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.
Processed meat and red meat and NPC risk

**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 I² 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 ≤ 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

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Study design</th>
<th>Cases, age</th>
<th>Quality score</th>
<th>Category (servings/week)</th>
<th>RR (95% CI)</th>
<th>Adjustment or matched for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong et al. 1998</td>
<td>China</td>
<td>PCC</td>
<td>282, Cases: 45.29, Controls: 44.82</td>
<td>6</td>
<td>Red meat: Weekly vs Ever</td>
<td>1.98 (0.97-4.05)</td>
<td>Age, sex, residence and marital status</td>
</tr>
<tr>
<td>Cheilleng et al. 2000</td>
<td>India</td>
<td>PCC</td>
<td>47, Cases: 43.7, Controls: 43.5</td>
<td>7</td>
<td>Processed meat: Frequently vs Never</td>
<td>10.8 (3.4-39.0)</td>
<td>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</td>
</tr>
<tr>
<td>Farrow et al. 1998</td>
<td>United States</td>
<td>PCC</td>
<td>133, 18-74</td>
<td>7</td>
<td>Processed meat: High vs Low</td>
<td>1.54 (0.71-3.33)</td>
<td>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</td>
</tr>
<tr>
<td>Feng et al. 2007</td>
<td>Africa</td>
<td>HCC</td>
<td>636, Cases: 42.6, Controls: 43.5</td>
<td>7</td>
<td>Processed meat: ≥ 1 vs &lt; 1</td>
<td>1.5 (0.6-3.8)</td>
<td>Age, sex, socio-economic status variables and exposure to toxic substances</td>
</tr>
<tr>
<td>Ghosh et al. 2014</td>
<td>India</td>
<td>HCC</td>
<td>64, Na</td>
<td>8</td>
<td>Processed meat: Yes vs No</td>
<td>2.00 (1.02-3.93)</td>
<td>Age, gender, occupation and nature of consuming tobacco-betel quid habit (smoking or smokeless) and alcohol intake</td>
</tr>
<tr>
<td>Jia et al. 2010</td>
<td>China</td>
<td>HCC</td>
<td>1387, Cases: 46.92, Controls: 47.34</td>
<td>7</td>
<td>Processed meat: Weekly vs Ever</td>
<td>9.69 (6.39-14.7)</td>
<td>Age, sex, education, dialect and household type</td>
</tr>
<tr>
<td>Polesel et al. 2013</td>
<td>Italy</td>
<td>HCC</td>
<td>198, Cases: 52, Controls: 52</td>
<td>8</td>
<td>Red meat: 6.50 vs 1.75 Processed meat: 6.00 vs 1.50</td>
<td>1.28 (0.74-2.23), 1.40 (0.85-2.29)</td>
<td>Age, sex, place of living, year of interview, education, tobacco, smoking, alcohol drinking, and non-alcohol energy</td>
</tr>
<tr>
<td>Turkoz et al. 2011</td>
<td>Turkey</td>
<td>HCC</td>
<td>183, Cases: 44.9, Controls: 43.9</td>
<td>8</td>
<td>Processed meat: Weekly vs Never</td>
<td>1.05 (0.57-1.93)</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Uzcedun et al. 2002</td>
<td>Spain</td>
<td>HCC</td>
<td>232, Cases: 57.96, Controls: 58.96</td>
<td>7</td>
<td>Processed meat: Frequently vs Never</td>
<td>1.70 (1.02-2.70)</td>
<td>Adjusted for tobacco smoking and alcoholic beverage drinking and their percentage contribution to risk</td>
</tr>
<tr>
<td>Ward et al. 2000</td>
<td>China</td>
<td>PCC</td>
<td>375, ≤ 75</td>
<td>7</td>
<td>Processed meat: &gt; 0 vs 0</td>
<td>1.1 (0.6-2.0)</td>
<td>Age, gender and ethnicity</td>
</tr>
<tr>
<td>Yuan et al. 2000</td>
<td>China</td>
<td>PCC</td>
<td>935, 15-74</td>
<td>6</td>
<td>Processed meat: Weekly vs Less than monthly</td>
<td>1.77 (1.12-2.79)</td>
<td>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)</td>
</tr>
</tbody>
</table>

Abbreviations: PCC: population-based case-control study; HCC: hospital-based case-control study; Na: not available.
Processed meat and red meat and NPC risk

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

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No. cases</th>
<th>No. studies</th>
<th>Risk estimate (95% CI)</th>
<th>Heterogeneity test</th>
<th>I² (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processed meat</td>
<td>4186</td>
<td>10</td>
<td>2.11 (1.21-3.70)</td>
<td>87.5</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Sources of control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population-based</td>
<td>1486</td>
<td>4</td>
<td>2.01 (1.03-3.92)</td>
<td>72.5</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Hospital-based</td>
<td>2700</td>
<td>6</td>
<td>2.08 (0.91-4.76)</td>
<td>91.0</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Geographic locations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>2991</td>
<td>6</td>
<td>2.64 (1.12-6.19)</td>
<td>92.0</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>430</td>
<td>2</td>
<td>1.48 (0.98-2.25)</td>
<td>0.0</td>
<td>0.966</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>765</td>
<td>2</td>
<td>1.52 (0.84-2.76)</td>
<td>0.0</td>
<td>0.676</td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200</td>
<td>621</td>
<td>5</td>
<td>1.85 (1.07-3.18)</td>
<td>66.5</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>3565</td>
<td>5</td>
<td>2.22 (1.08-4.61)</td>
<td>92.1</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Red meat

410 2 1.51 (0.97-2.33) 0.0 0.344

Note: Weights are from random effects analysis.

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 | I² (%) | 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  |
Processed meat and red meat 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 (I² = 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 = 2.64 (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, I² = 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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