	449	TR, Pr, NP EAC
Gao, Y. et al[13] [c]	2011	CC	Hospital/ Population	1997-2005	Median Controls 58 Median Cases 59	2,114	600	1,514	R, C, F/ ESCC
O'Doherty et al[14] [d]	2011	CC	Hospital	2002-2005	Mean Controls 63 Mean EAC 64	480	224	480	R, FR, W, Pr, F EAC
Navarro Silvera, S. A., et al[15] [b]	2011	CC	Population	1993-1995	Total 30-79	1,782	537	687	TM ESCC/EAC
Cross. A. J., et al[16] [b]	2011	Co	Population	1995-1996 (10 year f/u)	Red Median 61.7-63.0 White Median 61.8-63.2	494,979	845		R, W, Pr ESCC, EAC
Mulholland, H.G.[17] [d]	2011	CC	Population	2002-2005	Control 67.8 EAC 64.4	470	218	252	TR EAC
Ibiebele, T.I. et al[18] [e]	2010	CC	Population	2001-2005	Control = 60+ (56%) EAC 60+ (67%) ESCC 60+ (70%)	2,316	524	1,472	Ba ESCC, EAC
Fan, Y. et al[19] [c]	2008	Co	Population	1986-1989	Mean Control 55.3 EC 56.9	18,244	101		TM, F/Se EC
Sapkota, A. et al[20] [f]	2008	CC	Hospital	1999-2003	Control 45-54 (27%), 55-64 (33%), 65-74 (28%), ESCC 45-54 (29%), 55-64 (46%),	2,176	1,135	1,228	AM, R, NP, H, Sl, Su, P, F ESCC
Wu. A.H et al[21] [b]	2007	CC	Population	1992-1997	Total 30-74	1,514	206	1308	TMF, TMNF, R, Pr, Po, FSH/ EAC

Gonzalez C.A. et al[22] [g]	2006	Co	Population	1991 (6.5 yr f/u)	Mean Cohort 51.7, R 49.4-52.4, P 50.4-52.0, Pr 50.4-51.3	521,457	67		TM, R, P, Pr EAC
Hung, H. et al[23] [h]	2004	CC	Hospital	1996-2002	Mean Control 60.8, Mean ESCC 62.4	898	365	532	CM (Su/H), Sm (M/F)/ESCC
De Stefani, E. et al[24] [i]	2003	CC	Hospital	1998-2001	Both Control & ESCC 50-59 (21%), 60-69 (36%), 70-79 (29%),	830	166	664	R, W, F, Sa, St ESCC
Chen, H. et al[25] [b]	2002	CC	Hospital	1988-1993	Control 59.8, EAC 62.3	697	124	449	TM, Pr, R, P, F EAC
Bosetti, C. et al[26][k]	2000	CC	Hospital	1992-1997	Control 50-69 (75%) ESCC 50-69 (76%)	1,047	304	743	R, P, Pr, F ESCC
Levi, F. et al[27][k]	2000	CC	Hospital	1992-1999	Control <55 (38%), 55-64 (31%), 65-74 (31%), ESCC - <55 (31%), 55-64 (30%),	428	101	327	P, R, Po/Pr F ESCC, EAC
De Stefani, E. et al[28][i]	1999	CC	Hospital	1996-1997	Control 50-69 (62%), EC –50-69 (63%),	526	133	393	R, W, Pr, Sa, TM/EC
Brown, L.M. et al[29] [b]	1998	CC	Population	1986-1989	Control + ESCC 30-79	1,571	333	1,238	M, P, F, R, L, P ESCC
Ward, M. et al[30] [b]	1997	CC	Population	1988-1993	EAC > 21	821	143	502	TR, Pr, B/EAC
Zhang, Z. et al[31] [b]	1997	CC	Hospital	1992-1994	Not reported	227	95	132	TM, P, F, R, Pr EAC
Tzonou, A. et al[32] [l]	1996	CC	Hospital	1989-1991	Control < 60 (28%), 60-69 (34%), >70 (38%), ESCC <60 (16%), 60-69 (47%),	299	99	200	M & F ESCC, EAC
Rolon, P. A., et al[33] [m]	1995	CC	Hospital	1988-1991	Control 46-65 (54%), ≥ 66 (39%) EC 46-65 (54%), ≥56 (40%)	512	131	381	R, B, F EC
Guo, W. et al[35] [c]	1994	CC	Population	1986-1991	Controls + EC <50 (19%), 50-59 (43%), >60 (38%)	30,763	640	29,584	M EC

