World Cancer Research Fund International Systematic Literature Review

The Associations between Food, Nutrition and Physical Activity and the Risk of Mouth, Pharynx and Larynx cancer

Imperial College London

Continuous Update Project Team Members

Teresa Norat
Elli Polemiti
Doris Chan
Leila Abar
Snieguole Vingeliene
Ana Rita Vieira
Dagfinn Aune

WCRF Coordinator:

Rachel Thompson

Statistical advisor:

Darren C. Greenwood

Data manager:

Christophe Stevens

Date completed:
October 2015

Date reviewed:
February 2016

Date revised:
April 2016

Table of Contents

List of Figures

List of Tables

List of abbreviations

ACS	American Cancer Society
aMED	alternative Mediterranean Diet
BMI	Body Mass Index
CI	Confidence Interval
CUP	Continuous Update Project
FFQ	Food Frequency Questionnaire
HC	Hip Circumference
HEI-2005	Healthy Eating Index-2005
HNC	Head and Neck cancer
HR	Hazard Ratio
HRR	Hazard Rate Ratio
INHANCE	International Head and Neck Cancer Epidemiology
NCI	National Cancer Institute
NOS	Not otherwise specified
NPC	Nasopharyngeal Cancer
OR	Odds Ratio
RO	Relative Odds
RR	Relative Risk
SCC	Squamous Cell Carcinoma
SIR	Standardised Incidence Ratio
SLR	Systematic Literature Review
SMR	Standardised Morbidity Ratio
UADT	Upper Aerodigestive Tract
WC	Waist Circumference
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research
WHR	Waist to Hip Ratio

List of Abbreviations of cohort study names

AMORIS	Swedish Apolipoprotein Mortality Risk
APCSC	Asia-Pacific Cohort Studies Collaboration
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention
BRHS	British Regional Heart Study
CCHS	Copenhagen City Heart Study
EPIC	European Prospective Investigation into Cancer and Nutrition
HHP	Hawaiian Prospective UADT Study
IWHS	Iowa Women's Health Study Cohort
JACC	Japan Collaborative Cohort study
JAMS	Japanese Alcoholic Men Study
KCS	Kangwha Cohort Study

KNHIC	Korean National Health Insurance Corporation
KPMCP	Kaiser Permanente Medical Care Program
KRIS-MHDPS	Kaunas Rotterdam Intervention Study and Multifactorial Ischemic Heart Disease Prevention Study
MCCS	Melbourne Collaborative Cohort Study
MWS	Million Women Study
NHS	Nurse Health Study
NIH-AARP	National Institute of Health – (formerly known as) American Association of Retired Person Diet and Health Study
NLCS	Netherlands cohort study
PLCO	Prostate, Lung, Colorectal, Ovarian cancer screening trial
SCHS	Singapore Chinese Health Study
TOCSS	Trivandrum Oral Cancer Screening study
WHI	Women's Health Initiative

Background

The main objective of the present systematic literature review (SLR) is to update the 2005 WCRF/AICR review of epidemiologic studies on the association between foods, nutrients, physical activity, body adiposity and the risk of mouth, larynx and pharynx cancer and for combination of those cancers in men and women (Figure 1).

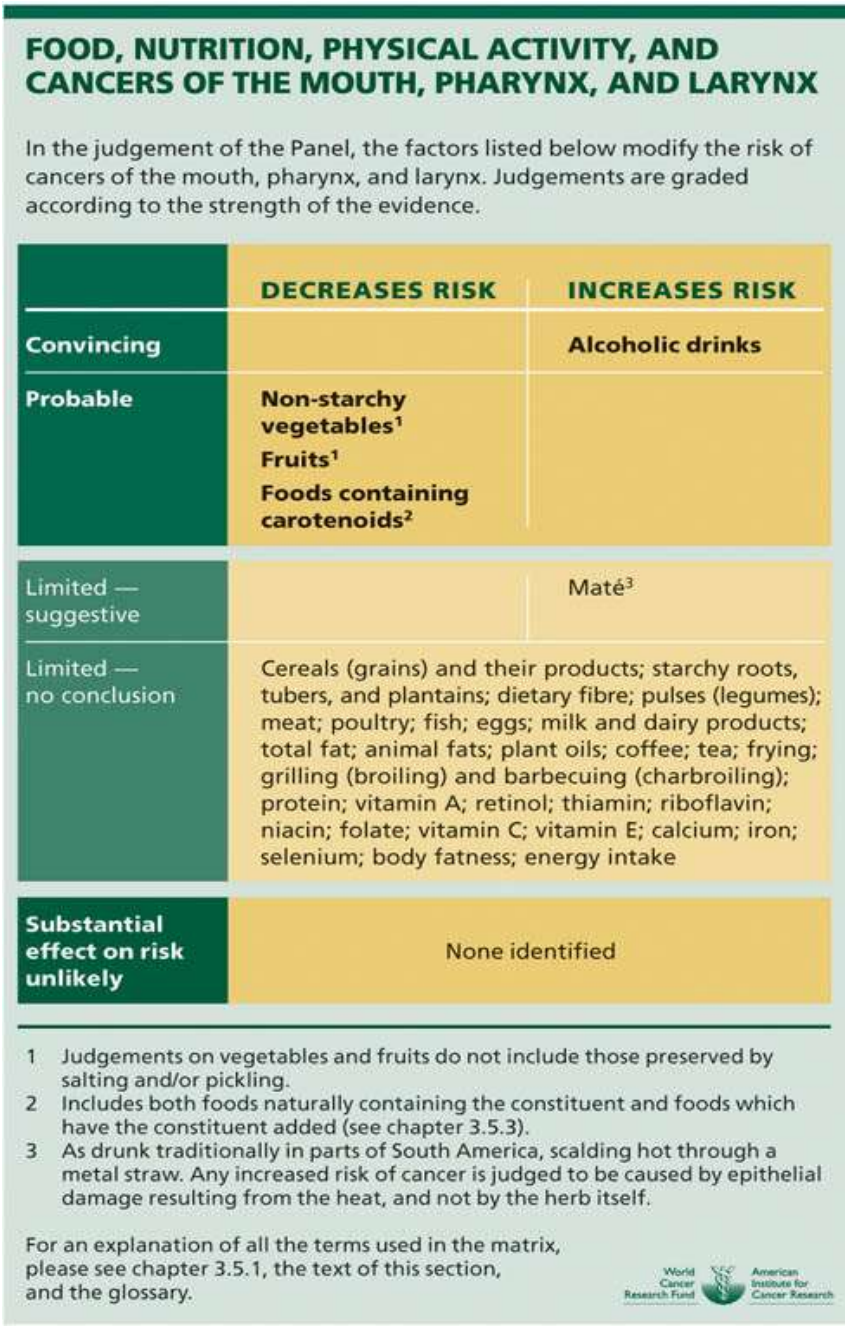
The methods of the CUP SLR are described in details in the protocol for the CUP review on mouth, larynx and pharynx cancer (version 2, August 2013 in Annex).

This CUP 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.

Modifications to the protocol

Case-control studies were not included individually in the review. Instead, the pooled results of the International Head and Neck Cancer Epidemiology (INHANCE) consortium of case-control studies are described. Case-control studies were reviewed for mate intake because this exposure is only present in specific populations and has not been investigated in the INHANCE consortium.

Figure 1. Summary of judgements of the WCRF-AICR Second Expert Report, 2007



FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCERS OF THE MOUTH, PHARYNX, AND LARYNX

In the judgement of the Panel, the factors listed below modify the risk of cancers of the mouth, pharynx, and larynx. Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing		**Alcoholic drinks**
Probable	**Non-starchy vegetables[1]** **Fruits[1]** **Foods containing carotenoids[2]**	
Limited — suggestive		Maté[3]
Limited — no conclusion	Cereals (grains) and their products; starchy roots, tubers, and plantains; dietary fibre; pulses (legumes); meat; poultry; fish; eggs; milk and dairy products; total fat; animal fats; plant oils; coffee; tea; frying; grilling (broiling) and barbecuing (charbroiling); protein; vitamin A; retinol; thiamin; riboflavin; niacin; folate; vitamin C; vitamin E; calcium; iron; selenium; body fatness; energy intake	
Substantial effect on risk unlikely	None identified	

1 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
2 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
3 As drunk traditionally in parts of South America, scalding hot through a metal straw. Any increased risk of cancer is judged to be caused by epithelial damage resulting from the heat, and not by the herb itself.

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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Notes on methods

- In the document, CUP or CUP SLR refers to the updated systematic literature review (SLR) that is the content of this document; 2005 SLR refers to the SLR conducted for the 2007 Second Expert Report.
- The article search and WCRF database update for the Second Expert Report ended in December 30th 2005. The CUP team at IC updated the search from January 1st 2006 up to April 30th 2015 (see Figure 2).
- Subsections and headings for randomised controlled trials (RCT) are indicated only for exposures in which RCT were identified.
- Linear dose-response meta-analyses were updated when at least two new publications with enough data for dose-response meta-analysis were identified during the CUP and if there were in total five cohort studies or five randomised controlled trials. The meta-analyses include studies identified during 2005 SLR and studies identified during the CUP SLR.
- Exposures for which the evidence was judged as convincing, probable or limited-suggestive in the Second Expert Report were reviewed even if the number of publications was below the previous figures; in most cases, the new data on these exposures are tabulated and no meta-analyses were conducted.
- The increment units used in the linear dose-response analyses were chosen to be consistent with other CUP SLRs, which may not be comparable with those used in the meta-analyses in the previous MPL 2005 SLR. However, if most of the identified studies reported servings, times, these were used as increment unit, as indicated in the Protocol.
- The statistical methods to derive missing data are described in the protocol.
- The interpretation of heterogeneity tests should be cautious as the number of studies is low. Visual inspection of the forest plots is recommended.
- The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity. Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for substantially more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects.
- Only summary relative risks estimated with random effect models are shown.
- Highest vs lowest forest plots show the relative risk estimates for the highest vs the reference category in each study. The overall summary estimate was not calculated.
- The dose-response forest plots show the relative risk per unit of increase for each study (most often derived by the CUP review team from categorical data). The relative risk is denoted by a box (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows the summary relative risk estimate and corresponding 95% CI. The unit of increase is indicated in each figure and in the summary table for each exposure.

- Dose-response plots of each study showing the RR estimates for each exposure level are also presented. The relative risks estimates were plotted in the mid-point of each category level (x-axis) and connected through lines.
- Exploratory nonlinear dose-response meta-analyses were conducted only when there were five or more studies with three or more categories of exposure – a requirement of the method. Nonlinear meta-analyses are not performed for this report.

Outcomes identified

The results of the studies are presented by cancer site under each exposure. However, when only one or two studies were identified for several cancer sites, the results for the different cancer sites were summarised in a single section.

The exposure code is that used in SLR guidelines (for instance for comparability with other WCRF SLR).
The cancer sites reviewed are:

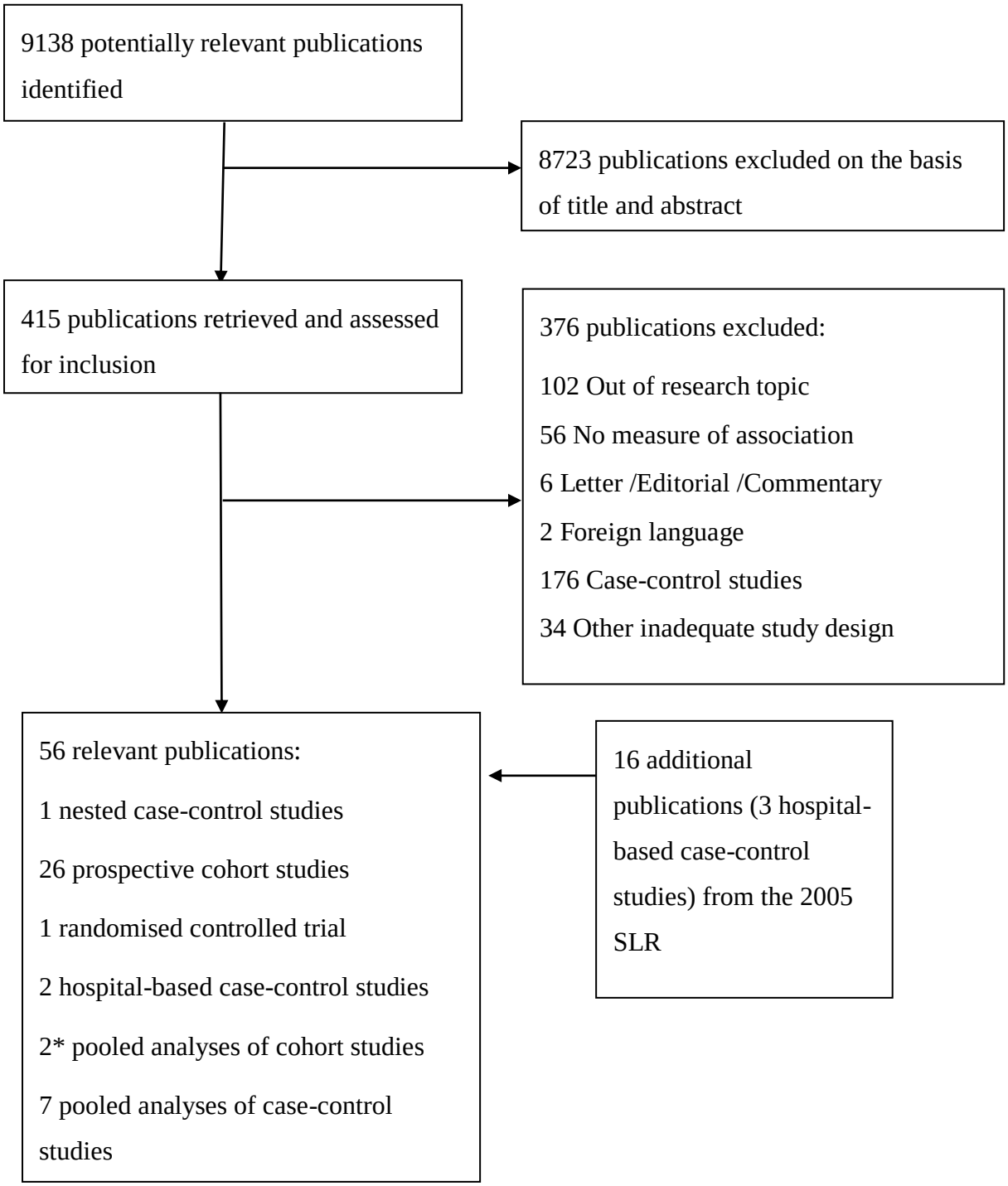
- Cancers of the oral cavity: include malignancies of the lips, the tongue, the inside lining of the cheeks (buccal mucosa), the floor of the mouth, the gums (gingiva), the palate, and the salivary glands. Most studies excluded cancer of the lip and salivary glands.
- Cancer of the pharynx: includes tumours of the nasopharynx, the oropharynx (including tonsils) and the hypopharynx. Studies on nasopharyngeal cancer were not reviewed.
- Cancers of the larynx.
- Head and neck cancer (HNC): includes cancers of the oral cavity, pharynx (but not nasopharynx) and larynx.
- Cancers of the upper aerodigestive tract (UADT): include head and neck cancers and oesophageal cancer.

