World Cancer Research Fund International
Systematic Literature Review

The Associations between Food, Nutrition and
Physical Activity and the Risk of Nasopharyngeal
Cancer

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Date completed:
02 December 2016
Date reviewed:
17 March 2017
Date revised:
26 January 2018
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASIR</td>
<td>Age standardised incidence rate</td>
</tr>
<tr>
<td>ASMR</td>
<td>Age standardised mortality rate</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CUP</td>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr Virus</td>
</tr>
<tr>
<td>FFQ</td>
<td>Food Frequency Questionnaire</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>NPC</td>
<td>Nasopharyngeal Cancer</td>
</tr>
<tr>
<td>OR</td>
<td>Odd Ratio</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SLR</td>
<td>Systematic Literature Review</td>
</tr>
<tr>
<td>SIR</td>
<td>Standardised Incidence Ratio</td>
</tr>
<tr>
<td>WCRF/AICR</td>
<td>World Cancer Research Fund/American Institute for Cancer Research</td>
</tr>
</tbody>
</table>
Background
The main objective of the present systematic literature review is to update the evidence from prospective cohort studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of nasopharyngeal cancer in men and women.

This SLR does not present conclusions or judgements on the strength of the evidence. The CUP Panel will discuss and judge the evidence presented in this review.

The methods of the SLR are described in detail in the protocol for the CUP review on nasopharyngeal cancer (see Appendix 1).
Figure 1 Conclusions from the evidence for nasopharyngeal cancer in the WCRF/AICR Second Expert Report (2007)

**FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE NASOPHARYNX**

In the judgement of the Panel, the factors listed below modify the risk of cancer of the nasopharynx. Judgements are graded according to the strength of the evidence.

<table>
<thead>
<tr>
<th></th>
<th>DECREASES RISK</th>
<th>INCREASES RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Convincing</strong></td>
<td></td>
<td>Cantonese-style salted fish¹</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td></td>
<td>Non-starchy vegetables² Fruits²</td>
</tr>
<tr>
<td><strong>Limited — suggestive</strong></td>
<td></td>
<td>Cereals (grains) and their products; nuts and seeds; herbs, spices, and condiments; meat; fish; shellfish and seafood; eggs; plant oils; tea; alcohol; salted plant food; Chinese-style pickled cabbage; pickled radish; pickled mustard leaf; Chinese-style preserved salted eggs; fermented tofu and soya products</td>
</tr>
<tr>
<td><strong>Limited — no conclusion</strong></td>
<td></td>
<td>None identified</td>
</tr>
</tbody>
</table>

¹ This style of preparation is characterised by treatment with less salt than typically used, and fermentation during the drying process due to relatively high outdoor temperature and moisture levels. This conclusion does not apply to fish prepared (or salted) by other means.

² Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

Source: WCRF/AICR Second Expert Report

** Modifications to the existing protocol**

The protocol on nasopharyngeal cancer was prepared in 2013 (see Appendix 1). The following modifications had been introduced:

**Review team:** Elli Polemiti joined the team as research assistant. Christophe Stevens joined the team as database manager.

**Timeline:** The current review comprises publications included in PubMed up to June 1st 2016.

**Methods:** Four cohort studies published after the 2005 SLR were identified in the literature search. There were no relevant randomised controlled trials and pooled studies. Because evidence was limited, the studies were reviewed narratively, along with the review of relevant published meta-analyses (all on case-control studies). Case-control studies are not reviewed in the CUP, apart from those on salted fish intake and preserved vegetable intake.
Salted fish intake was reviewed, as it was judged in the Second Expert Report that there was probable evidence that Cantonese-style salted fish is causally associated with nasopharyngeal cancer risk, and this judgement was based in case-control studies. Preserved vegetables intake was reviewed, at the request of the Expert Panel.

**Continuous Update Project: Results of the search**

**Figure 2 Flow chart of the search for nasopharyngeal cancer – Continuous Update Project**

Search period January 1\(^{st}\) 2006 – June 1\(^{st}\) 2016

*Two publications on multiple cancers including nasopharyngeal cancer were identified in the searches of other SLRs (Wen, 2014; Samanic, 2004).*
Results by exposure

Table 1 Number of relevant publications identified during the 2005 SLR and the 2016 CUP Update and total number of publications by exposure.

<table>
<thead>
<tr>
<th>Exposure Code</th>
<th>Exposure Name</th>
<th>Number of publications</th>
<th>Total number of publications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2005 SLR</td>
<td>CUP</td>
</tr>
<tr>
<td>2.</td>
<td>Foods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2.1.5</td>
<td>Preserved vegetables</td>
<td>12 case-control</td>
<td>3 case-control</td>
</tr>
<tr>
<td>2.3</td>
<td>Pulses (legumes)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2.5.2.1</td>
<td>Salted fish, adulthood consumption</td>
<td>1 cohort</td>
<td>0 cohort</td>
</tr>
<tr>
<td>2.5.2.1</td>
<td>Salted fish, childhood consumption (aged around 10 years)</td>
<td>16 case-control</td>
<td>1 cohort</td>
</tr>
<tr>
<td>3.</td>
<td>Beverages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.7.1</td>
<td>Alcohol consumption</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3.7.1</td>
<td>Alcohol and smoking</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>5.</td>
<td>Dietary constituents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.6.2</td>
<td>Iron in blood</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8.</td>
<td>Anthropometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1.2</td>
<td>Obesity</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

1The exposure code is the exposure identification in the database.
2Number of publications with a cohort design unless otherwise stated.
3Exposures with new publications identified during the CUP were reviewed in the current report.
2 Foods
2.2.1 Vegetables

Cohort studies
No new studies were identified during the CUP.

Published meta-analysis
Two published meta-analyses of case-control studies were identified (Jin, 2014; Gallicchio, 2006).

Jin, 2014 reported a significant 40% decrease in risk of nasopharyngeal cancer with total or fresh vegetable consumption (summary relative risk [RR] for the highest vs the lowest consumption = 0.60, 95% confidence interval [CI] = 0.47-0.76) (11 studies) (Jin, 2014). The high heterogeneity between studies ($I^2 = 50\%$, $P = 0.03$) could partly be explained by the source of controls. The association was stronger for the hospital-based studies (summary RR = 0.47, 95% CI = 0.38-0.58, $I^2 = 39\%$, $P = 0.18$) (4 studies) than for the population-based studies (summary RR = 0.80, 95% CI = 0.65-0.99, $I^2 = 0\%$, $P = 0.84$) (7 studies).

The other meta-analysis reported a significant inverse association between non-preserved vegetables intake and nasopharyngeal cancer risk (summary RR for the highest vs the lowest consumption = 0.64, 95% CI = 0.48-0.85, $I^2 = 50\%$, $P = 0.09$) (5 studies) (Gallicchio, 2006). The meta-analysis was published by the WCRF Second Expert Report SLR centre (John Hopkins University), based on the studies identified in the 2005 WCRF SLR.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of studies</th>
<th>Total number of cases</th>
<th>Studies country, area</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95%CI)</th>
<th>Heterogeneity (I², p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jin, 2014</td>
<td>11 case-control</td>
<td>3,749 cases</td>
<td>Africa, China, Italy, United States</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Highest vs lowest total or fresh vegetable intake</td>
<td>0.60 (0.47-0.76)</td>
<td>50%, 0.03</td>
</tr>
<tr>
<td></td>
<td>4 case-control</td>
<td></td>
<td></td>
<td></td>
<td>Hospital-based studies</td>
<td>0.47 (0.38-0.58)</td>
<td>39%, 0.18</td>
</tr>
<tr>
<td></td>
<td>7 case-control</td>
<td></td>
<td></td>
<td></td>
<td>Population-based studies</td>
<td>0.80 (0.65-0.99)</td>
<td>0%, 0.84</td>
</tr>
<tr>
<td>Gallicchio, 2006*</td>
<td>5 case-control</td>
<td>1,623 cases</td>
<td>Algeria, China, Malaysia, Singapore, Taiwan, Tunisia, United States</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Highest vs lowest intake, Non-preserved vegetables</td>
<td>0.64 (0.48-0.85)</td>
<td>50%, 0.09</td>
</tr>
</tbody>
</table>

*The meta-analysis was conducted by the WCRF Second Expert Report SLR centre (John Hopkins University)
2.2.1.5 Preserved vegetables
The section on preserved vegetables was prepared, at the request of the Expert Panel.

Cohort studies
No new cohort studies were identified during the CUP.

Case-control studies
Summary
Main results:
Fifteen publications from 14 case-control studies were identified. This included 12 publications (12 studies) from the 2005 SLR and three publications (2 studies) from the CUP. Five studies could be included in the dose-response meta-analysis.

Preserved vegetables intake during adulthood was statistically significantly positively associated with nasopharyngeal cancer risk (summary RR per 1 time/week = 1.42, 95% CI = 1.04-1.93). There was evidence of high heterogeneity between studies ($I^2 = 76\%$, $P<0.01$). Subgroup analysis was not conducted due to low number of studies.

There was no significant evidence of publication bias or small study bias ($P$ for Egger’s test = 0.18), but the test was low in statistical power. The funnel plot shows asymmetry, with two outlying studies reporting a strong positive association (Jia, 2010; Lee, 1994).

Nine studies did not have sufficient data to be included in the dose-response meta-analysis. Four studies reported a significant association (Zou, 1999; Armstrong, 1998; Huang, 1997; Zheng, 1993), one significant regression slope (Duan, 2000), and four no significant associations (Laouamri, 2001; Chen, 1997; Zheng, 1994; Ning, 1990).

Sensitivity analyses:
The summary RR became non-significant when Fachiroh, 2012 (summary RR = 1.46, 95% CI = 0.98-2.19), Jia, 2010 (1.31, 0.95-1.80), and Lee, 1994 (1.28, 0.97-1.68) were omitted in turn in influence analysis.

A significant 72% increased risk was observed for the comparison of the highest versus the lowest intake (summary RR = 1.72, 95% CI = 1.33-2.23) ($I^2 = 61\%$, $P = 0.01$) (9 studies).

Study quality:
Most studies were from China or among Chinese populations. Recruitment was mostly based in hospitals and the cases were ascertained histologically. Preserved vegetables were defined differently between the studies. Intake was mostly assessed in studies using a FFQ, with participants being interviewed in some studies. Most studies adjusted for age and sex. One study adjusted for salted fish intake reported a significant positive association (Jia, 2010). One study restricted the analysis to EBV positive cases and controls, and found a non-
significant positive association; the association was null when the whole study population was included (Hsu, 2012).

**Published meta-analysis**

One published meta-analysis of case-control studies was identified (Gallicchio, 2006). The meta-analysis was published by the WCRF Second Expert Report SLR centre (John Hopkins University), based on the studies identified in the 2005 WCRF SLR.

Preserved vegetables intake was significantly positively associated with nasopharyngeal cancer risk (summary RR for the highest vs the lowest consumption = 2.04, 95% CI = 1.43-2.92, $I^2 = 63\%$, $P = 0.02$) (6 studies).

The statistically significant between-study heterogeneity was not explained by factors such as source of controls, country of study, number of cases, dietary assessment method, or adjustment for foods other than vegetables.

**Table 3 Preserved vegetables intake during adulthood and nasopharyngeal cancer risk. Number of studies in the CUP SLR**

<table>
<thead>
<tr>
<th>Studies identified</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (15 publications)</td>
<td></td>
</tr>
<tr>
<td>Studies included in forest plot of highest compared with lowest exposure</td>
<td>9 (9 publications)</td>
</tr>
<tr>
<td>Studies included in linear dose-response meta-analysis</td>
<td>5 (5 publications)</td>
</tr>
<tr>
<td>Studies included in non-linear dose-response meta-analysis</td>
<td>Not enough studies</td>
</tr>
</tbody>
</table>

**Table 4 Preserved vegetables intake during adulthood and nasopharyngeal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2017 CUP**

<table>
<thead>
<tr>
<th>2005 SLR</th>
<th>CUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
</tr>
<tr>
<td>Cases</td>
<td>-</td>
</tr>
<tr>
<td>RR (95%CI)</td>
<td>-</td>
</tr>
<tr>
<td>Heterogeneity ($I^2$, p-value)</td>
<td>-</td>
</tr>
<tr>
<td>P value Egger test</td>
<td>-</td>
</tr>
</tbody>
</table>

...
Table 5 Preserved vegetables and nasopharyngeal cancer risk. Results of meta-analyses published after the 2005 SLR

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of studies</th>
<th>Total number of cases</th>
<th>Studies country, area</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95% CI)</th>
<th>Heterogeneity (I², p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallicchio, 2006*</td>
<td>6 case-control studies</td>
<td>1 695 cases</td>
<td>Algeria, China, Malaysia, Singapore, Taiwan, Tunisia, United States</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Highest vs lowest intake, Preserved vegetables</td>
<td>2.04 (1.43-2.92)</td>
<td>63%, 0.02</td>
</tr>
</tbody>
</table>

*The meta-analysis was conducted by the WCRF Second Expert Report SLR centre (John Hopkins University). All six studies were included in the current review.
<table>
<thead>
<tr>
<th>Author, Year, WCRF Code, Country</th>
<th>Study name, characteristics</th>
<th>Cases/controls</th>
<th>Case ascertainment</th>
<th>Exposure assessment</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95% CI) P trend</th>
<th>Adjustment factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fachiroh, 2012 NAS06062 Thailand</td>
<td>Hospital-based case-control study, Age: 48 years, M/W Thai</td>
<td>1 045/1 078</td>
<td>Hospital records</td>
<td>Questionnaire, interview Salted vegetables (hua-chai-poe)</td>
<td>Incidence, nasopharyngeal</td>
<td>≥ weekly vs never to rarely</td>
<td>1.34 (0.83-2.18) P trend:0.94</td>
<td>Age, sex, alcohol consumption, education years, smoking status, study center</td>
</tr>
<tr>
<td></td>
<td></td>
<td>358/97</td>
<td></td>
<td>Fermented vegetables (prak-kad-dorg)</td>
<td></td>
<td></td>
<td>1.78 (1.24-2.55) P trend:0.005</td>
<td></td>
</tr>
<tr>
<td>Hsu, 2012 NAS06053 Taiwan</td>
<td>Case-control study, (community controls) Age: 46 years, M/W</td>
<td>367/319</td>
<td>Hospital records</td>
<td>FFQ Preserved vegetables</td>
<td>Incidence, nasopharyngeal, EBV positive</td>
<td>≥0.41 vs ≤0.04 times/week</td>
<td>1.00 (0.67-1.48) P trend:1.0</td>
<td>Age, sex, educational level, ethnicity, family history of NPC, formaldehyde, total energy intake, wood dust, years of smoking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>358/97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.23 (0.68-2.23) P trend:0.49</td>
<td></td>
</tr>
<tr>
<td>Jia, 2010 NAS06052 Guangdong, China</td>
<td>Hospital-based case-control study, Age: 47 years, M/W</td>
<td>1 378/1 459</td>
<td>Hospital records</td>
<td>Interview Salted vegetables in adulthood</td>
<td>Incidence, nasopharyngeal</td>
<td>≥weekly vs &lt;monthly</td>
<td>1.79 (1.19-2.68)</td>
<td>Age, sex, dialect group, educational level, fruits intake, herbal tea, preserved vegetables, processed meat intake, residential (urban/rural), salted fish consumption, slow-cooked soup</td>
</tr>
<tr>
<td>Yuan, 2000 NAS00577 Shanghai, China</td>
<td>Population-based case-control study, Age: 15-74 years, M/W</td>
<td>935/1 032</td>
<td>Cancer registry</td>
<td>FFQ Preserved leafy vegetables, preserved stem vegetables, preserved root vegetables, all</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>≥201 vs 0-40 times/year</td>
<td>1.43 (1.11-1.86)</td>
<td>Age, gender, level of education, cigarette smoking, cooking exposures, occupational exposures, history of</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI) Ptrend</td>
<td>Adjustment factors</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------</td>
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<td>-------------------</td>
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<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Lee, 1994, NAS01056 Singapore</td>
<td>Hospital-based case-control study, Age: ≤44 years, M/W, Singapore Chinese</td>
<td>200/406</td>
<td>-</td>
<td>preserved vegetables FFQ Preserved green leafy vegetable, preserved cabbage, preserved Chinese radish, canned, salted, or pickled vegetables, salted Chinese tuber, salted mustard greens, preserved turnip root</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>1-3 times/week vs none</td>
<td>4.9 (1.8-12.9)</td>
<td>chronic ear and nose condition</td>
</tr>
<tr>
<td>Laouamri, 2001, NAS00424 Algeria</td>
<td>Population-based case-control study, Age: 9-70 years, M/W</td>
<td>72/72</td>
<td>Cancer registry</td>
<td>Vegetables in brine as seasoning, salted dried tomatoes as seasoning</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Current vs none</td>
<td>1.25 (0.64-2.41)</td>
<td>Age, sex, area of residence</td>
</tr>
<tr>
<td>Duan, 2000, NAS06002 Wuhan, China</td>
<td>Hospital-based case-control study, M/W</td>
<td>100/100</td>
<td>Hospital records</td>
<td>Questionnaire Pickled vegetables</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>-</td>
<td>Significant correlation r²=0.015</td>
<td>Environmental factors, gas range, pungent foods, socioeconomic status</td>
</tr>
</tbody>
</table>