Castelletto, R et al[34] [n]	1994	CC	Hospital	1986-1989	Control 55-74 (65%), ESCC 55-74 (65%),	393	131	262	B, Ba, P ESCC
Hu, J. et al[36] [c]	1994	CC	Hospital	1985-1989	Controls 40-59 (61%), >60 (35%) EC <40 (3%), 40-59 (60%) >60 (37%)	588	196	392	M EC
Brown, L.M, et al[37] [b]	1988	CC	Hospital	1977-1984		629	207	422	M/P, F/Sh, L EC
Yu, M et al[38][b]	1988	CC	Population	1975-1981	EC 20-64 years, Control matched (within 5 years)	550	275	275	B, FB, Ba/Sm EC
Cook-Mozaffari, P et al[39] [o]	1979	CC	Population	1974-1976	EC 18-80, Control matched (within 5 years)	1,032	344	688	M, P, F EC

[a] – a = Netherlands, b – United States c – China, d – Ireland, , e – Australia, f – Russia, Romania, Poland, Hungary, Slovakia, Czech Republic, g – Denmark, France, Germany, Greece, Netherlands, Norway, Spain, Sweden, UK, h – Taiwan, i – Uruguay, j – Italy, k – Switzerland, l – Greece, m – Paraguay, n – Argentina, o – Iran

[b] - Study Design– CC = Case Control, Co = Cohort

[c] - Types of Cancer – ESCC = Esophageal Squamous Cell Carcinoma, EAC = Esophageal Adenocarcinoma, EC = Esophageal Cancer

[d] - Types of Meat – M = Meat, TM = Total Meat, R = Red, C=Chicken, FR = Fresh Red, P=Poultry, Pr=Processed, CM = Cured Meat, Sm = Smoked, W=White, F= Fish, Sa=Salted, St= Stewed, Po=Pork, L=Liver, B=Beef, TR = Total Red, Ba=Barbecue, Shellfish=Sh, FB = Fried Bacon or Ham, Se=Seafood, AM = All Meat, NP=non-processed, H = Ham, Sl=Salami, Su=Sausage, TMF=Total Meat + Fish, TMNF – Total Meat No Fish, FSH- Fish/Shellfish

Statistical Analysis

Pooled odds ratios and 95% confidence intervals were calculated for the effect of different meats on the development of esophageal cancer using a random effects model[40]. We tested heterogeneity with Cochran's *Q* statistic, with P<0.10 indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25, 50 and 75% corresponded to low, moderate and high degrees of heterogeneity, respectively[41]. Further analysis was not completed if heterogeneity was found. We quantified publication bias using the Egger's regression model[42], with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the p<0.05 level. Publication bias is generally regarded as a concern if the fail-safe number is less than 5n+10, with n being the number of studies included in the meta-analysis[43]. All analyses were performed with Comprehensive Meta-analysis (version 2.0),Biostat, Englewood NJ (2005).