Continuous Update Project: Results of the search

Figure 2. Flow chart of the search for mouth, pharynx and larynx cancer – Continuous Update Project

Search period January 1st 2006 – April 30th 2015

Cohort studies. Results by exposure



*One pooled analysis of cohort studies was published online after the date of literature search

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

The exposure code is the exposure identification in the database.

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
1	Patterns of diet	5	5	10
2.1.2	Starchy roots, tuber and plantains	1	2	3
2.2	Total fruits and vegetables	0	4	4
2.2.1	Total vegetables	0	3	3
2.2.1.1	Other types of vegetables	2	4	6
2.2.2	Fruits	2	3	5
2.2.2.1	Citrus fruits	1	3	4
2.2.2.2	Other fruits	1	1	2
2.2.3	Pulses (legumes)	2	0	2
2.5.1	Meat	1	1	2
2.5.1.2	Processed meat	3	2	5
2.5.1.3	Red meat	1	2	3
2.5.1.4	Poultry	0	2	2
2.5.2	Fish	2	2	4
2.5.7	Milk and dairy products	2	1	3
3.4	Soft drinks	0	1	1
3.5	Fruit juices	1	1	2
3.6.1	Coffee	2	4	6
3.6.2	Tea	1	3	4
3.6.2.2	Green tea	1	1	2
3.6.3	Mate	3	2	5
3.7.1	Total alcoholic drinks	7	23	30
3.7.1.1	Beers	2	3	5
3.7.1.2	Wines	2	4	6
3.7.1.3	Spirits	2	0	2
3.7.1.4	Other alcoholic drinks	0	5	5
4.3	Food processing methods	1	0	1
4.4.2	Acrylamide	0	1	1
5.5.1.1	Retinol	2	0	2
5.5.1.2	Provitamin A carotenoids (serum levels)	2	0	2
5.5.1.2	Dietary carotenoids	1	0	1
5.5.2	Non-provitamin A carotenoids	1	0	1
5.5.10	Vitamin D (and calcium)	0	3	3
5.5.11	VItamin E	3	0	3
5.6.3	Calcium (and vitamin D)	1	1	2
6.1.1.2	Recreational physical activity	0	5	5
8.1.1	BMI	0	7	7

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
8.2.1	Waist circumference	0	1	1
8.2.2	Hip circumference	0	1	1
8.2.3	Waist to hip ratio	0	1	1
8.3.1	Height	0	4	4

Note: the number of publications identified for other exposures is 1 or null (not shown in the table)

1. Patterns of diet

Cohort studies

Summary

Ten publications from eight cohorts (from which five publications identified in the 2005 SLR) have investigated dietary patterns in relation to oral cancers (four publications from three cohorts), cancers of the pharynx (one cohort), mouth and pharynx (three publications from two cohorts), larynx (three publications from two cohorts), head and neck (HN) (two cohorts) and upper aero-digestive tract (UADT) (two cohorts). Some significant inverse associations with patterns that can be considered "healthy" and patterns rich in plant foods were observed in women but not in men and others only in smokers. The studies were adjusted for smoking and alcohol intake and other potential confounders. No meta-analysis was conducted because the patterns investigated in the studies were not comparable. The study characteristics and results are described and tabulated.

Healthy Diet Indices

No cohort studies were identified in the 2005 SLR. Three publications (from two cohort studies) on healthy diet indices and oral cavity, pharyngeal cancer, laryngeal, HN and UADT cancers were identified in CUP (Kabat, 2015; Li, 2014; Romaguera, 2012).

Three indices of healthy diets (ACS, HEI-2005, aMed) were investigated in one cohort study (NIH-AARP) in relation to the risk of cancers of the mouth, pharynx and larynx and the WCRF score and risk of UADT cancers was investigated in EPIC.

The HEI-2005 score assess concordance with 2005 Dietary Guidelines for Americans, and includes intakes of plant foods, milk, meat, saturated fat, sodium, energy from solid fat, alcohol, and added sugar.

The aMed score is a modified Mediterranean Diet score that includes intakes of vegetables (excluding potatoes), legumes, fruit, nuts, whole grains, fish, ratio of monounsaturated to saturated fat, red and processed meat and alcohol. Adherence to the score and risk of cancers of the oral cavity were investigated in the NIH-AARP.

The ACS score (American Cancer Society cancer prevention guidelines) includes maintaining a healthy body weight, engaging in moderate to vigorous physical activity, healthy dietary choices and limiting alcohol intake.

The WCRF score was constructed based on the WCRF/AICR recommendations on weight management, physical activity, foods and drinks that promote weight gain, plant foods, animal foods, alcoholic drinks, and breastfeeding (in women).

<u>Oral cavity</u>

In the NIH-AARP cohort higher adherence to the HEI-2005, the aMed and the ACS guidelines were related to lower risk of squamous cell carcinomas of the oral cavity in women but not in men. For the HEI-2005, the hazard ratios were 0.84; 95% CI 0.63-1.14, p-

trend= 0.25 in men and 0.58; 95% CI 0.36-0.96, p-trend= 0.004 in women for the comparison of scores 7-9 to 0-2. For the same comparison of the aMed, the hazard ratios were 0.95; 95% CI 0.66- 1.37, p-trend= 0.31 in men and 0.47; 95% CI 0.24- 0.93, p< 0.0001 in women (Li, 2014). The numbers of cases in the analyses were 572 in men and 208 in women. Analyses were adjusted for age, race, smoking, alcohol intake, education, BMI, physical activity, usual activity, and total energy intake. No effect modification by smoking or alcohol was observed, although no association with head and neck cancers was found in never-smokers men (data for oral cancers not shown). The authors reported that it was not clear why associations may have differed across subgroups of smoking status and sex. In the same cohort (NIH-AARP) (Kabat, 2015), for the ACS (for score 8-11 compared to 0-3) the hazard ratios were 0.79; 95% CI 0.64-0.97, p-trend= 0.06 in men, 862 cases and HR=0.71; 95% CI 0.48-1.06, p-trend= 0.03 in women, 292 cases. The adjustments factors included age, educational, level, ethnicity, smoking status, marital status and energy intake.

Oro-hypopharynx cancer

The NIH-AARP evaluated the associations of the HEI-2005 and the aMed scores and risk of SCC of oro/hypopharynx (Li, 2014). No significant associations were observed.

For HEI-2005, the hazard ratios for scores 7-9 compared to 0-2 were 0.64; 95% CI 0.41-1.01, p-trend= 0.008 in men and 0.42; 95% CI 0.17-1.08, p-trend= 0.054 in women. For the aMed score, the hazard ratios were 0.91; 95% CI 0.54-1.52, p-trend= 0.046 in men 0.68; 95% CI 0.35, 1.32, p-trend= 0.079 in women (7-9 and 5-6 highest scores in men and women respectively compared to 0-2). Adjustment factors included age, race, smoking, alcohol intake, education, BMI, vigorous physical activity, usual activity and total energy intake. The numbers of cases were 263 in men and 74 in women. No effect modification by smoking or alcohol was observed, although no association with head and neck cancers was found in never-smokers men (data for pharyngeal cancers not shown). The authors reported that it was not clear why associations may have differed across subgroups of smoking status and sex.

Laryngeal cancer

The NIH-AARP evaluated the associations of the HEI-2005 (Li, 2014), aMed scores (Li, 2014) and the ACS (Kabat, 2015), and risk of SCC of the larynx. An inverse significant association was observed only for the HEI-2005 in men and women.

The hazard ratios for the comparison of HEI-2005 scores 7-9 with 0-2 were 0.70; 95% CI 0.51-0.96, p-trend= 0.098 in men and 0.40; 95% CI 0.17-0.93, p-trend= 0.0007 in women. For the aMed score, the hazard ratios were 0.68; 95% CI 0.45-1.03, p-trend= 0.059 in men and 0.59; 95% CI 0.18-2.01, p-trend= 0.075 in women (7-9 scores compared to 0-2). Adjustment factors included age, race, smoking, alcohol intake, education, BMI, vigorous physical activity, usual activity and total energy intake. The numbers of cases were 526 in men and 96 in women. The authors reported no effect modification by smoking or alcohol for head and neck cancers, although an association with head and neck cancers was observed in smokers and former smokers men and women (data for laryngeal cancers not shown) but not

in never-smokers men. It was not clear why associations may have differed across subgroups of smoking status and sex

For ACS guidelines, in another publication of the NIH-AARP including 620 cases of laryngeal cancer, the HR for score 8-11compared to score 0-3 in men and women was 0.82; 95% CI 0.64-1.05 p-trend= 0.06. Adjustments factors included age, educational, level, ethnicity, smoking status, marital status and energy intake (Kabat, 2015).

Head and Neck cancer

The NIH-AARP examined the association between the HEI-2005 and the aMED score and the risk of or associations or trends were observed. For HEI-2005, the hazard ratios comparing score 7-9 to 0-3 were 0.74; 95% CI 0.61-0.89; p-trend= 0.008 in men and 0.48; 95% CI 0.33-0.70; p-trend< 0.0001 in women. For the aMED the hazard ratios for scores 7-9 compared to 0-2 were 0.80; 95% CI 0.64-1.01; p-trend= 0.002 in men and 0.42; 95% CI 0.24-0.74; p-trend< 0.0001 in women. A total of 1868 HNC cases were identified during follow-up. Adjustment factors included age, race, smoking, alcohol intake, education, BMI, vigorous physical activity, usual activity and total energy intake.

Hazard ratios appeared similar across subgroups of alcohol intake and education (all P-interaction< 0.05), but there was a null association with the HEI-2005 and the aMed in never smokers and an inverse association in former and current smokers in men, although these associations were not significantly different from each other (P-interaction= 0.24). For women, in contrast, the associations were similar across smoking status, although associations did not reach statistical significance in never smokers (P-interaction= 0.13). The authors reported that it was not clear why associations may have differed across subgroups of smoking status and sex.

UADT cancer

The EPIC study (Romaguera, 2012) investigated the association of a score of concordance with the WCRF guidelines and risk of UADT cancers. There was a significant inverse association of higher concordance with the recommendations and UADT risk. The HR was 0.69 (95% CI 0.50-0.95) for the highest compared to the lowest quintile of the score and 0.82 (95% CI 0.74-0.90) for each increment of one point of the score. The analyses were adjusted for age, sex, centre, smoking status and duration, pack-years of cigarettes, educational level, energy intake, and presence of chronic disease at baseline. Models were further adjusted for use of contraceptive pills, use of hormone replacement therapy, age at first menarche, age at pregnancy and menopausal status for women.

Adventists Diet

Three cohort studies from four publications (one for oral cancer, three for mouth and pharyngeal cancer and one for laryngeal cancer) were identified in 2005 SLR and no new studies were identified during the CUP.

Oral cancer

In a cohort study of non-Hispanic, white California Seventh-day Adventists, the SMR of cancer of the buccal cavity was 0.24; 95% CI 0.08-0.54 in men and 0.41; 95% CI 0.12-1.01 in women in comparison to the general population (Mills, 1994).

Mouth and pharynx

In a Japanese study, participants were classified according to lifestyle similar to the lifestyle of Seven Days Adventists (SDA-like: daily neither smoke, drink alcohol, nor eat meat, but did eat green and yellow vegetables). The SDA-like group had lower mortality for cancers of the mouth and pharynx compared to non SDA-like participants (Hirayama, 1985a; Hirayama, 1985b).

In a historical cohort study of males in Denmark, people with Seventh Day Adventist diet had a non-significant increased risk for cancer of buccal cavity and pharynx combined (OR 2.20; 95% CI 0.80-4.80) compared to diet of member of other temperance societies (Jensen, 1983).

Laryngeal cancer

In a Japanese prospective cohort study, participants were classified according to lifestyle similar to the lifestyle of Seven Days Adventists (Hirayama, 1985a). Participants who were not smoking daily, drinking alcohol, eating meat and were eating daily green and yellow vegetables had lower mortality for laryngeal cancer compared to participants who were smoking daily, drinking alcohol, consuming meat and were not consuming daily green and yellow vegetables (OR 0.07; 95% CI: are not reported).

Organic food consumption

No cohort studies were identified in the 2005 SLR and one cohort study on oral cancer was identified in CUP

Oral cancer

In the Million Woman study (Bradbury, 2014), women were asked whether they eat organic food and the analyses were restricted to women who reported usually or always consuming organic food compared to women who never consume organic food. Risk of cancers of the oral cavity was not related to consumption of organic food (RR usual or always vs none 1.04; 95% CI 0.78-1.39).

Diet preferences

No studies were identified in the 2005 SLR. One study was identified in the CUP.

Head and neck cancer

In a study of 444,963 Korean men, the hazard ratio of HNC in men who reported preference for vegetables or a mixture of vegetables and meat compared to preference for meat was not associated to HNC (RR 0.97; 95% CI 0.72-1.31) (Yun, 2008). Adjustment factors included

age, leisure physical activity, smoking status, amount of alcohol drinking, body mass index, employment and fasting blood sugar. For the same comparison, the RR was 1.11; 95% CI 0.62-2.00 in never/former smokers and 0.91; 95% CI 0.64-1.29 in current smokers.

Food temperature

One study on UADT cancer was identified in 2005 SLR and no new studies were identified during the CUP.

UADT cancer

A small study (84 cases) in a Japanese population reported non-significant increased risk of UADT cancers in men preferring hot/boiling hot food compared to those preferring cool/warm food (RR=1.44 ; 95% CI 0.91-2.26) (Chyou, 1995).

