World Cancer Research Fund International Systematic Literature Review

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

Analysing research on cancer prevention and survival

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List of abbreviations

ASIR	Age standardised incidence rate
ASMR	Age standardised mortality rate
BMI	Body Mass Index
CI	Confidence Interval
CUP	Continuous Update Project
EBV	Epstein-Barr Virus
FFQ	Food Frequency Questionnaire
HR	Hazard Ratio
NPC	Nasopharyngeal Cancer
OR	Odd Ratio
RR	Relative Risk
SLR	Systematic Literature Review
SIR	Standardised Incidence Ratio
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research

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.

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Cantonese-style salted fish**[1]
Limited — suggestive	Non-starchy vegetables[2] Fruits[2]	
Limited — no conclusion	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	
Substantial effect on risk unlikely	None identified	

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.

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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.

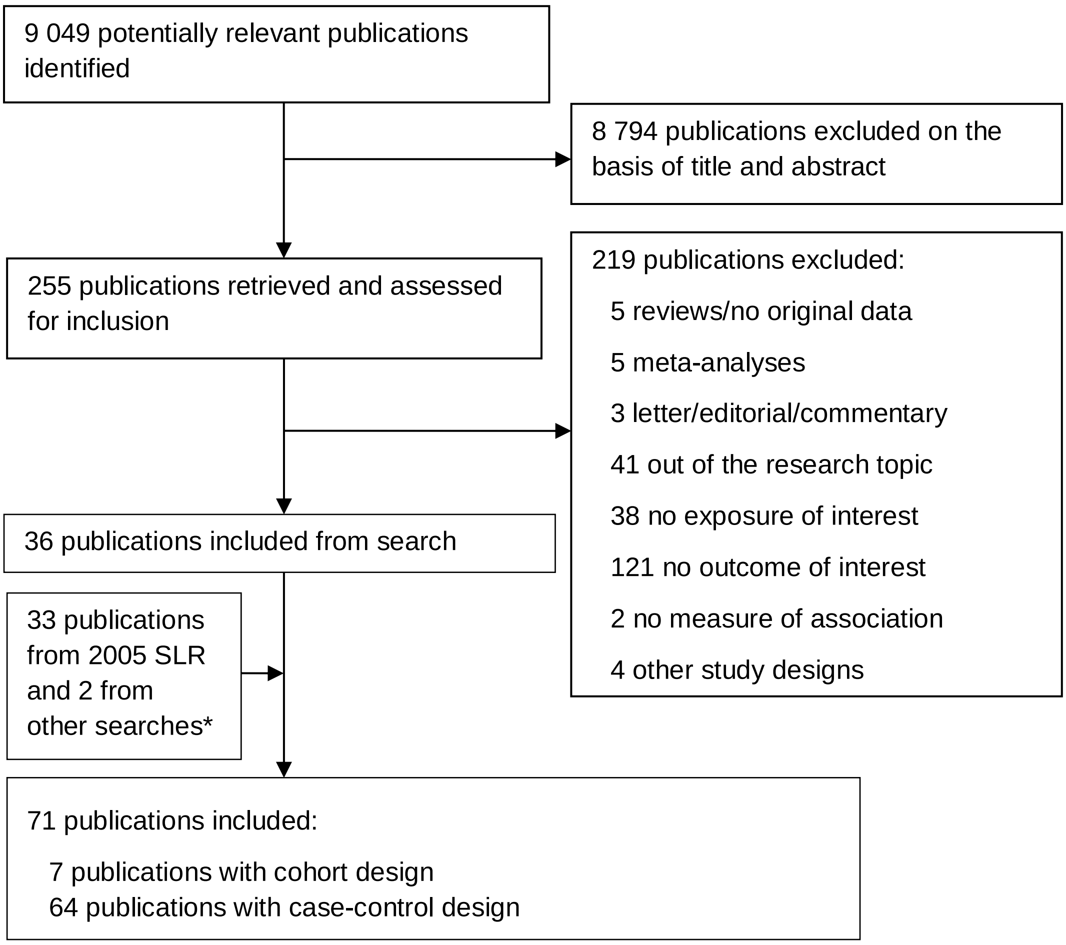
Methods: Four cohort studies published after the 2005 SLR were identified in the literature search. There were no relevant randomised controlled trials and pooled studies. Because evidence was limited, the studies were reviewed narratively, along with the review of relevant published meta-analyses (all 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 1st 2006 – June 1st 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.

Exposure Code[1]	Exposure Name	Number of publications[2]		Total number of publications
		2005 SLR	CUP[3]	
2.	**Foods**			
2.2.1.5	Preserved vegetables	12 case-control	3 case-control	15 case-control
2.3	Pulses (legumes)	1	0	1
2.5.2.1	Salted fish, adulthood consumption	1 cohort 21 case-control	0 cohort 12 case-control	1 cohort 33 case-control
2.5.2.1	Salted fish, childhood consumption (aged around 10 years)	1 cohort 16 case-control	0 cohort 1 case-control	1 cohort 17 case-control
3.	**Beverages**			
3.7.1	Alcohol consumption	1	1	2
3.7.1	Alcohol and smoking	0	2	2
5.	**Dietary constituents**			
5.6.2	Iron in blood	0	1	1
8.	**Anthropometry**			
8.1.2	Obesity	0	1	1

[1]The exposure code is the exposure identification in the database.

[2]Number of publications with a cohort design unless otherwise stated.

[3]Exposures 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 vegetables 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 2 Vegetables and nasopharyngeal cancer risk. Results of meta-analyses published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Jin, 2014	11 case-control studies	3 749 cases	Africa, China, Italy, United States	Incidence, nasopharyngeal cancer	Highest vs lowest total or fresh vegetable intake	0.60 (0.47-0.76)	50%, 0.03
	4 case-control studies			Hospital-based studies		0.47 (0.38-0.58)	39%, 0.18
	7 case-control studies			Population-based studies		0.80 (0.65-0.99)	0%, 0.84
Gallicchio, 2006*	5 case-control studies	1 623 cases	Algeria, China, Malaysia, Singapore, Taiwan, Tunisia, United States	Incidence, nasopharyngeal cancer	Highest vs lowest intake, Non-preserved vegetables	0.64 (0.48-0.85)	50%, 0.09

*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

	Number
Studies identified	14 (15 publications)
Studies included in forest plot of highest compared with lowest exposure	9 (9 publications)
Studies included in linear dose-response meta-analysis	5 (5 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

	2005 SLR	**CUP**
Increment unit used	**-**	**Per 1 time/week**
Studies (n)	-	5
Cases	-	3 924
RR (95%CI)	-	1.42 (1.04-1.93)
Heterogeneity (I^2, p-value)	-	76%, <0.01
P value Egger test	-	0.18

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

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Gallicchio, 2006*	6 case-control studies	1 695 cases	Algeria, China, Malaysia, Singapore, Taiwan, Tunisia, United States	Incidence, nasopharyngeal cancer	Highest vs lowest intake, Preserved vegetables	2.04 (1.43-2.92)	63%, 0.02

*****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 6 Preserved vegetables intake during adulthood and nasopharyngeal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Fachiroh, 2012 NAS06062 Thailand	Hospital-based case-control study, Age: 48 years, M/W Thai	1 045/ 1 078	Hospital records	Questionnaire, interview Salted vegetables (hua-chai-poe)	Incidence, nasopharyngeal	≥ weekly vs never to rarely	1.34 (0.83-2.18) Ptrend:0.94 (included in analysis)	Age, sex, alcohol consumption, education years, smoking status, study center
				Fermented vegetables (prak-kad-dorng)			1.78 (1.24-2.55) Ptrend:0.005	
Hsu, 2012 NAS06053 Taiwan	Case-control study, (community controls) Age: 46 years, M/W	367/ 319	Hospital records	FFQ Preserved vegetables	Incidence, nasopharyngeal,	≥0.41 vs ≤0.04 times/week	1.00 (0.67-1.48) Ptrend:1.0	Age, sex, educational level, ethnicity, family history of NPC, formaldehyde, total energy intake, wood dust, years of smoking
		358/ 97			EBV positive		1.23 (0.68-2.23) Ptrend:0.49	
Jia, 2010 NAS06052 Guangdong, China	Hospital-based case-control study, Age: 47 years, M/W	1 378/ 1 459	Hospital records	Interview Salted vegetables in adulthood	Incidence, nasopharyngeal	≥weekly vs <monthly	1.79 (1.19-2.68)	Age, sex, dialect group, educational level, fruits intake, herbal tea, preserved vegetables, processed meat intake, residential (urban/rural), salted fish consumption, slow-cooked soup
Yuan, 2000 NAS00577 Shanghai, China	Population-based case-control study, Age: 15-74 years, M/W	935/ 1 032	Cancer registry	FFQ Preserved leafy vegetables, preserved stem vegetables, preserved root vegetables, all	Incidence, nasopharyngeal cancer	≥201 vs 0-40 times/year	1.43 (1.11-1.86)	Age, gender, level of education, cigarette smoking, cooking exposures, occupational exposures, history of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
				preserved vegetables				chronic ear and nose condition
Lee, 1994 NAS01056 Singapore	Hospital-based case-control study, Age: ≤44 years, M/W, Singapore Chinese	200/ 406	-	FFQ Preserved green leafy vegetable, preserved cabbage, preserved Chinese radish, canned, salted, or pickled vegetables, salted Chinese tuber, salted mustard greens, preserved turnip root	Incidence, nasopharyngeal cancer	1-3 times/week vs none	4.9 (1.8-12.9)	Age, sex, educational level, dialect group

Table 7 Preserved vegetables intake during adulthood and nasopharyngeal cancer risk. Main characteristics of studies excluded in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Laouamri, 2001 NAS00424 Algeria	Population-based case-control study, Age: 9-70 years, M/W	72/ 72	Cancer registry	- Vegetables in brine as seasoning, salted dried tomatoes as seasoning	Incidence, nasopharyngeal cancer	Current vs none	1.25 (0.64-2.41)	Age, sex, area of residence	Excluded, two exposure categories only
Duan, 2000 NAS06002 Wuhan, China	Hospital-based case-control study, M/W	100/ 100	Hospital records	Questionnaire Pickled vegetables	Incidence, nasopharyngeal cancer	-	Significant correlation r^2=0.015	Environmental factors, gas range, pungent foods, socio-economic status	Excluded, no measure of association