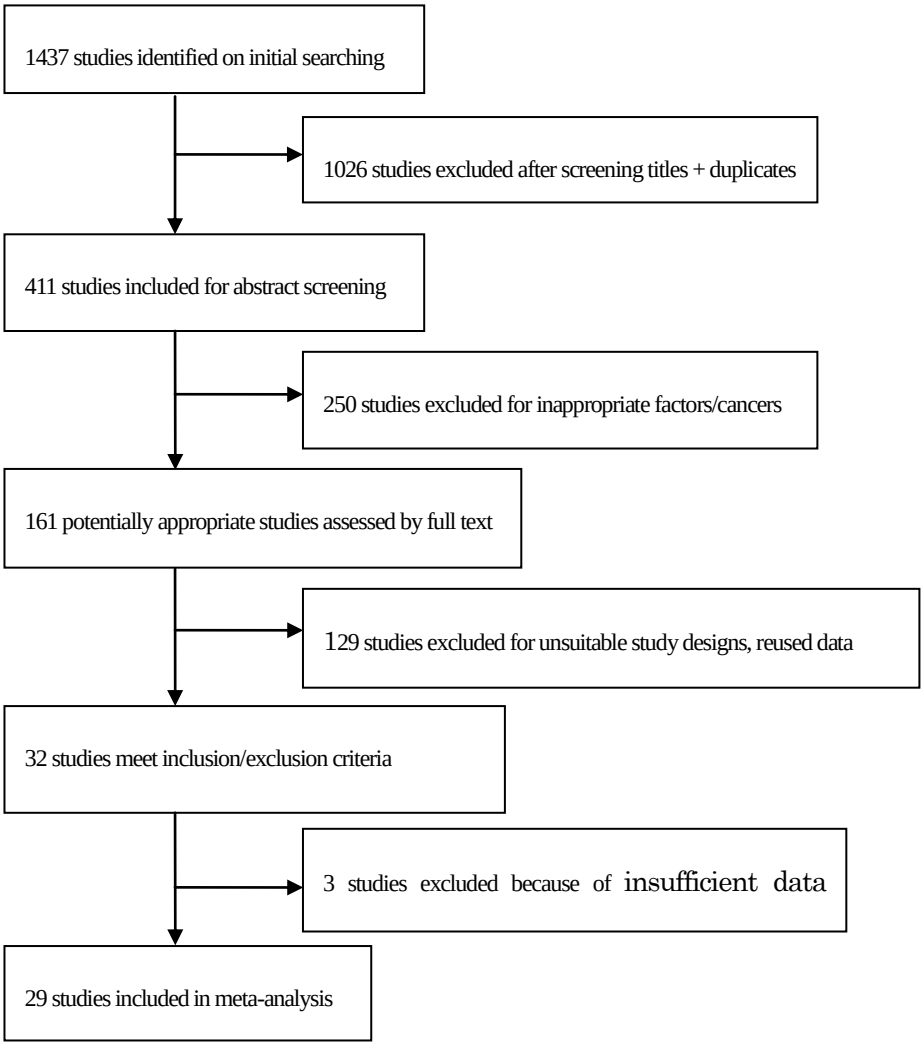

Figure 1 Flowchart of included studies

Results

Literature search

From the 1,437 studies identified, thirty-two studies were incorporated in the final data analysis after meeting inclusion criteria. All studies included were published in English, and included twenty-eight case control studies and four cohort studies (Figure 1). Three studies were subsequently excluded[44-46], as they did not provide sufficient data points or required confidence intervals for our final analysis. The individual study characteristics for all included studies are outlined in Table 2. Fourteen studies reported data on EAC, twelve studies reported on ESCC, and nine studies did not distinguish between the two subtypes and this data was subsequently referred to as esophageal cancer (EC).

Demographics

The total number in our study population was 1,208,768 individuals from all case control and cohort studies, including a combined total of 8,620 cases and 44,574 controls. The four cohort studies included 1,265 cases, while 7,355 cases were from case control studies. There were 2,128 EC cases, 2,895 ESCC cases & 4,712 EAC cases included in the analysis. The average age of the controls was 58.3 years old, and 60.7 years old for the cases.

Meat Types

Various types of meats being compared in the studies included red meat, chicken, fish, white meat, processed meat, barbecued meat, seafood, ham, salami, sausages, poultry, cured meat, salted meat, pork, liver, fried bacon or ham, non-processed meat and stewed meat. For the purposes of our analysis, classifications of red meat, fresh red, and total red meat was pooled as "red", white meat, chicken and poultry were pooled as "white", seafood, shellfish and fish were pooled as "fish". Salami, sausages, cured meat, salted meat, stewed meat, ham, fried bacon and ham and processed meat were all categorized as "processed". Studies that did not differentiate between meats were grouped under the category of "all meat". Liver, pork, and non-processed meat were also grouped into "all meat". An overall analysis including all groups was also completed.