Table 7 Preserved vegetables intake during adulthood and nasopharyngeal cancer risk. Main characteristics of studies excluded in the linear dose-response meta-analysis
<table>
<thead>
<tr>
<th>Author, Year, WCRF Code, Country</th>
<th>Study name, characteristics</th>
<th>Cases/ Controls</th>
<th>Case ascertainment</th>
<th>Exposure assessment</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95% CI) Ptrend</th>
<th>Adjustment factors</th>
<th>Inclusion/exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward, 2000 NAS00531 Taiwan</td>
<td>Population-based case control study, Age: &lt;75 years, M/W</td>
<td>371/321</td>
<td>Hospital records</td>
<td>FFQ Preserved vegetables</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Ever vs never</td>
<td>Not significant</td>
<td>Age, sex, ethnicity, subjects w/ mothers questionnaire, total calories</td>
<td>Superseded by Hsu, 2012, NAS06053</td>
</tr>
<tr>
<td>Zou, 1999 NAS06023 Yangjiang area, Guangdong province, China</td>
<td>Population-based case-control study, Age: 14-82 years, M/W</td>
<td>102/202</td>
<td>Death certificate</td>
<td>FFQ Salted other non-starchy vegetables, salted vegetables</td>
<td>Mortality, nasopharyngeal cancer</td>
<td>≥1/3.3 days vs others</td>
<td>2.28 (1.40-3.73)</td>
<td>Matched by sex and age</td>
<td>Excluded, two exposure categories only</td>
</tr>
<tr>
<td>Armstrong, 1998 NAS00749 Malaysia</td>
<td>Hospital-based case-control study, Age: 45 years, M/W, Malaysian Chinese</td>
<td>282/282</td>
<td>Histology reports</td>
<td>FFQ Salted leafy vegetables, salted root, 5 years pre-diagnosis</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>≥weekly vs &lt;monthly</td>
<td>3.33 (1.84-6.01) Ptrend:0.001</td>
<td>Age, gender, residence history</td>
<td>Excluded, missing cases and controls per category</td>
</tr>
<tr>
<td>Chen, 1997 NAS00825 Guangzhou, China</td>
<td>Hospital-based case-control study, Age: 25-54 years, M/W</td>
<td>104/104</td>
<td>-</td>
<td>FFQ Salted vegetables, 3 years ago</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>-</td>
<td>Not significant</td>
<td>Age, sex, area of residence</td>
<td>Excluded, no measure of association</td>
</tr>
<tr>
<td>Huang, 1997 NAS06024 Guangzhou province and Heilongjiang province, China</td>
<td>Population-based case-control study, M/W</td>
<td>104/104</td>
<td>Hospital records</td>
<td>FFQ Preserved green leafy vegetables</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Yes vs no</td>
<td>1.81 (1.01-3.33)</td>
<td>Age, sex, family history of cancer, number of separate kitchens, other nutrients, foods or supplements</td>
<td>Excluded, two exposure categories only</td>
</tr>
<tr>
<td>Zheng, 1994b NAS01113</td>
<td>Case-control study (from</td>
<td>88/</td>
<td>Histology</td>
<td>FFQ Salted, dried, or</td>
<td>Incidence, nasopharyngeal</td>
<td>-</td>
<td>Not significant</td>
<td>-</td>
<td>Excluded, no measure of</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/ Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI) Ptrend</td>
<td>Adjustment factors</td>
<td>Inclusion/exclusion</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>---------------------</td>
<td>---------</td>
<td>------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Wuzhou city, Zangwu county, Guangxi province, China</td>
<td>neighbourhood controls) Age: 42 years, M/W</td>
<td>176</td>
<td>reports</td>
<td>tinned vegetables in brine</td>
<td>cancer</td>
<td>-</td>
<td>&gt;0.1 Significant</td>
<td>-</td>
<td>association</td>
</tr>
<tr>
<td>Zheng, 1993 NAS01190 Guangzhou, China</td>
<td>Hospital-based case-control study, M/W</td>
<td>205/205</td>
<td>Hospital records</td>
<td>FFQ Salted vegetables</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>-</td>
<td>Not significant</td>
<td>Age, sex, area of residence</td>
<td>Excluded, limited information</td>
</tr>
<tr>
<td>Ning, 1990 NAS01922 Tianjin city, Northern China</td>
<td>Case-control study, (from the patients neighbourhood) Age: 45 years, M/W</td>
<td>100/292</td>
<td>Cancer registry</td>
<td>FFQ 3 years prior to diagnosis, Salted vegetables</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>-</td>
<td>Not significant</td>
<td>Age, sex, area of residence</td>
<td>Excluded, no measure of association</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pickled vegetables</td>
<td>-</td>
<td>Not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dried vegetables</td>
<td>-</td>
<td>Not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 3 RR estimates of nasopharyngeal cancer by preserved vegetables intake during adulthood

![Figure 3](image_url)

Figure 4 RR (95% CI) of nasopharyngeal cancer for the highest compared with the lowest level of preserved vegetables intake during adulthood*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>RR (95% CI)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fachiroh</td>
<td>2012</td>
<td>Thailand</td>
<td>1.34 (0.83, 2.18)</td>
<td>weekly vs never/rarely</td>
</tr>
<tr>
<td>Hsu</td>
<td>2012</td>
<td>Taiwan</td>
<td>1.00 (0.67, 1.49)</td>
<td>0.01 vs 0.04 times/week</td>
</tr>
<tr>
<td>Jia</td>
<td>2010</td>
<td>Guangdong, China</td>
<td>1.79 (1.19, 2.68)</td>
<td>weekly vs &lt;monthly</td>
</tr>
<tr>
<td>Laouamri</td>
<td>2001</td>
<td>Algeria</td>
<td>1.25 (0.64, 2.41)</td>
<td>Current vs none</td>
</tr>
<tr>
<td>Yuan</td>
<td>2000</td>
<td>Shanghai, China</td>
<td>1.43 (1.11, 1.86)</td>
<td>0-40 times/year</td>
</tr>
<tr>
<td>Zou</td>
<td>1999</td>
<td>Guangdong, China</td>
<td>2.28 (1.40, 3.73)</td>
<td>1 per 3.3 days vs others</td>
</tr>
<tr>
<td>Armstrong</td>
<td>1998</td>
<td>Malaysia</td>
<td>3.33 (1.84, 6.01)</td>
<td>weekly vs &lt;monthly</td>
</tr>
<tr>
<td>Huang</td>
<td>1997</td>
<td>Guangzhou, Heilongjiang, China</td>
<td>1.81 (1.01, 3.33)</td>
<td>Yes vs no</td>
</tr>
<tr>
<td>Lee</td>
<td>1994</td>
<td>Singapore</td>
<td>4.90 (1.80, 12.90)</td>
<td>3 times/week vs none</td>
</tr>
</tbody>
</table>

*When pooled, the summary RR was 1.72 (95% CI = 1.33-2.23) (I² = 61%, P=0.01)
Figure 5 Relative risk of nasopharyngeal cancer for 1 time per week increase of preserved vegetables intake during adulthood

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fachiroh</td>
<td>2012</td>
<td>Thailand</td>
<td>1.27 (0.84, 1.92)</td>
<td>19.52</td>
</tr>
<tr>
<td>Hsu</td>
<td>2012</td>
<td>Taiwan</td>
<td>0.99 (0.49, 1.98)</td>
<td>11.97</td>
</tr>
<tr>
<td>Jia</td>
<td>2010</td>
<td>Guangdong, China</td>
<td>1.85 (1.30, 2.65)</td>
<td>21.36</td>
</tr>
<tr>
<td>Yuan</td>
<td>2000</td>
<td>Shanghai, China</td>
<td>1.10 (1.04, 1.16)</td>
<td>29.45</td>
</tr>
<tr>
<td>Lee</td>
<td>1994</td>
<td>Singapore</td>
<td>2.23 (1.39, 3.58)</td>
<td>17.70</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.42 (1.04, 1.93)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Figure 6 Funnel plot of studies included in the dose response meta-analysis of preserved vegetables intake during adulthood and nasopharyngeal cancer risk

Funnel plot with pseudo 95% confidence limits

p Egger's test = 0.18
2.2.2 Fruits

Cohort studies
No new studies were identified during the CUP.

Published meta-analysis
One published meta-analysis of case-control studies and a cohort study of nasopharyngeal cancer patients was identified (Jin, 2014).

Within the case-control studies, Jin, 2014 reported a significant decreased risk of nasopharyngeal cancer with total or fresh fruit consumption (summary RR for the highest vs the lowest consumption = 0.61, 95% CI = 0.54-0.69) (9 studies) (Jin, 2014). There was no evidence of significant heterogeneity between studies ($I^2 = 0\%$, $P = 0.84$), and the summary RRs for the hospital-based studies (summary RR = 0.63, 95% CI = 0.54-0.74, $I^2 = 0\%$, $P = 0.96$) (5 studies) and the population-based studies (summary RR = 0.58, 95% CI = 0.47-0.71, $I^2 = 3\%$, $P=0.38$) (4 studies) were similar.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of studies</th>
<th>Total number of cases</th>
<th>Studies country, area</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95%CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jin, 2014</td>
<td>9 case-control studies</td>
<td>4622 cases</td>
<td>China, Italy, Turkey, United States</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Highest vs lowest total or fresh fruit intake</td>
<td>0.61 (0.54-0.69)</td>
<td>0%, 0.84</td>
</tr>
<tr>
<td></td>
<td>5 case-control studies</td>
<td></td>
<td></td>
<td>Hospital-based studies</td>
<td>0.63 (0.54-0.74)</td>
<td>0%, 0.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 case-control studies</td>
<td></td>
<td></td>
<td>Population-based studies</td>
<td>0.58 (0.47-0.71)</td>
<td>3%, 0.38</td>
<td></td>
</tr>
</tbody>
</table>
2.5.1.2 Processed meat

Cohort studies
No new studies were identified during the CUP.

Published meta-analysis
One published meta-analysis of case-control studies was identified (Li, 2016).

In Li, 2016, nasopharyngeal cancer risk increased with increasing processed meat consumption. The summary RRs were 1.46 (95% CI = 1.31-1.64), 1.59 (95% CI = 1.33-1.90), and 2.11 (95% CI = 1.31-3.42) for <30, 30-60, and >60 g/week compared with never consumption, respectively (P trend <0.001). There was evidence of significant and unexplained between-study heterogeneity (all P heterogeneity <0.01). The authors of the review recalculated the RR estimates to corresponding exposure comparisons used in the meta-analyses. Overall, 13 publications were identified. The meta-analysis of <30 vs 0 g/week intake included 10 studies and 11 relative risk estimates. Exclusion reasons were not given. The definition of processed meat was not clear in the studies. The review included studies that examined salted fish only or combined meat and processed meat.

2.5.1.3 Red meat

Cohort studies
No new studies were identified during the CUP.

Published meta-analysis
One published meta-analysis of case-control studies was identified (Li, 2016).

Similar to processed meat consumption, Li, 2016 observed a positive trend in nasopharyngeal cancer risk with increasing red meat intake (Li, 2016). The summary RRs were 1.35 (95% CI = 1.21-1.51), 1.54 (95% CI = 1.35-1.76), and 1.71 (95% CI = 1.14-2.55) for <100, 100-300, >300 g/week compared with never consumption, respectively (P trend = 0.003). There was evidence of significant between-study heterogeneity (P heterogeneity = 0.98, 0.05, 0.01, respectively). Seven publications were identified and six were included in the meta-analysis of <100 vs 0 g/week intake. The excluded study reported an inverse association (RR for 65-100 vs <65 g/day = 0.89, 95% CI = 0.54-1.46). It was not clear how red meat was defined in the studies. The review included studies that examined fried meat only, and meat and combined oro-, hypo-, and nasopharyngeal cancers.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of studies</th>
<th>Total number of cases</th>
<th>Studies country, area</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95%CI)</th>
<th>Heterogeneity (I², p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li, 2016</td>
<td>13 case-control studies</td>
<td>5 434</td>
<td>Africa, China, Hong Kong, India, Italy, Malaysia, Tunisia</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Processed meat: &lt;30 g/week vs never</td>
<td>1.46 (1.31-1.64)</td>
<td>76%, &lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-60 g/week vs never</td>
<td>1.59 (1.33-1.90)</td>
<td>82%, &lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;60 g/week vs never</td>
<td>2.11 (1.31-3.42)</td>
<td>85%, &lt;0.01</td>
</tr>
<tr>
<td></td>
<td>7 case-control studies</td>
<td>1 858</td>
<td>Africa, China, Italy, Tunisia, Turkey, Spain</td>
<td></td>
<td>Red meat: &lt;100 g/week vs never</td>
<td>1.35 (1.21-1.51)</td>
<td>0%, 0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100-300 g/week vs never</td>
<td>1.54 (1.35-1.76)</td>
<td>57%, 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;300 g/week vs never</td>
<td>1.71 (1.14-2.55)</td>
<td>77%, 0.01</td>
</tr>
</tbody>
</table>
2.5.2.1 Salted Fish, adulthood consumption

**Cohort studies**

No new cohort studies were identified during the CUP. One was identified in the 2005 SLR (Zou, 1994, NAS06011). Meta-analyses of case-control studies on salted fish consumption were conducted in the CUP review as it was judged in the Second Expert Report that there was probable evidence that Cantonese-style salted fish is causally associated with nasopharyngeal cancer risk, and this judgement was based in the results of case-control studies.

The only cohort study identified (Zou, 1994) was a study from Sihui County, Guangdong Province, China, where populations are at high risk of developing nasopharyngeal cancer (17 incident cases from 505 men and women, age 35-64 years, followed for 9 years). Information on adult salted fish intake was assessed by dietary history questionnaire. Compared with less frequent consumption, the associations with nasopharyngeal cancer risk were significant for consumption ≥ 1/week in the 1960s and 1970s (P <0.001 and P = 0.014, respectively) and not significant for consumption ≥ 1/week in the 1980s (P = 0.21) (detailed results not shown in the publication, not tabulated).

**Case-control studies**

**Summary**

**Main results:**

Thirty-three publications from 27 case-control studies were identified, including 21 publications (19 studies) from the 2005 SLR and 12 publications (8 studies) from the CUP. Nine studies could be included in the dose-response meta-analysis.

Salted fish intake during adulthood was statistically significantly positively associated with nasopharyngeal cancer risk (summary RR per 1 time/week = 1.35, 95% CI = 1.15-1.59). There was evidence of high heterogeneity between studies ($I^2 = 76\%$, $P<0.001$).

The summary RR remained significant when restricted to Chinese studies (summary RR per 1 time/week Chinese-style salted fish intake = 1.52, 95% CI = 1.21-1.91) ($I^2 = 81\%$, P<0.001, 6 studies), but was not significant in other countries (summary RR per 1 time/week salted fish intake = 1.14, 95% CI = 0.90-1.43) ($I^2 = 56\%$, P = 0.10, 3 studies).

Proportion of between-study heterogeneity remained high (>50%) in the stratified analyses by geographic location, type of controls, publication year, number of cases, levels of intake, and adjustment for main confounding factors (age, sex, smoking, socioeconomic status) (summary RR ranged from 1.14 to 1.52). Stratified analysis showed a non-significant positive association in the adjusted studies (summary RR = 1.17, 95% CI = 0.85-1.61) ($I^2 = 62\%$, P = 0.07, 3 studies) and a significant positive association in the unadjusted studies (summary RR = 1.45, 95% CI = 1.18-1.78) ($I^2 = 81\%$, P <0.001, 6 studies).
There was no significant evidence of publication bias or small study bias (P for Egger’s test = 0.11). Visual inspection of the funnel plot shows asymmetry, which could be driven by smaller studies with a stronger than the average positive association.

Eighteen studies were excluded from the meta-analysis. One excluded study (Xu, 2012) consisted of study populations that overlapped with another study included in the meta-analysis (Jia, 2010). One study from the Maghrebian countries (Tunisia, Algeria, and Morocco) examined industrial preserved fish/unsalted canned fish (Feng, 2007). Since the processed fish in Feng, 2007 was different to the salted fish investigated in most other studies, Feng, 2007 was excluded (RR for ≥10 vs ≤9 times/year = 0.40, 95% CI = 0.20-0.70, Ptrend = 0.0045).

Sixteen studies did not have sufficient data to be included in the dose-response meta-analysis. Seven excluded studies reported significant positive associations (Lye, 2015; Ghosh, 2014; Zou, 1999; Armstrong, 1998; Chen, 1994; Wang, 1993; Ning, 1990). These included one Malaysian study with high percentage of ethnic Chinese (Lye, 2015), one Malaysian Chinese study (Armstrong, 1998), one Indian study on salted fish intake that is common to the North-eastern areas (Ghosh, 2014), and four Chinese studies from Guangdong (Zou, 1999), Guangxi (Chen, 1994), Tianjin (Ning, 1990), and Heilongjiang (Wang, 1993). Four excluded studies reported non-significant positive associations, including one study from India (Lakhanpal, 2015), one study from the Philippines (West, 1993), and two studies from China (Cai, 1996; Ye, 1995b). Three excluded studies, one of Malaysian Chinese (Armstrong, 1983), one of Chinese subjects in the US (Henderson, 1976), and one of Taiwanese (Yang, 2005) reported no significant associations.

One additional Taiwanese study (Hsu, 2012) reported a non-significant inverse association overall and a non-significant positive association among Epstein-Barr virus (EBV)-positive patients. One Chinese study from Guangxi reported low consumption in both cases and controls with no measure of association (Zheng, 1994b).

Sensitivity analyses:

The summary RR remained significant when each study was omitted in turn in influence analysis.

