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Original Article

Association between processed meat and red meat consumption and risk of nasopharyngeal carcinoma: evidence from a meta-analysis

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Abstract: Background: Whether processed meat and red meat consumption could increase the nasopharyngeal carcinoma (NPC) risk have produced inconsistent results. Thus, we conducted a meta-analysis from epidemiological studies to assess the associations between them. Methods: We searched the databases of PubMed and Web of Knowledge up to July 2015. A random-effects model was used to combine study-specific relative risks (RR) and 95% confidence interval (CI). Publication bias was assessed by Egger regression asymmetry test. Results: In total, 11 studies involving 4468 NPC cases were included in this meta-analysis. Ten studies reported processed meat consumption and NPC risk, and the RR of NPC risk was 2.11 (95% CI = 1.21-3.70) (P < 0.001). The association was significant in Asia [summary RR = 2.64, 95% CI = 1.12-6.19], but not in the other populations. Pooled results suggested that red meat consumption had an increased but not significant association for NPC risk. No publication biases were found. Conclusions: Our analysis indicated that higher category of processed meat consumption could increase the risk NPC, especially among Asia population. No association was found between red meat consumption and NPC risk, and the results need to be confirmed.

Keywords: Processed meat, red meat, nasopharyngeal carcinoma, meta-analysis

Introduction

Nasopharyngeal carcinoma (NPC) is a common malignant tumor in Southeast Asia, Southern China and North Africa, but is rare in most parts of the world [1, 2]. The incidence rate for males is more than 20 per 100,000 person-years and is as high as 25 to 40 per 100,000 person-years in some areas bordering the Xijiang River and the Pearl River [3-5]. Therefore, primary prevention of NPC is an important matter in the current society. NPC is thought to be caused by the combined effects of environmental carcinogens [6], genetic susceptibility [7] and some dietary intakes [8].

Meat is a major source of food for humans. Dietary meat intake, particular processed meat consumption, has been suggested to be an increased factor for some diseases, including type 2 diabetes [9], cardiovascular disease [10] and cancers [11, 12]. Processed meat is usually preserved with nitrite and may also contain N-nitroso compounds. N-nitroso compounds can further be formed endogenously in the stomach from nitrite and ingested amides in foods of animal origin [13]. To date, a number of epidemiologic studies have been published to explore the relationships between meat consumption, particularly processed meat consumption and NPC risk. However, the results are not consistent. Therefore, the aim of this study was to systematically examine whether processed and red meat consumption could increase the risk of NPC.

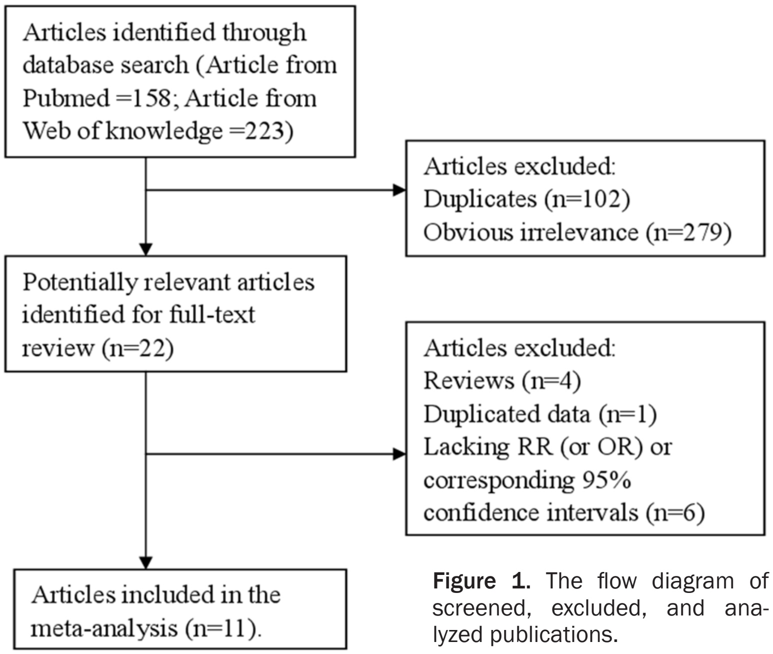

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

Materials and methods

Literature search

Two authors independently searched the databases of PubMed and Web of Knowledge for relevant articles published before July 2015 using the following search terms: 'nasopharyngeal' AND ('neoplasm' OR 'carcinoma' OR 'cancer') AND 'red meat' (unprocessed) AND/OR 'processed meat' with written in English. In addition, we reviewed references of obtained articles. Disagreements between the two authors were resolved by consensus with a third author.