Amount Consumed

The reporting of consumption was variable between the studies, including consumption rates of g/day[11, 12, 14, 21, 22], g/kcal[16], servings/year[24], servings/week[26, 27], times/week[23, 30, 38, 39], kg/year[36], portions/week[17] for example. In the majority of papers, they were reported in terms of tertiles[17, 19, 20, 22, 27, 37], quartiles[12, 14, 15, 21, 24, 25, 29-31, 33, 36] and quintiles[11, 16, 26, 32]. Based on this information, consumption was divided into 3 groups of low, medium or high consumption in order to simplify our analysis. These classifications were calculated after adjusting the consumptions reported to be equivalent with each other. High consumption represented >7 servings/week, medium represented 2-7 servings/week and low represented <2 servings/week. The findings from this analysis are found in Table 3. We found that at any level of consumption for both red meat and barbecued meat were significantly associated with the development of cancer. In the overall analysis, both medium consumption (OR: 1.13; 95% CI: 1.01-1.27) and high consumption (OR: 1.26; 95% CI: 1.11-1.43) were significantly associated. In the analysis of white meat, both medium consumption (OR: 0.83; 95% CI: 0.69-0.99) and high consumption (OR: 0.70; 95% CI: 0.55-0.89) were significantly found to reduce the risk. A risk reduction was also found in high consumption of fish (OR: 0.73; 95% CI: 0.55-0.95). There was a difference when looking at study design, only case control studies with high consumption levels demonstrated significant risk (OR: 1.24; 95% CI: 1.08-1.42).

Table 3 Results of analysis by amount of meat consumed.

Consumption Amount	Low[1] OR (95% CI)	Medium[2] OR (95% CI)	High[3] OR (95% CI)
		Continent	
Europe	1.16 (0.76 – 1.78)	1.19 (0.93 – 1.52)	1.31 (1.02 – 1.67)
North America	1.04 (0.94 – 1.15)	1.12 (0.97 – 1.29)	1.34 (1.11 – 1.61)
South America	1.21 (0.82 – 1.79)	1.27 (0.89 – 1.83)	1.47 (0.85 – 2.54)
Asia	0.92 (0.77 – 1.09)	0.96 (0.81 – 1.14)	0.93 (0.73 – 1.20)
		Study Design	
Cohort	1.22 (0.81-1.85)	1.27 (0.94 – 1.70)	1.34 (0.96 – 1.88)
Case Control	1.03 (0.93 – 1.14)	1.09 (0.98 – 1.22)	1.24 (1.08 – 1.42)
		Type of Meat	
All Meat	1.10 (0.95 – 1.26)	1.13 (1.01-1.27)	1.26 (1.11 – 1.43)
Red	1.20 (1.04 – 1.40)	1.30 (1.13 – 1.50)	1.59 (1.31 – 1.93)
Processed	1.25 (0.79 – 2.00)	1.28 (0.89 – 1.84)	1.75 (1.28 – 2.38)
White	0.91 (0.75 – 1.11)	0.83 (0.69-0.99)	0.70 (0.55-0.89)
Fish	0.82 (0.65-1.02)	0.88 (0.69 – 1.12)	0.73 (0.55 – 0.95)
Barbecue	1.26 (1.01 – 1.56)	1.36 (1.17 – 1.59)	1.54 (1.25 – 1.91)
Overall	1.10 (0.95 – 1.26)	1.13 (1.01-1.27)	1.26 (1.11 – 1.43)
		Population Type	
Population Based	1.14 (0.92 – 1.41)	1.23 (1.03 – 1.47)	1.41 (1.13 - 1.76)
Hospital Based	1.02 (0.86 – 1.21)	1.07 (0.92 – 1.24)	1.19 (1.01 – 1.14)
Combination	1 (0.66 – 1.52)	0.80 (0.36 – 1.74)	0.90 (0.48 – 1.69)

1 = <2 servings/week, 2 = 2-7 servings/week, 3 = >7 servings/week

OR = Odds Ratio, CI = Confidence Interval

Table 4 Results of analysis by the type of esophageal cancer.