1. Patterns of diet

Table 2. Dietary patterns and mouth, pharynx and larynx cancer risk. Main characteristics of studies identified in the search

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI)	Adjustment factors
Health scores								
Kabat, 2015 mou08583 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	862 men/ 292 women 566 401 10.5 years	Cancer registry	Semi-quantitative FFQ	Incidence, **Oral cancer** Men Women	ACS score Q5 vs Q1	0.79 (0.64-0.97) 0.71 (0.48-1.06)	Age, educational level, energy intake, ethnicity, marital status, smoking status
		620/ 566 401 10.5 years			Incidence, **Laryngeal cancer**		0.82 (0.64-1.05)	
Li, 2014 mou08579 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	1 466 men/ 402 women 494 967	Cancer registry	FFQ	Incidence, **Head and Neck cancer** Men Women	HEI-2005 score Q5 vs Q1	0.74 (0.61-0.89) 0.48 (0.33-0.70)	Age, alcohol intake, BMI, educational level, physical activity, race, smoking, total energy intake, usual activity
						Per increment of 10-score of the HEI-2005	0.91 (0.86-0.96) 0.75 (0.67-0.84)	
		237 732 431			Men smokers Never Former Current	Per increment of 10-score of the HEI-2005	1.00 (0.87-1.15) 0.91 (0.84-0.99) 0.87 (0.78-0.98)	Age, alcohol intake, BMI, educational level, physical activity, race, smoking, total energy intake, vigorous physical activity, usual activity
		70 127 188			Women smokers Never Former Current		0.80 (0.62-1.04) 0.79 (0.65-0.97) 0.74 (0.62-0.88)	
		326 555			Men, alcohol 0 drinks/day <0-1drinks/day		0.91 (0.81-1.01) 0.93 (0.86-1.02)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
		283 296			>1-3 drinks/day >3 drinks/day		0.96 (0.84-1.09) 0.73 (0.60-0.88)	
		112 180 66 42			Women, alcohol 0 drinks/day <0-1drinks/day >1-3 drinks/day >3 drinks/day		0.75 (0.62-0.92) 0.78 (0.67-0.92) 0.70 (0.52-0.95) 0.82 (0.45-1.48)	
Li, 2014 mou08579 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	572 men/ 208 women/ 494 967	Cancer registry	FFQ	Incidence, **Oral cancer**	HEI-2005 score Q5 vs Q1	0.84 (0.63-1.14) 0.58 (0.36-0.96)	Age, alcohol intake, BMI, educational level, physical activity, race, smoking, total energy intake, vigorous physical activity, usual activity
		526 men/ 96 women/			Incidence, **Laryngeal cancer**		0.70 (0.51-0.96) 0.40 (0.17-0.93)	
		263 men/ 74 women/			Incidence, **Pharyngeal cancer**		0.64 (0.41-1.01) 0.42 (0.17-1.08)	
Romaguera, 2012 oes00912 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark, Norway	EPIC, Prospective Cohort, Age: 25-70 years, M/W	602/ 386 355 11 years	Cancer registry, health insurance records, pathology rec & active follow up	FFQ and 24 hour recall	Incidence, **UADT cancer**	WCRF/AICR score Q5 vs Q1	0.69 (0.50-0.95)	Age, sex, disease at baseline, educational level, energy intake, smoking intensity, smoking status, study centre. Models for women were further adjusted for: use of contraceptive pills, use of hormone replacement therapy, age at first menarche, age at pregnancy, menopausal status
						Per increment of 1 point in WCRF/AICR score	0.82 (0.74-0.90)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
Li, 2014 mou08579 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	1 466/ men/ 402 women 494 967	Cancer registry	FFQ	Incidence, **Head and Neck cancer** Men Women	aMED score 7-9 vs 0-2	0.80 (0.64-1.01) 0.42 (0.24-0.74)	Age, alcohol intake, BMI, educational level, physical activity, race, smoking, total energy intake, usual activity
						Per increment of 1-score of the aMED score	0.94 (0.90-0.98) 0.82 (0.76-0.89)	
		237 732 431			Men smokers Never Former Current	Per increment of 1-score of the aMED score	1.00 (0.91-1.10) 0.93 (0.89-0.99) 0.91 (0.84-0.99)	Age, alcohol intake, BMI, educational level, physical activity, race, smoking, total energy intake, vigorous physical activity, usual activity
		70 127 188			Women smokers Never Former Current		0.91 (0.76-1.09) 0.75 (0.65-0.86) 0.87 (0.77-0.98)	
		326 555 283 296			Men, alcohol 0 drinks/day <0-1drinks/day >1-3 drinks/day >3 drinks/day		0.98 (0.90-1.07) 0.95 (0.89-1.01) 0.98 (0.89-1.07) 0.82 (0.73-0.91)	
		112 180 66 42			Women, alcohol 0 drinks/day <0-1drinks/day >1-3 drinks/day >3 drinks/day		0.82 (0.70-0.96) 0.85 (0.76-0.95) 0.77 (0.63-0.95) 0.84 (0.61-1.15)	
Li, 2014 mou08579 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	572 men/ 208 women/ 494 967	Cancer registry	FFQ	Incidence, **Oral cancer** Men Women	aMED score 7-9 vs 0-2	0.95 (0.66-1.37) 0.47 (0.24-0.93)	Age, alcohol intake, BMI, educational level, physical activity, race, smoking, total energy intake, vigorous physical activity, usual activity
		526 men/ 96 women/ 494 967			Incidence, **Laryngeal cancer** Men		0.68 (0.45-1.03) 0.59 (0.18-2.01)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
					Women			
		263 men/ 74 women/ 494 967			Incidence, **Pharyngeal cancer** Men Women		0.91 (0.54-1.52) 0.68 (0.35-1.32)*	
Diet preference								
Bradbury 2014 mou08585 UK	Million Women Study, Prospective Cohort W	633/ 623,080 9.3 years	National Health Service central registers	Questionnaire	Incidence, **Oral cancer**	Usually/always vs never consumption of organic food	1.04 (0.78- 1.39)	Age, region, deprivation category, smoking, BMI, physical activity, alcohol intake, height, parity, age at first child birth, fibre intake, meat
Yun, 2008 mou08596 Korea	KNHIC, Prospective Cohort, Age: 40- years, M	690/ 444 963 6 years	Cancer registry	FFQ	Incidence, men, **Head and Neck cancer**	Vegetables or mixture of vegetables and meat vs meat	0.97 (0.72-1.31)	Age, alcohol drinking, BMI, employment, fasting blood sugar, leisure time physical activity, smoking status
					Current smokers Never/ex-smokers		0.91 (0.64-1.29) 1.11 (0.62-2.00)	Age, alcohol drinking, BMI, fasting blood sugar, leisure time physical activity
Adventists diet								
Mills, 1994 mou08598 USA	AHS, Prospective Cohort, M/W, Seventh Day Adventists	9 men/ 7 women 31 208 6 years	Cancer registry	FFQ	Incidence, **Buccal cavity cancer** Men Women	Seventh Day Adventists vs General population	0.24 (0.08-0.54) 0.41 (0.12-1.01)	Age
Hirayama, 1985a mou02982 Japan	Japanese Prospective Cohort 1966-1982,	245 (total number of cases for all cancers)/	Unknown	Interview	Mortality, **Mouth and pharyngeal Laryngeal**	smoking, drinking, eating meat without green and yellow vegetables vs not smoking, drinking, eating	0.11 0.07	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors
	Prospective Cohort, M/W	265 118 17 years				meat with green and yellow vegetables		
Hirayama, 1985b mou02981 Japan	Japanese Prospective Cohort Study on Cancer and Death, 1966-1982, Prospective Cohort, M	26 889	Area residency lists	Questionnaire	Incidence, **Mouth and pharyngeal cancer**	smoking, drinking, eating meat without green and yellow vegetables vs not smoking, drinking, eating meat with green and yellow vegetables	9.11	
Jensen, 1983 mou03368 Denmark	DSDA, Historical Cohort, M, Temperance Society members	6/ 1 589 34 years		Unknown	Incidence, **Buccal cavity and pharyngeal cancer**	Seventh Day Adventists vs members of other temperance societies	2.20 (0.80-4.80)	
Food temperature								
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, M	84/ 7 995 25 years	Selective service roll	FFQ and 24 hour recall	Incidence, **UADT cancer**	Hot/boiling hot vs cool/warm	1.44 (0.91-2.26)	Age, alcohol consumption, smoking habits

* Hazard ratio for aMED scores 5-6 compared to 0-2 in women for pharyngeal cancer.

2. Foods

2.1.2 Starchy roots, tubers and plantains

Cohort studies

Summary

Two studies were identified in CUP and one in 2005 SLR (one study for HN and two for UADT cancer). No meta-analysis was conducted.

Head and Neck cancer

In the NIH-AARP study (Freedman, 2008), the HR for the highest compared to the lowest quintile of sweet potatoes and yams was 0.88 (95% CI 0.74-1.06).

UADT cancer

In the EPIC study (Boeing, 2006) the RR of UADT cancers per 8 g/day increment of consumption of root vegetables was 0.76 (95% CI 0.64-0.90) in men and 0.96 (95% CI 0.82-1.12) in women. In a Norwegian cohort, the RR for the highest compared to lowest intake of potatoes was 0.50 (95% CI 0.20-1.40) (Kjaerheim, 1998).

2.2 Total fruit and vegetables

Cohort studies

Summary

No cohort study was identified in the 2005 SLR. Four publications (from three cohorts) were identified in CUP. Fruit and vegetables intake in relation to the risk of oral cavity, oro/hypopharyngeal, laryngeal and HN cancer was investigated in the NIH-AARP (Freedman, 2008; George, 2009) and the Netherlands Cohort Study (NLCS) (Maasland, 2015). Another cohort study (EPIC; Boeing, 2006) investigated fruits and vegetables intakes and risk of cancers of UADT.

In the NIH-AARP (Freedman, 2008), 787 participants were diagnosed with squamous cell carcinomas of head and neck (319 oral cavity, 142 oro/hypopharyngeal, and 279 larynx) from 1995/1996 to 2000. Intake was categorized as servings/1000 calories. The median intake in the top and lowest quintiles were 5.8 servings/day and 1.5 servings/day, respectively. Analyses were adjusted for age at entry into cohort, alcohol intake, BMI, cigarette-smoke-dose, education, sex, total energy intake, usual activity throughout the day and vigorous physical activity.

In the NLCS (Maasland, 2015), after 20.3 years of follow-up, 415 cases of squamous cell carcinomas of head and neck (131 oral cavity, 88 oro/hypopharyngeal, three oral cavity/pharynx unspecified or overlapping and 193 larynx) and 3,898 sub-cohort members were available for case–cohort analyses. Intakes of fruits and vegetables were expressed as g/day. The median intakes in the top and lowest quartiles were 496 g/day and 552 g/day in

men and women, and 188 g/day and 227 g/day, respectively. Analyses were adjusted for age, sex, cigarette smoking status/ frequency/ duration and alcohol consumption.

In EPIC (ten European countries) (Boeing, 2006), 352 incident squamous cell cancer cases of the upper aero-digestive tract (oral cavity, pharynx, larynx, and oesophagus) were available for analyses since the study began (1990) to 2004. Intake was expressed in g/day. Analyses were adjusted for age, gender, centre, BMI, energy from fat sources, energy from non-fat sources, education, smoking status/ duration, alcohol drinking.

All studies used validated dietary questionnaires and case ascertainment was virtually complete. Cancers of the salivary glands, nasal cavity, paranasal sinuses and nasopharynx were excluded in all studies.

Oral cavity cancer

Significant inverse associations with fruits and vegetable intake were observed in the two cohort studies identified (NLCS and NIH-AARP).

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.46 (95% CI 0.27-0.81; p-trend= 0.005; 131 cases). The HR for 25 g/day increment of total fruit and vegetables intake was 0.95 (95% CI 0.92-0.99).

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 was 0.61 (95% CI 0.41–0.93; p-trend= 0.052; 319 cases). The HR for one serving/ 1000 calories of total fruit and vegetables was 0.93 (0.86-1.00).

Oro/hypopharyngeal cancer

Two cohort studies were identified (NLCS and NIH-AARP). Inverse associations with fruits and vegetable intake were observed in the NLCS and the NIH-AARP cohort but the only statistically significant result was the inverse trend in the NLCS.

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.51 (95% CI 0.26–1.00; p-trend= 0.005; 88 cases). The HR for 25 g/day increment of total fruit and vegetables intake was 0.96 (95% CI 0.90-1.01).

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 was 0.90 (95% CI 0.51–1.58; p-trend= 0.05; 142 cases). The HR for one serving/ 1000 calories of total fruit and vegetables was 0.95 (0.85-1.07).

Laryngeal cancer

Non-significant inverse associations with fruits and vegetable intake were observed in any of the two cohorts identified (NLCS and NIH-AARP).

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.80 (95% CI 0.51–1.23; p-trend= 0.32; 193 cases). The HR for 25 g/day increment of total fruit and vegetables intake was 0.99 (95% CI 0.96-1.02).

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 was 0.69 (95% CI 0.44–1.11; p-trend= 0.190; 279 cases). The HR for one serving/1000 calories of total fruit and vegetables was 0.95 (0.87-1.03).

Head and Neck cancer

Significant inverse associations with fruits and vegetable intake were observed in both cohorts (NLCS and NIH-AARP).

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.61 (95% CI 0.44–0.85; p-trend= 0.002; 415 cases). The HR for 25 g/day increment of total fruit and vegetables intake was 0.97 (95% CI 0.95-0.99). In the NLCS (Maasland, 2015) the association with fruit and vegetable intake and head and neck cancer risk was not modified by smoking (P-interaction= 0.10) or alcohol drinking status (P-interaction= 0.09). The HR (Q4 vs Q1) for total fruit and vegetable intake were 0.54 (95% CI 0.22–1.29) among never smokers, 0.72 (95% CI 0.44–1.18) in former smokers and 0.51 (95% CI 0.31–0.88) in current smokers. The HR for Q4 vs Q1 were 0.89 (95% CI 0.35–2.24) among abstainer, 0.79 (95% CI 0.49–1.28) in people drinking less than 15 g/day and 0.48 (95% CI 0.30–0.77) among people drinking more than 15 g/day

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 was 0.71 (95% CI 0.55–0.92; p-trend= 0.018; 787 cases). The HR for one serving/ 1000 calories of total fruit and vegetables was 0.94 (0.89-0.99). The association was similar in men and women.

In the NIH-AARP (Freedman, 2008) the association with fruit and vegetable intake and head and neck cancer risk was not modified by smoking (P-interaction= 0.32) or alcohol drinking status (P-interaction= 0.68). No significant differences by smoking status (never, former and current) were observed for total fruit and vegetable intake. The HR for total fruit and vegetable intake per serving/1,000 calories were 0.97 (95% CI 0.86–1.10) in never smokers, 0.90 (95% CI 0.84–0.97) in former smokers and 1.01 (95% CI, 0.94–1.10) in current smokers. The HR for total fruit and vegetable intake per serving/1,000 calories were 0.93 (95% CI, 0.77–1.13) among never smokers who did not drink alcohol (n=39 cases), 0.94 (95% CI 0.88–1.01) among ever smokers who also drank alcohol (n = 478 cases); 0.95 (0.89–1.01) among alcohol drinkers and 0.92 (0.85–1.01) among non-drinkers.

UADT cancer

In the EPIC study (Boeing, 2006) fruits and vegetables intake was significantly related to the risk of squamous carcinomas of the UADT. The HR for the highest compared to the lowest quintile intake of fruits and vegetables were 0.60 (95% CI 0.37–0.99; p-trend= 0.035) and 0.91 (95% CI: 0.83–1.00) for each increment of 80 g/day. The association was significant in men (RR for 80 g/day increment was 0.88; 95% CI 0.79-0.98) but not in women (RR 0.96; 95% CI 0.79-1.15). Relative risk estimates were similar in analyses by smoking status with slightly stronger inverse associations in non-smokers than in smokers (data not shown in the paper).

2.2.1 Vegetables

Cohort studies

Summary

In the 2005 SLR the summary OR for 50 g/d increment was 0.72 (95% CI 0.63-0.82) combining 5 case-control studies. No cohort study was identified in the 2005 SLR.

Two cohort studies on vegetables and risk of cancers of the oral cavity, oro/hypopharynx, larynx and neck and head were identified in the CUP: the NIH-AARP (George, 2009; Freedman, 2008) and the Netherlands Cohort Study (NLCS) (Maasland, 2015). Another cohort study (EPIC; Boeing, 2006) investigated vegetables intakes and risk of cancers of the upper aero-digestive tract. The pooled analysis of case-control studies (INHANCE) investigated vegetable intake and risk of head and neck cancers by cancer site (Chuang, 2012).

The study results are described in the text, shown in tables and in a summary figure. No dose-response meta-analyses were conducted.

Oral cavity

Inverse associations with vegetable intake were observed in two cohorts but the association was statistically significant only in the NIH-AARP.

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.71 (95% CI 0.41-1.24; p-trend= 0.36; 131 cases). The median intakes in the top and lowest quartiles were 271 g/day and 277 g/day in men and women, and 109 g/day and 113 g/day, respectively. The HR for 25 g/day increment of vegetables intake was 0.95 (95% CI 0.89-1.02).

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 (Median intake 3.2 vs 0.7 servings/1000 calories) was 0.56, 95% CI, 0.37–0.84; p-trend= 0.017; 319 cases). The HR for one serving/1000 calories of total vegetables was 0.84 (0.73-0.95).