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Ward, 2000 NAS00531 Taiwan	Population-based case control study, Age: <75 years, M/W	371/ 321	Hospital records	FFQ Preserved vegetables	Incidence, nasopharyngeal cancer	Ever vs never	Not significant	Age, sex, ethnicity, subjects w/ mothers questionnaire, total calories	Superseded by Hsu, 2012, NAS06053
Zou, 1999 NAS06023 Yangjiang area, Guangdong province, China	Population-based case-control study, Age: 14-82 years, M/W	102/ 202	Death certificate	FFQ Salted other non-starchy vegetables, salted vegetables	Mortality, nasopharyngeal cancer	≥1/3.3 days vs others	2.28 (1.40-3.73)	Matched by sex and age	Excluded, two exposure categories only
Armstrong, 1998 NAS00749 Malaysia	Hospital-based case-control study, Age: 45 years, M/W, Malaysian Chinese	282/ 282	Histology reports	FFQ Salted leafy vegetables, salted root, 5 years pre-diagnosis	Incidence, nasopharyngeal cancer	≥weekly vs <monthly	3.33 (1.84-6.01) Ptrend:0.001	Age, gender, residence history	Excluded, missing cases and controls per category
Chen, 1997 NAS00825 Guangzhou, China	Hospital-based case-control study, Age: 25-54 years, M/W	104/ 104	-	FFQ Salted vegetables, 3 years ago	Incidence, nasopharyngeal cancer	-	Not significant	Age, sex, area of residence	Excluded, no measure of association
Huang, 1997 NAS06024 Guangzhou province and Heilongjiang province, China	Population-based case-control study, M/W	104/ 104	Hospital records	FFQ Preserved green leafy vegetables	Incidence, nasopharyngeal cancer	Yes vs no	1.81 (1.01-3.33)	Age, sex, family history of cancer, number of separate kitchens, other nutrients, foods or supplements	Excluded, two exposure categories only
Zheng, 1994b NAS01113	Case-control study (from	88/	Histology	FFQ Salted, dried, or	Incidence, nasopharyngeal	-	Not significant	-	Excluded, no measure of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Wuzhou city, Zangwu county, Guangxi province, China	neighbourhood controls) Age: 42 years, M/W	176	reports	tinned vegetables in brine	cancer				association
Zheng, 1993 NAS01190 Guangzhou, China	Hospital-based case-control study, M/W	205/ 205	Hospital records	FFQ Salted vegetables	Incidence, nasopharyngeal cancer	-	>0.1 Significant	-	Excluded, limited information
Ning, 1990 NAS01922 Tianjin city, Northern China	Case-control study, (from the patients neighbourhood) Age: 45 years, M/W	100/ 292	Cancer registry	FFQ 3 years prior to diagnosis, Salted vegetables	Incidence, nasopharyngeal cancer	-	Not significant	Age, sex, area of residence	Excluded, no measure of association
				Pickled vegetables		-	Not significant		
				Dried vegetables		-	Not significant		

Figure 3 RR estimates of nasopharyngeal cancer by preserved vegetables intake during adulthood

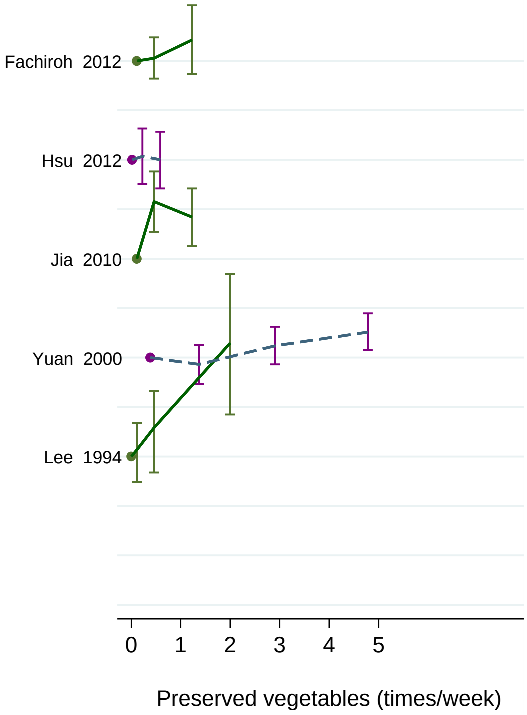
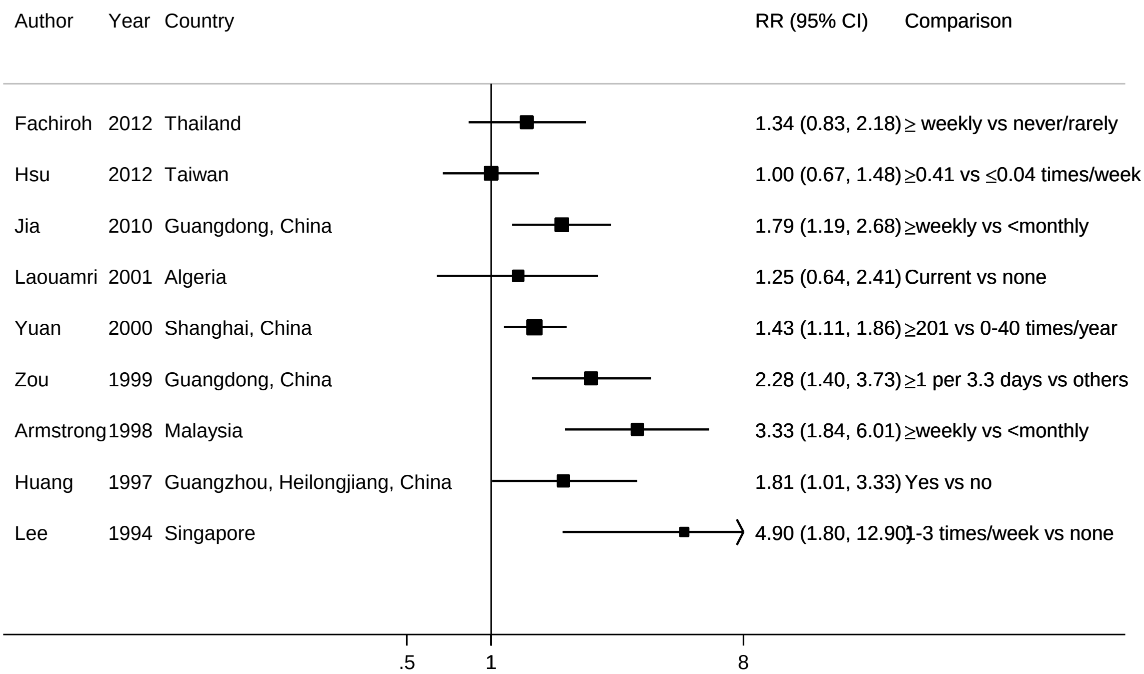


Figure 4 RR (95% CI) of nasopharyngeal cancer for the highest compared with the lowest level of preserved vegetables intake during adulthood*



*When pooled, the summary RR was 1.72 (95% CI = 1.33-2.23) (I^2 = 61%, P=0.01)

Figure 5 Relative risk of nasopharyngeal cancer for 1 time per week increase of preserved vegetables intake during adulthood

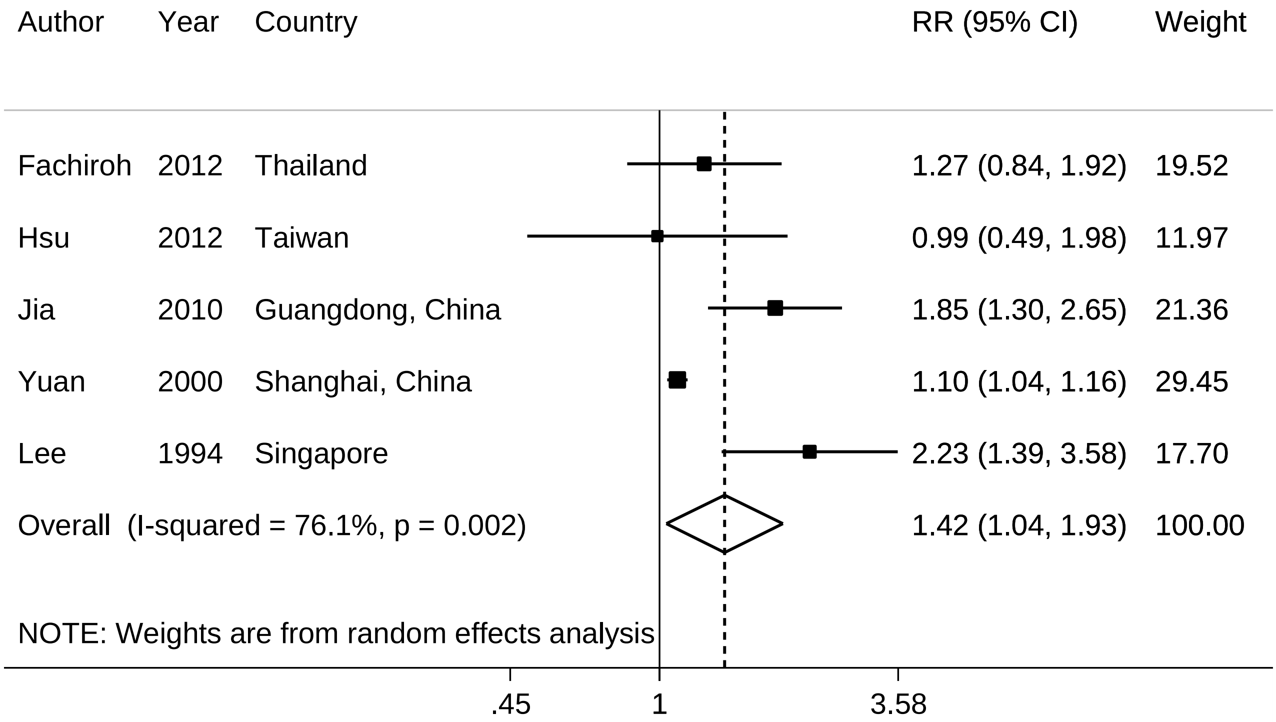
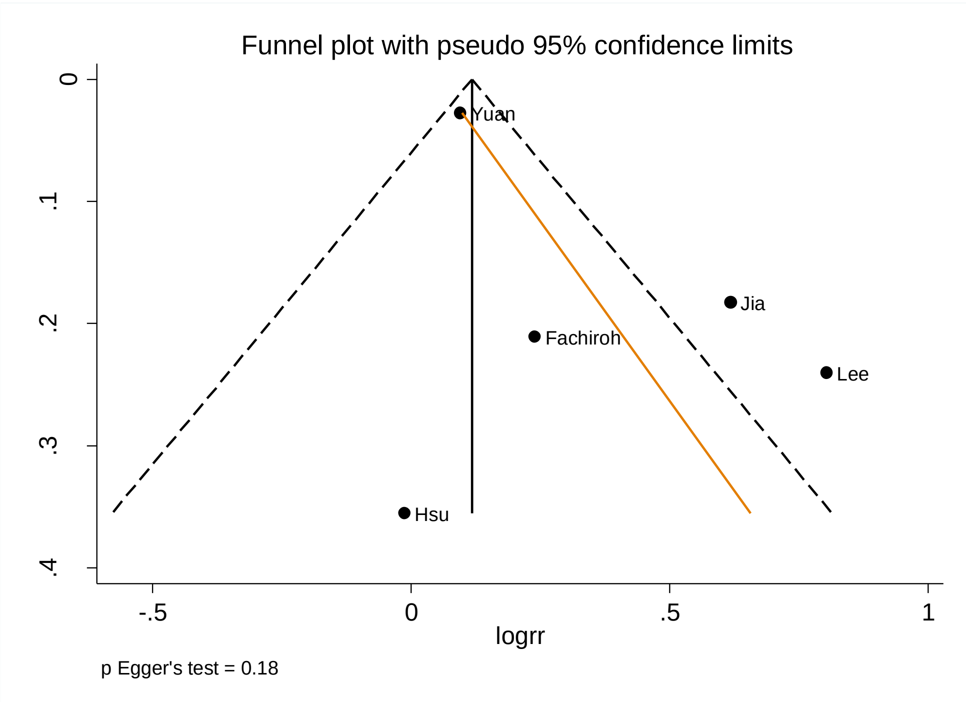