Cancer Type	EAC[1] OR (95% CI)	ESCC[2] OR (95% CI)	EC[3] OR (95% CI)
		Continent	
Europe	1.17 (1.03 – 1.33)	1.17 (0.89 – 1.53)	1.79 (0.92 – 3.48)
North America	1.11 (1.01 – 1.21)	1.15 (0.96 – 1.37)	1.46 (1.18 – 1.79)
South America		1.05 (0.81 – 1.37)	1.63 (1.20 – 2.20)
Asia		0.98 (0.84 – 1.14)	0.86 (0.76 – 0.97)
		Study Design	
Cohort	1.03 (0.94 – 1.13)	1.57 (1.09 – 2.27)	0.86 (0.66 – 1.13)
Case Control	1.16 (1.05 – 1.28)	0.99 (0.90 – 1.10)	1.31 (1.12 – 1.53)
		Type of Meat	
All Meat	1.53 (1.16 – 2.03)	1.19 (0.95– 1.50)	0.97 (0.83-1.13)
Red	1.19 (1.08 – 1.33)	1.41 (1.24 – 1.61)	2.27 (1.58 – 3.24)
Processed	1.11 (1 – 1.23)	1.54 (1.06 – 2.23)	2.05 (0.80 – 5.26)
White	0.87 (0.75 – 0.99)	0.73 (0.65 -0.83)	0.92 (0.80 – 1.06)
Fish	0.79 (0.54 – 1.15)	0.66 (0.58 – 0.76)	1.03 (0.85 – 1.26)
Barbecue	1.23 (1.07-1.42)	1.33 (1.15 – 1.45)	2.11 (1.47 – 3.04)
Overall	1.12 (1.04 – 1.21)	1.10 (0.97 – 1.26)	1.25 (1.08-1.44)
		Population Type	
Population Based	1.22 (1.08 – 1.38)	1.07 (0.92 – 1.25)	0.94 (0.81 – 1.09)
Hospital Based	1.06 (0.90 – 1.24)	0.98 (0.87 – 1.12)	1.49 (1.22 – 1.82)
Combination		0.94 (0.77 - 1.15)	

1 = Esophageal Adenocarcinoma, 2 = Esophageal Squamous Cell Carcinoma, 3 = Esophageal Cancer
OR = Odds Ratio, CI = Confidence Interval

Cancer Type

Table 4 shows the results of comparing the development of EAC, ESCC and EC to measured variables. The consumption of both red meat and barbecue meat groups were significantly associated

with increased risk in all 3 types of cancer groups. Consumption of all meat was shown to have a significant relationship to EAC (OR: 1.53; 95% CI: 1.16-2.03), Processed meat was found to be a significant risk factor for ESCC (OR: 1.54; 95% CI: 1.06-2.23). White meat was found to be a protective factor against EAC (OR: 0.87; 95% CI: 0.75-0.99), ESCC (OR: 0.73; 95% CI: 0.65-0.83), and fish was shown to be protective against ESCC (OR: 0.66; 95% CI: 0.58-0.76). Fish as a protective factor for esophageal cancer overall (OR: 0.80; 95% CI: 0.70-0.91) was significant and is reported in Figure 2. Overall, meat consumption had a significant risk associated with EAC (OR: 1.12; 95% CI: 1.04-1.21) and EC (OR: 1.25; 95% CI: 1.08-1.44). In terms of a continental relationship, Europe had a significant risk for EAC (OR: 1.28; 95% CI: 1.09-1.51) and both North America (OR: 1.46; 95% CI: 1.18-1.79) and South America (OR: 1.63; 95% CI: 1.20-2.20) had a significant risk for EC. Neither South America nor Asia reported studies investigating EAC, and the studies from Asia demonstrated no risk for development of EC (OR: 0.86; 95% CI: 0.76-0.97).