Study selection

Studies were eligible for analysis if they met the following criteria: (1) the studies were of case-control or cohort design; (2) the exposure was processed meat and/or red meat; (3) the end point was NPC; (4) written in English; and (5) there was sufficient data generated to make a relative risk (RR) or odds ratio (OR) with 95% confidence intervals (CI). In the present study, 'red meat' was defined as unprocessed meat from beef, pork, mutton and lamb, and excluding poultry, fish or eggs; 'processed meat' was defined as any meat preserved by smoking, curing or salting or addition of chemical preservatives, such as bacon, salami, sausages, hot dogs or processed deli or luncheon meats, and excluding fish or eggs [14]. When multiple publications from the same study population were available, we included the most recent publication.

Data extraction

We extracted data from the included articles, with particular regards to: the last name of the first author, publication year, country of region, study design, type of controls, study population, age for cases and participants, number of cases and participants, the most fully adjusted RR and 95% CI, and statistical adjustment for the main confounding or mediating factors. Otherwise, the crude RR with their 95% CI was extracted.

Statistical analysis

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI, to assess the association between processed meat and red meat and the risk of NPC. A random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [15]. Heterogeneity across the studies were tested by using the I^2 statistic [16], which is a quantitative measure of inconsistency across studies, with suggested thresholds for low (25%-50%), moderate (50%-70%) and high (> 75%) heterogeneity, respectively [17]. Meta-regression and subgroup analyses were performed to assess the potentially important covariates that might exert substantial impact on between-study heterogeneity [17]. Sensitivity analysis was conducted to describe how robust the pooled estimator was to removal of individual studies [18]. We used the Egger regression asymmetry test to evaluate the publication bias [19]. All statistical analyses were performed using Stata 10.0 (Stata Corp, College Station, Texas, USA). Two-tailed $P \leq 0.05$ was accepted as statistically significant.

Results

Literature search

A total of 381 papers were retrieved from the electronic databases. After initial screening of

Table 1. Characteristics of studies on processed meat and red meat with the risk of NPC

First author, year	Country	Study design	Cases, age	Quality score	Category (servings/week)	RR (95% CI)	Adjustment or matched for
Armstrong et al. 1998	China	PCC	282, Cases: 45.29 Controls: 44.82	6	Red meat: Weekly vs. Ever	1.98 (0.97-4.05)	Age, sex, residence and marital status
Chelleng et al. 2000	India	PCC	47, Cases: 43.7 Controls: 43.5	7	Processed meat: Frequently vs. Never	10.8 (3.4-39.0)	Adjusted for type of house, number of windows in the house, kitchen inside/outside, presence of soot in the living room, smoking status, smokeless tobacco use, type of cooking fuel used, habit of chewing betel nut and drinking alcohol
Farrow et al. 1998	United States	PCC	133, 18-74	7	Processed meat: High vs. Low	1.54 (0.71-3.33)	Age, alcohol consumption (0-6, 7-13, 14-20, or 21+ drinks per week), cigarette smoking (never, former, current with history of 1-34 pack years, current with history of 35-59 pack years or current with history of 60+ pack years), total caloric intake, broccoli, cauliflower, spinach, mustard or turnip greens, coleslaw, winter squash, carrots, yams
Feng et al. 2007	Africa	HCC	636, Cases: 42.6 Controls: 43.5	7	Processed meat: ≥ 1 vs. < 1	1.5 (0.6-3.8)	Age, sex, socio-economic status variables and exposure to toxic substances
Ghosh et al. 2014	India	HCC	64, Na	8	Processed meat: Yes vs. No	2.00 (1.02-3.93)	Age, gender, occupation and nature of consuming tobacco-betel quid habit (smoking or smokeless) and alcohol intake
Jia et al. 2010	China	HCC	1387, Cases: 46.92 Controls: 47.34	7	Processed meat: Weekly vs. Ever	9.69 (6.39-14.7)	Age, sex, education, dialect and household type
Polesel et al. 2013	Italy	HCC	198, Cases: 52 Controls: 52	8	Red meat: 6.50 vs. 1.75 Processed meat: 6.00 vs. 1.50	1.28 (0.74-2.23) 1.40 (0.85-2.29)	Age, sex, place of living, year of interview, education, tobacco, smoking, alcohol drinking, and non-alcohol energy
Turkoz et al. 2011	Turkey	HCC	183, Cases: 44.9 Controls: 43.9	8	Processed meat: Weekly vs. Never	1.05 (0.57-1.93)	Age and sex
Uzcudun et al. 2002	Spain	HCC	232, Cases: 57.96 Controls: 58.96	7	Processed meat: Frequently vs. Never	1.70 (1.02-4.70)	Adjusted for tobacco smoking and alcoholic beverage drinking and their percentage contribution to risk
Ward et al. 2000	China	PCC	375, ≤ 75	7	Processed meat: > 0 vs. 0	1.1 (0.6-2.0)	Age, gender and ethnicity
Yuan et al. 2000	China	PCC	935, 15-74	6	Processed meat: Weekly vs. Less than monthly	1.77 (1.12-2.79)	Age, gender, level of education, cigarette smoking, exposure to smoke from heated rapeseed oil and burning coal during cooking, occupational exposure to chemical fumes and history of chronic ear and nose condition (see text for more detailed description of confounding variables)