Oro/hypopharyngeal cancer

Inverse non-significant associations with vegetable intake were observed in the two cohorts identified.

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.52 (95% CI 0.24-1.10; p-trend= 0.10; 88 cases). The median intakes in the top and lowest quartiles were 271 g/day and 277 g/day in men and women, and 109 g/day and 113 g/day, respectively. The HR for 25 g/day increment of vegetables intake was 0.94 (95% CI 0.85-1.04).

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 (Median intake 3.2 vs 0.7 servings/1000 calories) was 0.56, 95% CI, 0.31–1.01; p-trend= 0.082; 142 cases). The HR for one serving/ 1000 calories of total fruit and vegetables was 0.90 (0.74-1.09).

Laryngeal cancer

Non-significant associations with vegetable intake were observed in both cohorts.

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.83 (95% CI 0.53-1.29; p trend= 0.39; 193 cases). The median intakes in the top and lowest quartiles were 271 g/day and 277 g/day in men and women, and 109 g/day and 113 g/day, respectively. The HR for 25 g/day increment of vegetables intake was 0.98 (95% CI 0.92-1.04).

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 (Median intake 3.2 vs 0.7 servings/1000 calories) was 0.77, 95% CI, 0.49–1.22; p-trend= 0.242; 279 cases). The HR for one serving/ 1000 calories of total vegetables was 0.91 (0.79-1.05).

Head and Neck cancer

Significant inverse associations with vegetable intake were observed in both cohorts.

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.71, 95% CI, 0.51–0.99; p-trend= 0.07; 415 cases). The median intakes in the top and lowest quartiles were 271 g/day and 277 g/day in men and women, and 109 g/day and 113 g/day, respectively. The HR for 25 g/day increment of vegetables intake was 0.96 (95% CI 0.92-1.01).

In the NIH-AARP study (George, 2009), the RR Q5 vs Q1 (Median intake 1.10-3.25 vs <0.44 cup equivalents/1000 calories) was 0.98, 95% CI, 0.80–1.19; p-trend= 0.897; 1029 cases) for men and 0.79 (0.53-1.16; p-trend=0.158) for women (Q5:1.43-4.38 vs Q1:0-0.56 cup equivalents/1000 calories).

UADT cancer

In the EPIC study (Boeing, 2006) vegetables intake was inversely but not significantly related to the risk of squamous carcinomas of the UADT. The HR for the highest compared to the lowest quintile intake of vegetables were 0.80 (95% CI 0.49–1.31; p-trend= 0.459) and 0.89 (95% CI 0.78–1.02) for each increment of 40 g/day. The association was significant in men (RR for 40 g/day increment was 0.83; 95% CI 0.71-0.99) but not in women (RR 0.93; 95% CI 0.74-1.18).

Pooled analysis of case-control studies

In the International Head and Neck Cancer Epidemiology (INHANCE) consortium, non-starchy vegetable intake was related to decreased risk of squamous carcinoma of head and neck. The pooled odds ratio for the highest compared to the lowest centre specific quartile of intake was 0.66 (95% CI 0.49–0.90; p-trend= 0.03) (Chuang, 2012). The analysis included individual participants data from 20 case–control studies for a total of 12 315 cases and 19 387 controls. There was significant heterogeneity across centres (p<0.01). The associations between vegetables and HNC were observed mostly in smokers or heavy drinkers. Among never smokers that were also light drinkers (1015 cases), the pooled OR for the same comparison was 0.85 (9%% CI 0.60–1.19, p-trend= 0.15).

Similar associations were observed across cancer sites. The pooled OR for the highest compared to the lowest quartile of vegetables were 0.69 (0.61-0.79) for cancers of the oral cavity; 0.62 (0.47-0.81) for pharynx; 0.62 (0.48-0.80) for oropharynx; and 0.55 (0.35-0.86) for larynx.

2.2.1.1 Other types of vegetables

Cohort studies

Summary

Two studies were identified in the 2005 SLR: a cohort on American postmenopausal women (Kasum, 2002) and a Norwegian study in men (Kjaerheim, 1998) that investigated specific types of vegetables and risk of UADT (see Table 3 for study details).

Four publications from three cohorts were identified in CUP: the NIH-AARP cohort (Freedman, 2008; George, 2009) and the Netherlands Cohort Study (NLCS) (Maasland, 2015) on head and neck cancer and its subsites and the EPIC study on UADT cancers (Boeing, 2006). The INHANCE pooling project of case-control studies investigated different types of fruits and vegetables as well.

In the NLCS (Maasland, 2015), no significant associations with cancers of the oral cavity, oro/hypopharynx, larynx and head and neck were observed for the following vegetables: cooked leafy vegetables; brassica vegetables; allium vegetables; (raw) string/French beans; cauliflower; carrots (cooked); endive (cooked); brussel sprouts, sauerkraut; tomatoes; onion; beetroot; and kale (results are not detailed in this SLR). Intake of leafy vegetables was inversely related to risk of head and neck cancers (HR for 25 g/day= 0.66; 95% CI= 0.47-0.96) and oro/hypopharyngeal cancer (HR for Q4 vs Q1= 0.46; 95% CI 0.23-0.93; p-trend= 0.11 and HR per 25 g/day= 0.53; 95% CI= 0.21-1.34) and inversely but not significantly related to risk of cancers of the oral cavity and larynx. Intake of spinach was not related with any of the cancer sites mentioned except with larynx, for which the HR for 25 g/day was 1.54 (95% CI 1.03-2.29). Intake of lettuce was inversely and significantly related to HNC (RR for 25g/day increment 0.58; 95% CI 0.35-0.95) but not to other cancer sites risk. Analyses were additionally adjusted for total vegetable and total fruit intake. Many comparisons were made and these associations could be chance findings.

In the NIH-AARP (Freedman, 2008), the risk of head and neck cancer was significantly inversely related to intake of carrots (HR for highest vs lowest tertile= 0.73; 95% CI 0.60-0.89; p-trend= 0.001), and tomatoes and peppers (HR for highest vs lowest tertile= 0.82; 95% CI 0.69-0.98; p-trend= 0.023), and not related to intake of spinach (raw, cooked); lettuce; and cruciferous vegetables (results are not tabulated).

In the EPIC study (Boeing, 2006), UADT cancer risk was inversely related to intake of root vegetables (HR for highest vs lowest quintile was 0.65 (95% CI 0.41–1.01); p-trend= 0.02) and not related to intake of fruiting vegetables, leafy vegetables, cabbages and onion/garlic (results are not tabulated).

In a cohort of postmenopausal women in United States (Kasum, 2002), the intake of yellow/orange vegetables was related to significantly decreased risk of UADT cancers (HR for 3.5 to 106 servings/week vs <0 to 1 serving/week= 0.58; 95% CI 0.39–0.87; p-trend= 0.01).

In a prospective cohort of 10,900 Norwegian men followed from 1968 through 1992, in which period a total of 71 upper aerogastric tract cancers occurred, UADT cancer was not related to intake of tomato, lettuce, cauliflower, cabbage, and carrots (Kjaerheim, 1998).

Pooled analysis of case-control studies

In the INHANCE consortium of 22 case-control studies (Chuang, 2012) the risk of head and neck cancer was inversely related to consumption of carrots (pooled OR for highest vs lowest quartile 0.64 (95% CI 0.57–0.72) p-trend=0.01); non-starchy vegetables (same comparison as before, 0.68 (0.51–0.90) p-trend= 0.03); green vegetables (0.65 (0.53–0.81) p-trend= 0.01); allium vegetables (0.66 (0.54–0.81) p-trend= 0.02); green salad (pooled OR for 7 times/week of more compared to less than once/week 0.60 (95% CI 0.45–0.79) p-trend= 0.13; lettuce (same comparison as before 0.52 (0.36–0.76) p-trend=0.02); fresh tomatoes (0.77 (0.64–0.92) p-trend= 0.05) and not significantly related to intake of cruciferous vegetables; beans of peas; spinach; cabbage; broccoli; and pumpkin.

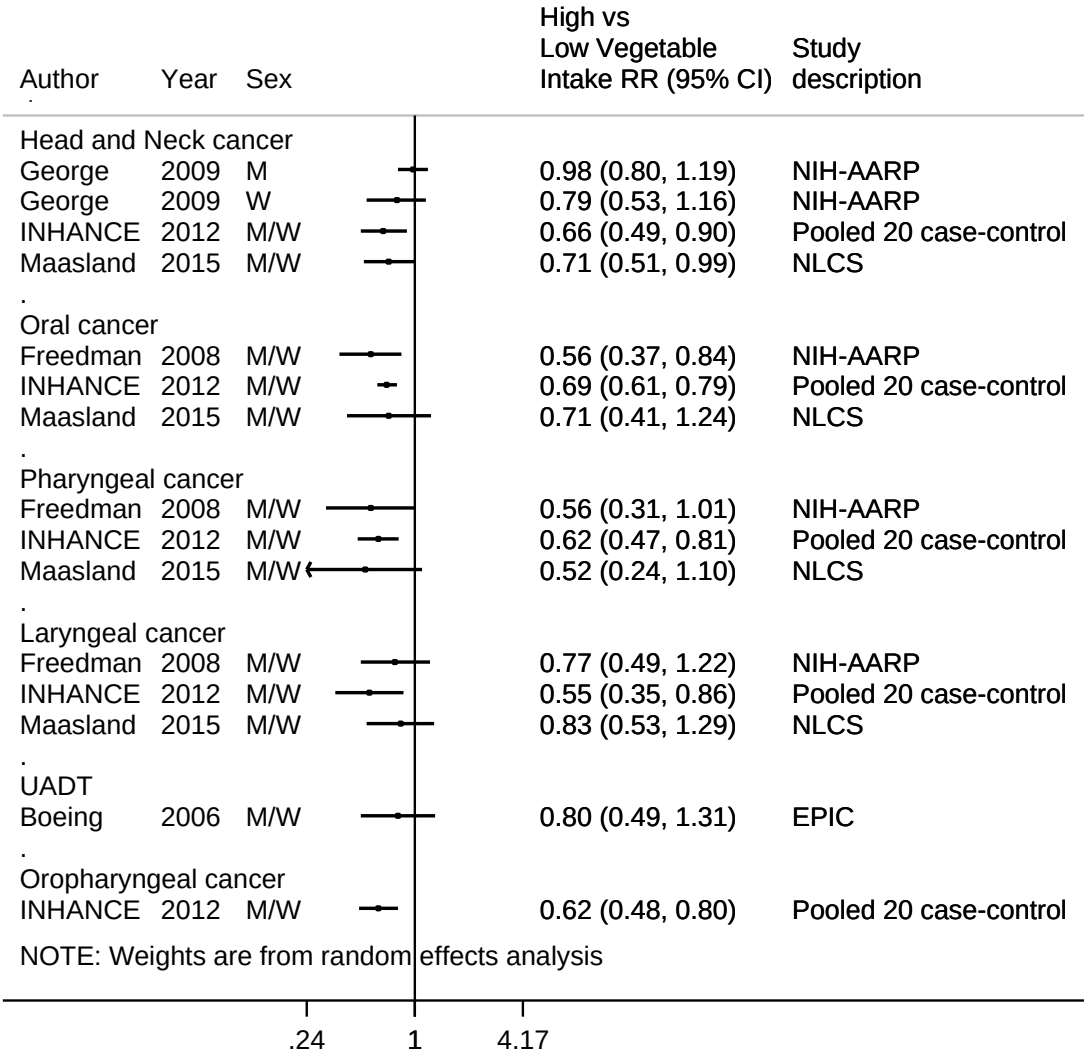
Table 3. Vegetable intake and its subcategories and mouth, pharynx and larynx cancer risk. Main characteristics of studies identified in the search

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI)	Adjustment factors	Included/ Reason of exclusion
Maasland 2015 Mou08607 Netherlands	NLCS, Case-cohort, Age:55-69 years, M/W,	415/ 120852	Linkage with cancer registry and pathology registry	FFQ	Incidence **Head and Neck cancer**	Q4 vs Q1 Per 25g/day	0.71 (0.51-0.99) 0.96 (0.92-1.01)	Age, sex, smoking status and dose, smoking duration, alcohol consumption, fruit intake	Included in HvsL analysis
		131/ 120852			Incidence **Oral cavity cancer**	Q4 vs Q1 Per 25g/day	0.71 (0.41-1.24) 0.95 (0.89-1.02)		
		88/ 120852			Incidence **Oro/hypopharyngeal cancer**	Q4 vs Q1 Per 25g/day	0.52 (0.24-1.10) 0.94 (0.85-1.04)		
		193/ 120852			Incidence **Laryngeal cancer**	Q4 vs Q1 Per 25g/day	0.83 (0.53-1.29) 0.98 (0.92-1.04)		
George, 2009 mou08593 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	1 029 men/ 318 women/ 483 338	Linkage with 11 state cancer registry databases	FFQ	Incidence, **Head and Neck cancer** Men Women	1.1-3.25 vs ≤0.44 cup/1000 kcal/day	0.98 (0.80-1.19) 0.79 (0.53-1.16)	Age, alcohol, BMI, educational level, energy Intake, family history of cancer, fruit Intake, marital status, physical activity, race, smoking	Included in HvsL analysis
						1.44-4.38 vs ≤0.56 cup/1000 kcal/day		Additionally adjusted: Menopausal oestrogen use	
Freedman, 2008 mou08573 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	787/ 490 802 4.5 years	Cancer registry	FFQ	Incidence, **Head and Neck cancer**	3.2 vs 0.7 serving/1000 kcal	0.65 (0.50-0.85)	Sex, age at baseline, alcohol intake, BMI, educational level, smoking dose, total energy intake,	Superseded from George 2009
						Per serving per 1000 calories	0.89 (0.82-0.97)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI)	Adjustment factors	Included/ Reason of exclusion
								usual activity, vigorous activity, fruit intake	
		109 334 317			Smoking status Never smoker Former smoker Current smoker	Per serving per 1000 calories	1.11 (0.94-1.32) 0.83 (0.73-0.94) 0.88 (0.77-1.02)	Sex, age at baseline, alcohol intake, BMI, smoking dose, education, total energy intake, usual activity and vigorous physical activity	
		219 568			Alcohol use No Yes		0.84 (0.72-0.98) 0.92 (0.83-1.01)		
Freedman, 2008 mou08573 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	319/ 490 802 4.5 years	Cancer registry	FFQ	Incidence, **Oral cancer**	3.2 vs 0.7 serving/1000 kcal	0.56 (0.37-0.84)	Sex, age at baseline, alcohol intake, BMI, educational level, smoking dose, total energy intake, usual activity, vigorous activity, fruit intake	Included in HvsL analysis for oral, laryngeal and oro/hypopharyngeal cancer
						Per serving per 1000 calories	0.84 (0.73-0.95)		
		279/			Incidence, **Laryngeal cancer**	3.2 vs 0.7 serving/1000 kcal	0.77 (0.49-1.22)		
						Per serving per 1000 calories	0.91 (0.79-1.05)		
		142/			Incidence, **Oro/hypopharyngeal cancer**	3.2 vs 0.7 serving/1000 kcal	0.56 (0.31-1.01)		
						Per serving per 1000 calories	0.90 (0.74-1.09)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI)	Adjustment factors	Included/ Reason of exclusion
Boeing, 2006 oes00910 Denmark, Germany, Italy, Netherlands, Spain, Sweden, UK	EPIC, Prospective Cohort, M/W	255 men/ 97 women/ 345 904 2 182 560 person-years	Cancer and pathology registry, active follow up, health Insurance record, mortality registry and contact of participants or next-of-kin		Incidence, **UADT cancer** Men Women Combined	239.2 vs 99.8 g/day per 40 g/day	0.80 (0.49-1.31) 0.83 (0.71-0.99) 0.93 (0.74-1.18) 0.89 (0.78-1.02)	Age, baseline alcohol intake, BMI, centre location, duration of smoking, educational level, energy from fat sources, energy from non-fat sources, gender, lifetime alcohol consumption, non-consumer status, smoking status	Included in HvsL analysis
Kasum 2002 Mou03561 USA	Iowa Women's Health Study	74 34 351 14 years	Driver's license list	127-item FFQ	Incidence, **UADT cancer** Yellow/orange vegetables	3.5-106 vs 0-1 servings/week	0.58 (0.39-0.87)	Whole grains, refined grains, alcohol intake, smoking, age, energy intake	Not included in HvsL analysis. It does not report result for total vegetable intake
Kjaerheim, 1998 oes00130 Norway	Norway 1968-1992 UADT, Prospective Cohort, M	71/ 10 900 25 years	Population survey	FFQ	Incidence, **UADT cancer** Carrots Tomatoes Cabbage Swedish turnip Cauliflower Rhubarb Lettuce	≥6 vs ≤1 times/month	1.90 (0.60-6.00) 1.70 (0.80-3.70) 1.90 (0.80-4.10) 0.80 (0.30-2.30) 0.80 (0.30-2.10) 0.60 (0.10-4.30) 1.00 (0.40-2.40)	Age, alcohol consumption, smoking habits	Not included in HvsL analysis. It does not report result for total vegetable intake

Figure 3. RR (95%) for the highest compared with the lowest level of vegetable intake, by cancer type



Note: Median intakes in the top and lowest quintiles were in the NLCS, 271g/day, 277 g/day and 109 g/day, 113 g/day in men and women; in NIH-AARP, 3.2 and 0.7 servings/1000 calories. M: men; W: women; M/W: men and women.