Figure 6 Funnel plot of studies included in the dose response meta-analysis of preserved vegetables intake during adulthood and nasopharyngeal cancer risk



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 8 Fruits and nasopharyngeal cancer risk. Results of meta-analyses published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Jin, 2014	9 case-control studies	4 622 cases	China, Italy, Turkey, United States	Incidence, nasopharyngeal cancer	Highest vs lowest total or fresh fruit intake	0.61 (0.54-0.69)	0%, 0.84
	5 case-control studies			Hospital-based studies		0.63 (0.54-0.74)	0%, 0.96
	4 case-control studies			Population-based studies		0.58 (0.47-0.71)	3%, 0.38

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 9 Processed meat and red meat and nasopharyngeal cancer risk. Results of meta-analyses published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Li, 2016	13 case-control studies	5 434	Africa, China, Hong Kong, India, Italy, Malaysia, Tunisia	Incidence, nasopharyngeal cancer	Processed meat: <30 g/week vs never	1.46 (1.31-1.64)	76%, <0.01
					30-60 g/week vs never	1.59 (1.33-1.90)	82%, <0.01
					>60 g/week vs never	2.11 (1.31-3.42)	85%, <0.01
	7 case-control studies	1 858	Africa, China, Italy, Tunisia, Turkey, Spain		Red meat: <100 g/week vs never	1.35 (1.21-1.51)	0%, 0.98
					100-300 g/week vs never	1.54 (1.35-1.76)	57%, 0.05
					>300 g/week vs never	1.71 (1.14-2.55)	77%, 0.01

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

	Number
Studies identified	27 (33 publications)
Studies included in forest plot of highest compared with lowest exposure	21 (21 publications)
Studies included in linear dose-response meta-analysis	9 (9 publications)
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

	2005 SLR	**CUP**
Increment unit used	**Per 1 time/week**	**Per 1 time/week**
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 (I^2, p-value)	75%	76%, <0.001
P value Egger test	-	0.11

Stratified analysis in the CUP		
Geographic locations	**China**	**Other countries**
Studies (n)	6	3
Cases	4 043	1 001
RR (95%CI)	1.52 (1.21-1.91)	1.14 (0.90-1.43)
Heterogeneity (I^2, p-value)	81%, <0.001	56%, 0.10
Type of controls	**Hospital controls**	**Other controls***
Studies (n)	4	5
Cases	2 376	2 668
RR (95%CI)	1.26 (0.97-1.64)	1.47 (1.14-1.89)
Heterogeneity (I^2, p-value)	77%, 0.004	79%, 0.001
Publication year	**<2000**	**≥2000**
Studies (n)	5	4
Cases	1 081	3 963
RR (95%CI)	1.33 (1.10-1.60)	1.43 (0.95-2.15)
Heterogeneity (I^2, p-value)	76%, 0.002	80%, 0.002

Number of cases	**<450 cases**	**≥450 cases**
Studies (n)	5	4
Cases	1 081	3 963
RR (95%CI)	1.33 (1.10-1.60)	1.43 (0.95-2.15)
Heterogeneity (I^2, p-value)	76%, 0.002	80%, 0.002
Difference between the highest and the lowest mean of intake category	**≤3 times/week**	**>3 times/week**
Studies (n)	4	5
Cases	3 963	1 081
RR (95%CI)	1.43 (0.95-2.15)	1.33 (1.10-1.60)
Heterogeneity (I^2, p-value)	80%, 0.002	76%, 0.002
Main adjustment**	**Adjusted**	**Not adjusted**
Studies (n)	3	6
Cases	1 736	3 308
RR (95%CI)	1.17 (0.85-1.61)	1.45 (1.18-1.78)
Heterogeneity (I^2, p-value)	62%, 0.07	81%, <0.001

*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

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Fachiroh, 2012 NAS06062 Thailand	Hospital-based case-control study, Age: 48 years, M/W Thai	681/ 1 078	Hospital records	Questionnaire, interview Salted fish (pla-kem) (Included in dose-response analysis)	Incidence, nasopharyngeal cancer	≥ weekly vs never to rarely	0.92 (0.68-1.25) Ptrend:0.48	Age, sex, alcohol consumption, education years, smoking status, study center
				Unsalty fermented fish (pla-ra)			1.03 (0.75-1.41) Ptrend:0.57	
				Salty fermented fish (pla-som)			0.90 (0.58-1.40) Ptrend:0.89	
Jia, 2010 NAS06052 Guangdong, China	Hospital-based case-control study, Age: 47 years, M/W Chinese	1 375/ 1 450	Hospital records	Interview Adult canton-style salted fish intake	Incidence, nasopharyngeal cancer	≥weekly vs <monthly	1.58 (1.20-2.09) Ptrend:<0.001	Age, sex, dialect group, educational level, residential (urban/rural)
Guo, 2009 NAS06051 Guangxi, China	Case-control study, (controls from health screening program) Age: 46 years, M/W Chinese	972/ 785	Hospital records	Questionnaire, interview Salted fish	Incidence / prevalence, nasopharyngeal cancer	≥3 vs ≤0 times/month	1.90 (1.05-3.47)	Family history of nasopharyngeal cancer, occupational exposure, processed meat, smoking, wood stove use
Yuan, 2000 NAS00577	Population-based case-control study,	935/ 1032	Cancer registry	FFQ	Incidence, nasopharyngeal	≥weekly vs less than monthly	1.82 (0.86-3.88)	Age, sex, educational level, environmental factors, non-

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Shanghai, China	Age: 15-74 years, M/W Chinese			Chinese salted fish	cancer			nutrient chemicals, presence of other diseases, smoking habits
Lee, 1994 NAS01056 Singapore	Hospital-based case-control study, Age: ≤44 years, M/W Singapore Chinese	200/ 406	Hospital records	FFQ Salted fish	Incidence, nasopharyngeal cancer	≥3 vs ≤0	4.40 (0.70-25.90)	Age, sex, educational level, ethnicity
Zheng, 1994a NAS01141 Guangzhou, China	Case-control study, (controls from friends of the cases or an individual living in the area) Age: -55 years, M/W Chinese	205/ 205	Hospital records	FFQ Salted fish soft meat (Included in dose-response analysis)	Incidence, nasopharyngeal cancer	Weekly and daily vs never and yearly	17.20 (4.10-152.10)	Age, sex, area of residence
				Salted fish tough meat			11.20 (4.60-32.0)	
Sriamporn, 1992 NAS01248 Thailand	Hospital-based case-control study Age: 47 years, M/W Thai	120/ 120	Histology reports	FFQ Salted fish	Incidence, nasopharyngeal cancer	Sea-salted fish, at least once a week vs only freshwater fish	2.50 (1.20-5.20)	Age, sex, alcohol consumption, area of residence, environmental factors, smoking habits, occupation
				Salted fish 3 years prior to diagnosis		Weekly/daily vs never	Not significant P=0.41	
Yu, 1989 NAS01459 Guangzhou, China	Case-control study, (population controls from the patients neighbourhood)	306/ 306	Hospital records	FFQ Salted fish 3 years prior to diagnosis	Incidence, nasopharyngeal cancer	daily vs rarely	1.80 (0.90-3.60)	Age, sex, area of residence

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Age: ≤49 years, M/W Chinese							
Yu, 1986 NAS01608 Hong Kong	Case-control study, (controls from friends of the case) Age: 29 years, M/W Chinese	250/ 250	Hospital records	FFQ Cantonese-style salted fish	Incidence, nasopharyngeal cancer	daily vs rarely	7.50 (0.90-65.30)	Age, sex

Table 13 Salted fish intake during adulthood and nasopharyngeal cancer risk. Main characteristics of studies excluded in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclu sion
Lakhanpal, 2016 NAS06060 Imphal, Manipur, India	Hospital-based case- control study, Age: 46.5 years, M/W Indian	120/ 100	Hospital records	Questionnaire, interview Dry salted fish	Incidence, nasopharyngeal cancer	consumers vs non-consumers	1.29 (0.62-2.71)	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