Abbreviations: PCC: population-based case-control study; HCC: hospital-based case-control study; Na: not available.

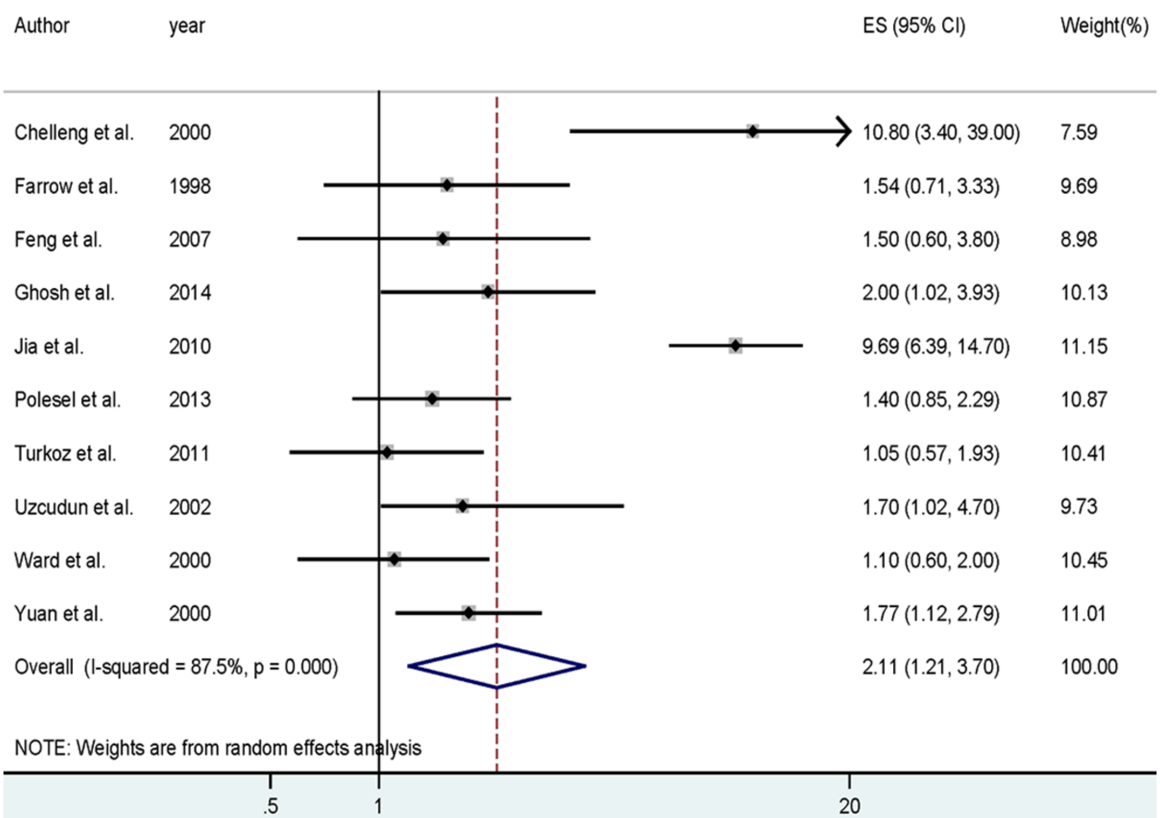

Figure 2. The multivariate-adjusted risk of NPC risk for the highest versus lowest categories of processed meat consumption.