2.2.2 Fruits

Cohort studies

In the 2005 SLR two cohort studies (Kjaerheim, 1998; Chyou, 1995), investigating the association between fruit intake and UADT cancer were identified. The summary OR of UADT of 7 case-control studies was 0.72 (95% CI 0.59-0.87) for 100 g/d increment of fruits intake.

Two cohort studies on fruits intake and risk of cancers of the oral cavity, oro/hypopharynx, larynx and neck and head were identified in the CUP: the NIH-AARP (Freedman, 2008) and the Netherlands Cohort Study (NLCS) (Maasland, 2015). Another cohort study (EPIC; Boeing, 2006) investigated fruit intake and risk of cancers of the upper aero-digestive tract.

The study results are described in the text, shown in tables and in a summary figure. No dose-response meta-analyses were conducted.

Oral cavity

In categorical analysis, inverse associations with fruit intake were observed in the NLCS and the NIH-AARP that were statistically significant only in the NLCS. No significant associations were observed for continuous increments of fruit intake.

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.56 (95% CI 0.33-0.97; p-trend= 0.07; 131 cases). The median intakes in the top and lowest quartiles were 271 g/day and 325 g/day in men and women, and 41 g/day and 75 g/day, respectively. The HR for 25 g/day increment of fruits intake was 0.95 (95% CI 0.91-1.01).

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 (Median intake 3.2 vs 0.4 servings/1000 calories) was 0.81, 95% CI, 0.54–1.22; p-trend= 0.268; 319 cases. The HR for one serving/ 1000 calories of total fruit and fruits was 0.96 (0.82-1.12).

Oro/hypopharyngeal cancer

In categorical analysis, non-significant inverse associations with fruit intake were observed in the NLCS and the NIH-AARP. No significant associations were observed for continuous increments of fruit intake.

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.73 (95% CI 0.39-1.37; p-trend= 0.25; 88 cases). The median intakes in the top and lowest quartiles were 271 g/day and 325 g/day in men and women, and 41 g/day and 75 g/day, respectively. The HR for 25 g/day increment of fruits intake was 0.97 (95% CI 0.89-1.05).

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 (Median intake 3.2 vs 0.4 servings/1000 calories) was 0.72, 95% CI, 0.37–1.39; p-trend= 0.181; 142 cases). The HR for one serving/ 1000 calories of total fruit and fruits was 0.89 (0.69-1.15).

Laryngeal cancer

No significant associations were observed in the two cohorts.

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.95 (95% CI 0.63-1.42; p-trend= 0.80; 193 cases). The median intakes in the top and lowest quartiles were 271 g/day and 325 g/day in men and women, and 41 g/day and 75 g/day, respectively. The HR for 25 g/day increment of fruits intake was 0.99 (95% CI 0.95-1.03).

In the NIH-AARP study (Freedman, 2008), the HR Q5 vs Q1 (Median intake 3.2 vs 0.4 servings/1000 calories) was 0.77, 95% CI, 0.49–1.22; p-trend= 0.393; 279 cases). The HR for one serving/ 1000 calories of total fruit and fruits was 0.96 (0.80-1.14).

Head and Neck cancer

Non-significant inverse associations with fruit intake were observed in both cohorts.

In the NLCS (Maasland, 2015), the HR Q4 vs Q1 was 0.77, 95% CI, 0.56–1.04; p-trend= 0.09; 415 cases). The median intakes in the top and lowest quartiles were 271 g/day and 325 g/day in men and women, and 41 g/day and 75 g/day, respectively. The HR for 25 g/day increment of fruits intake was 0.97 (95% CI 0.94-1.00).

In the NIH-AARP study (George, 2009), the RR for the comparison of 1.59-5.13 vs less than 0.44 cup equivalents/1000 calories was 0.84 (0.68-1.04; p-trend=0.064) in men. For women, for the comparison of 1.90-5.58 vs less than 0.06 cup equivalents/1000 calories, the RR was 0.70 (0.48-1.02; p-trend=0.057).

UADT cancer

In the EPIC study (Boeing, 2006) fruits intake was inversely but not significantly related to the risk of squamous carcinomas of the UADT categorical analysis. The HR for the highest compared to the lowest quintile intake of fruits were 0.60 (95% CI 0.38–0.97; p-trend= 0.041) and 0.97 (95% CI 0.92–1.02) for each increment of 40 g/d. The relationship was similar in men (RR for 40 g/day increment was 0.96; 95% CI 0.91-1.02) and women (RR 0.98; 95% CI 0.86-1.12).

In a cohort study of 10,900 Norwegian men, no significant association was found between sum-scores of fruit consumption and UADT cancer (data not shown in the paper; Kjaerheim, 1998).

In a cohort study in Japanese-American in which 92 cases of UADT cancers were identified, fruit intake was inversely but not significantly related to risk of these cancers (HR for eating fruits 5 times or more per week compared to one or less 0.65 (95% CI 0.39-1.07) p-trend= 0.097) (Chyou, 1995).

Pooled analysis of case-control studies

In the International Head and Neck Cancer Epidemiology (INHANCE) consortium, fruit intake was related to decreased risk of squamous carcinoma of head and neck. The pooled odds ratio for the highest compared to the lowest centre specific quartile of intake was 0.52

(95% CI 0.43–0.62; p-trend= 0.01) (Chuang, 2012). The analysis included individual participants data from 20 case–control studies for a total of 12 315 cases and 19 387 controls. There was significant heterogeneity across centres (p< 0.01). Fruit intake was related to HNC among never smokers that were also light drinkers (1 015 cases), the pooled OR for the same comparison as above was 0.66 (95% CI 0.48–0.92, p-trend= 0.27).

Similar associations were observed across cancer sites. The pooled OR for the highest compared to the lowest quartile of fruits were 0.46 (0.38-0.56) for cancers of the oral cavity; 0.59 (0.50-0.69) for pharynx; 0.60 (0.51-0.69) for oropharynx; and 0.59(0.45-0.79) for larynx.

2.2.2.1 Citrus fruits

Cohort Studies

A Norwegian study in men investigating citrus fruits (orange) intake and risk of UADT cancer was identified in 2005 SLR (Kjaerheim, 1998). Two studies (NLCS; Maasland, 2015; NIH-AARP; Freedman, 2008) on cancers of oral cavity, oro/hypopharynx, laryngeal and HN and one study on UADT cancer (EPIC; Boeing, 2006) were identified in CUP.

In the NLCS (Maasland, 2015), no associations were observed with cancers of the oral cavity and oro/hypopharynx (HRs for 25 g/day increment were 1.02 (95% CI 0.92-1.13) and 1.12 (95% CI 0.99-1.25), respectively) but there was an inverse association of fruits intake and laryngeal cancer in categorical analysis (HR for highest vs lowest quartile 0.48; 95% CI 0.28-0.83; and for 25 g/day increment, HR 0.93; 95% CI 0.85-1.02). Intake of citrus fruits was not significantly related to risk of HNC (HR for highest vs lowest quartile 0.71; 95% CI 0.49-1.03; and for 25 g/day increment, HR 1.00; 95% CI 0.94-1.06).

In the NIH-AARP (Freedman, 2008), the risk of head and neck cancer was not significantly related to intake of citrus fruits (HR for highest vs lowest tertile 0.90; 95% CI 0.75-1.08; p-trend= 0.293).

In the EPIC study (Boeing, 2006), UADT cancer risk was non-significantly inversely related to citrus fruits intake (HR for highest vs lowest quintile was 0.76 (95% CI 0.51–1.13; p-trend= 0.12). The HR for 8 g/day increase was 0.98 (95% CI 0.85–1.13).

A marginal inverse association of UADT with intake of oranges was observed in a cohort of Norwegian men. The RR for the highest compared to the lowest intake was 0.50; 95% CI 0.30-1.00 (Kjaerheim, 1998).

Pooled analysis of case-control studies

In the INHANCE consortium of 16 case-control studies in the analysis (Chuang, 2012) the risk of head and neck cancer was inversely related to consumption of citrus fruits (pooled OR for highest vs lowest quartile 0.66 (95% CI 0.56–0.77) p-trend= 0.01).

Also, within the INHANCE consortium pooled data set, data from 10 case-control studies was used to investigate the associations between vitamin C intake derived from natural sources and oral and pharyngeal cancer, and laryngeal cancer (Edefonti, 2015). The analysis

included a total of 5 959 cases and 12 248 controls. There was significant heterogeneity among studies (p<0.1). Comparisons of highest versus lowest non-alcohol energy-adjusted vitamin C intake quintiles revealed an inverse significant association with both oral and pharyngeal cancer, and laryngeal cancer (OR 0.54; 95% CI 0.45-0.65, p trend< 0.001; OR 0.52; 95% CI 0.40-0.68, p trend 0.006, respectively). Analyses were adjusted for age, sex, education, race/ethnicity, study centre, cigarette smoking status, cigarette intensity, cigarette duration, cigar smoking status, pipe smoking status, alcohol drinking intensity and the interaction between cigarette intensity and alcohol drinking intensity.

In stratified analyses by tobacco consumption, alcohol consumption the inverse significant association for oral and pharyngeal cancer persisted (HvsL OR for current tobacco users 0.62; 95% CI 0.49-0.80; HvsL OR for heavy drinkers 0.46; 95% CI 0.33-0.65; HvsL OR for current tobacco users/heavy drinkers 0.55; 95% CI 0.35-0.87) and for laryngeal cancer (HvsL OR for current tobacco users 0.55; 95% CI 0.41-0.72; HvsL OR for heavy drinkers 0.38; 95% CI 0.25-0.59; HvsL OR for current tobacco users/heavy drinkers 0.48; 95% CI 0.26-0.90).

2.2.2.2 Other fruits

One study on UADT cancer was identified in 2005 SLR and one study on HNC was identified in CUP.

Head and Neck cancer

In the NIH-AARP study (Freedman, 2008) HNC risk was significantly inversely associated with consumption of fruits from the botanical group Rosaceae (apples, pears, peach, nectarines, plums, strawberries) (HR 0.60; 95% CI 0.49-0.73) and not significantly associated with intake of bananas (HR 0.92; 95% CI 0.77-1.09); cucurbitaceae (cantaloupe, watermelon, melon) (HR 0.96; 95% CI 0.80-1.14); grapes (HR 0.87; 95% CI 0.73-1.04) (results are not tabulated).

UADT cancer

In a prospective cohort of Norwegian men, UADT cancer was inversely but not significantly associated with consumption of apples (RR 0.70; 95% CI 0.40-1.30); garden berries (RR 0.80; 95% 0.40-1.60); grapes (RR 0.90; 95% CI 0.30-2.60), and bananas (RR 0.40; 95% CI 0.10-1.00). There was no association with wild berries (RR 1.00; 95% CI 0.40-2.20) (Kjaerheim, 1998) (All RRs are for the comparison of highest with lowest intake).

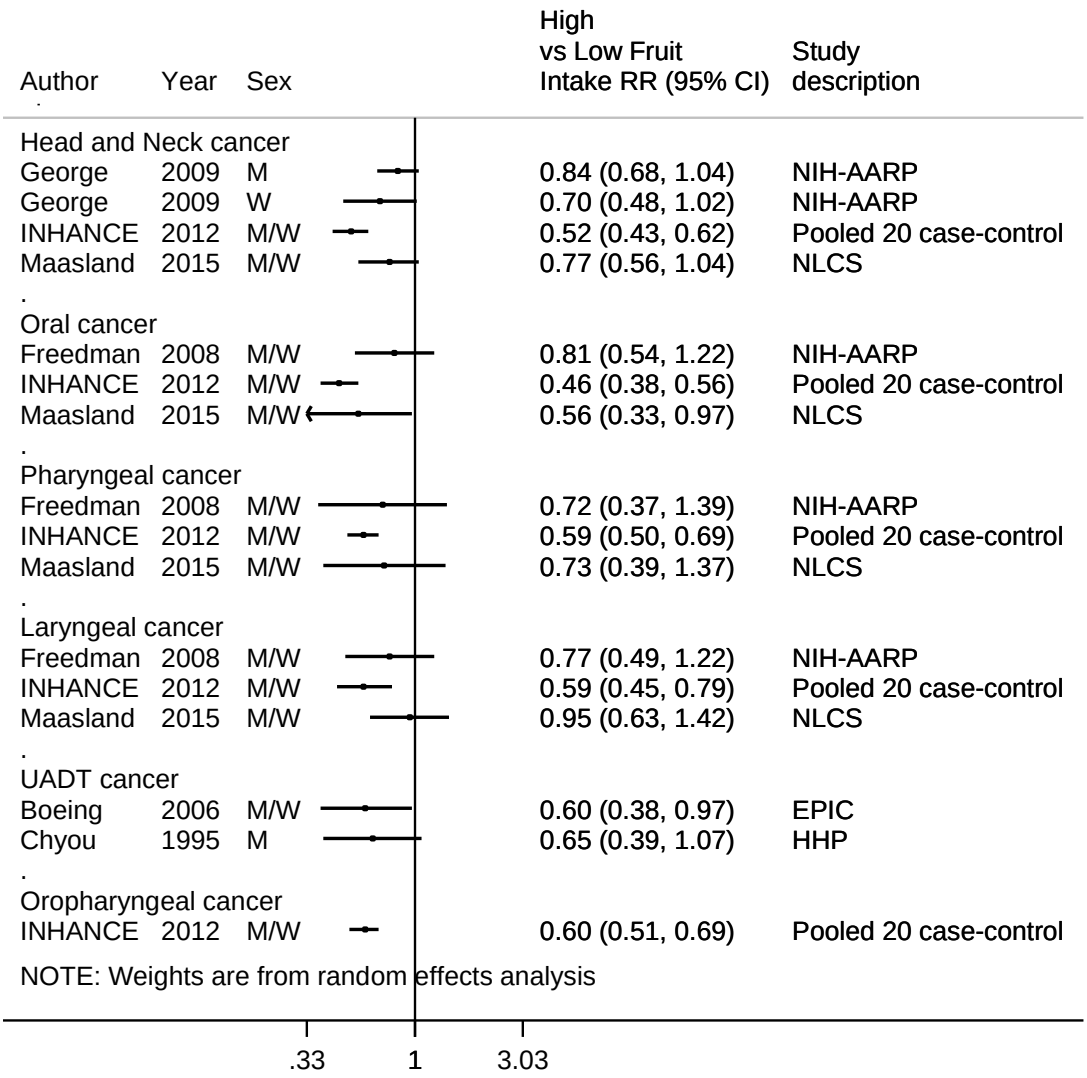
Table 4. Fruit intake and its subcategories and mouth, pharynx and larynx cancer risk. Main characteristics of studies identified in the search