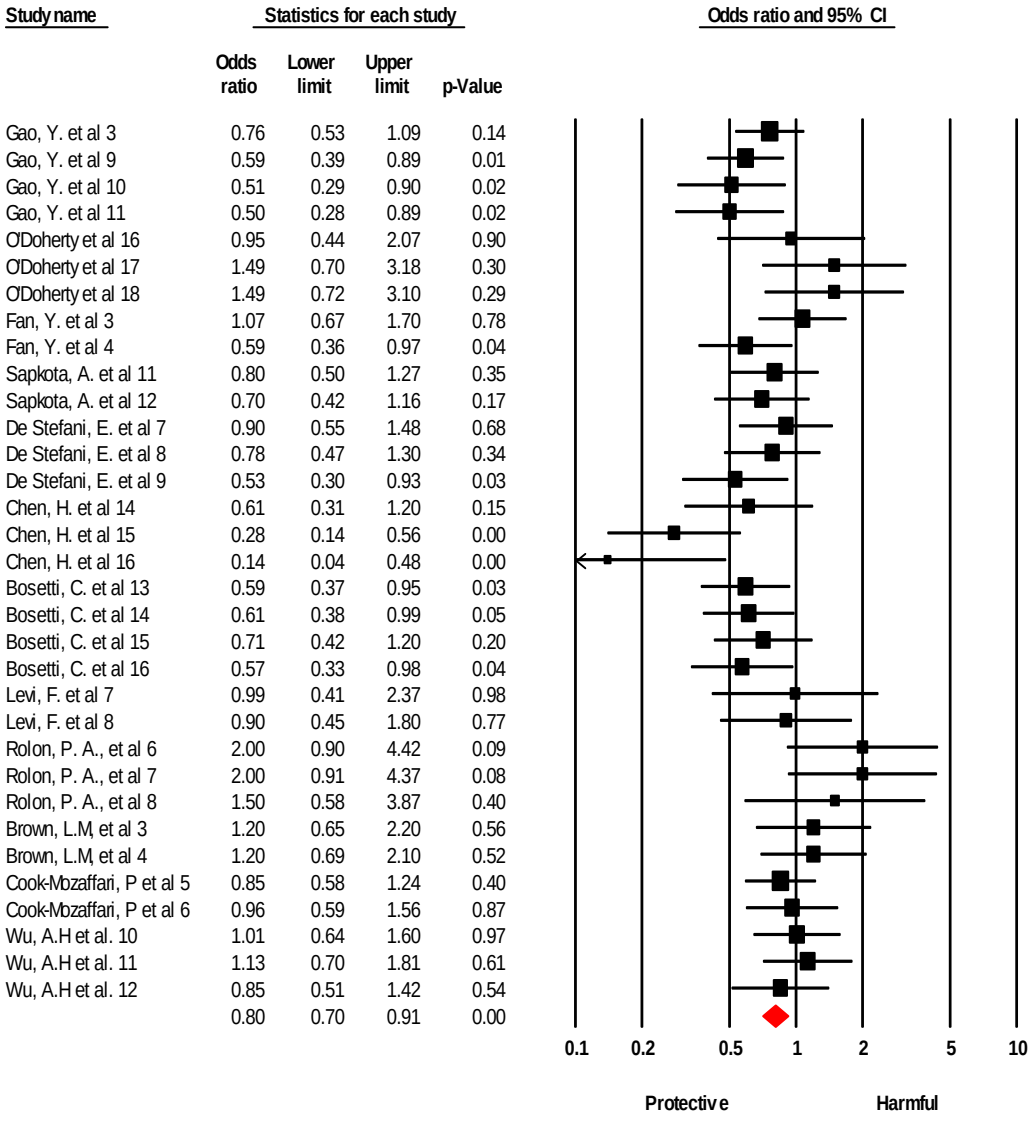

Figure 2 Forest plot (fish vs. overall cancer risk).

Heterogeneity

There were moderate levels of heterogeneity amongst studies looking for risk of cancer overall in all meat (I^2=51.23%, p<0.001), fish (I^2=46.84%, p=0.002) and white meat (I^2=44.17%, p=0.007). There were low levels of heterogeneity amongst the studies exploring red meat (I^2=24.69%, p=0.04) and processed meat (I^2=35.79%, p=0.02). When analyzing by cancer type, high levels of heterogeneity were observed when looking at ESCC (I^2=84.25%, p<0.001) and EC (I^2=60.62%, p<0.001), but only moderate heterogeneity was present in studies looking at EAC (I^2=41.50%, p<0.001).