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								ventilation	
Lakhanpal, 2015 NAS06059 Imphal, Manipur, India	Hospital-based case- control study, Age: 12-80 years, M/W Indian	120/ 100	Hospital records	Questionnaire, interview Dry salted fish	Incidence, nasopharyngeal cancer	consumers vs non-consumers	1.32 (0.61-2.85)	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	Excluded, result was for yes vs no comparison
Lye, 2015 NAS06058 Malaysia	Hospital-based case- control study, Age: 53 years, M/W 70.2% ethnic Chinese, 28.4% Malays	356/ 356	Hospital records	- Salted fish	Incidence, nasopharyngeal cancer	Ever vs never	1.76 (1.23-2.51)	Age, sex, alcohol consumption, ethnicity, genotype (XPD K751Q), cigarette smoking	Excluded, result was for ever vs never comparison
Ghosh, 2014 NAS06061 Manipuri, Naga and Mizo, India	Hospital-based case-control study, M/W India	64/ 100	Hospital records	Medical record and interviewed Salted fish	Incidence, nasopharyngeal cancer	yes vs no	2.61 (1.17-5.81)	Unknown adjustment, matched for ethnicity	Excluded, result was for yes vs no comparison
Hsu, 2012 NAS06053 Taiwan	Case-control study, (community	371/ 327	Hospital records	66-item FFQ, for diet 3 -10 years before	Incidence, nasopharyngeal cancer	yes vs no	0.88 (0.35-2.21)	Age, sex, educational level, ethnicity,	Excluded, result was for yes vs no comparison

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	controls) Age: 46 years, M/W Chinese	358/ 327		ascertainment Cantonese-style salted fish	Incidence, nasopharyngeal cancer, EBV positive	yes vs no	4.80 (0.55-42.30)	family history of nasopharyngeal cancer, formaldehyde, total energy intake, wood dust, years of smoking	
Xu, 2012 NAS06057 Guangdong, China	Guangdong case-control study, hospital-based case-control study Age: 14-80 years, M Chinese	1 311/ 1 571	Hospital records	Questionnaire, interview Salted fish	Incidence, nasopharyngeal cancer	weekly or more vs < monthly	1.74 (1.29-2.35) Ptrend:<0.001	Age, educational level	Excluded, study population overlapped with Jia, 2010, NAS06052
Ekburanawat, 2010 NAS06055 Thailand	Hospital-based case-control study, Age: 48 years, M/W Thai	327/ 327	Hospital records	Questionnaire, interview Salted fish consumption	Incidence, nasopharyngeal cancer	≥1 vs ≤0.9 times/week	1.38 (0.84-2.25)	Educational years, smoking	Superseded by Fachiroh, 2012, NAS06062
Ren, 2010 NAS06056 Guangdong, China	Hospital-based case-control study Age: 13-80 years, M/W Chinese	1 834/ 2 251	Hospital records	Questionnaire, interview Salt-preserved fish consumption	Incidence, nasopharyngeal cancer	Ever salted fish and family history of nasopharyngeal cancer vs Never/rarely salted fish and no family	9.38 (5.37-16.38)	Age, sex, education, smoking, consumption of alcohol, number of siblings, and number of children	Superseded by Jia, 2010, NAS06052 that was included in the dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						history of nasopharyngeal cancer			
Feng, 2007 NAS06054 Tunisia, Algeria, Morocco	Hospital-based case-control study, Age: 43 years, M/W Maghrebian populations	559/ 523	Hospital records	Questionnaire, interview Adult industrial preserved fish, unsalted canned fish	Incidence / prevalence, nasopharyngeal cancer	≥10 vs ≤9 times/year	0.40 (0.20-0.70) Ptrend:0.0045	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	Excluded, industrial preserved fish/ unsalted canned fish
Yang, 2005 NAS05679 Taiwan	Case-control study, Age: 47 years, M/W Families with two or more affected members Chinese	502/ 1 942	Cancer registry, hospitals, outpatients clinics	Dietary questionnaire, interview (self-/proxy respondents) Guangdong moldy salted fish intake between age 10 and 30 years	Incidence/mortality	Yes vs no	Similar salted fish (moldy and firm) intake after age 10 in cases and controls	Age, Sex, Family history of nasopharyngeal cancer	Excluded, no measure of association
Ward, 2000 NAS00531	National Cancer Institute Case	375/	Hospital records	Dietary history questionnaire	Incidence, nasopharyngeal	Per 5 g/week	0.80 (0.50-1.20)	Age, sex, ethnicity,	Superseded by Hsu, 2012,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Taiwan	Control (1987-1990), hospital-based case-control study, Age: 0-74 years, M/W Chinese	327		Salted fish other than Guandong salted fish	cancer			subjects w/ mothers questionnaire, total calories	NAS06053 that was included in the dose-response meta-analysis
Zou, 1999 NAS06023 Yangjiang area, Guangdong province, China	Case Control Study, Age: 14-82 years, M/W Chinese	97/ 197	Death certificate	Questionnaire Salted fish	Mortality, nasopharyngeal cancer	≥1/3.3 days vs other	3.07 (1.66-5.70)	Age, sex, educational level, environmental factors, family history of cancer, presence of other diseases	Excluded, two exposure categories only; outcome was mortality
Armstrong, 1998 NAS00749 Malaysia	Hospital-based case-control study, Age: 45 years, M/W Malaysian Chinese	282/ 282	Histology reports	Dietary history questionnaire Salted fish intake 5 years prior	Incidence, nasopharyngeal cancer	≥weekly vs <monthly	4.22 (2.23-7.99)	-	Excluded, missing cases and controls per category
Cai, 1996 NAS06010 Fujian province , China	Hospital-based case-control study, Age: 16-68 years, M/W Chinese	115/ 115	Hospital records	Dietary history questionnaire Salted fish	Incidence, nasopharyngeal cancer	≥3 vs 0-2.99 times/week	1.32 (0.99-1.79)	Age, sex, area of residence	Excluded, two exposure categories only
Ye, 1995a NAS06003	Hospital-based case-control	135/	Hospital records	Dietary history questionnaire	Incidence, nasopharyngeal	>1 vs ≤1 time/week	5.0 (1.26-19.6)	Matching factors: age, sex,	Excluded, two exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
S. Fujian province, China	study, Age: 21-75 years, M/W Chinese	135		Salted fish	cancer			area of residence	categories only (Same study as Ye, 1995b NAS06009)
Ye, 1995b NAS06009 Minan prefecture, Fujian province, China	Hospital-based case-control study, Age: 14-68 years, M/W Chinese	135/ 135	Hospital records	Questionnaire Salted fish	Incidence, nasopharyngeal cancer	>1 vs ≤1 time/week	2.74 (0.82-9.13)	Matching factors: age, sex, area of residence, multivariate adjusted	Excluded, two exposure categories only (Same study as Ye, 1995a NAS06003)
Chen, 1994 NAS06021 Guangxi province, China	Population-based Case-control study, M/W Chinese	28/ 113	Health records or death certificates	Questionnaire Salted fish	Incidence, nasopharyngeal cancer	yes vs no	5.51 (1.74-17.46)	Age, sex	Excluded, result was for yes vs no comparison
Zheng, 1994b NAS01113 Wuzhou city, Zangwu county, Guangxi province, China	Case-control study (from neighbourhood controls) Age: 42 years, M/W Chinese	88/ 176	Histology reports	FFQ Salted fish year before diagnosis	Incidence, nasopharyngeal cancer	yes vs no	Consumption during the year preceding cancer was very low for both cases (2.3%) and controls (0.6%)	Age, sex, area of residence, socioeconomic status	Excluded, no measure of association
Wang, 1993 NAS06022 Heilongjiang province, China	Population-based case-control study Age: 13-70 years, M/W Chinese	122/ 122	Pathology reports	Questionnaire Salted fish	Nasopharyngeal cancer	frequently consumed vs less consumed	8.99 P-value: 0.0127	Age, sex, environmental factors, non-nutrient chemicals, other nutrients, foods or supplements,	Excluded, missing cases and controls per category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								other nutrients, foods or supplements, other nutrients, foods or supplements, socio-economic status, vegetable intake, vegetable intake	
West, 1993 NAS01153 Philippines	Hospital-based case-control study Age: 11-83 years, M/W Filipino	104/ 101	Histology reports	Interview Salted fish	Incidence, nasopharyngeal cancer	high tertile vs low tertile	1.30 (0.69-2.60)	Age, sex, other, other nutrients, foods or supplements, other nutrients, foods or supplements	Excluded, exposure ranges not quantified
Zheng, 1993 NAS01190 Guangzhou, China	Hospital-based case-control study, M/W Chinese	205/ 205	Hospital records	FFQ Highest consumption of salted fish from: last 7 years, at age 10, and in the first 3 years	Incidence, nasopharyngeal cancer	-	Significant	-	Superseded by Zheng, 1994a, NAS01141 that was included in the dose-response meta-analysis
Ning, 1990 NAS01922 Tianjin city, Northern China	Case Control Study, (from the patients neighbourhood) Age: 45 years, M/W Chinese	100/ 300	Cancer registry	FFQ Salted fish ever consumed	Incidence, nasopharyngeal cancer	ever vs never	2.20 (1.30-3.70)	Age, sex, area of residence	Excluded, result was for ever vs never comparison
				Salted fish 3 years prior to diagnosis		Weekly/daily vs never	Not significant P=0.41		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Armstrong, 1983 NAS02182 Malaysia	Case-control study, (from neighbourhood of the case) M/W Malaysian Chinese	100/ 100	Histology reports	- Salted fish, current consumption as adult	Incidence, nasopharyngeal cancer	-	Not significant	Age, sex, area of residence, ethnicity	Excluded, no measure of association
Henderson, 1976 NAS04928 USA	Population-based case-control study, Age: 52 years, M/W Chinese	156/ 267	Cancer registry	- Current use of salted fish	Incidence, nasopharyngeal cancer	-	Not significant	Age, sex, area of residence, socio-economic status	Excluded, no measure of association

Figure 7 RR estimates of nasopharyngeal cancer by salted fish intake during adulthood