Study quality:

Most studies were from China or among Chinese populations. Recruitment was mostly based in hospitals and the cases were ascertained histologically. Salted fish intake was mostly assessed in studies using a general questionnaire, with participants being interviewed in some studies. Participants reported their current salted fish intake or recalled the past adulthood intake. No individual study had shown strong influence in the sensitivity analysis. Stratified analysis showed that studies not adjusted for main confounding factors found slightly stronger positive association on average compared with studies adjusted for the factors. EBV status was not included as an adjustment in the studies.
Table 10 Salted fish intake during adulthood and nasopharyngeal cancer risk. Number of studies in the CUP SLR

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies identified</td>
<td>27 (33 publications)</td>
</tr>
<tr>
<td>Studies included in forest plot of highest compared with lowest exposure</td>
<td>21 (21 publications)</td>
</tr>
<tr>
<td>Studies included in linear dose-response meta-analysis</td>
<td>9 (9 publications)</td>
</tr>
<tr>
<td>Studies included in non-linear dose-response meta-analysis</td>
<td>Not enough studies</td>
</tr>
</tbody>
</table>

Table 11 Salted fish intake during adulthood and nasopharyngeal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2017 CUP

<table>
<thead>
<tr>
<th></th>
<th>2005 SLR</th>
<th>CUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increment unit used</td>
<td>Per 1 time/week</td>
<td>Per 1 time/week</td>
</tr>
</tbody>
</table>
| Studies (n)          | 9        | 9            |}
| Cases                | 2 363    | 5 044        |
| RR (95% CI)          | 1.28 (1.13-1.44) | 1.35 (1.15-1.59) |
| Heterogeneity (I², p-value) | 75%     | 76%, <0.001 |
| P value Egger test   | -        | 0.11         |

Stratified analysis in the CUP

<table>
<thead>
<tr>
<th>Geographic locations</th>
<th>China</th>
<th>Other countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Cases</td>
<td>4 043</td>
<td>1 001</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.52 (1.21-1.91)</td>
<td>1.14 (0.90-1.43)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>81%, &lt;0.001</td>
<td>56%, 0.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of controls</th>
<th>Hospital controls</th>
<th>Other controls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cases</td>
<td>2 376</td>
<td>2 668</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.26 (0.97-1.64)</td>
<td>1.47 (1.14-1.89)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>77%, 0.004</td>
<td>79%, 0.001</td>
</tr>
</tbody>
</table>

Publication year

<table>
<thead>
<tr>
<th></th>
<th>&lt;2000</th>
<th>≥2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Cases</td>
<td>1 081</td>
<td>3 963</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.33 (1.10-1.60)</td>
<td>1.43 (0.95-2.15)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>76%, 0.002</td>
<td>80%, 0.002</td>
</tr>
<tr>
<td>Number of cases</td>
<td>&lt;450 cases</td>
<td>≥450 cases</td>
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</tr>
<tr>
<td>Studies (n)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Cases</td>
<td>1 081</td>
<td>3 963</td>
</tr>
<tr>
<td>RR (95%CI)</td>
<td>1.33 (1.10-1.60)</td>
<td>1.43 (0.95-2.15)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>76%, 0.002</td>
<td>80%, 0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference between the highest and the lowest mean of intake category</th>
<th>≤3 times/week</th>
<th>&gt;3 times/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cases</td>
<td>3 963</td>
<td>1 081</td>
</tr>
<tr>
<td>RR (95%CI)</td>
<td>1.43 (0.95-2.15)</td>
<td>1.33 (1.10-1.60)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>80%, 0.002</td>
<td>76%, 0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Main adjustment**</th>
<th>Adjusted</th>
<th>Not adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Cases</td>
<td>1 736</td>
<td>3 308</td>
</tr>
<tr>
<td>RR (95%CI)</td>
<td>1.17 (0.85-1.61)</td>
<td>1.45 (1.18-1.78)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>62%, 0.07</td>
<td>81%, &lt;0.001</td>
</tr>
</tbody>
</table>

*Other controls included neighbours, families, and those from a screening programme and the general population.

**Adjusted simultaneously for age, sex, smoking, and socioeconomic status.
Table 12 Salted fish intake during adulthood and nasopharyngeal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

<table>
<thead>
<tr>
<th>Author, Year, WCRF Code, Country</th>
<th>Study name, characteristics</th>
<th>Cases/Controls</th>
<th>Case ascertainment</th>
<th>Exposure assessment</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95% CI)</th>
<th>Ptrend</th>
<th>Adjustment factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fachiroh, 2012 NAS06062 Thailand</td>
<td>Hospital-based case-control study, Age: 48 years, M/W Thai</td>
<td>681/1 078</td>
<td>Hospital records</td>
<td>Questionnaire, interview Salted fish (pla-kem) (Included in dose-response analysis)</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>≥ weekly vs never to rarely</td>
<td>0.92 (0.68-1.25) Ptrend:0.48</td>
<td></td>
<td>Age, sex, alcohol consumption, education years, smoking status, study center</td>
</tr>
<tr>
<td>Jia, 2010 NAS06052 Guangdong, China</td>
<td>Hospital-based case-control study, Age: 47 years, M/W Chinese</td>
<td>1 375/1 450</td>
<td>Hospital records</td>
<td>Interview Adult canton-style salted fish intake</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>≥weekly vs &lt;monthly</td>
<td>1.58 (1.20-2.09) Ptrend:&lt;0.001</td>
<td></td>
<td>Age, sex, dialect group, educational level, residential (urban/rural)</td>
</tr>
<tr>
<td>Guo, 2009 NAS06051 Guangxi, China</td>
<td>Case-control study, (controls from health screening program) Age: 46 years, M/W Chinese</td>
<td>972/785</td>
<td>Hospital records</td>
<td>Questionnaire, interview Salted fish</td>
<td>Incidence / prevalence, nasopharyngeal cancer</td>
<td>≥3 vs ≤0 times/month</td>
<td>1.90 (1.05-3.47)</td>
<td></td>
<td>Family history of nasopharyngeal cancer, occupational exposure, processed meat, smoking, wood stove use</td>
</tr>
<tr>
<td>Yuan, 2000 NAS00577</td>
<td>Population-based case-control study,</td>
<td>935/1032</td>
<td>Cancer registry</td>
<td>FFQ</td>
<td>Incidence, nasopharyngeal</td>
<td>≥weekly vs less than monthly</td>
<td>1.82 (0.86-3.88)</td>
<td></td>
<td>Age, sex, educational level, environmental factors, non-</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/ Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI) Ptrend</td>
<td>Adjustment factors</td>
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<tr>
<td>Shanghai, China</td>
<td>Age: 15-74 years, M/W Chinese Hospital-based case-control study, Age: ≤44 years, M/W Singapore Chinese</td>
<td>200/406</td>
<td>Hospital records</td>
<td>Chinese salted fish</td>
<td>cancer</td>
<td>≥3 vs ≤0</td>
<td>4.40 (0.70-25.90)</td>
<td>nutrient chemicals, presence of other diseases, smoking habits</td>
<td></td>
</tr>
<tr>
<td>Lee, 1994 NAS01056 Singapore</td>
<td></td>
<td></td>
<td></td>
<td>FFQ Salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td></td>
<td></td>
<td>Age, sex, educational level, ethnicity</td>
<td></td>
</tr>
<tr>
<td>Zheng, 1994a NAS01141 Guangzhou, China</td>
<td>Case-control study, (controls from friends of the cases or an individual living in the area) Age: ≤55 years, M/W Chinese</td>
<td>205/205</td>
<td>Hospital records</td>
<td>Salted fish soft meat (Included in dose-response analysis)</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Weekly and daily vs never and yearly</td>
<td>17.20 (4.10-152.10)</td>
<td>Age, sex, area of residence</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Salted fish tough meat</td>
<td></td>
<td></td>
<td>11.20 (4.60-32.0)</td>
<td></td>
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<tr>
<td>Sriamporn, 1992 NAS01248 Thailand</td>
<td>Hospital-based case-control study Age: 47 years, M/W Thai</td>
<td>120/120</td>
<td>Histology reports</td>
<td>FFQ Salted fish 3 years prior to diagnosis</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Sea-salted fish, at least once a week vs only freshwater fish Weekly/daily vs never</td>
<td>2.50 (1.20-5.20)</td>
<td>Age, sex, alcohol consumption, area of residence, environmental factors, smoking habits, occupation</td>
<td></td>
</tr>
<tr>
<td>Yu, 1989 NAS01459 Guangzhou, China</td>
<td>Case-control study, (population controls from the patients neighbourhood)</td>
<td>306/306</td>
<td>Hospital records</td>
<td>FFQ Salted fish 3 years prior to diagnosis</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>daily vs rarely</td>
<td>1.80 (0.90-3.60)</td>
<td>Age, sex, area of residence</td>
<td></td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI)</td>
<td>Ptrend</td>
<td>Adjustment factors</td>
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<tr>
<td>Yu, 1986 NAS01608 Hong Kong</td>
<td>Age: ≤49 years, M/W Chinese Case-control study, (controls from friends of the case) Age: 29 years, M/W Chinese</td>
<td>250/250</td>
<td>Hospital records</td>
<td>FFQ Cantonese-style salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>daily vs rarely</td>
<td>7.50 (0.90-65.30)</td>
<td></td>
<td>Age, sex</td>
</tr>
<tr>
<td>Lakhanpal, 2016 NAS06060 Imphal, Manipur, India</td>
<td>Hospital-based case-control study. Age: 46.5 years, M/W Indian</td>
<td>120/100</td>
<td>Hospital records</td>
<td>Questionnaire, interview Dry salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>consumers vs non-consumers</td>
<td>1.29 (0.62-2.71)</td>
<td></td>
<td>Age, sex, alcohol consumption, mode of cooking, genotypes (TNF-α, TNF-β, HSP 70-1, HSP 70-hom), type of household, smoked foods, smoking status, tobacco chewing, Superseded by Lakhanpal, 2015, NAS06059</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/ Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI) Ptrend</td>
<td>Adjustment factors</td>
<td>Inclusion/exclusion</td>
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<tr>
<td>Lakhanpal, 2015 NAS06059 Imphal, Manipur, India</td>
<td>Hospital-based case-control study, Age: 12-80 years, M/W Indian</td>
<td>120/100</td>
<td>Hospital records</td>
<td>Questionnaire, interview Dry salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>consumers vs non-consumers</td>
<td>1.32 (0.61-2.85)</td>
<td>ventilation Age, sex, alcohol consumption, location of household, mode of cooking, food habits, smoke exit facility, type of household, smoked foods, smoking status, tobacco chewing, ventilation</td>
<td>Excluded, result was for yes vs no comparison</td>
</tr>
<tr>
<td>Lye, 2015 NAS06058 Malaysia</td>
<td>Hospital-based case-control study, Age: 53 years, M/W 70.2% ethnic Chinese, 28.4% Malays</td>
<td>356/356</td>
<td>Hospital records</td>
<td>- Salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Ever vs never</td>
<td>1.76 (1.23-2.51)</td>
<td>Age, sex, alcohol consumption, ethnicity, genotype (XPD K751Q), cigarette smoking</td>
<td>Excluded, result was for ever vs never comparison</td>
</tr>
<tr>
<td>Ghosh, 2014 NAS06061 Manipuri, Naga and Mizo, India</td>
<td>Hospital-based case-control study, M/W India</td>
<td>64/100</td>
<td>Hospital records</td>
<td>Medical record and interviewed Salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>yes vs no</td>
<td>2.61 (1.17-5.81)</td>
<td>Unknown adjustment, matched for ethnicity</td>
<td>Excluded, result was for yes vs no comparison</td>
</tr>
<tr>
<td>Hsu, 2012 NAS06053 Taiwan</td>
<td>Case-control study, (community</td>
<td>371/327</td>
<td>Hospital records</td>
<td>66-item FFQ, for diet 3-10 years before</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>yes vs no</td>
<td>0.88 (0.35-2.21)</td>
<td>Age, sex, educational level, ethnicity,</td>
<td>Excluded, result was for yes vs no comparison</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/ Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI)</td>
<td>Ptrend</td>
<td>Adjustment factors</td>
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<tr>
<td>Xu, 2012 Guangdong, China</td>
<td>Guangdong case-control study, hospital-based case-control study Age: 14-80 years, M/W Chinese</td>
<td>1 311/ 1 571</td>
<td>Questionnaire, interview, Salted fish</td>
<td>Cantonese-style salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>yes vs no</td>
<td>4.80 (0.55-42.30)</td>
<td></td>
<td>family history of nasopharyngeal cancer, formaldehyde, total energy intake, wood dust, years of smoking</td>
</tr>
<tr>
<td>Ekburanawat, 2010 Thailand</td>
<td>Hospital-based case-control study, Age: 48 years, M/W Thai</td>
<td>327/ 327</td>
<td>Hospital records</td>
<td>Questionnaire, interview, Salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>weekly or more vs &lt; monthly</td>
<td>1.74 (1.29-2.35)</td>
<td>Ptrend:&lt;0.001</td>
<td>Age, educational level</td>
</tr>
<tr>
<td>Ren, 2010 Guangdong, China</td>
<td>Hospital-based case-control study, Age: 13-80 years, M/W Chinese</td>
<td>1 834/ 2 251</td>
<td>Hospital records</td>
<td>Questionnaire, interview, Salt-preserved fish consumption</td>
<td>Incident, nasopharyngeal cancer</td>
<td>≥1 vs ≤0.9 times/week</td>
<td>1.38 (0.84-2.25)</td>
<td></td>
<td>Educational years, smoking</td>
</tr>
<tr>
<td>Author, Year,</td>
<td>Study name, characteristics</td>
<td>Cases/ Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI)</td>
<td>Ptrend</td>
<td>Adjustment factors</td>
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<tr>
<td>Feng, 2007</td>
<td>Hospital-based case-control study, Age: 43 years, M/W Maghrebian populations</td>
<td>559/523</td>
<td>Hospital records</td>
<td>Questionnaire, interview Adult industrial preserved fish, unsalted canned fish</td>
<td>Incidence / prevalence, nasopharyngeal cancer</td>
<td>≥10 vs ≤9 times/year</td>
<td>0.40 (0.20-0.70)</td>
<td>Ptrend: 0.0045</td>
<td>Age, toxic substances, residential area (urban/rural) during childhood and adulthood, number of rooms or gourbi during childhood and adulthood, education level, occupation; stratified by sex and study centre</td>
</tr>
<tr>
<td>Yang, 2005</td>
<td>Case-control study, Age: 47 years, M/W Families with two or more affected members Chinese</td>
<td>502/1,942</td>
<td>Cancer registry, hospitals, outpatients clinics</td>
<td>Dietary questionnaire, interview (self-proxy respondents) Guangdong moldy salted fish intake between age 10 and 30 years</td>
<td>Incidence/mortality</td>
<td>Yes vs no</td>
<td>Similar salted fish (moldy and firm) intake after age 10 in cases and controls</td>
<td>Age, Sex, Family history of nasopharyngeal cancer</td>
<td>Excluded, no measure of association</td>
</tr>
<tr>
<td>Ward, 2000</td>
<td>National Cancer Institute Case</td>
<td>375/</td>
<td>Hospital records</td>
<td>Dietary history questionnaire</td>
<td>Incidence, nasopharyngeal</td>
<td>Per 5 g/week</td>
<td>0.80 (0.50-1.20)</td>
<td>Age, sex, ethnicity,</td>
<td>Superseded by Hsu, 2012,</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI) Ptrend</td>
<td>Adjustment factors</td>
<td>Inclusion/exclusion</td>
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<tr>
<td>Taiwan</td>
<td>Control (1987-1990), hospital-based case-control study, Age: 0-74 years, M/W Chinese</td>
<td>327</td>
<td></td>
<td>Salted fish other than Guandong salted fish</td>
<td>cancer</td>
<td></td>
<td></td>
<td>subjects w/ mothers questionnaire, total calories</td>
<td>NAS06053 that was included in the dose-response meta-analysis</td>
</tr>
<tr>
<td>Zou, 1999 NAS06023 Yangjiang area, Guangdong province, China</td>
<td>Case Control Study, Age: 14-82 years, M/W Chinese</td>
<td>97/197</td>
<td>Death certificate</td>
<td>Questionnaire Salted fish</td>
<td>Mortality, nasopharyngeal cancer</td>
<td>≥1/3.3 days vs other</td>
<td>3.07 (1.66-5.70)</td>
<td>Age, sex, educational level, environmental factors, family history of cancer, presence of other diseases</td>
<td>Excluded, two exposure categories only; outcome was mortality</td>
</tr>
<tr>
<td>Armstrong, 1998 NAS00749 Malaysia</td>
<td>Hospital-based case-control study, Age: 45 years, M/W Malaysian Chinese</td>
<td>282/282</td>
<td>Histology reports</td>
<td>Dietary history questionnaire Salted fish intake 5 years prior</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>≥weekly vs &lt;monthly</td>
<td>4.22 (2.23-7.99)</td>
<td>-</td>
<td>Excluded, missing cases and controls per category</td>
</tr>
<tr>
<td>Cai, 1996 NAS06010 Fujian province, China</td>
<td>Hospital-based case-control study, Age: 16-68 years, M/W Chinese</td>
<td>115/115</td>
<td>Hospital records</td>
<td>Dietary history questionnaire Salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>≥3 vs 0-2.99 times/week</td>
<td>1.32 (0.99-1.79)</td>
<td>Age, sex, area of residence</td>
<td>Excluded, two exposure categories only</td>
</tr>
<tr>
<td>Ye, 1995a NAS06003</td>
<td>Hospital-based case-control</td>
<td>135/</td>
<td>Hospital records</td>
<td>Dietary history questionnaire</td>
<td>Incidence, nasopharyngeal</td>
<td>&gt;1 vs ≤1 time/week</td>
<td>5.0 (1.26-19.6)</td>
<td>Matching factors: age, sex,</td>
<td>Excluded, two exposure</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/ Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI)</td>
<td>P trend</td>
<td>Adjustment factors</td>
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<tr>
<td>S. Fujian province, China</td>
<td>Age: 21-75 years, M/W Chinese</td>
<td>135</td>
<td>Hospital records</td>
<td>Salted fish</td>
<td>cancer</td>
<td>&gt;1 vs ≤1 time/week</td>
<td>2.74 (0.82-9.13)</td>
<td></td>
<td>area of residence</td>
</tr>
<tr>
<td>Ye, 1995b NAS06009 Minan prefecture, Fujian province, China</td>
<td>Age: 14-68 years, M/W Chinese</td>
<td>135/135</td>
<td>Questionnaire</td>
<td>Salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>yes vs no</td>
<td>5.51 (1.74-17.46)</td>
<td></td>
<td>Age, sex</td>
</tr>
<tr>
<td>Chen, 1994 NAS06021 Guangxi province, China</td>
<td>Age: 42 years, M/W Chinese</td>
<td>28/113</td>
<td>Questionnaire</td>
<td>Salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>yes vs no</td>
<td></td>
<td></td>
<td>Age, sex</td>
</tr>
<tr>
<td>Zheng, 1994b NAS01113 Wuzhou city, Zangwu county, Guangxi province, China</td>
<td>Age: 42 years, M/W Chinese</td>
<td>88/176</td>
<td>FFQ</td>
<td>Salted fish year before diagnosis</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>yes vs no</td>
<td>Consumption during the year preceding cancer was very low for both cases (2.3%) and controls (0.6%)</td>
<td></td>
<td>Age, sex, area of residence</td>
</tr>
<tr>
<td>Wang, 1993 NAS06022 Heilongjiang province, China</td>
<td>Age: 13-70 years, M/W Chinese</td>
<td>122/122</td>
<td>Questionnaire</td>
<td>Salted fish</td>
<td>Nasopharyngeal cancer</td>
<td>frequently consumed vs less consumed</td>
<td>8.99 P-value: 0.0127</td>
<td></td>
<td>Age, sex, environmental factors, non-nutrient chemicals, other nutrients, foods or supplements,</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI)</td>
<td>P trend</td>
<td>Adjustment factors</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------</td>
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<td>---------</td>
<td>------------</td>
<td>-------------</td>
<td>---------</td>
<td>-------------------</td>
</tr>
<tr>
<td>West, 1993 NAS01153 Philippines</td>
<td>Hospital-based case-control study Age: 11-83 years, M/W Filipino</td>
<td>104/101</td>
<td>Histology reports</td>
<td>Interview Salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>high tertile vs low tertile</td>
<td>1.30 (0.69-2.60)</td>
<td>-</td>
<td>other nutrients, foods or supplements, other nutrients, foods or supplements, socio-economic status, vegetable intake</td>
</tr>
<tr>
<td>Zheng, 1993 NAS01190 Guangzhou, China</td>
<td>Hospital-based case-control study, M/W Chinese</td>
<td>205/205</td>
<td>Hospital records</td>
<td>FFQ Highest consumption of salted fish from: last 7 years, at age 10, and in the first 3 years</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>-</td>
<td>Significant</td>
<td>-</td>
<td>Age, sex, other, other nutrients, foods or supplements, other nutrients, foods or supplements</td>
</tr>
<tr>
<td>Ning, 1990 NAS01922 Tianjin city, Northern China</td>
<td>Case Control Study, (from the patients neighbourhood) Age: 45 years, M/W Chinese</td>
<td>100/300</td>
<td>Cancer registry</td>
<td>FFQ Salted fish ever consumed Salted fish 3 years prior to diagnosis</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>ever vs never</td>
<td>2.20 (1.30-3.70)</td>
<td>-</td>
<td>Age, sex, area of residence</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/ Controls</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI) Ptrend</td>
<td>Adjustment factors</td>
<td>Inclusion/exclusion</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>---------</td>
<td>------------</td>
<td>------------------</td>
<td>------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Armstrong, 1983 NAS02182 Malaysia</td>
<td>Case-control study, (from neighbourhood of the case) M/W Malaysian Chinese</td>
<td>100/100</td>
<td>Histology reports</td>
<td>- Salted fish, current consumption as adult</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>-</td>
<td>Not significant</td>
<td>Age, sex, area of residence, ethnicity</td>
<td>Excluded, no measure of association</td>
</tr>
<tr>
<td>Henderson, 1976 NAS04928 USA</td>
<td>Population-based case-control study, Age: 52 years, M/W Chinese</td>
<td>156/267</td>
<td>Cancer registry</td>
<td>- Current use of salted fish</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>-</td>
<td>Not significant</td>
<td>Age, sex, area of residence, socio-economic status</td>
<td>Excluded, no measure of association</td>
</tr>
</tbody>
</table>
Figure 7 RR estimates of nasopharyngeal cancer by salted fish intake during adulthood