Publication Bias

Egger's regression analysis showed that publication bias was not present with p=0.48, (Figure 3).

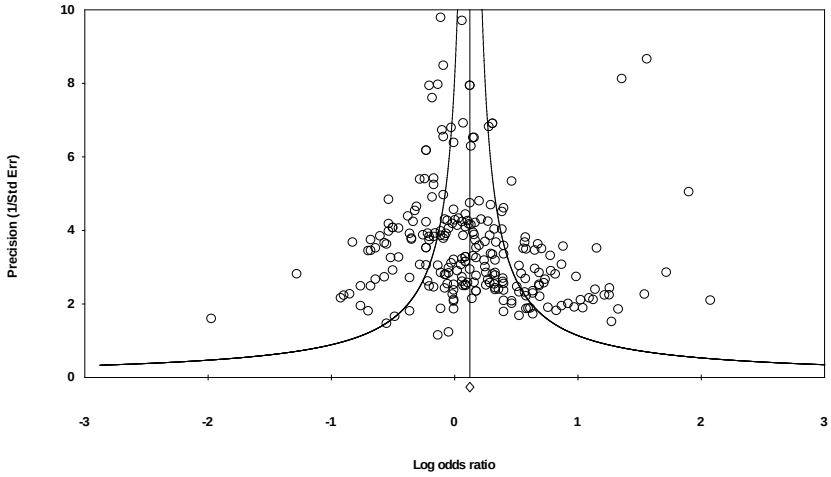

Figure 3 Funnel plot assessing publication bias. Std Err = Standard Error

Discussion

Our systematic review and meta-analysis supports the hypothesis that there is a statistically significant increase in the risk of esophageal cancer with the consumption of meat. Significant relationships were found between red meat, barbecued meat and ESCC, EAC and EC. Processed meat was also a significant risk factor for ESCC. Significant dose dependent relationships were demonstrated, where high levels of consumption of all, red, processed, and barbecued meat were associated with an increased risk of cancer (26%, 59%, 75% and 54%, respectively). Overall, a high amount of meat consumption was associated with a 26% increased risk of cancer.

An important distinction here is that our study revealed that while red meat is a risk factor for all cancer types studied, processed meat was only a significant risk factor for EAC. Some of the studies we included did consider dietary risks for ESCC, however, the current literature has not proven diet as a risk factor for ESCC[5]. The literature on the development of EAC is also controversial, with a recent review finding that although there is evidence that processed meat and red meat are associated with the development of EAC; this data is inconsistent[47]. It is especially difficult to study these risks in EAC, as there are many factors to consider, such as genetics and other environmental risks. Obesity is one of the established risk factors implicated for EAC, but the extent of this contribution is unclear. It has been suggested that obesity causes chronic reflux, which could indirectly contribute to the development of esophageal cancer via Barrett's Esophagus[48]. A recent review examining the progression of

Barrett's to EAC, shows that this is a complex relationship that may depend on distribution of fat, rather than BMI on its own[49].

There are many possible reasons why red meat and processed meat in particular lead to an increased risk of esophageal cancers. It has been postulated that this may be due to cooking methods, hormonal factors, or biochemical compounds such as hemeiron, or carcinogens such as heterocyclic amines and nitrosamine compounds. The production and impact of heterocyclic amines has been investigated[50, 51], but there the impact of their contribution is not clear. A large case-control study from Sweden found that heterocyclic amine intake might be associated with an increase risk by 50-70% of ESCC, although this risk was non-significant, and no association was found with risk of EAC[50]. Nitrite and n-nitrosamine compounds are strong animal carcinogens that are strongly present in processed meat[47]. Although it is possible that there is an effect of nitrite and nitrosamines in the development of esophageal cancer, the current evidence is insufficient to conclusively implicate them[52]. Another source of endogenous n-nitrosation, ingestion of heme iron may account for increased risk associated with red meat consumption and colorectal cancer. This may also account for the finding that dose dependent relationships between red meat and colorectal cancer may be related to the amount of heme ingestion[53]. There is still much uncertainty as to the pathogenesis of esophageal carcinoma, but the study of red meat has further implications as well; potential associations have been described with Diabetes Mellitus, cardiovascular disease, other cancers and mortality; so there are many reasons to continue research into this field and, potentially, for the recommendation of red meat free diets to the general population[54].