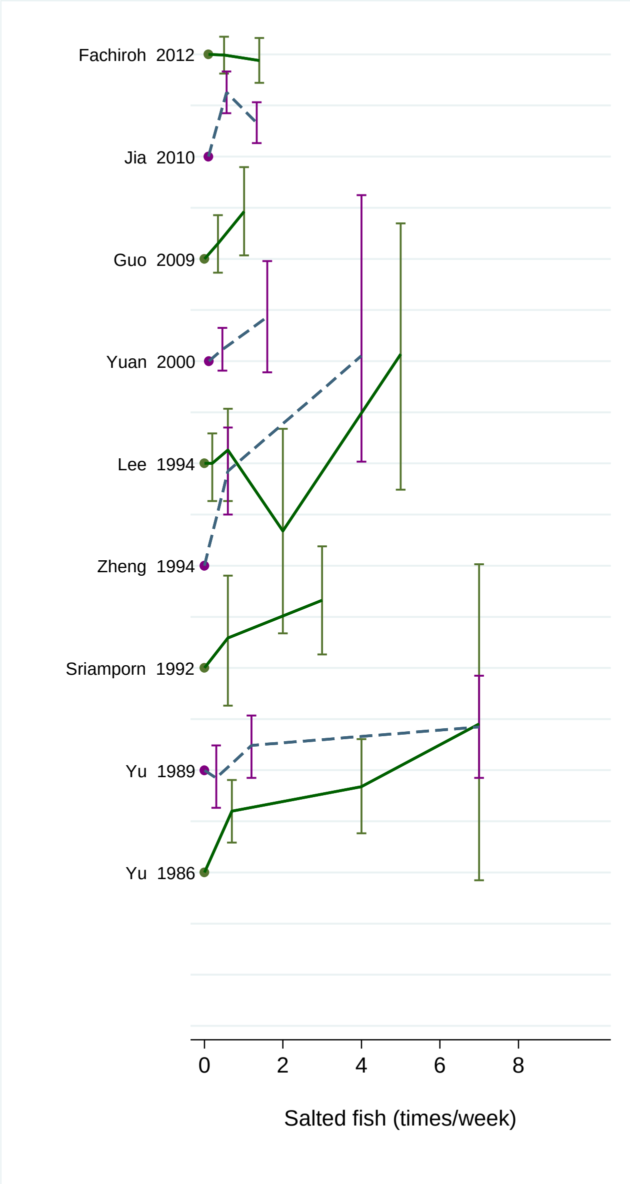
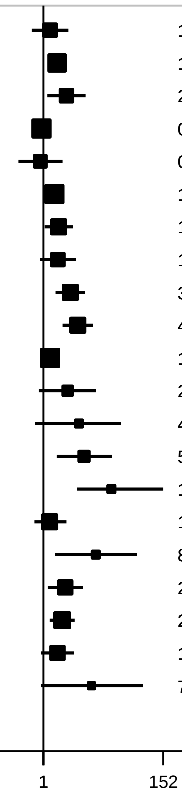


Figure 8 **RR (95% CI) of nasopharyngeal cancer for the highest compared with the lowest level of salted fish intake during adulthood**

Author	Year	Country	high vs low RR (95% CI)	Comparison
Lakhanpal	2015	India	1.32 (0.61, 2.85)	Consumers vs non-consumers
Lye	2015	Malaysia	1.76 (1.23, 2.51)	Ever vs never
Ghosh	2014	India	2.61 (1.17, 5.81)	Yes vs no
Fachiroh	2012	Thailand	0.92 (0.68, 1.25)	≥ weekly vs Never to rarely
Hsu	2012	Taiwan	0.88 (0.35, 2.21)	Yes vs no
Jia	2010	Guangdong, China	1.58 (1.20, 2.09)	Weekly or more vs < monthly
Guo	2009	Guangxi, China	1.90 (1.05, 3.47)	≥3 vs ≤0 times/month
Yuan	2000	Shanghai, China	1.82 (0.86, 3.88)	≥weekly vs <monthly
Zou	1999	Guangdong, China	3.07 (1.66, 5.70)	≥1 time/3.3 days vs other
Armstrong	1998	Malaysia	4.22 (2.23, 7.99)	≥weekly vs <monthly
Cai	1996	Fujian , China	1.32 (1.00, 1.79)	≥3 vs 0-2.99 times/week
Ye	1995	Fujian , China	2.74 (0.82, 9.13)	>1 vs ≤1 time/week
Lee	1994	Singapore	4.40 (0.70, 25.90)	≥3 vs ≤0 times/week
Chen	1994	Guangxi, China	5.51 (1.74, 17.46)	Yes vs no
Zheng	1994	Guangzhou, China	17.20 (4.10, 152.10)	Weekly and daily vs never and yearly
West	1993	Philippines	1.30 (0.69, 2.60)	Tertile 3 vs tertile 1
Wang	1993	Heilongjiang, China	8.99 (1.60, 50.57)	Frequently consumed vs less consumed
Sriamporn	1992	Thailand	2.50 (1.20, 5.20)	Sea-salted fish ≥1 times/week vs only freshweater fish
Ning	1990	Tianjin, China	2.20 (1.30, 3.70)	Ever vs never
Yu	1989	Guangzhou, China	1.80 (0.90, 3.60)	Daily vs rarely
Yu	1986	Hong Kong	7.50 (0.90, 65.30)	Daily vs rarely



*When pooled, the summary RRs were 1.98 (95% CI = 1.58-2.50) (I^2 = 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

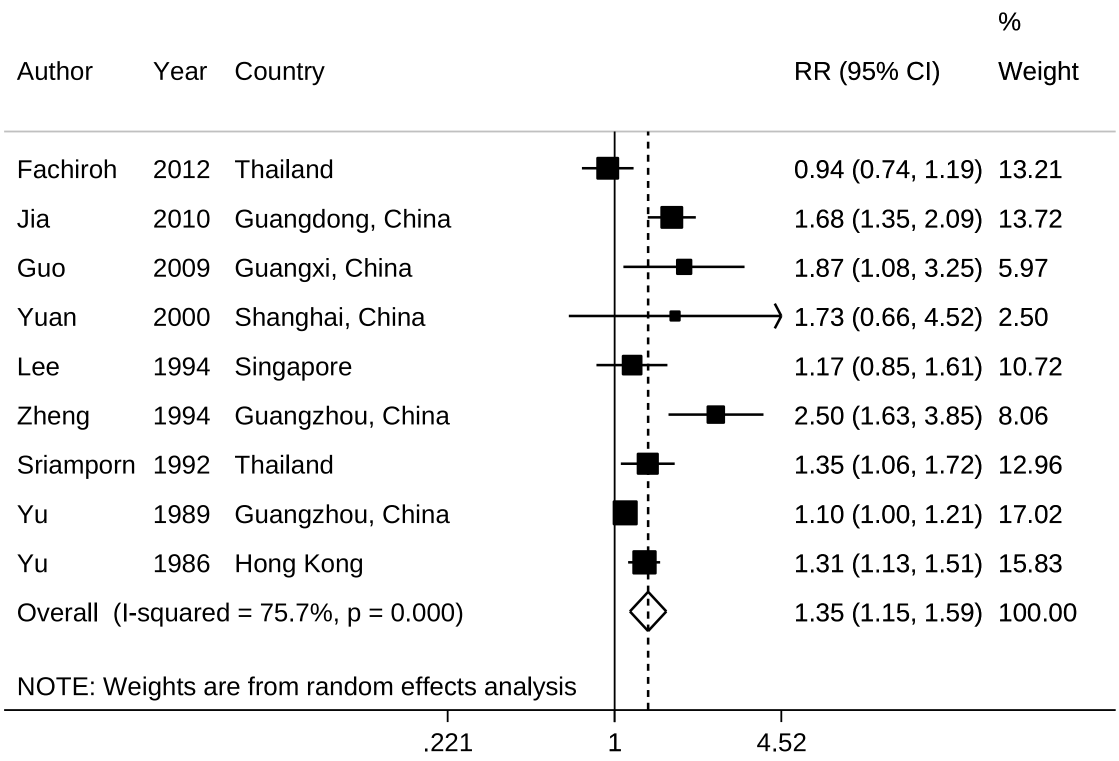


Figure 10 Funnel plot of studies included in the dose response meta-analysis of salted fish intake during adulthood and nasopharyngeal cancer risk