![Graph showing RR estimates of nasopharyngeal cancer by salted fish intake during adulthood.](image)
Figure 8: RR (95% CI) of nasopharyngeal cancer for the highest compared with the lowest level of salted fish intake during adulthood

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>RR (95% CI)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lakhanpal</td>
<td>2015</td>
<td>India</td>
<td>1.32 (0.61, 2.85)</td>
<td>Consumers vs non-consumers</td>
</tr>
<tr>
<td>Lye</td>
<td>2015</td>
<td>Malaysia</td>
<td>1.76 (1.23, 2.51)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Ghosh</td>
<td>2014</td>
<td>India</td>
<td>2.61 (1.17, 5.81)</td>
<td>Yes vs no</td>
</tr>
<tr>
<td>Fachiroh</td>
<td>2012</td>
<td>Thailand</td>
<td>0.92 (0.68, 1.25)</td>
<td>Weekly vs Never to rarely</td>
</tr>
<tr>
<td>Hsu</td>
<td>2012</td>
<td>Taiwan</td>
<td>0.88 (0.35, 2.21)</td>
<td>Yes vs no</td>
</tr>
<tr>
<td>Jia</td>
<td>2010</td>
<td>Guangdong, China</td>
<td>1.58 (1.20, 2.09)</td>
<td>Monthly or more vs &lt; monthly</td>
</tr>
<tr>
<td>Guo</td>
<td>2009</td>
<td>Guangxi, China</td>
<td>1.90 (1.05, 3.47)</td>
<td>3 vs 0 times/month</td>
</tr>
<tr>
<td>Yuan</td>
<td>2000</td>
<td>Shanghai, China</td>
<td>1.82 (0.86, 3.88)</td>
<td>Weekly vs &lt; monthly</td>
</tr>
<tr>
<td>Zou</td>
<td>1999</td>
<td>Guangdong, China</td>
<td>3.07 (1.86, 5.70)</td>
<td>&gt;1 time/3.3 days vs other</td>
</tr>
<tr>
<td>Armstrong</td>
<td>1998</td>
<td>Malaysia</td>
<td>4.22 (2.23, 7.99)</td>
<td>Weekly vs &lt; monthly</td>
</tr>
<tr>
<td>Cai</td>
<td>1996</td>
<td>Fujian, China</td>
<td>1.32 (1.00, 1.79)</td>
<td>3 vs 0-2.99 times/week</td>
</tr>
<tr>
<td>Ye</td>
<td>1995</td>
<td>Fujian, China</td>
<td>2.74 (0.82, 9.13)</td>
<td>&gt;1 time/week</td>
</tr>
<tr>
<td>Lee</td>
<td>1994</td>
<td>Singapore</td>
<td>4.40 (0.70, 25.90)</td>
<td>3 vs 0 times/week</td>
</tr>
<tr>
<td>Chen</td>
<td>1994</td>
<td>Guangxi, China</td>
<td>5.51 (1.74, 17.46)</td>
<td>Yes vs no</td>
</tr>
<tr>
<td>Zheng</td>
<td>1994</td>
<td>Guangzhou, China</td>
<td>17.20 (4.10, 152.10)</td>
<td>Weekly and daily vs never and yearly</td>
</tr>
<tr>
<td>West</td>
<td>1993</td>
<td>Philippines</td>
<td>1.30 (0.69, 2.60)</td>
<td>Tertile 3 vs tertile 1</td>
</tr>
<tr>
<td>Wang</td>
<td>1993</td>
<td>Heilongjiang, China</td>
<td>8.99 (1.60, 50.57)</td>
<td>Frequently consumed vs less consumed</td>
</tr>
<tr>
<td>Sriampon</td>
<td>1992</td>
<td>Thailand</td>
<td>2.50 (1.20, 5.20)</td>
<td>Sea-salted fish &gt;1 times/week vs only freshwater fish</td>
</tr>
<tr>
<td>Ning</td>
<td>1990</td>
<td>Tianjin, China</td>
<td>2.20 (1.30, 3.70)</td>
<td>Ever vs never</td>
</tr>
<tr>
<td>Yu</td>
<td>1989</td>
<td>Guangzhou, China</td>
<td>1.80 (0.90, 3.60)</td>
<td>Daily vs rarely</td>
</tr>
<tr>
<td>Yu</td>
<td>1986</td>
<td>Hong Kong</td>
<td>7.50 (0.90, 65.30)</td>
<td>Daily vs rarely</td>
</tr>
</tbody>
</table>

*When pooled, the summary RRs were 1.98 (95% CI = 1.58-2.50) (I² = 63%, P<0.001) overall; 2.08 (95% CI = 1.57-2.76) (54%, 0.01) among the Chinese studies (13 studies); and 1.86 (95% CI = 1.23-2.81) (73%, <0.001) among the studies of other regions (8 studies).
Figure 9 Relative risk of nasopharyngeal cancer for 1 time per week increase of salted fish intake during adulthood

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fachiroh</td>
<td>2012</td>
<td>Thailand</td>
<td>0.94 (0.74, 1.19)</td>
<td>13.21</td>
</tr>
<tr>
<td>Jia</td>
<td>2010</td>
<td>Guangdong, China</td>
<td>1.68 (1.35, 2.09)</td>
<td>13.72</td>
</tr>
<tr>
<td>Guo</td>
<td>2009</td>
<td>Guangxi, China</td>
<td>1.87 (1.08, 3.25)</td>
<td>5.97</td>
</tr>
<tr>
<td>Yuan</td>
<td>2000</td>
<td>Shanghai, China</td>
<td>1.73 (0.66, 4.52)</td>
<td>2.50</td>
</tr>
<tr>
<td>Lee</td>
<td>1994</td>
<td>Singapore</td>
<td>1.17 (0.85, 1.61)</td>
<td>10.72</td>
</tr>
<tr>
<td>Zheng</td>
<td>1994</td>
<td>Guangzhou, China</td>
<td>2.50 (1.63, 3.85)</td>
<td>8.06</td>
</tr>
<tr>
<td>Sriamporn</td>
<td>1992</td>
<td>Thailand</td>
<td>1.35 (1.06, 1.72)</td>
<td>12.96</td>
</tr>
<tr>
<td>Yu</td>
<td>1989</td>
<td>Guangzhou, China</td>
<td>1.10 (1.00, 1.21)</td>
<td>17.02</td>
</tr>
<tr>
<td>Yu</td>
<td>1986</td>
<td>Hong Kong</td>
<td>1.31 (1.13, 1.51)</td>
<td>15.83</td>
</tr>
</tbody>
</table>

Overall (I-squared = 75.7%, p = 0.000)  
1.35 (1.15, 1.59) 100.00  

NOTE: Weights are from random effects analysis

Figure 10 Funnel plot of studies included in the dose response meta-analysis of salted fish intake during adulthood and nasopharyngeal cancer risk

Funnel plot with pseudo 95% confidence limits

p Egger’s test = 0.11
Figure 11 Relative risk of nasopharyngeal cancer for 1 time per week increase of salted fish intake during adulthood, by geographic location

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jia</td>
<td>2010</td>
<td>Guangdong, China</td>
<td>1.68 (1.35, 2.09)</td>
<td>21.48</td>
</tr>
<tr>
<td>Guo</td>
<td>2009</td>
<td>Guangxi, China</td>
<td>1.87 (1.08, 3.25)</td>
<td>10.59</td>
</tr>
<tr>
<td>Yuan</td>
<td>2000</td>
<td>Shanghai, China</td>
<td>1.73 (0.66, 4.52)</td>
<td>4.71</td>
</tr>
<tr>
<td>Zheng</td>
<td>1994</td>
<td>Guangzhou, China</td>
<td>2.50 (1.63, 3.85)</td>
<td>13.80</td>
</tr>
<tr>
<td>Yu</td>
<td>1989</td>
<td>Guangzhou, China</td>
<td>1.10 (1.00, 1.21)</td>
<td>25.40</td>
</tr>
<tr>
<td>Yu</td>
<td>1986</td>
<td>Hong Kong</td>
<td>1.31 (1.13, 1.51)</td>
<td>24.02</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>1.52 (1.21, 1.91)</td>
<td>100.00</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fachiroh</td>
<td>2012</td>
<td>Thailand</td>
<td>0.94 (0.74, 1.19)</td>
<td>36.73</td>
</tr>
<tr>
<td>Lee</td>
<td>1994</td>
<td>Singapore</td>
<td>1.17 (0.85, 1.61)</td>
<td>27.52</td>
</tr>
<tr>
<td>Sriampon</td>
<td>1992</td>
<td>Thailand</td>
<td>1.35 (1.06, 1.72)</td>
<td>35.75</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>1.14 (0.90, 1.43)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.

2.5.2.1 Salted Fish, childhood consumption

Cohort studies

No new cohort studies were identified during the CUP. One nested case-control study was identified in the 2005 SLR (Zou, 1994, NAS06011).

Zou, 1994 was a study from Sihui County, Guangdong Province, China, where populations are at high risk of developing nasopharyngeal cancer (17 incident cases and 488 non-cases from 11,552 men and women after 3-year follow-up, age 35-64 years). Information on childhood salted fish intake was assessed by dietary history questionnaire. Compared with less frequent consumption, the association with nasopharyngeal cancer risk was significant for consumption ≥ 1/week (P = 0.038) (results not shown in study, not tabulated).

Case-control studies

One new case-control study was identified during the CUP (Jia, 2010).
Childhood salted fish intake (prior to aged 12 years) was statistically significantly positively associated with nasopharyngeal cancer risk (RR for ≥weekly vs <monthly = 1.57, 95% CI = 1.16-2.13) in the hospital-based case-control study from Guangdong province, China, an area with the highest incidence rate of nasopharyngeal cancer (Jia, 2010). Cases (n = 1,387) were ascertained from the medical records of the largest cancer centre in Guangzhou and were histologically confirmed. Controls (n = 1,459) were recruited among those who requested health examinations in the largest general hospitals in the province and were matched to cases by age, sex, education, dialect, and household type. Participants were interviewed following a structured questionnaire which included the assessment of salted fish intake prior to 12 years of age and adulthood.
Table 14 Salted fish intake during childhood and nasopharyngeal cancer risk. Main characteristics of studies identified in the CUP.

<table>
<thead>
<tr>
<th>Author, Year, WCRF Code, Country</th>
<th>Study name, characteristics</th>
<th>Cases/ Controls</th>
<th>Case ascertainment</th>
<th>Exposure assessment</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95% CI) Ptrend</th>
<th>Adjustment factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jia, 2010 NAS06052 Guangdong, China</td>
<td>Hospital-based case-control study, Age: 47 years, M/W Chinese</td>
<td>1387/1459</td>
<td>Hospital records</td>
<td>Interview Childhood (≤aged 12 years) canton-style salted fish intake</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>≥Weekly vs &lt;monthly</td>
<td>1.57 (1.16-2.13)</td>
<td>Age, sex, dialect group, educational level, fresh fruits in childhood, herbal tea habit, salted vegetables in childhood, salted vegetables in adulthood, preserved and cured meat in adulthood, residential (urban/rural), slow-cooked soup habit</td>
</tr>
</tbody>
</table>
3 Beverages
3.6.1 Tea

Cohort studies
No new studies were identified during the CUP.

Published meta-analysis
One published meta-analysis of Chinese case-control and cohort studies was identified (Li, 2013).

For tea drinkers vs non-drinkers, Li, 2013 reported an inverse association with nasopharyngeal cancer risk among Chinese populations (summary RR for drinkers = 0.53, 95% CI = 0.43-0.60, I²=18%, P = 0.30) (Li, 2013).

The authors of the review calculated the RR estimates for all but one study before pooling them in a meta-analysis, therefore, these results were unadjusted for confounding factors. When the one study that reported an odd ratio (OR) was excluded in a sensitivity analysis, the summary RR was 0.62 (95% CI = 0.46-0.83, I² = 59%, P = 0.09).

There was limited information on the studies included in the meta-analysis. The main focus of the review was on alcohol consumption (see section 3.7.1 Alcohol consumption).

3.7.1 Alcohol consumption

Cohort studies
Two prospective studies were identified (Friborg, 2007; Boffetta, 2001), one during the CUP (Friborg, 2007). Statistically non-significant increased risks of nasopharyngeal cancer were reported.

The Singapore Chinese Health Study observed a RR of 1.20 (95% CI = 0.60-2.30) (P trend = 0.70) when comparing daily drinkers with non-drinkers (Friborg, 2007). For higher consumption (>7 drinks/week vs non-drinkers), the RR was 1.30 (95% CI = 0.80-2.30) (P trend = 0.58). Only 173 nasopharyngeal cancer cases among 61 320 men and women (aged ≥45 years) were identified, through Cancer Registry and the Singapore Registry of Births and Deaths, after an average follow-up of 12 years. Multiple confounding factors were adjusted for in the study, including age, sex, educational, number of years of smoking, intakes of protein-rich preserved food, and fresh vegetables, and other factors. Only baseline information on the use of tobacco and alcohol were available, thus misclassification of an individual’s exposure status was possible. The study also reported results on combined levels of alcohol consumption and duration of smoking in current smokers (see 3.7.1 Alcohol and smoking).
The study identified during the 2005 SLR was a Swedish historical cohort of alcoholics (Boffetta, 2001). 173,665 men and women who were diagnosed of alcoholism in hospitals were followed for an average of 10.6 years. Only 21 nasopharyngeal cancer cases (19 men and 2 women) were identified. Compared with the general public, alcoholics were associated with a non-significant increased risk. The age and calendar year-adjusted standardised incidence ratio (SIR) were 1.56 (95% CI = 0.97-2.39) overall, 1.53 (95% CI = 0.92-2.39) in men, and 2.03 (95% CI = 0.25-7.33) in women.

Published meta-analysis

Three published meta-analyses were identified (Li, 2013; Li, 2011; Chen, 2009), of which two were in Chinese populations only (Li, 2013; Li, 2011). Positive associations were observed between alcohol consumption and nasopharyngeal cancer risk.

In Li, 2013, the summary RR for Chinese drinkers vs non-drinkers was 1.12 (95% CI = 0.98-1.26, I² = 45%, P = 0.04) (3 prospective studies, 11 case-control studies) (Li, 2013). Two of the included studies reported a measure of association (OR) (summary RR = 1.18, 95% CI = 1.07-1.30, I² = 23%, P = 0.22 when excluded), whereas RR estimates of the other studies were calculated by the authors of the review using raw numbers in a 2x2 table, therefore these results were unadjusted for confounding factors. In this study, positive association was observed for regular drinkers (summary RR = 1.18, 95% CI = 1.00-1.38, I² = 0%, P = 0.58) and not for occasional drinkers (summary RR = 0.76, 95% CI = 0.65-0.89, I² = 33%, P = 0.21) compared with non-drinkers (4 case-control studies).

The earlier meta-analysis reported slightly stronger positive association (summary RR for drinkers vs non-drinkers = 1.21, 99% CI = 1.00-1.46, I² = 55%, P = 0.08) (Li, 2011), but only four Chinese case-control studies (also in Li, 2013) could be included at the time.