Table 2. Summary risk estimates of the association between processed meat and red meat consumption and the risk of NPC

Subgroups	No. cases	No. studies	Risk estimate (95% CI)	Heterogeneity test	
				I^2 (%)	*P*-value
Processed meat	4186	10	2.11 (1.21-3.70)	87.5	0.000
Sources of control					
Population-based	1486	4	2.01 (1.03-3.92)	72.5	0.012
Hospital-based	2700	6	2.08 (0.91-4.76)	91.0	0.000
Geographic locations					
Asia	2991	6	2.64 (1.12-6.19)	92.0	0.000
Europe	430	2	1.48 (0.98-2.25)	0.0	0.966
Others	765	2	1.52 (0.84-2.76)	0.0	0.676
Number of cases					
< 200	621	5	1.85 (1.07-3.18)	66.5	0.018
≥ 200	3565	5	2.22 (1.08-4.61)	92.1	0.000
Red meat	410	2	1.51 (0.97-2.33)	0.0	0.344

titles and abstracts using the aforementioned criteria, 22 articles were identified for full-text review. Of these, 11 were further excluded, leaving 11 eligible articles (**Figure 1**). Hence, eleven articles involving 4468 NPC cases were included in the final analysis [20-30]. All of the included studies were case-control design. Three studies were come from China, 2 from India, 1 from United States, 1 from Italy, 1 from Spain, 1 from Turkey and 1 from Africa. The characteristics of these included studies are presented in **Table 1**.

Processed meat

For processed meat consumption and the risk of NPC, data from 10 studies [21-30] including 4186 NPC cases were used. Five of the ten studies reported a positive association between processed meat consumption and the risk of NPC, while 5 studies found no significant association between them. **Figure 2** presents the each RR with their 95% CI for all 10 studies assessing the association between processed meat consumption and NPC risk. The pooled

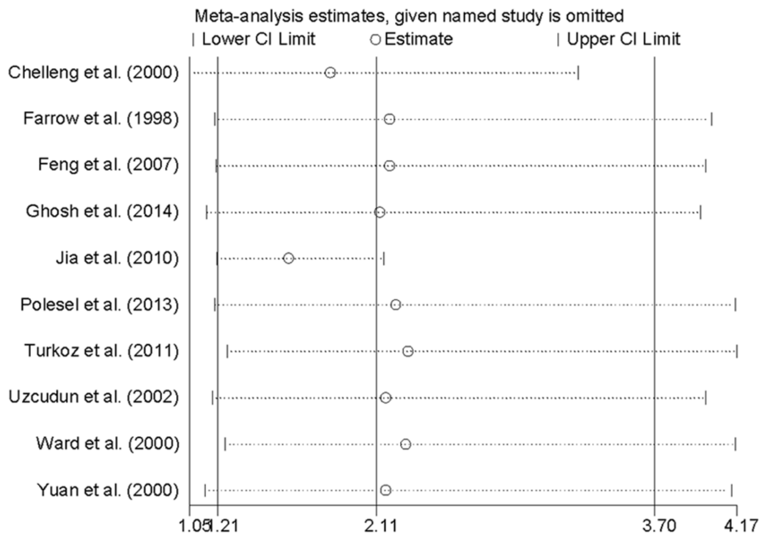

Figure 3. Analysis of influence of individual study on the association between processed meat consumption and NPC risk.

RR of 2.11 (95% CI = 1.21-3.70) (P < 0.001) shows that higher category of processed meat consumption was associated with increased the risk of NPC, with high heterogeneity detected (I^2 = 87.5%, $P_{heterogeneity}$ = 0.000).

Meta-regression and subgroup analyses

In our pooled results, high heterogeneity was found between processed meat consumption and NPC risk. Thus, we used univariate meta-regression with the covariates of publication year, geographic locations, and number of cases and source of controls to explore the high between-study heterogeneity founded in the analysis. However, no significant findings were found in the above-mentioned analysis.