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Included/ Reason of exclusion
Maasland 2015 Mou08607 Netherlands	NLCS, Case-cohort, Age:55-69 years, M/W,	415/ 120852	Linkage with cancer registry and pathology registry	FFQ	Incidence **Head and Neck cancer** Total fruit Citrus fruit	Q4 vs Q1 Per 25g/day	0.77 (0.56-1.04) 0.97 (0.94-1.00) 0.71 (0.49-1.03) 1.00 (0.94-1.06)	Age, sex, smoking status and dose, smoking duration, alcohol consumption, vegetable intake	Included in HvsL analysis
		131/ 120852			Incidence **Oral cavity cancer** Total fruit Citrus fruit	Q4 vs Q1 Per 25g/day	0.56 (0.33-0.97) 0.95 (0.91-1.01) 0.94 (0.52-1.71) 1.02 (0.92-1.13)		
		88/ 120852			Incidence **Oro/hypopharyngeal cancer** Total fruit Citrus fruit	Q4 vs Q1 Per 25g/day	0.73 (0.39-1.37) 0.97 (0.89-1.05) 1.08 (0.57-2.04) 1.12 (0.99-1.25)		
		193/ 120852			Incidence **Laryngeal cancer** Total fruit Citrus fruit	Q4 vs Q1 Per 25g/day	0.95 (0.63-1.42) 0.99 (0.95-1.03) 0.48 (0.28-0.83) 0.93 (0.85-1.02)		
George, 2009 mou08593 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	1 029men/ 318women/ 483 338	Linkage with 11 state cancer registry databases	FFQ	Incidence, **Head and Neck cancer** Men Women	1.6-5.13 vs ≤0.44 cup/1000 kcal/day 1.91-5.58 vs ≤0.6 cup1000 kcal/day	0.84 (0.68-1.04) 0.70 (0.48-1.02)	Age, alcohol, BMI, educational level, energy Intake, family history of cancer, marital status, physical activity, race, smoking, vegetable intake and in women for menopausal oestrogen use	Included in the HvsL analysis for HNC

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Included/ Reason of exclusion
Freedman, 2008 mou08573 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	787/ 490 802 4.5 years	Cancer registry	FFQ	Incidence, **Head and Neck cancer** Fruits and fruit juice Whole fruits	5.2-6.8 vs 1.2-1.8 serving/1000 kcal	0.87 (0.68-1.11) 0.77 (0.59-1.00)	Sex, age at baseline, alcohol Intake, BMI, educational level, smoking dose, total energy intake, usual activity throughout the day, vigorous activity. Fruit and fruit juices were further adjusted for vegetable intake. Whole fruits are additionally adjusted for vegetable intake and fruit juice intake	Included in the HvsL analysis for oral cavity, oro/hypopharyngeal and laryngeal cancer
						Per serving per 1000 kcal	0.98 (0.91-1.06) 0.94 (0.85-1.04)		
		109 334 317			Fruits and fruit juice Never smoker Former smoker Current smoker	Per serving per 1000 kcal	0.85 (0.70-1.03) 0.97 (0.87-1.08) 1.13 (1.01-1.27)		
					Whole fruit Never smoker Former smoker Current smoker		0.77 (0.59-1.01) 1.02 (0.89-1.18) 0.99 (0.82-1.20)		
		219 568			Fruits and fruit juice Non-drinkers Drinkers	Per serving per 1000 kcal	0.99 (0.88-1.12) 0.97 (0.89-1.06)		
					Whole fruit Non-drinkers Drinkers		0.92 (0.77-1.10) 0.94 (0.83-1.07)		
		787			Citrus fruit	1.1 vs 0.1 serving/ 1000 Kcal	0.90 (0.75-1.08)		
Freedman, 2008 mou08573 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	319/ 490 802 4.5 years	Cancer registry	FFQ	Incidence**, Oral cancer** Fruits and fruit juice Whole fruit	5.2-6.8 vs 1.2-1.8 serving/1000 kcal	0.84 (0.57-1.25) 0.81 (0.54-1.22)	Sex, age at baseline, alcohol intake, BMI, educational level, smoking dose, total energy Intake, usual activity throughout the day, vigorous activity,	
						Per serving per 1000 kcal	1.00 (0.90-1.12) 0.96 (0.82-1.12)		
		279/ 490 802			Incidence**, Laryngeal cancer**	5.2-6.8 vs 1.2-1.8 serving/1000 kcal	0.80 (0.51-1.23) 0.77 (0.49-1.22)		

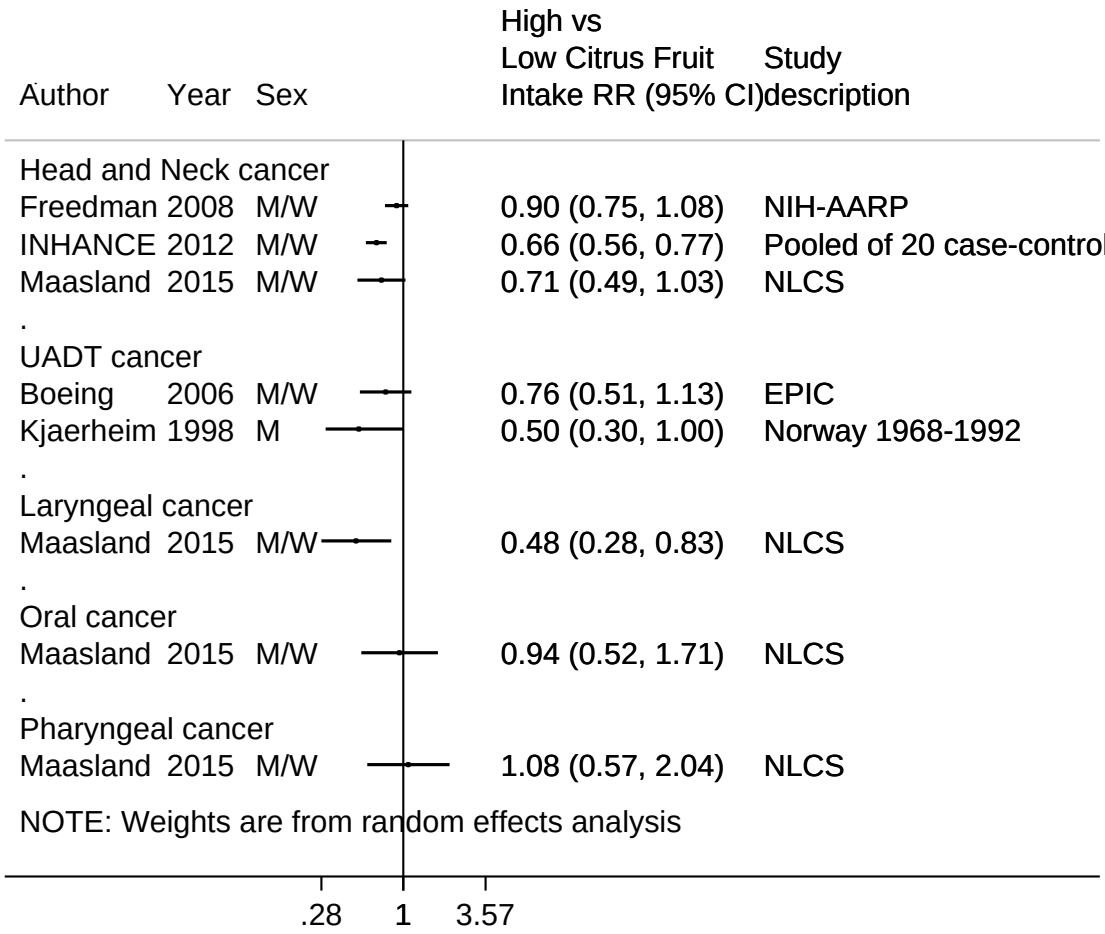
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Included/ Reason of exclusion
		4.5 years			Fruits and fruit juice Whole fruit	Per serving per 1000 kcal	0.98 (0.86-1.11) 0.96 (0.80-1.14)	vegetable intake. Whole fruits are additionally adjusted: fruit juice intake	
		142/ 490 802 4.5 years			Incidence, **oro/hypopharyngeal cancer** Fruits and fruit juice Whole fruit	5.2-6.8 vs 1.2-1.8 serving/1000 kcal Per serving per 1000 kcal	1.19 (0.68-2.08) 0.72 (0.37-1.39) 1.00 (0.84-1.18) 0.89 (0.69-1.15)		
Boeing, 2006 oes00910 Denmark, Germany, Italy, Netherlands, Spain, Sweden, UK	EPIC, Prospective Cohort, M/W	255men/ 97women/ 345 904 2 182 560 person-years	Cancer and pathology registry, active follow up, health insurance record, mortality registry and contact of participants or next-of-kin		Incidence, **UADT cancer** Total fruits Citrus fruits	104.4 vs 4.5 g/day 403.7 vs 80.8 g/day	0.60 (0.38-0.97) 0.76 (0.51-1.13)	Age, baseline alcohol intake, BMI, centre location, duration of smoking, educational level, energy from fat sources, energy from non-fat sources, gender, lifetime alcohol consumption, non-consumer status, smoking status	Included in the HvsL analysis
					Total fruits Men Women Combined	per 40 g/day	0.96 (0.91-1.02) 0.98 (0.86-1.12) 0.97 (0.92-1.02)		
					Citrus fruits Men Women Combined	per 8 g/day	0.93 (0.78-1.11) 1.23 (0.95-1.61) 0.98 (0.85-1.13)		
Kjaerheim, 1998 oes00130 Norway	Norway 1968-1992 UADT, Prospective Cohort, M	69/ 10 900 25 years	Population survey	FFQ	Incidence, **UADT cancer**	≥6 vs ≤1 times/month Garden berries Wild berries Citrus fruits Apples Bananas Grapes Canned fruits	 0.80 (0.40-1.60) 1.00 (0.40-2.20) 0.50 (0.30-1.00) 0.70 (0.40-1.30) 0.40 (0.10-1.00) 0.90 (0.30-2.60) 0.40 (0.10-2.60)	Age, alcohol consumption, smoking habits	Not included in HvsL analysis. It does not report result for total fruit intake
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, M	92/ 7 995 25 years	Selective service roll	FFQ and 24 hour recall	Incidence, **UADT cancer**	≥5 vs ≤1 servings/week	0.65 (0.39-1.07)	Age, alcohol consumption, smoking habits	Included in the HvsL analysis

Figure 4. RR (95%) for the highest compared with the lowest quintile of fruits intake by cancer type



Note: Median intakes in the top and lowest quintiles were in the NLCS, 271g/day, 325 g/day and 41 g/day, 75 g/day in men and women; in NIH-AARP, 3.2 and 0.4 servings/1000 calories. M: men; W: women; M/W: men and women.

Figure 5. RR (95%) for the highest compared with the lowest quintile of citrus fruits intake by cancer type



Note: M: men; W: women; M/W: men and women

2.2.3 Pulses

Cohort studies

Summary

Two publications on UADT cancer were identified in the 2005 SLR and no study was identified in the CUP. Dose-response meta-analysis was not conducted.

In a cohort study of 10,900 Norwegian men, no association was found between monthly consumption of beans and UADT cancer (RR 1.10; 95% CI 0.60-2.00) (Kjaerheim, 1998). In a Japanese-American cohort (Chyou, 1995), a non-significant decreased risk for UADT cancer was found with higher consumption of tofu, a product made out of soy milk (RR 0.49; 95% CI 0.07-3.54).

2.5 Meat, poultry, fish and eggs

A limited number of studies was identified. The study results are described in text. No figures or tables are presented.

2.5.1 Meat

Cohort studies

Summary

One study on UADT cancer was identified in the 2005 SLR and one study on oral/pharyngeal, laryngeal and UADT cancer was identified in CUP.

Meta-analyses were not conducted.

In the EPIC study (Steffen, 2012) meat intake (including red meat, processed meat and poultry) was not related to the risk of laryngeal cancer (HR for an increment of 20g/1000 kcal of total meat 0.91; 95% CI 0.79-1.04), but was significantly related to increased risk of oral cavity/pharyngeal cancer (HR for 20g/1000 kcal increment 1.13; 95% CI 1.02-1.24) and UADT cancer (HR for 20g/1000 kcal increment 1.09; 95% CI 1.02-1.17). The association was significant in former smokers and current smokers (HR for 20 g/1000 kcal 1.20; 95% CI 1.04-1.38; RR 1.12; 95% CI 1.03-1.22, respectively) but not in lifelong non-smokers (RR 0.98; 95% CI 0.81-1.18).

In a Japanese-American cohort (Chyou, 1995), the HR of UADT cancer risk for consumption of meat 5 times per week or more was 0.77; 95% CI 0.44-1.36, compared to less than once per week meat consumption.

Pooled analysis of case-control studies

In the International Head and Neck Cancer Epidemiology (INHANCE) consortium, the OR for the highest compared the lowest quartile of intake of meats was 1.05 (95% CI 0.87–1.27); p-trend= 0.36; 21 cohorts; p-heterogeneity <0.01 (Chuang, 2012).

2.5.1.2 Processed meat

Cohort studies

Summary

Three studies on UADT cancer were identified in the 2005 SLR and two on oral/pharyngeal, laryngeal and UADT cancer in the CUP.

Meta-analyses were not conducted.

Oral/pharyngeal cancer

In the EPIC study (Steffen, 2012) intake of processed meat was not significantly related to increased risk of oral/pharyngeal cancer (HR for 10g/1000 kcal increase was 1.09; 95% CI 1.00-1.19).

In the NIH-AARP study (Cross, 2007), the hazard ratio of oral/pharyngeal cancer for the highest compared to the lowest intake of processed meat was 1.17; 95% CI 0.94-1.45.

Laryngeal cancer

In the EPIC study (Steffen, 2012) intake of processed meat was not related to the risk of laryngeal cancer (HR for 10g/1000 kcal increase was 1.03; 95% CI 0.91-1.16).

In the NIH-AARP study (Cross, 2007), intake of processed meat was positively but not significantly related to the risk of laryngeal cancer. The hazard ratio for the highest compared to the lowest intake of processed meat was 1.33; 95% CI 0.93-1.91.