The third meta-analysis was conducted by the WCRF Second Expert Report SLR centre (John Hopkins University), based on the studies identified in the 2005 SLR (Chen, 2009). For total alcohol intake, the summary RR for the highest vs the lowest category was 1.33 (95% CI = 1.09-1.62, I² = 17%, P = 0.28) (11 case-control studies). Studies controlling for smoking on average observed weaker association (summary RR = 1.26, 95% CI = 0.99-1.62) than in studies not controlling for smoking (summary RR = 1.47, 95% CI = 1.02-2.12). The association was also weaker in the Chinese populations (summary RR = 1.21, 95% CI = 0.98-1.62) than in the US populations (summary RR = 1.50, 95% CI = 1.08-2.10). The dose-response meta-analysis showed a J-shape trend, with nasopharyngeal cancer risk decreasing with up to 15 drinks/week and increasing with higher intake.
Table 15 Alcohol consumption and nasopharyngeal cancer risk. Results of meta-analyses published after the 2005 SLR.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of studies</th>
<th>Total number of cases</th>
<th>Studies country, area</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95%CI)</th>
<th>Heterogeneity (I², p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li, 2013</td>
<td>14 studies (3 prospective studies, 11 case-control studies)</td>
<td>4 718 cases</td>
<td>China</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Drinkers vs non-drinkers</td>
<td>1.12 (0.98-1.26)</td>
<td>45%, 0.04</td>
</tr>
<tr>
<td></td>
<td>4 case-control studies</td>
<td></td>
<td></td>
<td></td>
<td>Regular drinkers vs non-drinkers</td>
<td>1.18 (1.00-1.38)</td>
<td>0%, 0.58</td>
</tr>
<tr>
<td></td>
<td>4 case-control studies</td>
<td></td>
<td></td>
<td></td>
<td>Occupational drinkers vs non-drinkers</td>
<td>0.76 (0.65-0.89)</td>
<td>33%, 0.21</td>
</tr>
<tr>
<td>Li, 2011</td>
<td>4 case-control studies</td>
<td>1 698 cases</td>
<td>China</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Drinkers vs non-drinkers</td>
<td>1.21 (1.00-1.46)</td>
<td>55%, 0.08</td>
</tr>
<tr>
<td>Chen, 2009*</td>
<td>11 case-control studies</td>
<td>2 898 cases</td>
<td>China, Hong Kong, Malaysia, Singapore, Taiwan, Thailand, United States</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Highest vs lowest alcohol intake</td>
<td>1.33 (1.09-1.62)</td>
<td>17%, 0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Studies adjusted for smoking</td>
<td></td>
<td>1.26 (0.99-1.62)</td>
<td>-</td>
</tr>
</tbody>
</table>
Studies not adjusted for smoking 1.47 (1.02-2.12) -
Chinese studies 1.21 (0.98-1.62) -
American studies 1.50 (1.08-2.10) -

*The meta-analysis was conducted by the WCRF Second Expert Report SLR centre (John Hopkins University)

Table 16 Alcohol consumption and nasopharyngeal cancer risk. Main characteristics of studies identified in the CUP.

<table>
<thead>
<tr>
<th>Author, Year, WCRF Code, Country</th>
<th>Study name, characteristics</th>
<th>Cases/Study size (Follow-up years)</th>
<th>Case ascertainment</th>
<th>Exposure assessment</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95%CI) Ptrend</th>
<th>Adjustment factors</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friborg, 2007 NAS06047 Singapore</td>
<td>Singapore Chinese Health Study (SCHS), Prospective Cohort, Age: 45-74 years, M/W, Hokkien and Cantonese dialect</td>
<td>173/61 320 12 years</td>
<td>Cancer registry, birth and death registry</td>
<td>Semi-quantitative FFQ</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Daily vs non-drinkers</td>
<td>1.20 (0.60-2.30) Ptrend:0.70</td>
<td>Age, sex, dialect group, educational level, history of familial nasopharyngeal carcinoma, year of interview, number of years of smoking, intakes of protein-rich preserved food, intakes of fresh vegetables</td>
<td></td>
</tr>
<tr>
<td>Boffetta, 2001 NAS00381 Sweden</td>
<td>Swedish Alcoholic Study, Historical</td>
<td>21/173 665 10.6 years</td>
<td>Hospital records</td>
<td>Diagnosis of alcoholism in hospital discharge</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>Alcoholic vs non-alcoholic</td>
<td>1.56 (0.97-2.39)</td>
<td>Age, sex, calendar year</td>
<td>Standardised incidence ratio, compared to the general</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Author, Year, WCRF Code, Country</th>
<th>Study name, characteristics</th>
<th>Cases/Study size Follow-up (years)</th>
<th>Case ascertainment</th>
<th>Exposure assessment</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95% CI)</th>
<th>Ptrend</th>
<th>Adjustment factors</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort, Age: ≥20 years, M/W, Alcoholics</td>
<td>138 195 records</td>
<td>2/35 470</td>
<td>records</td>
<td>Women</td>
<td></td>
<td>2.03 (0.25-7.33)</td>
<td>year</td>
<td>populations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.7.1 Alcohol and smoking

Cohort studies

Two prospective studies were identified during the CUP (Lin, 2015; Friborg, 2007).

In Lin, 2015, alcohol consumption was only examined jointly with smoking as the main focus of the study was on smoking, which the amount and cumulative use was reported to be statistically significantly associated with increased risk of nasopharyngeal cancer mortality (Lin, 2015). When examining the joint status that compared with never smokers and never drinkers, positive associations were observed, and were only significant for daily smokers and never drinkers; however the numbers of deaths were very limited in the categories, ranging from 1 to 12 deaths. The RRs were 3.38 (95% CI = 0.95-11.97) for daily smokers and daily drinkers; 2.95 (95% CI = 1.01-8.68) for daily smokers and never drinkers; and 4.19 (95% CI = 0.47-37.22) for never smokers and daily drinkers. In this study, 101 823 factory workers and drivers who attended medical examinations in Guangzhou, China (a high risk region) were followed for an average of 7.3 years. Deaths within two years of follow-up were excluded. Only 34 nasopharyngeal cancer deaths (30 men, 4 women) were identified through factory records, public statistics office, funeral homes, and police station. The results were adjusted for age, sex, education, and occupational status, and accounted for smoking-drinking interaction (P = 0.26).

Similarly, compared with non-smokers and non-drinkers, a significant positive association with nasopharyngeal cancer risk was observed for long-term current smokers (≥40 years) and non-drinkers in the Singapore Chinese Healthy Study (RR = 2.0, 95% CI = 1.1-3.6) (Friborg, 2007). Among long-term smokers, drinkers were also at increased risks. The RRs were 2.3 (95% CI = 0.9-5.9) with 1-7 drinks/week; and 1.8 (95% CI = 0.5-5.9) with >7 drinks/week.

Among short-term smokers (< 40 years), the associations were less clear. The RRs were 1.2 (95% CI = 0.7-2.1) for non-drinkers, 0.7 (95% CI = 0.3-1.8) for drinkers with 1-7 drinks/week; and 1.2 (95% CI = 0.5-3.1) with >7 drinks/week. In this study, smoking for ≥ 40 years and not smoking intensity and age at smoking initiation significantly increased the risk of nasopharyngeal cancer. The numbers of cases were limited in the analysis, ranging from 3 to 20 cases in the categories. Overall, only 173 nasopharyngeal cancer cases among 61 320 men and women (aged ≥45 years) were identified, through cancer, and birth and death registries, after an average follow-up of 12 years. Multiple confounding factors were adjusted for in the study, including age, sex, educational, intakes of protein-rich preserved food, and fresh vegetables, and other factors. Only baseline information on the use of tobacco and alcohol were available, thus misclassification of an individual’s exposure status was possible. For results on alcohol consumption, see 3.7.1 Alcohol consumption.
### Table 17 Alcohol and smoking and nasopharyngeal cancer risk. Main characteristics of studies identified in the CUP.

<p>| Author, Year, WCRF Code, Country | Study name, characteristics | Cases/Study size Follow-up (years) | Case ascertainment | Exposure assessment | Outcome | Comparison | RR (95% CI) | Ptrend | Adjustment factors | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lin, 2015 NAS06050 China | Guangzhou Occupational Cohort, Prospective Cohort, Age: 30-60+ years, M/W | 34/101 823 7.3 years (27 deaths in the analysis) | Factories, public health bureau statistics office, funeral homes, and local police stations | Workers’ records | Mortality, nasopharyngeal cancer | Daily smokers and daily drinkers vs never smokers and never drinkers | 3.38 (0.95-11.97) | | Age, sex, education, occupational status with smoking and alcohol interaction terms | 6 deaths among the daily smokers and daily drinkers |
| | | | | | | Daily smokers and never drinkers vs never smokers and never drinkers | 2.95 (1.01-8.68) | | | 12 deaths among the daily smokers and never drinkers |
| | | | | | Never smokers and daily drinkers vs never smokers and never drinkers | 4.19 (0.47-37.22) | | | 1 death among the never smokers and daily drinkers |
| Friborg, 2007 NAS06047 Singapore | Singapore Chinese Health Study (SCHS), Prospective Cohort, Age: 45-74 | 173/61 320 12 years | Cancer registry, birth and death registry | Semi-quantitative FFQ | Incidence, nasopharyngeal cancer | 1-39 years of smoking and non-drinkers vs non-smokers and non-drinkers | 1.2 (0.7-2.1) | | Age, sex, dialect group, educational level, history of familial nasopharyngeal | 20 cases among those with 1-39 years of smoking and non-drinkers |</p>
<table>
<thead>
<tr>
<th>Author, Year, WCRF Code, Country</th>
<th>Study name, characteristics</th>
<th>Cases/Study size</th>
<th>Follow-up (years)</th>
<th>Case ascertainment</th>
<th>Exposure assessment</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95%CI)</th>
<th>P trend</th>
<th>Adjustment factors</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/W, Hokkien and Cantonese dialect Current smokers</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>1-39 years of smoking and 1 – 7 drinks/week vs non-smokers and non-drinkers</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7 (0.3-1.8)</td>
<td></td>
<td>carcinoma, year of interview, intakes of protein-rich preserved food, intakes of fresh vegetables</td>
</tr>
<tr>
<td></td>
<td>1-39 years of smoking and ≥7 drinks/week vs non-smokers and non-drinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.2 (0.5-3.1)</td>
<td></td>
<td>5 cases among those with 1-39 years of smoking and ≥7 drinks/week</td>
</tr>
<tr>
<td></td>
<td>≥40 years of smoking and non-drinkers vs non-smokers and non-drinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.0 (1.1-3.6)</td>
<td></td>
<td>16 cases among those with ≥40 years of smoking and non-drinkers</td>
</tr>
<tr>
<td></td>
<td>≥40 years of smoking and 1 – 7 drinks/week vs non-smokers and non-drinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.3 (0.9-5.9)</td>
<td></td>
<td>5 cases among those with ≥40 years of smoking and 1 – 7 drinks/week</td>
</tr>
<tr>
<td>Author, Year, WCRF Code, Country</td>
<td>Study name, characteristics</td>
<td>Cases/Study size Follow-up (years)</td>
<td>Case ascertainment</td>
<td>Exposure assessment</td>
<td>Outcome</td>
<td>Comparison</td>
<td>RR (95% CI)</td>
<td>P trend</td>
<td>Adjustment factors</td>
<td>Remarks</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>≥40 years of smoking and &gt;7 drinks/week vs non-smokers and non-drinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.8 (0.5-5.9)</td>
<td></td>
<td></td>
<td>3 cases among those with ≥40 years of smoking and &gt;7 drinks/week</td>
<td></td>
</tr>
</tbody>
</table>
5 Dietary constituents

5.6.2 Iron in blood

Cohort studies

One prospective study was identified during the CUP.

In the Taiwanese cohort of 309,443 men and women who participated in a private medical screening programme, nasopharyngeal cancer risk was non-statistically significantly increased with both high and low serum iron levels (RR for ≥120 vs 60-79 μg/dL = 1.43, 95 CI = 0.79-2.57 and RR for <60 vs 60-79 μg/dL = 1.69, 95 CI = 0.85-3.37, respectively) (Wen, 2014). Elevated risks were also observed for other serum iron levels. For the extreme comparison of ≥140 vs 60-79 μg/dL, the RR was 1.09 (95% CI = 0.54-2.18). Only 165 cases were identified through record linkage to cancer and death registries after an average of 7.1 years of follow-up. The results were adjusted for age, sex, BMI, smoking, alcohol consumption, physical activity, and other metabolic factors. Serum iron level was only measured once at the initial examination.

8 Anthropometry

8.1.2 Obesity

Cohort studies

One prospective study, published in 2004 and not in the 2005 SLR, was identified during the CUP.

Male US veterans hospitalised with a diagnosis of obesity were non-significantly inversely associated with nasopharyngeal cancer risk compared with those hospitalised for other reasons (Samanic, 2004). The inverse association was slightly stronger among black veterans (RR for obese vs non-obese = 0.76, 95% CI = 0.34-1.73) than white veterans (RR = 0.91, 95% CI = 0.64-1.31), but the difference was not statistically significant (P>0.05). After following up for an average of 12 years, 171 and 610 cases were identified among 832,214 and 3,668,486 black and white veterans, respectively. Cases diagnosed during the first year of follow-up or within one year of obesity diagnosis were excluded. The results were only age and calendar year adjusted.
### Table 18 Iron in blood and nasopharyngeal cancer risk. Main characteristics of studies identified in the CUP.

<table>
<thead>
<tr>
<th>Author, Year, WCRF Code, Country</th>
<th>Study name, characteristics</th>
<th>Cases/Study size (Follow-up years)</th>
<th>Case ascertainment</th>
<th>Exposure assessment</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95% CI)</th>
<th>Ptrend</th>
<th>Adjustment factors</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wen, 2014 NAS06049 Taiwan</td>
<td>Taiwan cohort study, Prospective Cohort, Age: ≥20 years, Mean age: 41.8 years M/W</td>
<td>165/309 443 7.07 years</td>
<td>Cancer registry and death certificates</td>
<td>Serum iron was measured by a Nitroso-PSAP method</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>≥120 vs 60-79 μg/dL</td>
<td>1.43 (0.79-2.57)</td>
<td></td>
<td>Age, gender, BMI, systolic blood pressure, total cholesterol, C-reactive protein, hemoglobin, smoking, alcohol consumption, physical activity</td>
<td>46 cases vs 19 cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥140 vs 60-79 μg/dL</td>
<td>1.09 (0.54-2.18)</td>
<td></td>
<td>20 cases vs 19 cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;60 vs 60-79 μg/dL</td>
<td>1.69 (0.85-3.37)</td>
<td></td>
<td>22 cases vs 19 cases</td>
<td></td>
</tr>
</tbody>
</table>

### Table 19 Obesity and nasopharyngeal cancer risk. Main characteristics of studies identified in the CUP.

<table>
<thead>
<tr>
<th>Author, Year, WCRF Code, Country</th>
<th>Study name, characteristics</th>
<th>Cases/Study size (Follow-up years)</th>
<th>Case ascertainment</th>
<th>Exposure assessment</th>
<th>Outcome</th>
<th>Comparison</th>
<th>RR (95% CI)</th>
<th>Ptrend</th>
<th>Adjustment factors</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samanic, 2004 NAS06048 USA</td>
<td>Veterans Obesity and Cancer Study, Prospective Cohort, Age: 18-100 years, M, Black and white male veterans</td>
<td>610/3 668 486 12 years</td>
<td>Hospital records</td>
<td>Discharge diagnosis of obesity made by veterans’ hospital</td>
<td>Incidence, nasopharyngeal cancer</td>
<td>White men Obese vs non-obese</td>
<td>0.91 (0.64-1.31)</td>
<td></td>
<td>Age, calendar year</td>
<td>Compared to men hospitalised for other reasons; RRs were not significantly different (P&gt;0.05) between black and white men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>171/832 214 12 years</td>
<td></td>
<td></td>
<td></td>
<td>Black men</td>
<td>0.76 (0.34-1.73)</td>
<td></td>
<td>20 cases vs 19 cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22 cases vs 19 cases</td>
<td></td>
</tr>
</tbody>
</table>
Reference list


Appendix 1 Nasopharyngeal cancer continuous update protocol

Protocol Version 2

Continuous Update and Systematic Literature Review of Randomised Controlled Trials, Prospective Studies and Case-control Studies on Food, Nutrition, Physical Activity and the Risk of Nasopharyngeal Cancers.

Prepared by: CUP Team, Imperial College London, December 2013

INTRODUCTION

The Continuous Update Project.

The World Cancer Research Fund/ American Institute for Cancer Research: (WCRF/AICR) has been a global leader in elucidating the relationship between food, nutrition, physical activity and cancer. The First and Second Expert Reports (1;2) represent the most extensive analyses of the existing science on the subject to date.

The Second Expert Report features eight general and two special recommendations based on solid evidence which, when followed, will be expected to reduce the incidence of cancer. More recently, empirical evidence from a large European cohort study showed that people with lifestyle in agreement with the WCRF/AICR recommendations experienced decreased risk of cancer after an average follow-up time of ten years (3). The main risk reductions were for cancers of the colon and rectum, and oesophageal cancer, and significant associations were observed for cancers of the breast, endometrium, lung, kidney, upper aerodigestive tract, liver, and oesophagus.

The Second Expert Report was informed by a process of seventeen systematic literature reviews (SLRs) all of the evidence published. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project (CUP) in collaboration with Imperial College London (ICL). The CUP [http://www.wcrf.org/cancer_research/cup/index.php] is an on-going systematic literature review on food, nutrition, physical activity and body fatness, and cancer risk. The project ensures that the evidence, on which the WCRF/AICR recommendations are based, continues to be the most-up-to-date and comprehensive available.

WCRF/AICR has convened a panel of experts for the CUP consisting of leading scientists in the field of diet, physical activity, obesity and cancer, who will consider the evidence produced by the systematic literature reviews conducted by the research team at ICL. The CUP Panel will judge the evidence, draw conclusions and make recommendations for cancer prevention. The entire CUP process will provide an impartial analysis and interpretation of
the data as a basis for reviewing and where necessary revising the 2007 WCRF/AICR's cancer prevention recommendations (Figure 1).

**Figure 1. The Continuous Update Process**

The CUP builds on the foundations of the Second Expert Report to ensure a consistent approach to reviewing the evidence (4). A team at ICL conducts the CUP SLRs, where a central database has been created by merging the cancer-specific databases generated in the 2007 SLR’s. A key step of the CUP is the update of the central database with the results of randomised controlled trials and prospective studies for most cancer sites. These study designs are considered to be less prone to bias and the 2007 WCRF recommendations had been mainly based on the results of randomised controlled trials and prospective cohort studies. However, the number of published cohort studies is sparse for some cancers with relative low incidence rates. For these cancers, the CUP SLR will include case-control studies.

The WCRF database has been updated at ICL in a rolling programme. The CUP started in 2007 with breast cancer, followed by prostate and colorectal cancers. When a cancer site is included in the CUP, the team at ICL keeps updating the database for that cancer and all the other cancers already included in the CUP (Figure 2). Currently, the central database is being updated for cancers of the breast, prostate, colon and rectum, pancreas, ovary, endometrium, bladder, kidney, gallbladder, liver and stomach.

Periodically, the CUP team at ICL prepares SLR reports with updated meta-analyses by request of the CUP Panel and Secretariat. The protocols and reports of systematic literature reviews by the IC team are available at [http://www.dietandcancerreport.org/cancer_resource_center/continuous_update_project.php](http://www.dietandcancerreport.org/cancer_resource_center/continuous_update_project.php).