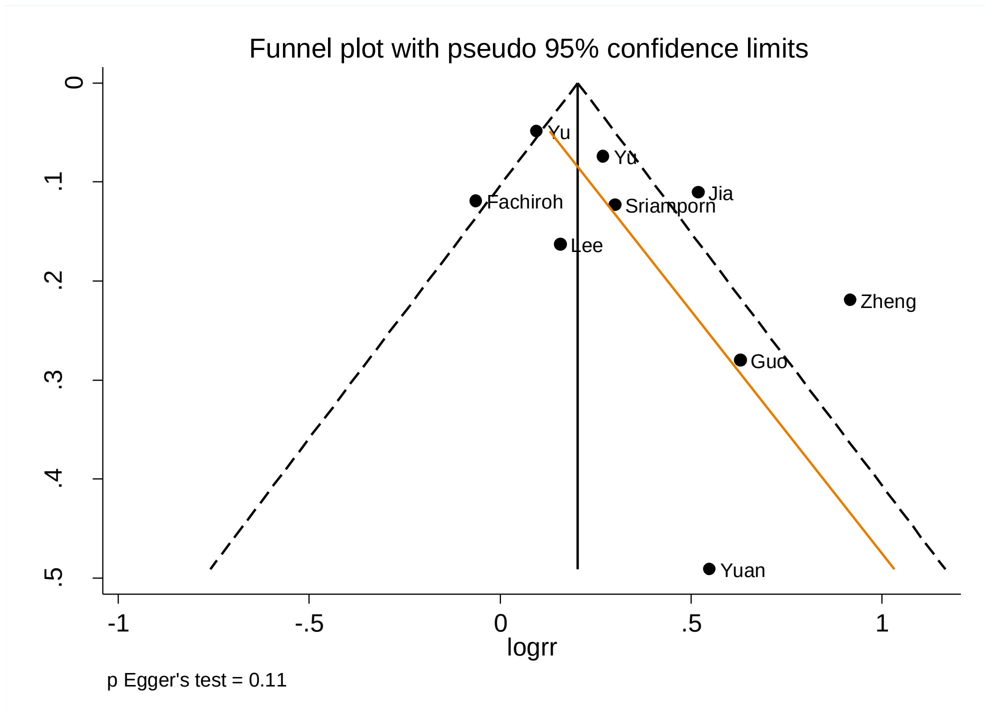
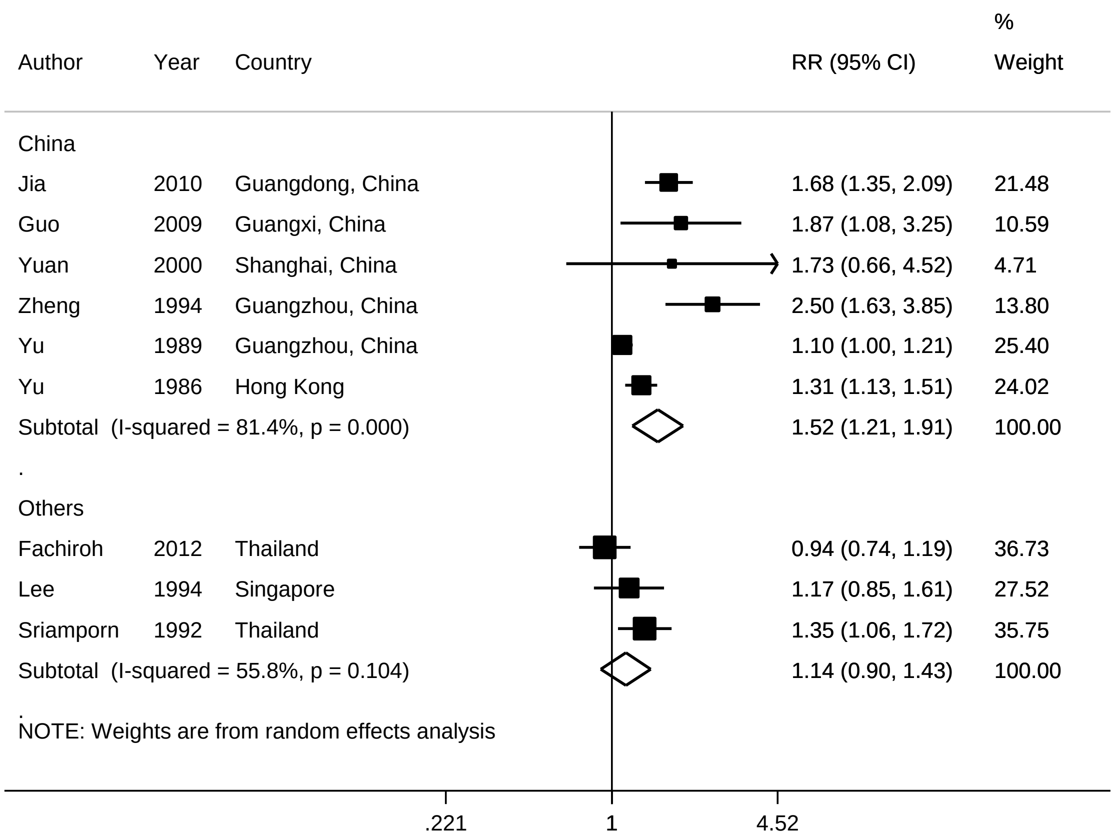


Figure 11 Relative risk of nasopharyngeal cancer for 1 time per week increase of salted fish intake during adulthood, by geographic location



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.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Controls	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Jia, 2010 NAS06052 Guangdong, China	Hospital-based case-control study, Age: 47 years, M/W Chinese	1 387/ 1 459	Hospital records	Interview Childhood (≤aged 12 years) canton-style salted fish intake	Incidence, nasopharyngeal cancer	≥Weekly vs <monthly	1.57 (1.16-2.13)	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

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, I^2=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, I^2 = 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) were1.56 (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, I^2 = 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, I^2 = 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, I^2 = 0%, P = 0.58) and not for occasional drinkers (summary RR = 0.76, 95% CI = 0.65-0.89, I^2 = 33%, P = 0.21) compared with non-drinkers (4 case-control studies).

The earlier meta-anaylsis reported slightly stronger positve association (summary RR for drinkers vs non-drinkers = 1.21, 99% CI = 1.00-1.46, I^2 = 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, I^2 = 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.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Li, 2013	14 studies (3 prospective studies, 11 case-control studies)	4 718 cases	China	Incidence, nasopharyngeal cancer	Drinkers vs non-drinkers	1.12 (0.98-1.26)	45%, 0.04
	4 case-control studies				Regular drinkers vs non-drinkers	1.18 (1.00-1.38)	0%, 0.58
	4 case-control studies				Occupational drinkers vs non-drinkers	0.76 (0.65-0.89)	33%, 0.21
Li, 2011	4 case-control studies	1 698 cases	China	Incidence, nasopharyngeal cancer	Drinkers vs non-drinkers	1.21 (1.00-1.46)	55%, 0.08
Chen, 2009*	11 case-control studies	2 898 cases	China, Hong Kong, Malaysia, Singapore, Taiwan, Thailand, United States	Incidence, nasopharyngeal cancer	Highest vs lowest alcohol intake	1.33 (1.09-1.62)	17%, 0.28
				Studies adjusted for smoking		1.26 (0.99-1.62)	-

				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.

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
Friborg, 2007 NAS06047 Singapore	Singapore Chinese Health Study (SCHS), Prospective Cohort, Age: 45-74 years, M/W, Hokkien and Cantonese dialect	173/ 61 320 12 years	Cancer registry, birth and death registry	Semi-quantitative FFQ	Incidence, nasopharyngeal cancer	Daily vs non-drinkers	1.20 (0.60-2.30) Ptrend:0.70	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	
						>7 drinks/week vs non-drinkers	1.30 (0.80-2.30) Ptrend:0.58		
Boffetta, 2001 NAS00381 Sweden	Swedish Alcoholic Study, Historical	21/ 173 665 10.6 years	Hospital records	Diagnosis of alcoholism in hospital discharge	Incidence, nasopharyngeal cancer	Alcoholic vs non-alcoholic	1.56 (0.97-2.39)	Age, sex, calendar year	Standardised incidence ratio, compared to the general
		19/			Men		1.53 (0.92-2.39)	Age, calendar	

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
	Cohort, Age: ≥20 years, M/W, Alcoholics	138 195		records				year	populations
		2/ 35 470			Women		2.03 (0.25-7.33)		

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.

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, cohort, 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

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
	years, M/W, Hokkien and Cantonese dialect Current smokers					1-39 years of smoking and 1 – 7 drinks/week vs non-smokers and non-drinkers	0.7 (0.3-1.8)	carcinoma, year of interview, intakes of protein-rich preserved food, intakes of fresh vegetables	5 cases among those with 1-39 years of smoking and 1 – 7 drinks/week
						1-39 years of smoking and >7 drinks/week vs non-smokers and non-drinkers	1.2 (0.5-3.1)		5 cases among those with 1-39 years of smoking and >7 drinks/week
						≥40 years of smoking and non-drinkers vs non-smokers and non-drinkers	2.0 (1.1-3.6)		16 cases among those with ≥40 years of smoking and non-drinkers
						≥40 years of smoking and 1 – 7 drinks/week vs non-smokers and non-drinkers	2.3 (0.9-5.9)		5 cases among those with ≥40 years of smoking and 1 – 7 drinks/week

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
						≥40 years of smoking and >7 drinks/week vs non-smokers and non-drinkers	1.8 (0.5-5.9)		3 cases among those with ≥40 years of smoking and >7 drinks/week

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.

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
Wen, 2014 NAS06049 Taiwan	Taiwan cohort study, Prospective Cohort, Age: ≥20 years, Mean age: 41.8 years M/W	165/ 309 443 7.07 years	Cancer registry and death certificates	Serum iron was measured by a Nitroso-PSAP method	Incidence, nasopharyngeal cancer	≥120 vs 60-79 µg/dL	1.43 (0.79-2.57)	Age, gender, BMI, systolic blood pressure, total cholesterol, C-reactive protein, hemoglobin, smoking, alcohol consumption, physical activity	46 cases vs 19 cases
						≥140 vs 60-79 µg/dL	1.09 (0.54-2.18)		20 cases vs 19 cases
						<60 vs 60-79 µg/dL	1.69 (0.85-3.37)		22 cases vs 19 cases

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

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
Samanic, 2004 NAS06048 USA	Veterans Obesity and Cancer Study, Prospective Cohort, Age: 18-100 years, M, Black and white male veterans	610/ 3 668 486 12 years	Hospital records	Discharge diagnosis of obesity made by veterans' hospital	Incidence, nasopharyngeal cancer White men	Obese vs non-obese	0.91 (0.64-1.31)	Age, calendar year	Compared to men hospitalised for other reasons; RRs were not significantly different (P>0.05) between black and white men
		171/ 832 214 12 years			Black men		0.76 (0.34-1.73)		

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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.

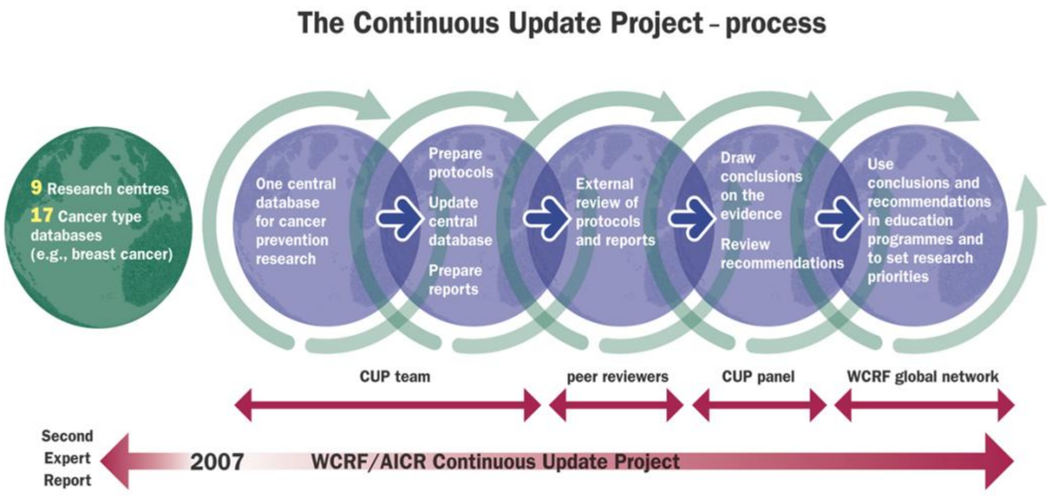
The World Cancer Research Fund/ American Institute for Cancer Research: (WCRF/AICR) has been a global leader in elucidating the relationship between food, nutrition, physical activity and cancer. The First and Second Expert Reports (1;2) represent the most extensive analyses of the existing science on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