UADT cancer

In the EPIC study (Steffen, 2012) intake of processed meat was significantly related to increased risk of UADT cancers (HR for 10g/1000 kcal increase was 1.13; 95% CI 1.06-1.20 and 1.41; 95% CI 1.03-1.94 for the highest compared to the lowest intake quintile). The significant positive association was observed in current smokers but not in lifelong non-smokers and former smokers (HR for 10g/1000 kcal increase 1.18; 95% CI 1.10-1.27; RR 0.87; 95% CI 0.69-1.08; RR 1.11; 95% CI 0.97-1.26, respectively). Overall, a positive association was found for ham (per 5g/1000 kcal, HR 1.11; 95% CI 1.02-1.20) but non-significant associations were found for meat balls, bacon and hamburger (RR 1.21; 95% CI 0.99-1.47; HR 1.00; 95% CI 0.98-1.02; RR 0.77; 95% CI 0.50-1.20, respectively).

In three other cohorts, positive but non-significant associations were observed: in a cohort study of Norwegian men (RR for six times or more compared to none :1.60; 95% CI 0.40-6.90) (Kjaerheim, 1998), in post-menopausal women in US (intake of processed meat and fish thirteen times or more/week compared to none, RR 1.30; 95% CI 0.6-3.2) (Zheng, 1995), and in a Japanese-American cohort (RR for 5 times per week or more compared to none 1.24; 95% CI 0.73-2.10) (Chyou, 1995).

Pooled analysis of case-control studies

In the International Head and Neck Cancer Epidemiology (INHANCE) consortium, the OR for the highest compared to the lowest quartile of intake of processed meats was 1.37 (95% CI 1.14–1.65); p-trend<0.01; 21 cohorts; p-heterogeneity <0.01 (Chuang, 2012).

2.5.1.3 Red meat

Cohort studies

Summary

One study on beef, pork and lamb and UADT cancer was identified in the 2005 SLR and two studies on red meat and oral/pharyngeal, laryngeal and UADT cancer were identified in CUP. Meta-analyses were not conducted.

Oral/pharyngeal cancer

Red meat was not related to risk of oral/pharyngeal cancer in the EPIC study (Steffen, 2012) (HR for 10g/1000 kcal increase was 1.04; 95% CI 0.96-1.12) and in the NIH-AARP study (Cross, 2007) (HR for the highest compared to the lowest intake of red meat was 1.03; 95% CI 0.82-1.28).

Laryngeal cancer

Red meat was not related to risk of laryngeal cancer in the EPIC study (Steffen, 2012) (HR for 10g/1000 kcal increase was 0.92; 95% CI 0.82-1.02) and was positively but not statistically significantly related to laryngeal cancer in the NIH-AARP study (Cross, 2007) (HR for the highest compared to the lowest intake of red meat was 1.43; 95% CI 0.99-2.07).

UADT cancer

Red meat was not related to risk of UADT in the EPIC study (Steffen, 2012) (HR for 10g/1000 kcal increase was 1.02; 95% CI 0.97-1.08 and 0.98; 95% CI 0.70-1.37 for the highest compared to the lowest quintile). A marginal positive association was observed in former smokers (HR 10g/1000 kcal 1.12; 95% CI 1.00-1.25) but not in lifelong smokers and current smokers (RR 1.03; 95% CI 0.89-1.20 and 1.03; 95% CI 0.96-1.10, respectively).

Beef, pork and lamb

In a cohort study of 10,900 Norwegian men (Kjaerheim, 1998), the risk of UADT cancer was positively but not significantly related to consumption of beef (RR 2.80; 95% CI 1.00-7.60), pork (RR 1.50; 95% CI 0.50-4.20) and lamb (RR 2.10; 95% CI 0.70-6.10). (All RRs are for the comparison of 6 times/ month or more to less than monthly).

Pooled analysis of case-control studies

In the International Head and Neck Cancer Epidemiology (INHANCE) consortium, the OR for the highest compared the lowest quartile of intake of beef/pork was 1.40 (95% CI, 1.13–1.74; p-trend= 0.13; 15 cohort studies, p-heterogeneity=0.010) (Chuang, 2012).

2.5.1.4 Poultry

Cohort studies

Summary

No studies were identified in the 2005 SLR and two studies were identified in CUP regarding oral cavity, oral/pharyngeal, laryngeal and UADT cancer. Meta-analyses were not conducted.

Oral cavity cancer

Poultry was not related to cancers of the oral cavity in the NIH-AARP study (Daniel, 2011) (HR for highest compared to lowest 1.05; 95% CI 0.87-1.26).

Oral/pharyngeal cancer

No association of poultry intake with oral/pharyngeal cancer was observed in the EPIC study (HR for 5g/1000 kcal increment= 1.01; 95% CI 0.95-1.08) (Steffen, 2012).

Laryngeal cancer

No association of poultry intake with laryngeal cancer was observed in the EPIC study (HR for 5g/1000 kcal increment= 0.92; 95% CI 0.83-1.01) (Steffen, 2012).

No association was observed in men in the NIH-AARP (HR for highest vs lowest 1.04; 95% CI 0.77-1.41 in men) and an inverse association was observed in women (HR 0.27; 95% CI 0.10-0.71) (Daniel, 2011).

UADT cancer

No association of poultry intake with UADT cancer was observed in the EPIC study in continuous analysis (HR for 5g/1000 kcal increment 0.96; 95% CI 0.91-1.01). An inverse association was observed in categorical analysis (HR for highest compared to lowest intake 0.70; 95% CI 0.51-0.96) (Steffen, 2012). The significantly inverse association was observed in current smokers (HR 0.91; 95% CI 0.84-0.98) but not in lifelong non-smokers and former smokers (HR 0.97; 95% CI 0.86-1.09; HR 1.03; 95% CI 0.94-1.12, respectively).

2.5.2 Fish

Cohort studies

Summary

Two studies on UADT cancer were identified in the 2005 SLR and two studies on oral cavity, oral/pharyngeal, laryngeal and UADT cancer in CUP.

Meta-analyses were not conducted.

Oral cavity cancer

Fish intake was not related to cancer of the oral cavity in the NIH-AARP study (Daniel, 2011) (HR for highest compared to lowest 0.90; 95% CI 0.75-1.09).

Oral/pharyngeal cancer

No association of fish intake with oral/pharyngeal cancer was observed in the EPIC study (HR for 5g/1000 kcal increment 0.99; 95% CI 0.88-1.10) (Steffen, 2012).

Laryngeal cancer

No association of fish intake with laryngeal cancer was observed in the EPIC study (HR for 5g/1000 kcal increment 0.97; 95% CI 0.85-1.12) (Steffen, 2012) and in the NIH-AARP (HR for highest vs lowest 1.03; 95% CI 0.79-1.36) (Daniel, 2011).

UADT cancer

No association of fish intake with UADT cancer was observed in the EPIC study in continuous analysis (HR for 5g/1000 kcal increment= 0.96; 95% CI 0.89-1.04) (Steffen, 2012). In analysis stratified by smoking status showed the hazard ratios for 10g/1000 kcal of fish intake were 0.96; 95% CI 0.79-1.16; RR 0.85; 95% CI 0.71-1.02; RR 1.01; 95% CI 0.91-1.11 in lifelong smokers, former smokers and current smokers, respectively.

In a Japanese-American cohort (Chyou, 1995), no significant positive association of consumption of fish 5 times per week or more compared to none and UADT cancer risk (RR 1.37; 95% CI 0.70-2.69).

A non-significant inverse association was observed in a cohort study of Norwegian men (RR 6 times per month or more compared to none 0.80; 95% CI 0.30-2.70) (Kjaerheim, 1998).

Pooled analysis of case-control studies

In the INHANCE consortium (Chuang, 2012), the OR of head and neck cancer for the highest compared the lowest quartile of intake of seafood intake was 0.83 (95% CI, 0.74-0.94; p-trend= 0.02; 19 cohort studies, p-heterogeneity<0.01).

2.5.7 Milk and dairy products

Cohort studies

Summary

One small study in Norway (Ursin, 1990) and one study in Japanese men in North America (Chyou, 1995) on milk intake and oral cavity, pharyngeal, laryngeal and UADT cancer were identified in the 2005 SLR. Furthermore, Chyou *et al.* (1995) reported results on dairy products and UADT cancer. The NIH-AARP (Park, 2009) on dairy products and HNC was identified during the CUP.

Meta-analyses were not conducted.

Milk

Oral cavity cancer

A Norwegian prospective cohort in which 10 cases of buccal cancer were identified after 11.5 years of follow-up (Ursin, 1990) showed no significant inverse association of milk intake and risk of cancer of the oral cavity. The RR for consumption of two or more glasses of milk (mainly whole milk, 3.8% fat) compared to less than one glass was 0.27, p-trend 0.09 in men and 0.35, p-trend 0.17 in men and women combined (CI are not reported).

Pharyngeal cancer

A positive association was suggested in the Norwegian study (Ursin, 1990) in an analysis including a total of 7 cases. The RR for two or more glasses of milk compared to less than one glass was 14.02, p-trend 0.10; OR 27.12, p-trend 0.03, in men and men and women combined, respectively.

Laryngeal cancer

In the Norwegian prospective cohort (Ursin, 1990) in which 12 cases of larynx cancer were identified, the RR for two or more glasses of milk compared to less than one glass were 1.17, p-trend 0.87 in men and 0.98, p-trend 1.00 in men and women combined.

UADT cancer

A Japanese-American cohort (Chyou, 1995), examined the association between risk of UADT cancer and intake of milk. The RR for drinking milk five or more times/week compared to less than once per week was 0.70; 95% CI 0.42-1.17. The number of cases of UADT cancer in the analysis was 92.

Dairy products

Head and Neck cancer

The NIH-AARP study (Park, 2009) showed that higher consumption of dairy products (including milk, yogurt, natural and processed cheese) was inversely but not significantly inverse associated with HNC risk (1038 cases) in men and women (HR 0.84; 95% CI 0.69-1.02; HR 0.89; 95% CI 0.63-1.27, respectively). The analyses were adjusted for several potential confounders including alcohol intake and smoking status, time since quitting smoking, smoking dose, and intake of fruits and vegetables.

UADT cancer

A cohort in American men of Japanese ancestry (Chyou, 1995), examined the association between risk of UADT cancer and intake of butter/margarine and ice cream. Consumption of those products did not show an association with UADT cancer (RR 1.08; 95% CI 0.64-1.80; RR 0.99; 95% CI 0.49-2.00, respectively).

Pooled analysis of case-control studies

In the International Head and Neck Cancer Epidemiology (INHANCE) consortium, milk and dairy products intake was not related to the risk of squamous carcinoma of head and neck. The pooled odds ratio for the highest compared to the lowest centre specific quartile of intake was 1.01 (95% CI 0.77–1.34) (Chuang, 2012). The analysis included individual participants data from 20 case–control studies for a total of 12 315 cases and 19 387 controls. There was significant heterogeneity across centres ($p<0.01$).

3 Beverages

3.4 Soft drinks

Cohort studies

Summary

No study was identified in the 2005 SLR and one study on oral, pharyngeal and laryngeal cancer (NIH-AARP) was identified during the CUP.

Meta-analyses were not conducted.

In the NIH-AARP study (Ren, 2010) consumption of carbonated soft drinks was not associated with the risk of oral cancer, pharynx and larynx cancers. For the comparison of one or more cans/day to none the HRs were: 0.77; 95% CI 0.54-1.09; p trend 0.33, 392 cases for oral cancers; 0.76; 95% CI 0.46-1.25, p trend 0.20, 178 cases for pharyngeal cancer; and 0.82; 95% CI 0.55-1.23, p value 0.55, 307 cases for laryngeal cancer. The analyses were adjusted for age, sex, tobacco smoking, alcohol drinking, BMI, education, ethnicity, usual physical activity throughout the day, vigorous physical activity and the daily intake of fruit, vegetables, red meat, white meat and calories.

3.5 Fruit juices

Cohort studies

Summary

One study on UADT cancer was identified in the 2005 SLR and one study on HNC in CUP.

Meta-analyses were not conducted.

In the NIH-AARP study (Freedman, 2008) intake of fruit juices was not related to the risk of cancers of head and neck cancers (787 cases) or any of the subsites. The HRs for one serving/1000 calories increment were 1.03; 95% CI 0.93-1.15 for head and neck cancer; 1.06; 95% CI 0.90-1.25 for oral cancer;1.12; 95% CI 0.88-1.43 for pharyngeal cancer and 1.00; 95% CI 0.82-1.21 for laryngeal cancer. The HR estimates for HNC were non-significant among never smokers and former smokers (HR 0.96; 95% CI 0.72-1.28, HR 0.88; 95% CI 0.73-1.07, respectively) and for alcohol users and non-drinkers (HR 1.01; 95% CI 0.88-1.16, HR 1.08; 95% CI 0.90-1.29, respectively), but they were significant for current smokers (HR 1.26; 95% 1.09-1.46).

In a cohort of Norwegian men in which 71 upper aerogastric tract cancers occurred, no association was found between UADT cancer and intake of lemonade (RR highest vs lowest 0.90; 95% CI 0.50-1.60) or red fruit drinks (RR highest vs lowest 1.20; 95% 0.60-2.20) (Kjaerheim, 1998).

3.6 Hot drinks

3.6.1 Coffee

Cohort studies

Summary

Two cohort studies on oral/pharyngeal and UADT cancer were identified in the 2005 SLR and four other cohort studies on oral cavity, oral/pharyngeal, pharyngeal, HN and UADT cancer were identified in the CUP.

The cancer sites investigated were oral cavity, pharynx and larynx in the NIH-AARP (Ren, 2010); fatal oral/pharyngeal cancers in the CPS II (Hildebrand, 2013) incident oral/pharyngeal cancers in the Miyagi Cohort Study (Naganuma, 2008) and a Norwegian cohort (Stensvold, 1994); HNC in the PLCO study (Hashibe, 2015); and UADT in the Miyagi Cohort Study (Naganuma, 2008) and in a cohort of American of Japanese ancestry (Chyou, 1995). Inverse associations were observed only for cancers of the oral cavity and oral/pharynx combined. All studies adjusted for smoking.

Oral cavity cancer

In the NIH-AARP study (Ren, 2010) the HR for consumption of more than 3 cups per day of coffee compared to less than one cup was 0.85; 95% CI 0.62-1.16; p-trend= 0.14; 392 cases.

Oral/pharyngeal cancer

In a prospective US cohort study on cancer mortality (Hildebrand, 2013) the risk of dying from oral/pharyngeal cancer was inversely related to coffee intake. The association was significant for caffeinated coffee (HR for more than 4 cups/day compared to no coffee or tea 0.58; 95% CI 0.37-0.92; p-trend= 0.01, 299 deaths in the analysis) and non-significant for decaffeinated coffee (HR for more than 2 cups/day compared to no coffee or tea 0.61; 95% CI 0.37-1.01; p-trend 0.24; 106 deaths in the analysis). The association was similar in men and women. There was no significant interaction with smoking or alcohol drinking. The HR for more than two cups per day were 0.36; 95% CI 0.23-0.58 in non-smokers; RR 0.64; 95% CI 0.50-0.81 in smokers and 0.63; 95%CI 0.40-1.01 in former smokers. Similar patterns of association were observed across strata of alcohol use (non-drinkers: RR 0.70; 95% CI 0.54-0.92, light drinkers: RR 0.45; 95% CI 0.33-0.61, moderate/heavy drinkers: RR 0.56; 95% CI 0.42-0.75).