The present document is the protocol for the continuous update of the WCRF database and the CUP SLR on food, nutrition, body fatness, physical activity and the risk of...
nasopharyngeal cancers. The peer-reviewed protocol will represent the agreed plan. Should departure from the agreed plan be considered necessary at a later stage, the CUP Expert Panel must agree this and the reasons be documented.

Figure 2. The Continuous Update Project-rolling programme

Note: Cancer types included in the CUP rolling program in 2013: Gallbladder, Liver, Stomach, Oesophageal. Protocols in preparation: Mouth, pharynx and larynx, and nasopharyngeal cancers.

Epidemiology and risk factors of nasopharyngeal cancer.

Nasopharyngeal carcinoma (NPC) is in general a rare epithelial tumour with a high incidence restricted to certain world regions (Figure 3). NPC ranked as the 18th and 23th most frequent cancer in men and women respectively (Figure 4). There were approximately 84,440 incidental cases of NPC and 51,600 NPC-related deaths in 2008 all over the world (Globocan, 2008 (5)). Approximately 80% of the NPC were diagnosed in southeastern Asia. Across countries, the highest incidence rates were seen in Malaysia (11.5 per 100,000 among males) (5) but in some cities in southern China (i.e., Sihui, Zhongshan, Guangzhou city) the incidence rates are the highest in the world (30.9, 22.2, 26.9 per 100,000 among males, respectively (6). Hong Kong is also a high-risk area with an incidence rate of 20.6 among males (6). High incidence rates have also been recorded also in North-east India, in the Kohima district of Nagaland State (19.4 per 100,000 among males) (7). Incidence rates are intermediate in several parts of Africa, where the highest rates are in Algeria (5.2 per 100,000 among males) and in the South African Republic (4.9 per 100,000 among males); this cancer is relatively frequent also in Greenlanders, and Alaskan Eskimos (8). The incidence of NPC in males is approximately 2- to 3-fold higher than that in females. Mortality rates show patterns similar to those of incidence rates throughout different areas. In high risk areas, NPC risk increases with age. However, in low-risk areas, incidence rates increase by age up to a
first peak in late adolescence and early adulthood (ages 15-24 years) that is followed by a subsequent decline in risk until the ages 30-39 years, from which the risk increase continuously up to a second peak later in life (ages 65-79 years) (9).

Tobacco smoking is a causal agent of NPC (10). Occupational exposure to wood dust and formaldehyde might increase the risk of NPC (11). The infection with Epstein Barr virus (EBV) is associated with NPC, in particular with poorly differentiated or undifferentiated NPC, which are the common histopathological types of NPC among southern Chinese (12);(13). However, only a fraction of the EBV-infected population develops NPC. Persons migrating from high- to low-risk countries retained incidence rates that were intermediate between natives of their host country and their country of origin (14). Taken together all this support a role of environmental and genetic factors, possibly interacting with EBV in the development of NPC.

Figure 3. Incidence rates of nasopharyngeal cancer by geographic area.

Figure 4. Worldwide age standardized rates of incidence and mortality from cancer in men and women.
Dietary factors
There is evidence that Cantonese-style salted fish probably increases the risk of nasopharyngeal cancer. In the WCRF/AICR Second Expert Report, the evidence of a potential protective effect of non-starchy vegetables and fruits was judged limited suggestive (Figure 4). The evidence on other dietary factors was limited and no conclusion was possible.

**Figure 4.** Matrix with the judgement of the Panel of Experts in the WCRF/AICR Second Expert Report for nasopharyngeal cancer.

Source: WCRF/AICR Second Expert Report (2)
1. RESEARCH QUESTION

The research topic is:
The associations between food, nutrition and physical activity and the risk of nasopharyngeal cancers.

The main objective is:
To summarize the evidence from case-control studies, prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of nasopharyngeal cancer in men and women.

2. REVIEW TEAM

<table>
<thead>
<tr>
<th>Name</th>
<th>Current position at IC</th>
<th>Role within team</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teresa Norat</td>
<td>Principal Research Fellow</td>
<td>Principal investigator</td>
</tr>
<tr>
<td>Doris Chan</td>
<td>Research Assistant</td>
<td>Supervisor of data extraction. Data analyst, SLR report preparation</td>
</tr>
<tr>
<td>Ana Rita Vieira</td>
<td>Research Assistant</td>
<td>Data analyst, SLR report preparation</td>
</tr>
<tr>
<td>Leila Abar</td>
<td>Research Assistant</td>
<td>Systematic search, article selection, data extraction</td>
</tr>
<tr>
<td>Deborah Navarro</td>
<td>Research Assistant</td>
<td>Systematic search, article selection, data extraction</td>
</tr>
<tr>
<td>Snieguole Vingeliene</td>
<td>Research Assistant</td>
<td>Systematic search, article selection, data extraction</td>
</tr>
</tbody>
</table>

Review coordinator, WCRF: Rachel Thompson
Statistical advisor: Darren Greenwood, senior Research Lecturer, University of Leeds

All the reviewers have been trained in the procedures for literature search, data selection and extraction. The reviewers that will conduct the data analyses have experience in meta-analyses. Selected SLRs published by members of the ICL team are in the References Section (15-29).

3. TIMELINE
The SLRs for the Second Expert Report ended in December 30th 2005. The SLR centre extracted all the data from relevant articles published up to this date for the Second Expert Report.

The CUP team at IC will search and extract data of the articles from case-control studies, prospective studies and randomised controlled trials published from January 1st 2006. The reviewers will verify that there are not duplicities in the database using a module for article search implemented in the interface for data entry.

**List of tasks and deadlines for the continuous update on nasopharyngeal cancer:**

<table>
<thead>
<tr>
<th>Task</th>
<th>Deadline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start Medline search of relevant articles published from January 1st 2006</td>
<td>January 4, 2014</td>
</tr>
<tr>
<td>Start review of title and abstracts of articles identified in electronic search and select papers for complete review</td>
<td>January 15, 2014</td>
</tr>
<tr>
<td>Download papers and select relevant papers for data extraction</td>
<td>January 30, 2014</td>
</tr>
<tr>
<td>Start data extraction</td>
<td>February 28, 2014</td>
</tr>
<tr>
<td>Start hand search of references</td>
<td>February 28, 2014</td>
</tr>
<tr>
<td>Start quantitative analysis of articles included in Pubmed up to 30th May 2014*</td>
<td>July 1, 2014</td>
</tr>
<tr>
<td>Start writing SLR report</td>
<td>September 1, 2014</td>
</tr>
<tr>
<td>Send SLR report for review to CUP secretariat</td>
<td>November 30, 2014</td>
</tr>
<tr>
<td>Review and modify SLR report according to reviewer’s comments</td>
<td>March-May 2015</td>
</tr>
<tr>
<td>Send reviewed SLR report to CUP secretariat</td>
<td>May 30, 2015</td>
</tr>
<tr>
<td>Transfer Endnote files to SLR CUP Secretariat</td>
<td>May 30, 2015</td>
</tr>
<tr>
<td>Panel meeting</td>
<td>June 2015</td>
</tr>
</tbody>
</table>

*Endate of the intermediate systematic literature review to the CUP Panel

**4. SEARCH STRATEGY**

**4.1. Search database**

The search will be conducted in Medline and in the Chinese Biomedical Literature Database System, and in Central and ClinicalTrials.gov. The Medline database will be searched using PubMed as platform. The rationale for searching in Medline is that the results of the SLR’s for the Second Expert Report indicated that searching reports in databases other than Medline was not cost effective (30). In the 2007 SLR for nasopharyngeal cancer (up to December 2005), only 56 case-control and 3 cohort studies had been identified in the searches, from which 32 case-control studies, had been conducted in China.
4.2. Hand searching for cited references

The review team will also hand search the references of reviews and meta-analyses identified during the search.

4.3 Search strategy for PubMed

The CUP review team will use the search strategy established in the SLR Guidelines for the WCRF-AICR Second Expert Report (4). A first search will be conducted using as date limits January 1st 2006 to September 30th 2013 and subsequent searches will be conducted every month.

The search will be conducted in three steps:

1) Searching for studies relating to food, nutrition and physical activity
2) Searching for studies relating to nasopharyngeal cancer
3) Searching for studies relating food, nutrition and physical activity, and nasopharyngeal cancer

The full search strategy is in Annex 1.

5. STUDY SELECTION CRITERIA FOR THE UPDATE OF THE DATABASE

5.1 Inclusion criteria

The articles to be included in the review:

- Studies in men, women or both, in which nasopharyngeal cancer is the first cancer.
- Studies in which the exposure refers to a period before cancer diagnosis.
- Must have as exposure/intervention: patterns of diet, foods, nutrients –dietary, supplemental or both-, other dietary constituents including phytochemicals, and other bioactive compounds, energy density of the diet, glycaemic index, glycaemic load, beverages, substances in foods formed during food production or processing, food additives and contaminants, diet biomarkers, indicators of body adiposity in early life, adolescence or adulthood, changes in body adiposity, height, breastfeeding, physical activity (Exposure list is in Annex 2)
- Must have as outcome of interest incidence or mortality of nasopharyngeal cancer
- Included in Medline from January 1st 2006
- Have to present results from an epidemiologic study in men and/or women of one of the following types:
  - Randomized controlled trial
  - Group randomized controlled trial (Community trial)
Prospective cohort study
Nested case-control study
Case-cohort study
Historical cohort study
Population based case-control study
Other case-control studies

† January 1st 2006 is the closure date of the database for the Second Expert Report.

5.2 Exclusion criteria

- Studies in which the only measure of the relationship between the relevant exposure and outcome is the mean difference of exposure (this is because the difference is not adjusted for main confounders).
- Studies in which the outcome include other cancers grouped with nasopharyngeal cancer.
- Studies in which the exposure is weight, waist circumference or hip circumference measured at the moment of cancer diagnosis or after cancer diagnosis (e.g. in some case-control studies).
- Studies in which the exposure is derived from weight, waist or hip circumference measured at or after cancer diagnosis.

6. ARTICLE SELECTION

First, all references obtained with the searches in PubMed will be imported in a Reference Manager Database using the filter Medline.

The article selection will follow three steps:

1. An electronic search will first be undertaken within Reference Manager to facilitate the identification of irrelevant records by using the terms indicated below. The relevance of the articles identified with the search words within Reference Manager will be assessed upon reading of the titles and abstracts.
List of terms for use within Reference Manager Database

Radiotherapy
Chemotherapy
Cisplatinum
Cisplatin
Docetaxel
Taxotere
Fluoracil
5-FU
Paclitaxel
Taxol
Gemcitabine
Cell
Inhibitor
Novel
Model
Receptor
Antibody
Transgenic
Mice
Hamster
Rat
Dog
Cat
In vitro

2. In a second step, two reviewers will assess the titles and abstracts of the remaining articles.

3. In a third step, the reviewers will assess the full manuscripts of all papers for which eligibility could not be determined by reading the title and abstract. The reviewers will solve any disagreements about the study or exposure relevance by discussion with the principal investigator.

6.1 Reference Manager Files

Four user-defined fields (Table 2) will be created in the Reference Manager database, where the reviewers will indicate:

1) if the study was selected upon reading of title and abstract, or entire article
2) the study design of articles relevant to the review
3) the status of data extraction of included articles
4) the WCRF code assigned to the studies in the database
5) reasons for exclusion of articles on exposures/interventions and outcomes relevant to the review

**Table 2.** User-defined fields and terms to be used in the Reference Manager database for identification of the status of articles identified in the searches.

<table>
<thead>
<tr>
<th>Field</th>
<th>Use</th>
<th>Terms</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>User Def 1</td>
<td>For all articles retrieved in the search</td>
<td>Excludedabti</td>
<td>Excluded: exclusion based on abstract and title</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excluded</td>
<td>Excluded: exclusion based on full paper text</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Included</td>
<td>Included</td>
</tr>
<tr>
<td>User Def 2</td>
<td>Only for EXCLUDED studies</td>
<td>Includes other cancers sites*</td>
<td>*Grouped with nasopharyngeal cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inadequate study design**</td>
<td>**Cross-sectional studies, case-only study, ecological study, other study designs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No measure of association</td>
<td>***If the article can’t be translated. Articles in Chinese will be assessed by a reviewer who speaks Chinese.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No original data</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Commentary, letter</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foreign article in [language]***</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meta-analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Already extracted</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer survivors</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MPL not primary cancer</td>
<td></td>
</tr>
<tr>
<td>User Def 3</td>
<td>Only for INCLUDED studies</td>
<td>Randomized controlled trial (RCT)</td>
<td>*Case-control study- other: the comparison populations are neighbors, friends, or other controls that are not population- or hospital-based.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospective cohort study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retrospective cohort study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nested case-control study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case cohort study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Population-based case-control study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital-based case-control study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case-control study-other*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pooled analysis of cohort studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pooled analysis of case-control studies</td>
<td></td>
</tr>
<tr>
<td>User Def 4</td>
<td>WCRF code</td>
<td>Only for INCLUDED</td>
<td>WCRF codes are assigned</td>
</tr>
</tbody>
</table>
7. DATA EXTRACTION

The IC team will update the WCRF-AICR central database using an interface created for this purpose (Figure 5). The application will automatically check that the paper has not already been extracted to the database using author name, publication year and journal references. The data extracted will be double-checked by a second reviewer.

The data to be extracted include among other: study design, study name, characteristics of study population, exclusion criteria, mean age, sex, study location, recruitment year, race/ethnicity, methods of exposure assessment, definition of exposure, definition of outcome, method of outcome assessment, study size, number of cases, number of comparison subjects, length of follow up, lost to follow-up, analytical methods and whether methods for correction of measurement error were used.

The reviewer will not do any calculation during data extraction. The ranges, means or median values for each exposure level will be extracted as reported in the paper.

For each result, the reviewers will extract the covariates and matching variables included in the analytical models and tumour characteristics, such as histological type (e.g., WHO type). Measures of association, number of cases and number of comparison individuals or person years for each category of exposure will be extracted for each analytical model reported. Stratified and subgroup analyses, and results of interaction analyses will be extracted (e.g. by sex, age group, smoking status, BMI category, alcohol intake level, etc.)

7.1 Study identifier

The CUP team will use the same labelling of articles used in the SLR process for the Second Expert Report: the unique identifier for an article will be constructed using a 3-letter code to represent the cancer site: NAS, followed by a 5-digit number that will be generated sequentially by the software during data extraction.

7.2 Codification of exposures/interventions.

The exposures/interventions will be codified during data extraction as in the Second Expert Report. The main headings and sub-headings codes are in Annex 2. Wherever possible, the reviewer will use the sub-heading codes. Additional codes have been programmed in the database to facilitate the data entry (all additional codes are not shown in the Annex).

The main headings for codification of the exposure groups are:

1. Patterns of diet, includes regionally defined diets, socio-economically defined diets, culturally defined diets, individual level dietary patterns, other dietary patterns, breastfeeding and other issues
2. **Foods**, including starchy foods; fruit and (non-starchy) vegetables; pulses (legumes); nuts and seeds; meat, poultry, fish and eggs; fats, oils and sugars; milk and dairy products; and herbs, spices, and condiments, and composite foods.

**Figure 5. CUP interface. Example of screen for data entry**

3. **Beverages**, including total fluid intake, water, milk, soft drinks, fruit juices, hot drinks and alcoholic drinks.

4. **Food production** including traditional methods and chemical contaminants, food preservation, processing and preparation.

5. **Dietary constituents**, including carbohydrate, lipids, protein, alcohol, vitamins, minerals, phytochemicals, nutrient supplements and other bioactive compounds

6. **Physical activity**, including total physical activity, physical inactivity and surrogate markers for physical activity.

7. **Energy balance**, including energy intake, energy density and energy expenditure.

8. **Anthropometry**, including markers of body composition, markers of body fat distribution, height and other skeletal measures, and growth in foetal life, infancy or childhood.
The reviewer should extract the description of the exposure/intervention definition in the free text box provided for that purpose in the data entry screen. The definition will be extracted as it appears in the paper.

7.2.1 Codification of biomarkers of exposure

During the SLR for the Second Expert Report, some review centres opted for including in the review only biomarkers for which there was strong evidence on reliability or validity whereas other centres opted for including results on all the biomarkers retrieved in the search, independently of their validity. For the evaluation of the evidence, the Panel of Experts took in consideration the validity of the reported biomarkers.

However, since the identification and validation of other biomarkers is an evolving topic (31), the CUP team will extract the data for all biomarkers of intake reported in the studies, independently of whether validity and reliability had been or not fully documented.

7.3 Codification of outcomes.

The reviewer will indicate under “outcome type”, whether the outcome for each results is incidence or mortality and in “outcome subtype”, the histology or other classification used by the authors (e.g. Squamous cell carcinoma, histology not reported, undifferentiated, etc.).

The reviewer should also extract the outcome definition in the free text box provided for that purpose in the data entry screen. The outcome definition will be extracted as it appears in the paper, including ICD codes if reported.

7.4 Extraction and labelling of study results

The reviewer will extract the measures of association (punctual estimates and confidence intervals) for the relevant exposures from all the analytical models shown in the paper, including subgroups, stratified analyses, interactions and sensitivity analyses. These results can be found in the paper in tables, in the text or as online supplemental information. The results for each analytical model will be extracted. Potential confounders of interest include age, gender, current and past smoking status, socioeconomic status, race and/or ethnicity, geographic location, alcohol intake, family history of nasopharyngeal cancer, dietary factors, and occupational exposures. Potential effect modifiers are age, gender, smoking status, race/ethnicity, and alcohol consumption. Information on genetic polymorphisms that may interact with nutrients or other dietary factors and modify the association between dietary factors of interest and nasopharyngeal cancer will be noted.

During data extraction, the reviewer should label each result as unadjusted, intermediately adjusted, or most adjusted model, as follows:

- The results of univariate models will be labelled “unadjusted”.
- The results obtained with the model including the higher number of covariables in the article will be labelled “most adjusted.”
• The results obtained using any multivariable model that is not the most adjusted model will be labelled “intermediately” adjusted.

In addition, the reviewer will indicate the “best model” for meta-analyses.

Sometimes, the researchers use models that include variables likely to be in the causal pathway with the purpose of exploring hypothetical mechanisms. When “mechanistic” models are reported by the authors, the most adjusted result that is not “mechanistic” will be indicated as “best model”’. The mechanistic” models will be extracted and labelled as most adjusted model, but not as best model for meta-analysis. If there are enough results with these models, they will be used in separate analysis.