Subgroup analysis by sources of control was performed. We extracted the detailed information for hospital based case-control studies or population based case-control studies. And the association was only significant in the population based case-control studies [summary RR = 2.01, 95% CI = 1.03-3.92], but not in the hospital based case-control studies [summary RR = 0.59, 95% CI = 0.39-0.88] between processed meat consumption and NPC risk. Studies were also stratified by geographic area, The RR were 2.64 (95% CI = 1.12-6.19) for studies conducted in Asia, 1.48 (95% CI = 0.98-2.25) for studies in Europe. Only 1 study conducted from America and 1 from Africa. We combined the results as other populations [summary RR = 1.52, 95% CI = 0.84-2.76]. In analysis stratified by number of cases (< 200 or ≥ 200), significant associations were found both in the subgroup of < 200 cases [summary RR = 1.85, 95% CI = 1.07-3.18] and ≥ 200 cases [summary RR = 2.22, 95% CI = 1.08-4.61]. The detailed results are summarized in **Table 2**.

Red meat

Two studies [20, 26] with 480 NPC cases were carried out for the association between red meat consumption and NPC risk. There was no statistically significant association between red meat consumption and NPC risk in overall studies [summary RR = 1.51, 95% CI = 0.97-2.33, I^2 = 0.0%, $P_{heterogeneity}$ = 0.344].

Sensitivity analysis and publication bias

Sensitivity analysis showed that no individual study had excessive influence on the NPC risk either in processed meat consumption (**Figure 3**) or red meat consumption. Egger regression asymmetry test showed no evidence of significant publication bias between NPC risk and processed meat consumption (*P* = 0.391) and red meat consumption (*P* = 0.282).

Discussion

In this study, data were available for large participants and 4468 NPC case. This work provided convincing evidence that processed meat consumption is associated with an increased risk of NPC. This relationship between processed meat consumption and NPC risk was consistent in Asia population and in the subgroup analysis of population based case-control studies. Furthermore, only 2 studies were conducted for red meat and NPC risk, and no significant association was found between them.

In our study, significant between-study heterogeneity was found between processed meat consumption and NPC risk. Previous paper [31] had reported that heterogeneity is common in the meta-analyses. To explore the potential sources of between-study heterogeneity is therefore an essential component of meta-analysis. The high degree of heterogeneity might have arisen from publication year, geographic locations, and number of cases and source of controls. Therefore, we used meta-regression to explore the causes of heterogeneity for covariates. However, no covariate had significant impact on between-study heterogeneity among those mentioned above. We then performed subgroup analyses by geographic locations, number of cases and source of controls to explore the source of heterogeneity. However, between-study heterogeneity persisted in some of the subgroups, suggesting the presence of other unknown confounding factors. Other genetic and environment variables, as well as their possible interaction, may well be potential contributors to the heterogeneity observed.

As a meta-analysis of published studies, our findings showed some advantages. First, a highlight of this study was that we found an increased association between processed meat consumption and NPC risk. Second, the current study included a large number of cases and participants, and this may derive a more precise estimation of the relationship between processed meat consumption and NPC risk. Third, no significant publication biases were detected in this meta-analysis.

There are some limitations in this meta-analysis should be concerned. First, all studies included in this meta-analysis were case-control design. Although case-control studies may suffer from recall bias and selection bias, case-control studies are important methods in etiology research. More studies with prospective design are wanted in the future studies. Second, as a meta-analysis of observational studies, we cannot rule out that individual studies may have failed to control for potential confounders, which may introduce bias in an unpredictable direction. Third, we did not do a dose-response analysis for processed meat consumption and the risk of NPC because of the limited data in the reported articles. Further studies with detailed dose for each category are wanted to assess this association. Fourth, for the subgroups of geographic locations, the association was only significant in the Asia, but not in the Europe and other populations between processed meat consumption and NPC risk. Only 2 studies were conducted from Europe, 1 from United States and 1 from Africa. Due to this limitation, the results are applicable to Asia, but cannot be extended to populations elsewhere. More studies originating in other countries are required to investigate the association between processed meat consumption and NPC risk. Fifth, we did not find significant association between red meat consumption and risk of NPC because little studies were included. Further studies should be conducted to assess the association between red meat consumption and NPC risk.

In summary, findings from this meta-analysis indicated that processed meat consumption might increase the risk of NPC, especially in Asia. No association was found between red meat consumption and NPC risk.

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Disclosure of conflict of interest

None.

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