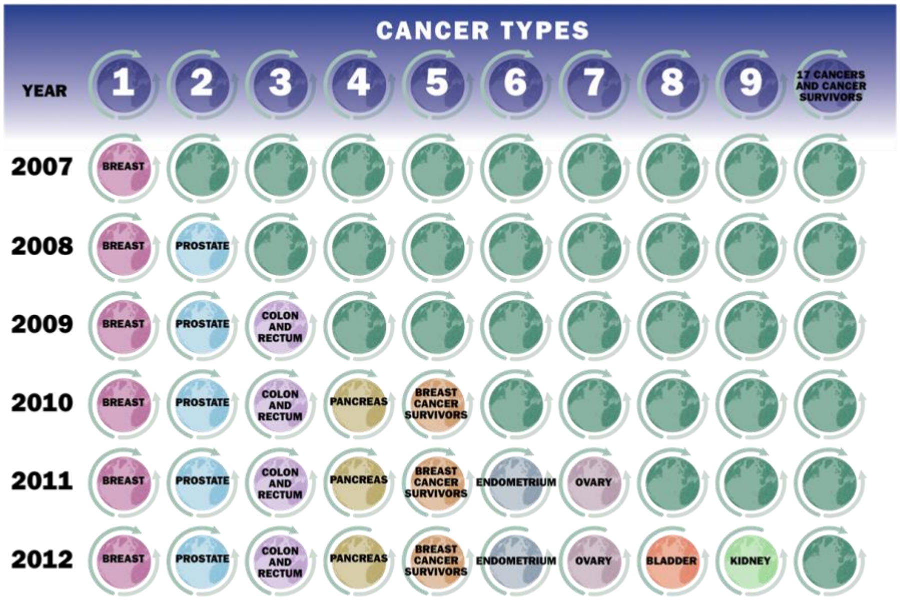
The WCRF database has been updated at ICL in a rolling programme. The CUP started in 2007 he first cancer to be updated was breast cancer, followed by prostate and colorectal cancers. When a cancer site is included in the CUP, the team at ICL keeps updating the database for that cancer and all the other 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).

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 incident 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 (30.94, 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.

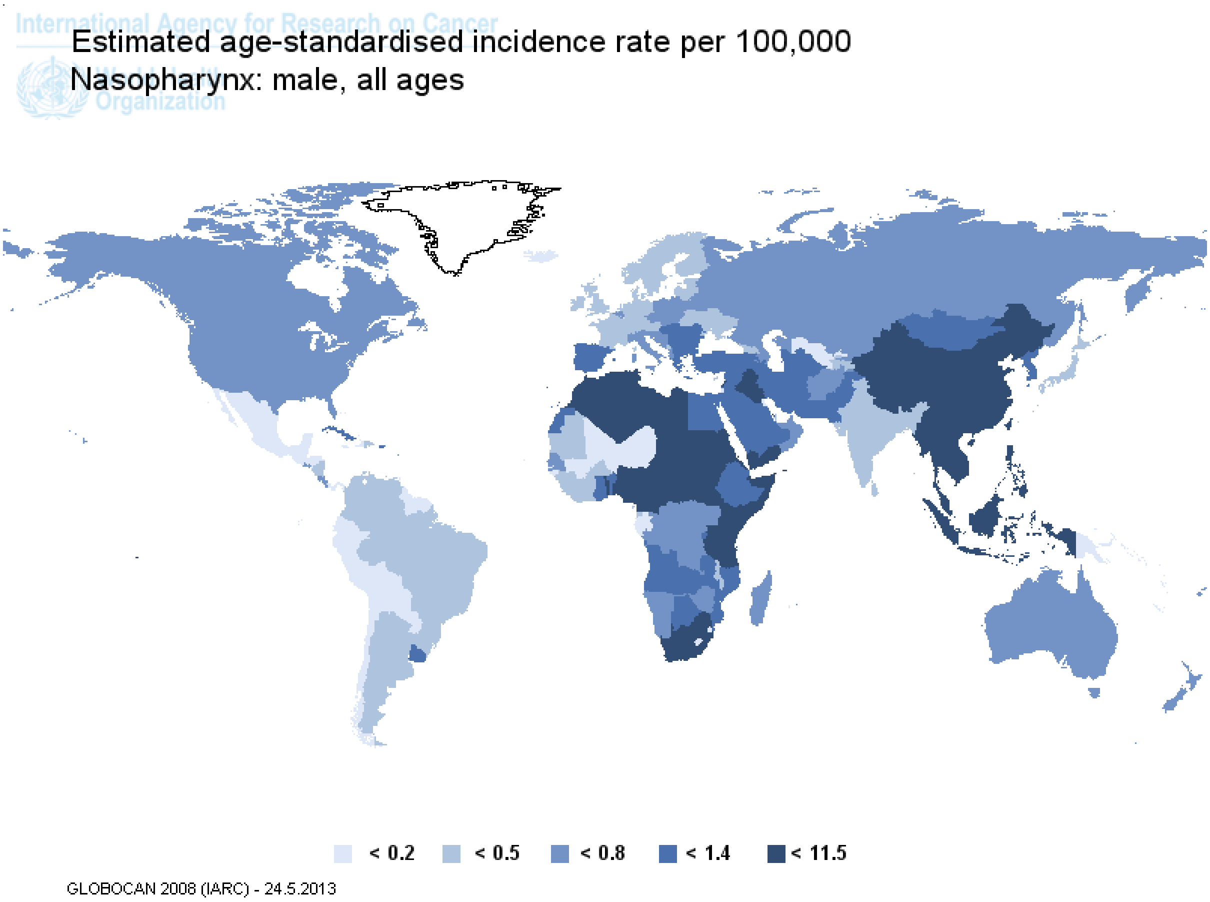
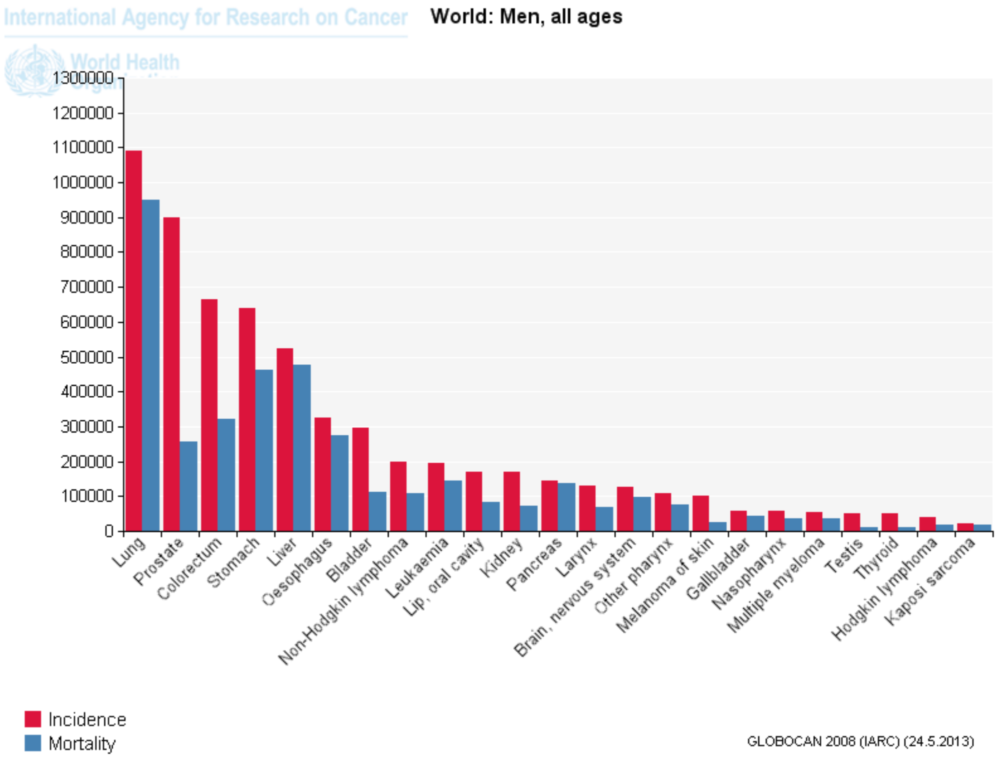
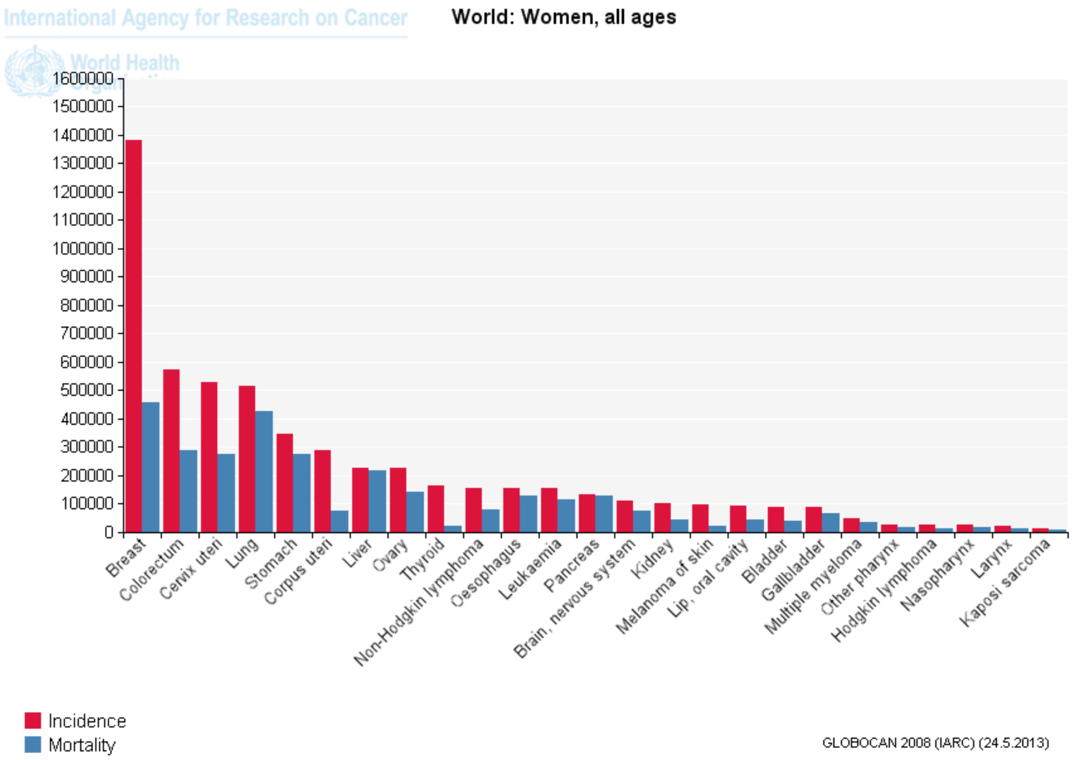


Figure 4. Worldwide age standardized rates of incidence and mortality from cancer in men and women.