In our analysis, white meat was found to be protective against EAC and ESCC, but fish was only found to be protective significantly against ESCC. Although it is uncertain why white meat has this protective effect, it has been suggested and is plausible that this is due to a lack of heme iron in white meat[55]. Evidence exists for the protective nature of fish and fish n-3 polyunsaturated fatty acids in other cancers, such as breast and colorectal cancer. It has been demonstrated that an increase in the consumption of fish in industrialized countries may contribute to lower cancer risks[56]. The mechanisms of this protection have been discussed elsewhere[57]. A recent large Australian systematic review and meta-analysis found that higher consumption of poultry and fish could potentially reduce the risk of ovarian cancer[58].

Our meta-analysis had a number of strengths. We had well-defined objectives from the outset of the project with pre-determined outcomes, an appropriate and documented methodology including study identification and selection strategy. We searched multiple databases and included a large number of studies from a broad range of geographical locations and economical classes, and no publication bias was found. We used a random-effects model for our analysis, reducing our risk of variance within the studies. Finally, we used only adjusted ratios when they were provided, thus increasing our statistical power.

As with most meta-analyses, there were some limitations. We did not search for unpublished studies, increasing our risk for selection bias. Conducting a meta-analysis of observational studies makes our study susceptible to bias existing within the original studies. As the majority of our studies were case-control studies, they are prone to recall and selection bias as well. This is contrary to the prospective cohort studies that provide more protection against these types of biases. The case-control studies revealed a significant risk for cancer in the high consumption groups, and significant risks for EAC and EC overall, thecohort analysis revealed a significant risk for ESCC.It is possible that there was an influence of study design on our results; although this may be a product of the majority of our studies being case-control studies, and the lack of published cohort data being available. There were differences in sample size in our studies as well; the cohort studies had much larger numbers than the case-control studies, but

we did not stratify by sample size to test the stability of the results.

Another limitation our study faced was high levels of heterogeneity, especially in our studies of ESCC and EC, potentially having an impact on the validity of our results. We believe there are a number of reasons for this. Firstly, there were issues with regards to the classification of cancers. Two of the studies reported that even though their classification was EC, the majority of the cases (85-90%) comprised of ESCC compared to EAC[37, 38]. We left these as EC in our comparison, although it may have been more appropriate to study them as ESCC. The decision was made to keep them classified as EC to avoid potentially erroneous data. Secondly, it is also possible that our results are affected by imprecise measurement of meat consumption and misclassification within the studies themselves, and even perhaps on our part in our categorization. It has been reported that it is possible in case-control studies measuring dietary intake measurement error unrelated to disease status can give rise to differential misclassification resulting in a bias of the estimated relative risk towards or away from the null value[59]. We faced great challenges pooling data from the different study types as outlined in our methods, but grouped meats according to what we thought to be the most important groups for our analysis, and in reasonable consumption amounts reflecting what the original studies measured to the best of our ability. Third, combining both protective and risk factors may have confounded the effect of overall meat on the development of cancer. Finally, some other contributing factors may have been that we used study from many geographical locations, duration of follow-up in the cohort studies, where populations were derived from, and the play of chance cannot be excluded.

Conclusions

In conclusion, findings of this meta-analysis support the hypothesis that meat overall, red meat and barbecued meat likely increase the risk of EAC, with a suggestion of a dose dependent relationship in certain cases. Red, processed and barbecue are associated with increases in ESCC. Fish and poultry may have a protective effect, against ESCC, and white against EAC, although the mechanisms of these effects are complex and not completely understood as of yet. We also found that there is a dose dependent relationship in the analysis of red meat, processed meat and barbecued meat and their risk for the development of cancer. There are obviously a multitude of factors implicated in the development of esophageal cancers, and this study has implicated the potential effects of meat in the first meta-analysis of this topic to our knowledge.

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