8. QUALITY CONTROL OF THE ARTICLE SELECTION AND DATA EXTRACTION.

A second reviewer at ICL will check the article selection and the data extraction. If there are discrepancies between the reviewers, the discrepancy will be discussed with the Principal Investigator.

9. DATA ANALYSIS

9.1 Meta-analysis

The database manager will export from the WCRF/AICR database the data required for analysis. The CUP team at IC will update the meta-analyses conducted for the Second Report using studies included in the 2007 SLR and studies published after that review. The CUP SLR will not conduct meta-analysis using as contrast the highest vs. the lowest category of exposure/intervention except for specific exposures (e.g. breastfeeding categorised as yes vs. no, use of multivitamins categorised as yes vs. no) and for physical activity for which quantitative levels are often not provided.

The meta-analysis will be conducted separately for randomized controlled trials, cohort studies and case-control studies (if possible for population-based and hospital-based separately), and for studies on incidence and mortality as outcome separately and combined. Meta-analyses will be conducted for men, women and both gender in separate analyses and if the number of studies allows it, for smokers and non-smokers separately.

The data analyst will check that the same study population is not included twice in one meta-analysis. To check this, the database manager will export the location and recruitment years of the study population. For studies with overlapping location and recruitment years, the data analyst will check duplicity by examining other study characteristics such as gender, age range, race/ethnicity.
Where results from two or more studies are reported in the same paper, the results of each study will be included separately in the CUP meta-analysis instead of using the pooled result reported in the paper. The purpose is to look at heterogeneity across study results. If this is not possible, the overall result will be included and sensitivity analyses will be conducted excluding the overall results of pooling projects.

The results of the individual studies will be displayed graphically in forests plots of the highest vs. the lowest comparison for each study, but a summary estimate will not be calculated, to avoid pooling different exposure levels. In all forest plots, the studies will be ordered by publication year, with the most recent on the top.

Linear dose-response meta-analysis will be conducted to express the results of each study in the same increment unit for a given exposure. The results will be shown in a dose-response forest plots. For comparability, the increment units for the linear dose-response analyses will be those used in the meta-analyses in the previous SLRs (Table 3) but another increment may have to be used in the range of exposure in the identified papers is smaller than the recommended increment unit.

If most of the identified studies report servings, times, units these will be used as increment unit.

Non-linear dose-response meta-analyses will be conducted as exploratory analysis.

**Table 3. Recommended increment units for meta-analyses.**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Increment unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fruits and vegetables</td>
<td>100 g</td>
</tr>
<tr>
<td>Non starchy vegetables</td>
<td>100 g</td>
</tr>
<tr>
<td>Fruits</td>
<td>100 g</td>
</tr>
<tr>
<td>Citrus fruits</td>
<td>50 g</td>
</tr>
<tr>
<td>Red meat</td>
<td>100 g</td>
</tr>
<tr>
<td>Processed meat</td>
<td>50 g</td>
</tr>
<tr>
<td>Poultry</td>
<td>100 g</td>
</tr>
<tr>
<td>Fish</td>
<td>50 g</td>
</tr>
<tr>
<td>Eggs</td>
<td>25 g</td>
</tr>
<tr>
<td>Salt</td>
<td>1 g</td>
</tr>
<tr>
<td>Coffee</td>
<td>1 cup</td>
</tr>
<tr>
<td>Tea</td>
<td>1 cup</td>
</tr>
<tr>
<td>Alcoholic drinks</td>
<td>1 drink/day</td>
</tr>
<tr>
<td>Alcohol (as ethanol)</td>
<td>10 g</td>
</tr>
<tr>
<td>Dietary calcium</td>
<td>200 mg</td>
</tr>
<tr>
<td>Dietary fibre</td>
<td>10 g</td>
</tr>
<tr>
<td>Folate</td>
<td>100 µg</td>
</tr>
<tr>
<td>Blood selenium</td>
<td>10 µg/L</td>
</tr>
<tr>
<td>Beer</td>
<td>10 g/day (approx. one drink)</td>
</tr>
<tr>
<td>Wine</td>
<td>10 g/day (approx. one drink)</td>
</tr>
<tr>
<td>BMI</td>
<td>5 kg/m²</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Waist</td>
<td>2.5 cm (1 inch)</td>
</tr>
<tr>
<td>Waist-to-hip</td>
<td>0.1 unit</td>
</tr>
<tr>
<td>Height</td>
<td>5 cm</td>
</tr>
<tr>
<td>Physical activity</td>
<td>5 MET-h per week</td>
</tr>
</tbody>
</table>

9.2 Selection of exposures for a dose-response meta-analysis

The meta-analysis will include studies identified during the SLR and studies identified during the CUP.

For each exposure, a dose-response meta-analysis will be conducted when:

- at least two new reports of trials or cohort studies with enough data for dose-response meta-analysis have been published after the year 2005 (end date for the SLR for the Second Expert Report) and if the total number of studies that can be included in the meta-analysis is at least 5 in each study design
- at least 5 new reports of case-control studies have been published

The minimum number of studies was not derived statistically but it is a number of studies that can be reasonable expected to have been published after the Second Expert Report.

Where a particular study has published more than one paper on the same exposure, the analysis using the larger number of cases will be selected but if the most recent paper does not provide enough information for the dose-response meta-analysis, the previous publication with the required information will be used. The results section will indicate whether the reports of the same study are similar or not.

9.3 Selection of results for meta-analyses

The results based on “best” adjusted models will be used in the dose-response meta-analyses. When the linear dose-response estimate is reported in an article, this will be used in the CUP dose-response meta-analysis. If the results are presented only for categorical exposures/intervention (quantiles or pre-defined categories), the slope of the dose-response relationship for each study will be derived from the categorical data.

9.4 Derivation of data required for meta-analyses.

The data required to derive the dose-response slope from categorical data are:

1. Number of cases for each exposure category
2. Person-years -or number of controls - for each exposure category
3. Median, mean or cut-offs of exposure categories.

The information provided in the articles is often incomplete and this may result in exclusions of results from meta-analyses. For instance, in the SLR’s on oesophageal and prostate cancer for the Second Expert Report, only 64% of the cohort studies provided enough data to
be included in dose-response meta-analysis, and there was empirical evidence that studies that showed an association were more likely to be usable in dose-response meta-analysis than studies that did not show any evidence (30).

The failure to include all available evidence will reduce precision of summary estimates and may lead to bias if propensity to report results in sufficient detail is associated with the magnitude and/or direction of associations. To address the data incompleteness, a number of approaches will be undertaken to derive the missing data from the available data where possible (30). These approaches are summarized in Table 4.

For estimating the “dose-response” for each study, the means or medians of the exposure categories reported in the articles will be assigned as “dose”; if not reported, the midpoints of the exposure range in each category will be used. For lowest or highest open-ended categories the amplitude of the nearest category will be used to calculate the midpoint. If different measurement units of exposure have been used, these will be rescaled where possible (e.g. pounds to g; kg to g, weeks to days, etc). Where portion or serving sizes have to be rescaled, the standard portion sizes reported in the paper will be used but if not reported, the standard portion sizes used in the WCRF/AICR Second Expert Report (4) will be applied (Table 5) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108955/ - pone.0020456-World1. For studies reporting intakes in grams/1000 kcal/day, the intake in grams/day will be estimated using the average energy intake reported in the article.

Table 4. Approaches to derive missing information for meta-analyses in the CUP

<table>
<thead>
<tr>
<th>Type of data</th>
<th>Problem</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-response data</td>
<td>Serving size is not quantified or ranges are missing, but group descriptions are given</td>
<td>Use serving size recommended in SLR</td>
</tr>
<tr>
<td></td>
<td>Standard error missing</td>
<td>The p value (either exact or the upper bound) is used to estimate the standard error</td>
</tr>
<tr>
<td>Quantile-based data</td>
<td>Numbers of controls (or the denominator in cohort studies) are missing</td>
<td>Group sizes are assumed to be approximately equal if the quantiles are based in the distribution of controls. If quantiles are derived using both cases and controls, or this is not explicitly said, the approach indicated in “Category data” should be used</td>
</tr>
<tr>
<td></td>
<td>Confidence interval is missing</td>
<td>Use raw numbers of cases and controls (or the denominator in cohort studies) to calculate confidence interval (although doing so may result in a somewhat smaller standard error than would be</td>
</tr>
</tbody>
</table>
For estimating the “dose-response” for each study, the means or medians of the exposure categories reported in the articles will be assigned as “dose”; if not reported, the midpoints of the exposure range in each category will be used. For lowest or highest open-ended categories the amplitude of the nearest category will be used to calculate the midpoint.

If different measurement units of exposure have been used, these will be rescaled where possible (e.g. pounds to g; kg to g, weeks to days, etc). Where portion or serving sizes have to be rescaled, the standard portion sizes reported in the paper will be used but if not reported, the standard portion sizes used in the WCRF/AICR Second Expert Report will be applied (4) (Table 5)http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108955/ - pone.0020456.World1.

For studies reporting intakes in grams/1000 kcal/day, the intake in grams/day will be estimated using the average energy intake reported in the article.

**Table 5. List of conversion units**

<table>
<thead>
<tr>
<th>Item</th>
<th>Conversion of one unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>400ml serving</td>
</tr>
<tr>
<td>Cereals</td>
<td>60g serving</td>
</tr>
<tr>
<td>Cheese</td>
<td>35g serving</td>
</tr>
<tr>
<td>Dried fish</td>
<td>10g serving</td>
</tr>
<tr>
<td>Eggs</td>
<td>55g serving (1 egg)</td>
</tr>
<tr>
<td>Fats</td>
<td>10g serving</td>
</tr>
<tr>
<td>Fruit &amp; Vegetables</td>
<td>80g serving</td>
</tr>
<tr>
<td>Fruit Juice</td>
<td>125ml serving</td>
</tr>
<tr>
<td>General drinks inc. soft &amp; hot drinks</td>
<td>200ml serving</td>
</tr>
<tr>
<td>Meat &amp; Fish</td>
<td>120g serving</td>
</tr>
</tbody>
</table>
Milk
Milk as beverage
Processed cheese slice
Processed meat
Shellfish
Spirits
Staple foods (rice, pasta, potatoes, beans & lentils, foods boiled in soy sauce)
Water & Fluid intake
Wine

50ml serving
200ml serving
10g serving
50g serving
60g serving
25ml serving
150g serving
8oz cup
125ml serving

9.5 Statistical Methods

If the dose response estimates are not reported in an article, this will be derived from categorical data using generalized least-squares for trend estimation (command GLST in Stata) (33). This method accounts for the correlation between relative risks estimates with respect to the same reference category (34). The dose-response model is forcing the fitted line to go through the origin and whenever the assigned dose corresponding to the reference group (RR=1) is different from zero, this will be rescaled to zero and the assigned doses to the other exposure categories will be rescaled accordingly.

The study specific log odds ratios per unit increase in exposure will be combined in a random effect model using the method of DerSimonian and Laird (35), with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model.

Publication and related bias (e.g. small study bias) will be explored through visual examination of funnel plots and Egger’s test (36). Funnel plots will be shown in the SLR when there are at least four studies included in the analysis.

Heterogeneity between studies will be quantified with the $I^2$ statistic with cut points for $I^2$ values of 30%, and 50% for low, moderate, and high degrees of heterogeneity (37). Heterogeneity will be assessed visually from forest plots and with statistical tests ($P$ value <0.05 will be considered statistically significant) but the interpretation will rely mainly in the $I^2$ values as the test has low power and the number of studies will probably be low.

Potential sources of heterogeneity will be explored by stratified analyses when the number of studies allows it (at least two studies in each stratum). The variables that will be explored as sources of heterogeneity are geographic area (if the number of studies allow it, by low-risk, intermediate risk and high risk area), level of control for smoking, alcohol intake and other confounders, publication year, length of follow-up (cohort studies), type of control population (for case-control studies). Meta-regression will be conducted when the number of studies allows it.

The interpretation of stratified analysis should be cautious. If a considerable number of study characteristics are investigated in a meta-analysis containing only a small number of studies,
then there is a high probability that one or more study characteristics will be found to explain heterogeneity, even in the absence of real associations.

Non-linear dose-response relationship will be explored using fractional polynomial models (38). The best fitting second order fractional polynomial regression model defined as the one with the lowest deviance will be determined. Non-linearity will be tested using the likelihood ratio test. A program in Stata prepared by D. Greenwood, statistical advisor of the project will be used.

All analyses will be conducted in Stata/SE 12.1.

9.7 Sensitivity analyses

Sensitivity analyses will be carried out to investigate how robust the overall findings of the CUP are relative to key decisions and assumptions that were made in the process of conducting the update. The purpose of doing sensitivity analyses is to strengthen the confidence that can be placed in the results.

Sensitivity analysis will be done as a minimum in the following cases:

- Including and excluding studies where there is some ambiguity as to whether they meet the inclusion criteria, for example it may be unclear if other cancer sites are included together with nasopharyngeal cancer.
- Including and excluding studies where exposure levels were inferred by the authors (for example assigning a standard portion size when this is not provided) or when other missing information was derived from the data.
- Influence-analyses where each individual study will be omitted in turn in order to investigate the sensitivity of the pooled estimates to inclusion or exclusion of particular studies (39).

10. SYSTEMATIC LITERATURE REVIEW REPORT

An updated SLR will be sent to the CUP Secretariat on May 30th 2015 for discussion in the Expert Panel.

The SLR report will include the following elements:

1. Modifications of the approved protocol
   Any modification required during the review will be described

2. Results of the search
   Flowchart with number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts, number of papers included and excluded, reasons for excluding papers.

3. Summary tables of studies identified in the continuous update
   Number of studies by study design and publication year.
   Number of studies by exposure (main heading and selected subheadings) and publication year
   Number of studies by exposure and outcome subtype

4. Tabulation of study characteristics and main study results by study design and outcome
The tables will include the information required by the Panel to judge the quality of the studies included in the analyses (Newcastle–Ottawa quality assessment scale (40) for observational studies and the Cochrane Collaboration’s tool for assessing risk of bias (41).

Example of table of study characteristics for cohort studies (in two parts below):

<table>
<thead>
<tr>
<th>Author, Year, country, WCRF Code</th>
<th>Study design</th>
<th>Country, Ethnicity, other characteristics</th>
<th>Age (mean)</th>
<th>Cases (n)</th>
<th>Non cases (n/person-years)</th>
<th>Case ascertainment</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment details</td>
<td>Category of exposure</td>
<td>Subgroup No cat</td>
<td>RR (95% CI)</td>
<td>p trend</td>
<td>Adjustment factors</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

10.6 Graphic presentation

Tabular presentation will be complemented with graphic displays when two or more new reports of randomized controlled trials or cohort studies or 5 new reports of case-control studies have been published after December 2006. Study results will be displayed in forest plots showing relative risk estimates and 95% confidence interval of “high versus low” comparisons for each study. Dose-response graphs will be given for individual studies for which the information is available. Funnel plots will be shown when there are at least four studies.

10.7 Results of the dose-response meta-analysis

Main characteristics of included and excluded studies in dose-response meta-analysis will be tabulated, and reasons for exclusions will be detailed.

The results of meta-analyses will be presented in tables and forest plots. The tables will include a comparison with the results of the meta-analyses undertaken during the SLR for the Second Expert Report.

All forest plots in the report will have the same format. Footnotes will provide quantified information (statistical tests and $I^2$ statistics) on the degree of heterogeneity.

Meta-regression, stratified analyses and sensitivity analyses results will be presented in tables and, if the number of studies justifies it, in forest plots.
Reference List


Annex 1. WCRF - PUBMED SEARCH STRATEGY

1) Searching for all studies relating to food, nutrition and physical activity:

**#1** diet therapy[MeSH Terms] OR nutrition[MeSH Terms]


**#3** food and beverages[MeSH Terms]


**#6** pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]


**#8** food preservation[MeSH Terms]


#10 cookery[MeSH Terms]


#12 ((carbohydrates[MeSH Terms] OR proteins[MeSH Terms]) and (diet*[tiab] or food*[tiab]))) OR sweetening agents[MeSH Terms]


#14 vitamins[MeSH Terms]


#16 physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] OR walking[MeSH Terms]


#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

#21 animal[MeSH Terms] NOT human[MeSH Terms]

#22 #20 NOT #21

2) Searching for all studies relating to cancers of nasopharyngeal cancer:

#23 Nasopharyngeal Neoplasms [MeSH]


#25 nasopharyngeal[tiab] OR nasal[tiab] or nasal sinus[tiab] or pharynx[tiab] OR head and neck[tiab] or aerodigestive[tiab]

#26 #24 AND #25

#27 #23 OR #26

3) Searching for all studies relating mouth, pharynx and larynx cancers, and food, nutrition, anthropometry and physical activity:

#28 #22 AND #27
Annex 2. LIST OF HEADINGS AND EXPOSURE CODES (minimum list)
*Indicates codes added during the CUP

1  Patterns of diet

1.1  Regionally defined diets
*1.1.1  Mediterranean diet

Include all regionally defined diets, evident in the literature. These are likely to include Mediterranean, Mesoamerican, oriental, including Japanese and Chinese, and "western type".

1.2  Socio-economically defined diets

To include diets of low-income, middle-income and high-income countries (presented, when available in this order). Rich and poor populations within low-income, middle-income and high-income countries should also be considered. This section should also include the concept of poverty diets (monotonous diets consumed by impoverished populations in the economically-developing world mostly made up of one starchy staple, and may be lacking in micronutrients).

1.3  Culturally defined diets

To include dietary patterns such as vegetarianism, vegan diets, macrobiotic diets and diets of Seventh-day Adventists.

1.4  Individual level dietary patterns

To include work on factor and cluster analysis, and various scores and indexes (e.g. diet diversity indexes) that do not fit into the headings above.

1.5  Other dietary patterns

Include under this heading any other dietary patterns present in the literature, that are not regionally, socio-economically, culturally or individually defined.

1.6  Breastfeeding

1.6.1  Mother

Include here also age at first lactation, duration of breastfeeding, number of children breastfed

1.6.2  Child

Results concerning the effects of breastfeeding on the development of cancer should be disaggregated into effects on the mother and effects on the child. Wherever possible detailed information on duration of total and exclusive breastfeeding, and of complementary feeding should be included.