Dietary factors

There is evidence that Cantonese-style salted fish probably increases the risk of nasophayngeal 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.

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.

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Cantonese-style salted fish[1]**
Limited — suggestive	Non-starchy vegetables[2] Fruits[2]	
Limited — no conclusion	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	
Substantial effect on risk unlikely	None identified	

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.

World Cancer Research Fund American Institute for Cancer Research

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

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

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:

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

*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 ClinialTrials.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

(http://www.dietandcancerreport.org/cancer_resource_center/downloads/SLR/Nasopharynx_SLR.pdf)

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.

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

		studies NAS+ consecutive digits	automatically by the data extraction software when performing the data extraction.

7. DATA EXTRACTION

The IC team will update the WCRF-AICR central database using an interface created or 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, esclusion 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.

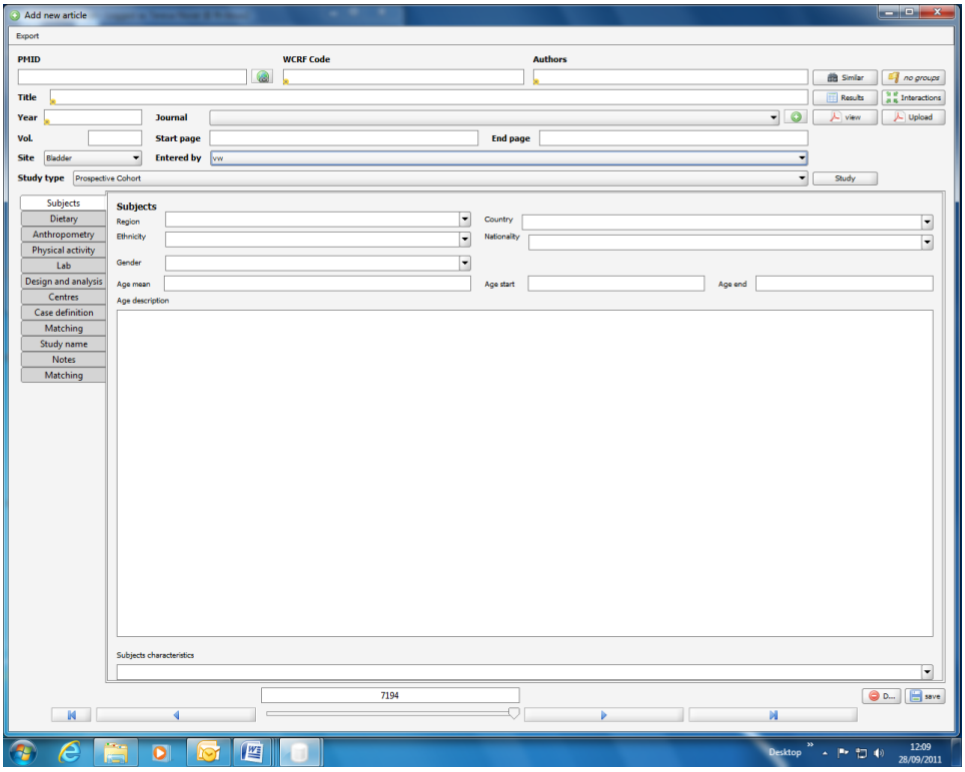
The exposures/interventions will be codified during data extraction as in the Second Expert Report. The main headings and sub-headings codes are in **Annex 2**. Wherever possible, the reviewer will use the sub-heading codes. Additional codes have been programmed in the database to facilitate the data 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.

Exposure	Increment unit
Total fruits and vegetables	100 g
Non starchy vegetables	100 g
Fruits	100 g
Citrus fruits	50 g
Red meat	100 g
Processed meat	50 g
Poultry	100 g
Fish	50 g
Eggs	25 g
Salt	1 g
Coffee	1 cup
Tea	1 cup
Alcoholic drinks	1 drink/day
Alcohol (as ethanol)	10 g
Dietary calcium	200 mg
Dietary fibre	10 g
Folate	100 µg
Blood selenium	10 µg/L
Beer	10 g/day (approx. one drink)
Wine	10 g/day (approx. one drink)

BMI	5 kg/m^2
Waist	2.5 cm (1 inch)
Waist-to-hip	0.1 unit
Height	5 cm
Physical activity	5 MET-h per week

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 of 5 in each study design
- at least 5 new reports of case-control studies have been published

The minimum number of o 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](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

Type of data	Problem	Approach
Dose-response data	Serving size is not quantified or ranges are missing, but group descriptions are given	Use serving size recommended in SLR
	Standard error missing	The p value (either exact or the upper bound) is used to estimate the standard error
Quantile-based data	Numbers of controls (or the denominator in cohort studies) are missing	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
	Confidence interval is missing	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

		obtained in an adjusted analysis)
	Group mean are missing	This information may be estimated by using the method of Chêne and Thompson (32) with a normal or lognormal distribution, as appropriate, or by taking midpoints (scaled in unbounded groups according to group numbers) if the number of groups is too small to calculate a distribution (3-4 groups)
Category data	Numbers of controls (or the denominator in cohort studies) is missing	Derive these numbers from the numbers of cases and the reported odds ratios (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

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

Item	Conversion of one unit
Beer	400ml serving
Cereals	60g serving
Cheese	35g serving
Dried fish	10g serving
Eggs	55g serving (1 egg)
Fats	10g serving
Fruit & Vegetables	80g serving
Fruit Juice	125ml serving
General drinks inc. soft & hot drinks	200ml serving
Meat & Fish	120g serving

Milk	50ml serving
Milk as beverage	200ml serving
Processed cheese slice	10g serving
Processed meat	50g serving
Shellfish	60g serving
Spirits	25ml serving
Staple foods (rice, pasta, potatoes, beans & lentils, foods boiled in soy sauce)	150g serving
Water & Fluid intake	8oz cup
Wine	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 counfounders, 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):

Author, Year, country, WCRF Code	Study design	Country, Ethnicity, other characteristics	Age (mean)	Cases (n)	Non cases (n/person-years)	Case ascertainment	Follow-up (years)

Assessment details	Category of exposure	Subgroup	No cat	RR	(95% CI)	p trend	Adjustment factors						
							A	B	C	D	E	F	G

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.

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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]

#2 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab]

#3 food and beverages[MeSH Terms]

#4 food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR

wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut*[tiab] OR groundnut*[tiab] OR (seeds[tiab] and (diet*[tiab] OR food*[tiab])) OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR ((fat[tiab] OR fats[tiab] OR fatty[tiab]) AND (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR (oils[tiab] AND and (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab]or serum[tiab] or plasma[tiab])) OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab] OR tomato*[tiab]

#5 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR (ethanol[tiab] and (drink*[tiab] or intake[tiab] or consumption[tiab])) OR yerba mate[tiab] OR ilex paraguariensis[tiab]

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

#7 pesticide*[tiab] OR herbicide*[tiab] OR DDT[tiab] OR fertiliser*[tiab] OR fertilizer*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate*[tiab] OR veterinary drug*[tiab] OR polychlorinated dibenzofuran*[tiab] OR PCDF*[tiab] OR polychlorinated dibenzodioxin*[tiab] OR PCDD*[tiab] OR polychlorinated biphenyl*[tiab] OR PCB*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated hydrocarbon*[tiab] OR microbial contamination*[tiab]

#8 food preservation[MeSH Terms]

#9 mycotoxin*[tiab] OR aflatoxin*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack*[tiab] OR refrigerate*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive*[tiab] OR colouring*[tiab] OR coloring*[tiab] OR flavouring*[tiab] OR flavoring*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment*[tiab] OR processed[tiab] OR antioxidant*[tiab] OR genetic modif*[tiab] OR genetically modif*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]

#10 cookery[MeSH Terms]

#11 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR (microwave[tiab] and (diet*[tiab] or food*[tiab])) OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab] OR dietary acrylamide[tiab]

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

#13 salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR ((linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab]) AND (diet*[tiab] or food*[tiab] or adipose [tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#14 vitamins[MeSH Terms]

#15 supplements[tiab] OR supplement[tiab] OR vitamin*[tiab] OR retinol[tiab] OR carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR (sodium[tiab] AND (diet*[tiab] or food*[tiab])) OR iron[tiab] OR ((calcium[tiab] AND (diet*[tiab] or food*[tiab] or supplement*[tiab])) OR selenium[tiab] OR (iodine[tiab] AND and (diet*[tiab] or food*[tiab] or supplement*[tiab] or deficiency)) OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab] OR lycopene[tiab]

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

#17 recreational activit*[tiab] OR household activit*[tiab] OR occupational activit*[tiab] OR physical activit*[tiab] OR physical inactivit*[tiab] OR exercise[tiab] OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy balance[tiab] OR energy density[tiab]

#18 body weight [MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms] OR obesity [MeSH Terms] OR obesity [MeSH Terms]

#19 weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio*[tiab] OR weight change [tiab] OR adiposity [tiab] OR abdominal fat [tiab] OR body fat distribution [tiab] OR body size [tiab] OR waist-to-hip ratio [tiab]

#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]

#**24** malign*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR neoplasm*[tiab]

#**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 breast-fed

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.

2.3Pulses (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

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

3.4 Soft drinks

Soft drinks that are both carbonated and sugary should be reported under this general heading. Drinks that contain artificial sweeteners should be reported separately and labelled as such.

3.4.1 Sugary (not carbonated)

3.4.2 Carbonated (not sugary)

The precise definition used by the studies should be highlighted, as definitions used for various soft drinks vary greatly.

*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, oOesophageal and pancreas, it may be important to report results about specific cured foods, cured meats and smoked meats. N-*nitrososamines 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