1.7  Other issues

For example results related to diet diversity, meal frequency, frequency of snacking, dessert-eating and breakfast-eating should be reported here. Eating out of home should be reported here.

2  Foods

*2.0.1 Plant foods
2.1 Starchy foods
2.1.1 Cereals (grains)
  * 2.1.1.0.1 Rice, pasta, noodles
  * 2.1.1.0.2 Bread
  * 2.1.1.0.3 Cereal

* Report under this subheading the cereals when it is not specified if they are wholegrain or refined cereals (e.g. fortified cereals)

2.1.1.1 Wholegrain cereals and cereal products
  * 2.1.1.1.1 Wholegrain rice, pasta, noodles
  * 2.1.1.1.2 Wholegrain bread
  * 2.1.1.1.3 Wholegrain cereal

2.1.1.2 Refined cereals and cereal products
  * 2.1.1.2.1 Refined rice, pasta, noodles
  * 2.1.1.2.2 Refined bread
  * 2.1.1.2.3 Refined cereal

2.1.2 Starchy roots, tubers and plantains
  * 2.1.2.1 Potatoes

2.1.3 Other starchy foods

*Report polenta under this heading

2.2 Fruit and (non-starchy) vegetables

Results for “fruit and vegetables” and “fruits, vegetables and fruit juices” should be reported here. If the definition of vegetables used here is different from that used in the first report, this should be highlighted.

2.2.1 Non-starchy vegetables

This heading should be used to report total non-starchy vegetables. If results about specific vegetables are reported they should be recorded under one of the sub-headings below or if not covered, they should be recorded under ‘2.2.1.5 other’.

2.2.1.1 Non-starchy root vegetables and tubers
  *2.2.1.1.1 Carrots

2.2.1.2 Cruciferous vegetables

2.2.1.3 Allium vegetables

2.2.1.4 Green leafy vegetables (not including cruciferous vegetables)

2.2.1.5 Other non-starchy vegetables
  *2.2.1.5.13 Tomatoes
  *2.2.1.5.1 Fresh beans (e.g. string beans, French beans) and peas
Other non-starchy vegetables’ should include foods that are botanically fruits but are eaten as vegetables, e.g. courgettes. In addition vegetables such as French beans that do not fit into the other categories, above.

If there is another sub-category of vegetables that does not easily fit into a category above eg salted root vegetables (ie you do not know if it is starchy or not) then report under 2.2.1.5. and note the precise definition used by the study. If in doubt, enter the exposure more than once in this way.

2.2.1.6 Raw vegetables

This section should include any vegetables specified as eaten raw. Results concerning specific groups and type of raw vegetable should be reported twice i.e. also under the relevant headings 2.2.1.1 – 2.2.1.5.

2.2.2 Fruits

*2.2.2.0.1 Fruit, dried
*2.2.2.0.2 Fruit, canned
*2.2.2.0.3 Fruit, cooked

2.2.2.1 Citrus fruit

2.2.2.1.1 Oranges

2.2.2.1.2 Other citrus fruits (e.g. grapefruits)

2.2.2.2 Other fruits

*2.2.2.2.1 Bananas
*2.2.2.2.4 Melon
*2.2.2.2.5 Papaya
*2.2.2.2.7 Blueberries, strawberries and other berries
*2.2.2.2.8 Apples, pears
*2.2.2.2.10 Peaches, apricots, plums
*2.2.2.2.11 Grapes

If results are available that consider other groups of fruit or a particular fruit please report under ‘other’, specifying the grouping/fruit used in the literature.

2.3 Pulses (legumes)

*2.3.1 Soya, soya products

*2.3.1.1 Miso, soya paste soup
*2.3.1.2 Soya juice
*2.3.1.4 Soya milk
*2.3.1.5 Tofu

*2.3.2 Dried beans, chickpeas, lentiles

*2.3.4 Peanuts, peanut products

Where results are available for a specific pulse/legume, please report under a separate heading.
2.4 Nuts and Seeds
To include all tree nuts and seeds, but not peanuts (groundnuts). Where results are available for a specific nut/seed, e.g. brazil nuts, please report under a separate heading.

2.5 Meat, poultry, fish and eggs
Wherever possible please differentiate between farmed and wild meat, poultry and fish.

2.5.1 Meat
This heading refers only to red meat: essentially beef, lamb, pork from farmed domesticated animals either fresh or frozen, or dried without any other form of preservation. It does not refer to poultry or fish.

Where there are data for offal (organs and other non-flesh parts of meat) and also when there are data for wild and non-domesticated animals, please show these separately under this general heading as a subcategory.

2.5.1.1 Fresh Meat
2.5.1.2 Processed meat

*2.5.1.2.1 Ham
*2.5.1.2.1.7 Burgers
*2.5.1.2.8 Bacon
*2.5.1.2.9 Hot dogs
*2.5.1.2.10 Sausages

Repeat results concerning processed meat here and under the relevant section under 4. Food Production and Processing. Please record the definition of ‘processed meat’ used by each study.

2.5.1.3 Red meat

*2.5.1.3.1 Beef
*2.5.1.3.2 Lamb
*2.5.1.3.3 Pork

*2.5.1.3.6 Horse, rabbit, wild meat (game)

Where results are available for a particular type of meat, e.g. beef, pork or lamb, please report under a separate heading.

Show any data on wild meat (game) under this heading as a separate sub-category.

2.5.1.4 Poultry

Show any data on wild birds under this heading as a separate sub-category.

*2.5.1.5 Offals, offal products (organ meats)

2.5.2 Fish

*2.5.2.3 Fish, processed (dried, salted, smoked)
*2.5.2.5 Fatty Fish
*2.5.2.7 Dried Fish
*2.5.2.9 White fish, lean fish
2.5.3 Shellfish and other seafood
2.5.4 Eggs
2.6 Fats, oils and sugars
2.6.1 Animal fats
*2.6.1.1 Butter
*2.6.1.2 Lard
*2.6.1.3 Gravy
*2.6.1.4 Fish oil
2.6.2 Plant oils
2.6.3 Hydrogenated fats and oils
*2.6.3.1 Margarine
Results concerning hydrogenated fats and oils should be reported twice, here and under 4.3.2 Hydrogenation
2.6.4 Sugars
This heading refers to added (extrinsic) sugars and syrups as a food, that is refined sugars, such as table sugar, or sugar used in bakery products.
2.7 Milk and dairy products
Results concerning milk should be reported twice, here and under 3.3 Milk
*2.7.1 Milk, fresh milk, dried milk
*2.7.1.1 Whole milk, full-fat milks
*2.7.1.2 Semi skimmed milk, skimmed milk, low fat milk, 2% Milk
*2.7.2 Cheese
*2.7.2.1 Cottage cheese
*2.7.2.2 Cheese, low fat
*2.7.3 Yoghurt, buttermilk, sour milk, fermented milk drinks
*2.7.3.1 Fermented whole milk
*2.7.3.2 Fermented skimmed milk
*2.7.7 Ice cream
2.8 Herbs, spices, condiments
*2.8.1 Ginseng
*2.8.2 Chili pepper, green chili pepper, red chili pepper
2.9 Composite foods
Eg, snacks, crisps, desserts, pizza. Also report any mixed food exposures here ie if an exposure is reported as a combination of 2 or more foods that cross categories (eg bacon and eggs). Label each mixed food exposure.
*2.9.1 Cakes, biscuits and pastry
*2.9.2 Cookies
*2.9.3 Confectionery
*2.9.4 Soups
*2.9.5 Pizza
*2.9.6 Chocolate, candy bars
*2.9.7 Snacks

3 Beverages
3.1 Total fluid intake
3.2 Water
3.3 Milk

*3.4 Soft drinks

For results concerning milk please report twice, here and under 2.7 Milk and Dairy Products.

*3.5 Fruit and vegetable juices
*3.5.1 Citrus fruit juice
*3.5.2 Fruit juice
*3.5.3 Vegetable juice
*3.5.4 Tomato juice

3.6 Hot drinks
3.6.1 Coffee
3.6.2 Tea

Report herbal tea as a sub-category under tea.

3.6.2.1 Black tea
3.6.2.2 Green tea
3.6.3 Maté
3.6.4 Other hot drinks

3.7 Alcoholic drinks
3.7.1 Total
3.7.1.1 Beers
3.7.1.2 Wines
3.7.1.3 Spirits
3.7.1.4 Other alcoholic drinks

4 Food production, preservation, processing and preparation

4.1 Production

4.1.1 Traditional methods (to include ‘organic’)

4.1.2 Chemical contaminants

Only results based on human evidence should be reported here (see instructions for dealing with mechanistic studies). Please be comprehensive and cover the exposures listed below:

4.1.2.1 Pesticides

4.1.2.2 DDT

4.1.2.3 Herbicides

4.1.2.4 Fertilisers

4.1.2.5 Veterinary drugs

4.1.2.6 Other chemicals

4.1.2.6.1 Polychlorinated dibenzofurans (PCDFs)

4.1.2.6.2 Polychlorinated dibenzodioxins (PCDDs)

4.1.2.6.3 Polychlorinated biphenyls (PCBs)

4.1.2.7 Heavy metals

4.1.2.7.1 Cadmium

4.1.2.7.2 Arsenic

4.1.2.8 Waterborne residues

4.1.2.8.1 Chlorinated hydrocarbons

4.1.2.9 Other contaminants

Please also report any results that cover the cumulative effect of low doses of contaminants in this section.

4.2 Preservation

4.2.1 Drying

4.2.2 Storage

4.2.2.1 Mycotoxins

4.2.2.1.1 Aflatoxins

4.2.2.1.2 Others

4.2.3 Bottling, canning, vacuum packing

4.2.4 Refrigeration

4.2.5 Salt, salting

4.2.5.1 Salt

4.2.5.2 Salting
4.2.5.3 Salted foods
4.2.5.3.1 Salted animal food
4.2.5.3.2 Salted plant food
4.2.6 Pickling
4.2.7 Curing and smoking
4.2.7.1 Cured foods
4.2.7.1.1 Cured meats
4.2.7.1.2 Smoked foods

For some cancers e.g. colon, rectum, oesophagus and pancreas, it may be important to report results about specific cured foods, cured meats and smoked meats. N-nitrosamines should also be covered here.

4.3 Processing
4.3.1 Refining

Results concerning refined cereals and cereal products should be reported twice, here and under 2.1.1.2 refined cereals and cereal products.
4.3.2 Hydrogenation

Results concerning hydrogenated fats and oils should be reported twice, here and under 2.6.3 Hydrogenated fats and oils.
4.3.3 Fermenting
4.3.4 Compositional manipulation
4.3.4.1 Fortification
4.3.4.2 Genetic modification
4.3.4.3 Other methods
4.3.5 Food additives
4.3.5.1 Flavours

Report results for monosodium glutamate as a separate category under 4.3.5.1 Flavours.
4.3.5.2 Sweeteners (non-caloric)
4.3.5.3 Colours
4.3.5.4 Preservatives
4.3.5.4.1 Nitrites and nitrates
4.3.5.5 Solvents
4.3.5.6 Fat substitutes
4.3.5.7 Other food additives

Please also report any results that cover the cumulative effect of low doses of additives.
Please also report any results that cover synthetic antioxidants
4.3.6 Packaging
4.3.6.1 Vinyl chloride
4.3.6.2 Phthalates

4.4 Preparation

4.4.1 Fresh food

4.4.1.1 Raw
Report results regarding all raw food other than fruit and vegetables here. There is a separate heading for raw fruit and vegetables (2.2.1.6).

4.4.1.2 Juiced

4.4.2 Cooked food

4.4.2.1 Steaming, boiling, poaching

4.4.2.2 Stewing, casseroling

4.4.2.3 Baking, roasting

4.4.2.4 Microwaving

4.4.2.5 Frying

4.4.2.6 Grilling (broiling) and barbecuing

4.4.2.7 Heating, re-heating
Some studies may have reported methods of cooking in terms of temperature or cooking medium, and also some studies may have indicated whether the food was cooked in a direct or indirect flame. When this information is available, it should be included in the SLR report.

Results linked to mechanisms e.g. heterocyclic amines, acrylamides and polycyclic aromatic hydrocarbons should also be reported here. There may also be some literature on burned food that should be reported in this section.

5 Dietary constituents
Food constituents’ relationship to outcome needs to be considered in relation to dose and form including use in fortified foods, food supplements, nutrient supplements and specially formulated foods. Where relevant and possible these should be disaggregated.

5.1 Carbohydrate

5.1.1 Total carbohydrate

5.1.2 Non-starch polysaccharides/dietary fibre

5.1.2.1 Cereal fibre

5.1.2.2 Vegetable fibre

5.1.2.3 Fruit fibre

5.1.3 Starch

5.1.3.1 Resistant starch

5.1.4 Sugars

*5.1.5 Glycemic index, glycemic load
This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and also extrinsic sugars not incorporated into the cellular structure of foods. Results for
intrinsic and extrinsic sugars should be presented separately. Count honey and sugars in fruit juices as extrinsic. They can be natural and unprocessed, such as honey, or refined such as table sugar. Any results related to specific sugars e.g. fructose should be reported here.

5.2 Lipids
5.2.1 Total fat
5.2.2 Saturated fatty acids
5.2.3 Monounsaturated fatty acids
5.2.4 Polyunsaturated fatty acids
5.2.4.1 n-3 fatty acids

Where available, results concerning alpha linolenic acid and long chain n-3 PUFA should be reported here, and if possible separately.

5.2.4.2 n-6 fatty acids
5.2.4.3 Conjugated linoleic acid
5.2.5 Trans fatty acids
5.2.6 Other dietary lipids, cholesterol, plant sterols and stanols.

For certain cancers, e.g. endometrium, lung, and pancreas, results concerning dietary cholesterol may be available. These results should be reported under this section.

5.3 Protein
5.3.1 Total protein
5.3.2 Plant protein
5.3.3 Animal protein
5.4 Alcohol

This section refers to ethanol the chemical. Results related to specific alcoholic drinks should be reported under 3.7 Alcoholic drinks. Past alcohol refers, for example, to intake at age 18, during adolescence, etc.

*5.4.1 Total Alcohol (as ethanol)
*5.4.1.1 Alcohol (as ethanol) from beer
*5.4.1.2 Alcohol (as ethanol) from wine
*5.4.1.3 Alcohol (as ethanol) from spirits
*5.4.1.4 Alcohol (as ethanol) from other alcoholic drinks
* 5.4.1.5 Total alcohol (as ethanol), lifetime exposure
* 5.4.1.6 Total alcohol (as ethanol), past
5.5 Vitamins
*5.5.0 Vitamin supplements
*5.5.0.1 Vitamin and mineral supplements
*5.5.0.2 Vitamin B supplement
5.5.1 Vitamin A
5.5.1.1 Retinol
5.5.1.2 Provitamin A carotenoids
5.5.2 Non-provitamin A carotenoids

Record total carotenoids under 5.5.2 as a separate category marked Total Carotenoids.

5.5.3 Folates and associated compounds
*5.5.3.1 Total folate
*5.5.3.2 Dietary folate
*5.5.3.3 Folate from supplements

Examples of the associated compounds are lipotropes, methionine and other methyl donors.

5.5.4 Riboflavin
5.5.5 Thiamin (vitamin B1)
5.5.6 Niacin
5.5.7 Pyridoxine (vitamin B6)
5.5.8 Cobalamin (vitamin B12)
5.5.9 Vitamin C
5.5.10 Vitamin D (and calcium)
5.5.11 Vitamin E
5.5.12 Vitamin K
5.5.13 Other

If results are available concerning any other vitamins not listed here, then these should be reported at the end of this section. In addition, where information is available concerning multiple vitamin deficiencies, these should be reported at the end of this section under ‘other’.

5.6 Minerals
5.6.1 Sodium
5.6.2 Iron
5.6.3 Calcium (and Vitamin D)
5.6.4 Selenium
5.6.5 Iodine
5.6.6 Other

Results are likely to be available on other minerals e.g. magnesium, potassium, zinc, copper, phosphorus, manganese and chromium for certain cancers. These should be reported at the end of this section when appropriate under ‘other’.

5.7 Phytochemicals
5.7.1 Allium compounds
5.7.2 Isothiocyanates
5.7.3 Glucosinolates and indoles
5.7.4 Polyphenols
5.7.5 Phytoestrogens eg genistein
5.7.6 Caffeine
5.7.7 Other

Where available report results relating to other phytochemicals such as saponins and coumarins. Results concerning any other bioactive compounds, which are not phytochemicals should be reported under the separate heading ‘other bioactive compounds’. Eg flavonoids, isoflavonoids, glycoalkaloids, cyanogens, oligosaccharides and anthocyanins should be reported separately under this heading.

5.8 Other bioactive compounds

6 Physical activity
6.1 Total physical activity (overall summary measures)
6.1.1 Type of activity
6.1.1.1 Occupational
6.1.1.2 Recreational
6.1.1.3 Household
6.1.1.4 Transportation
6.1.2 Frequency of physical activity
*6.1.2.1 Frequency of occupational physical activity
*6.1.2.2 Frequency of recreational physical activity
6.1.3 Intensity of physical activity
*6.1.3.1 Intensity of occupational physical activity
*6.1.3.2 Intensity of recreational physical activity
6.1.4 Duration of physical activity
*6.1.4.1 Duration of occupational physical activity
*6.1.4.2 Duration of recreational physical activity
6.2 Physical inactivity
6.3 Surrogate markers for physical activity e.g. occupation

7 Energy balance
7.1 Energy intake
*7.1.0.1 Energy from fats
*7.1.0.2 Energy from protein
*7.1.0.3 Energy from carbohydrates
*7.1.0.4 Energy from alcohol
*7.1.0.5 Energy from all other sources
7.1.1 Energy density of diet
7.2 Energy expenditure
8 Anthropometry
8.1 Markers of body composition
8.1.1 BMI
8.1.2 Other weight adjusted for height measures
8.1.3 Weight
8.1.4 Skinfold measurements
8.1.5 Other (e.g. DEXA, bio-impedance, etc)
8.1.6 Change in body composition (including weight gain)
8.2 Markers of distribution of fat
8.2.1 Waist circumference
8.2.2 Hips circumference
8.2.3 Waist to hip ratio
8.2.4 Skinfolds ratio
8.2.5 Other e.g. CT, ultrasound
8.3 Skeletal size
8.3.1 Height (and proxy measures)
8.3.2 Other (e.g. leg length)
8.4 Growth in fetal life, infancy or childhood
8.4.1 Birthweight
8.4.2 Weight at one year