In the Miyagi Cohort Study (Naganuma, 2008) consumption of one or more cups of coffee per day compared to none was significantly inversely related to oral and pharyngeal cancer (HR 0.35; 95% 0.16-0.77; p-trend= 0.009).

In a Norwegian cohort (Stensvold, 1994) inverse non-significant inverse associations of coffee consumption and cancer of oral cavity and pharynx were observed for both men (33 cases) and women (12 cases) (RR 0.50 and 0.70, respectively. No confidence intervals are reported).

Pharyngeal cancer

In the NIH-AARP study (Ren, 2010) cancer of the pharynx (177 cases) was not related to coffee intake (HR for more than 3 cups/compared to less than one cup was 1.23; 95% CI 0.75-2.01; p-trend= 0.34).

Laryngeal cancer

In the NIH-AARP study (Ren, 2010) cancer of the larynx (306 cases) was not related to coffee intake (HR for more than 3 cups/compared to less than one cup was 1.01; 95% CI 0.71-1.44; p-trend= 0.95).

Head and neck cancer

In the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, of the 97 334 eligible individuals, 145 developed head and neck up to ten years of follow-up after the intervention ended in 2006. Head and neck cancer risk was not related with intake of coffee (HR for one cup/day increase 0.99; 95 % CI 0.91–1.09). The HR for two or more cups of coffee/day compared to less than one cup/day was 1.04 (95% CI 0.68-1.58, p-trend= 0.91). The analyses were adjusted for age, sex, race, education, smoking status, frequency, duration, years since quitting (former smokers) and alcohol drinking (Hashibe, 2015).

UADT cancer

In the Miyagi Cohort Study (Naganuma, 2008) a lower risk of oral, pharyngeal, and oesophageal cancers with higher coffee consumption was observed in both never and current alcohol drinkers, and in smokers and non-smokers, although the associations were non-significant in non-smokers (24 cases) and non-drinkers (20 cases). The HR for one or more cups of coffee per day compared with no consumption were 0.43 (95% CI: 0.13-1.41; p-trend= 0.17) for non-drinkers and 0.49 (95% CI: 0.31- 0.77; p-trend= 0.004) for current drinkers. The multivariate-adjusted hazard ratios for one or more cups of coffee/day compared with no consumption were 0.50 (95% CI: 0.14-1.81; p-trend= 0.29) for non-smokers and 0.49 (95% CI: 0.30- 0.79; p-trend= 0.008) for current smokers.

In a cohort in Japanese-American (Chyou, 1995), consumption of five or more servings of coffee/week compared to less than one/week had a non-significant positive association with UADT cancer (RR 1.44; 95% CI 0.63-3.32).

Pooled analysis of case-control studies

In a pooled analysis of individual-level data from nine case-control studies of head and neck cancers (INHANCE) including 5 139 cases and 9 028 controls, caffeinated coffee intake was inversely related with the risk of cancer of the oral cavity and pharynx: the ORs were 0.96 (95% CI, 0.94–0.98) for an increment of one cup per day and 0.61 (95% CI, 0.47–0.80) in drinkers of >4 cups per day versus non-drinkers (Galeone, 2010). The inverse association was observed in all cancer sites investigated. The OR for >4 cups per day versus none were 0.46; 95% CI, 0.30–0.71 for oral cavity; OR, 0.58; 95% CI, 0.41–0.82 for oro/hypopharynx; and OR, 0.61; 95% CI, 0.37–1.01 for oral cavity/pharynx not otherwise specified (NOS) and

across strata of selected covariates. No association of caffeinated coffee drinking was found with laryngeal cancer (OR, 0.96; 95% CI, 0.64–1.45 in drinkers of >4 cups per day versus non-drinkers). There was limited data on decaffeinated coffee.

3.6.2 Tea

Cohort studies

Summary

A cohort study on American men of Japanese ancestry and UADT cancer (Chyou, 1995) was identified in the 2005 SLR and three other cohort studies were identified in the CUP. The cancer sites investigated were oral cavity, pharynx and larynx in the NIH-AARP (Ren, 2010); fatal oral/pharyngeal cancers in the CPS II (Hildebrand, 2013); head and neck cancer in the PLCO study (Hashibe, 2015). An inverse association was observed only in one study for cancers of the oral cavity and for pharynx.

Oral cavity

In the NIH-AARP study (Ren, 2010) intake of tea was inversely but not significantly related to risk of cancer of the oral cavity. Compared to no consumption, the HR for consumption of one cup/day or more of hot tea was 0.75; 95% CI 0.53-1.06, p-trend= 0.083 and HR 0.89; 95% CI 0.67-1.19, p-trend=0.42 for iced tea.

Oral/pharyngeal cancer

The risk of fatal oral/pharyngeal cancer was not related to tea consumption in the CPS II (Hildebrand, 2013). The HR for more than two cups/day compared to none was RR 0.79; 95% CI 0.44-1.42, p-trend= 0.99).

Pharyngeal cancer

In the NIH-AARP study (Ren, 2010) intake of hot tea was inversely related to risk of cancer of the pharynx. Compared to no consumption, the HR for consumption of one cup/day or more of hot tea was 0.37; 95% CI 0.20-0.70, p-trend= 0.0003. No association with consumption of iced tea was observed (HR for same comparison, 0.99; 95% CI 0.63-1.55, p-trend= 0.68).

Laryngeal cancer

The risk of laryngeal cancer was not related to tea intake in the NIH-AARP study (Ren, 2010). The HR for one cup/day or more of hot tea compared to no consumption was 0.92; 95% CI 0.63-1.36, p-trend= 0.69 and for the same comparison of iced tea, the HR was 0.89; 95% CI 0.62-1.18 p-trend= 0.13.

Head and neck cancer

In the PLCO cancer screening trial, of the 97 334 eligible individuals, 145 developed HNC up to ten years of follow-up after the intervention. Follow-up ended in 2006. Head and neck

cancer risk was not related with intake of tea (HR for one cup/day= 1.01; 95% CI, 0.88–1.17). The analysis was adjusted for age, sex, race, education, smoking status, frequency, duration, years since quitting (former smokers) and alcohol drinking (Hashibe, 2015).

UADT cancer

In a Japanese-American cohort (Chyou, 1995), consumption of black tea (ever versus almost never) was non-significantly inversely associated with UADT cancer (RR 0.67; 95% CI 0.43-1.03).

Pooled analysis of case-control studies

In a pooled analysis of individual-level data from nine case-control studies of head and neck cancers (INHANCE) including 5,139 cases and 9,028 controls, tea intake was not related with the risk of cancer of the oral cavity and pharynx: the ORs for an increment of 1 cup/day were 0.99 (95% CI, 0.94–1.04) for HNC, 0.98 (95% CI 0.91–1.06) for oral cavity; 1.02 (95% CI 0.93–1.12) for oro/hypopharynx; and 1.06 (95% CI 0.97–1.16) for laryngeal cancer (Galeone, 2010).

3.6.2.2 Green tea

Cohort studies

Summary

One study on UADT cancer was identified in the 2005 SLR and one study on oral cancer was identified in CUP.

Oral cancer

In the JACC study (Ide, 2007), consumption of five or more cups/day of green tea was non-significantly inversely associated with oral cancer incidence in men, women and in the combined group (HR 0.61; 95% CI 0.18-2.06; HR 0.31; 95% CI 0.09-1.07; HR 0.44; 95% CI 0.19-1.04, respectively). In analysis stratified by smoking status in men, an inverse non-significant association was reported in current smokers and past smokers (HR for five or more cups/ day of green tea, compared with four or less, 0.31; 95% CI 0.06-1.54; HR 0.83; 95% CI 0.18-3.78, respectively), whereas for non-smokers a positive non-significant association was found (HR 1.85; 95% CI 0.30-11.46).

UADT cancer

Consumption of green tea (ever versus almost never, RR 1.14; 95% CI 0.68-1.91) was not related with UADT cancer in a cohort of American with Japanese ancestry (Chyou, 1995).

3.6.3 Mate

Summary

Three hospital-based case-control studies were identified in the 2005 SLR (on mouth and oral cavity cancer) and two (on oral cavity, oral cavity/oropharyngeal, hypopharyngeal/laryngeal and UADT cancer) during CUP. The study results are tabulated (Table 5). No cohort studies were identified.

In a large multicentre case-control study in Uruguay (Deneo-Pellegrini, 2013), drinking mate was not related to the risk of cancers of the oral cancer. The association was strengthened and became statistically significant when interaction terms of alcohol and smoking with mate were added to the models. The study reports results for oral cavity and pharyngeal cancer. However number of cases is not reported for these cancer sites. Furthermore, topography is not reported for any of the cancer sites.

In another large study in Argentina and Brazil (Szymanska, 2010), drinking mate was associated with higher risk of all UADT cancers investigated, although the association with quantity of mate was in general not statistically significant. The analysis of mate temperature was not conclusive.

Two other smaller studies in Brazil and one in Uruguay reported positive associations that were significant in two of the studies (Pintos, 1994; Franco, 1989; De Stefani, 1988).

Table 5 Summary of results of case-control studies on mate drinking and mouth, pharynx and larynx cancers

Author, location, sex, number of controls	Cancer site, number of cases	Contrast	OR (95% CI) P value linear trend	Adjustment
Deneo-Pellegrini, 2013 Uruguay Men 696 hospital based controls	Oral cancer 696 cases of squamous cell carcinoma	Ever vs never drinkers	1.05 (0.70–1.55)	Age, residence, urban/rural status, education, income, pack years of tobacco, alcohol years
		>1 l/day vs never	1.12 (0.75–1.69) p linear trend 0.24	
		>46 years drinking mate vs never	1.21 (0.77–1.89) p linear trend 0.31	
		Warm mate vs never Hot/very hot mate vs never	0.88 (0.53–1.49) 1.11 (0.74–1.66) p linear trend 0.37	
		Ever vs never drinkers	2.33 (1.27-4.27)	With additional terms for interaction (mate variable × pack years and alcohol years)
		>1 l/day vs never	3.47 (1.60–7.52) p linear trend 0.006	
		>46 years drinking mate vs never	3.28 (1.44-7.51) p linear trend 0.001	
		Warm mate vs never Hot/very hot mate vs never	1.25 (0.89-3.17) 2.95 (1.37-6.36) p linear trend 0.001	
		(all ORs for oral cavity and pharyngeal cancer were also statistically significant)		
Szymanska, 2010 Argentina, Brazil Men and women, 1026 hospital based controls	Oral cavity and oropharynx 628 cases	Ever vs never	1.48 (1.05-2.08)	Age, sex, education, tobacco pack-years, alcohol, centre
		>0.2 l/day vs never	1.35 (0.86-2.13) p linear trend 0.07	
		>40 years vs never	1.83 (1.19-2.81) p linear trend 0.003	
		Lifetime litres (highest vs never)	1.72 (1.08-2.76) p linear trend 0.07	
		Cold/warm vs never Hot/very hot vs never	2.89 (1.8-4.64) 1.15 (0.79-1.66) p linear trend 0.72	
	Hypopharynx and larynx 410 cases	Ever vs never drinkers	1.51 (1.05-2.18)	
		>0.2 l/day vs never	1.58 (0.98-2.53) p linear trend 0.019	
		>40 years vs never	1.75 (1.12-2.74) p linear trend 0.03	

		Lifetime litres (highest vs never)	1.66 (1.02-2.69) p linear trend 0.06	
		Cold/warm vs never	2.33 (1.39-3.91)	
		Hot/very hot vs never	1.28 (0.87-1.9) p linear trend 0.72	
	Upper aero-digestive tract	Ever vs never drinkers	2.29 (0.58-9.07) p linear trend 0.12	
		>0.2 l/day vs never	1.78 (0.30-10.68) p linear trend 0.12	
		>40 years vs never	4.55 (1.47-14.06) p linear trend 0.004	
	Never drinkers, never smokers 37 cases	Lifetime litres (highest vs never)	3.64 (1.1-12.06) p linear trend 0.055	
		Cold/warm vs never	5.35 (1.18-24.32)	
		Hot/very hot vs never	2.50 (0.93-6.74) p linear trend 0.095	
Franco, 1989 Brazil Men and women 464 controls	Oral cavity, 232 cases	>30 cups /month vs <1 cup/month	1.6 (0.8–3.3)	Smoking and alcohol
De Stefani,1988 Uruguay Men 286 controls	Oral/pharyngeal cancer 108 cases	>2 l/day vs <1 l/day	5.2 (2.1–13.1)	Age, smoking, alcohol
Pintos, 1994 Brazil Men and women 338 controls	Mouth 169 cases	> 3 gourd/day vs never	2.82 (1.2–6.6), p trend 0.038	Age, gender, income, smoking, alcohol, rural residence, diet, non-alcoholic beverages
	Pharynx 112 cases		1.32 (0.4-4.1), p trend 0.37	
	Larynx 97 cases		2.87 (1.0-8.3), p trend 0.009	
	UADT 378 cases		2.13 (1.3-3.4), p trend 0.001	

3.7 Alcoholic drinks

3.7.1 Total alcoholic drinks

Cohort studies

Summary

Thirty publications from twenty six cohorts (of which seven were identified in 2005 SLR) investigated alcohol consumption in relation to oral, pharyngeal and laryngeal cancer and for combinations of those cancers. Dose-response meta-analyses were conducted for oral, oral/pharyngeal, laryngeal and UADT cancer.

Oral cancer

Fourteen publications from twelve cohorts were identified. Six cohorts (5 617 cases) were included in the dose-response meta-analysis; (Hippisley-Cox, 2015; Hsu, 2014; Maasland, 2014; Shanmugham, 2010; Freedman, 2007; Boffetta, 1990), from which one is a study on cancer mortality (Boffetta, 1990). A standard conversion from drinks to grams was applied in two studies (Freedman, 2007; Boffetta, 1990) and from units to grams in one study (Hippisley-Cox, 2015). Seven studies were excluded from the dose response analyses due to lack of required data (Saieva, 2012; Cancela, 2009; Thygesen, 2009; Muwonge, 2008; Thygesen, 2005; Tonnesen, 1995; Adami, 1992). Furthermore, one study was further excluded due to considerably low range of alcohol consumption (Jayalekshmi, 2011). All studies reported positive associations although non-significant associations were found in two of them (Jayalekshmi, 2011; Muwonge, 2008). Of the excluded studies, four studies were on alcoholics (Saieva, 2012; Thygesen, 2009; Tonnesen, 1995; Adami, 1992) and one on brewery workers (Thygesen, 2005).

Significantly positive association was found between alcohol consumption (as ethanol, per 10 g/day increase) and oral cancer (RR 1.15; 95% CI 1.09-1.22).

There was high heterogeneity. The funnel plot shows that there were three outliers (Hsu, 2014; Maasland, 2014; Boffetta, 1990). Influence analysis showed that the summary RR did not change substantially when each study was excluded in turn from the meta-analysis.

Interactions with smoking and folate

In the Nurses' Health study (Shanmugham, 2010) a significant interaction between alcohol and folate intakes was observed (P-interaction= 0.02). The cancer risk for women with high alcohol (≥30 g/d) and low folate (<350 μg/d) intakes was significantly elevated (RR, 3.36; 95% CI, 1.57-7.20) as compared with non-drinkers with low folate intake. No association with high alcohol intake (≥30 g/d) was observed in the high-folate (≥350 μg/d) group as compared with non-drinkers with high folate intake (RR= 0.98; 95% CI, 0.35-2.70). The analysis of alcohol intake was adjusted by age, follow-up time, pack-years of smoking, current smoking status, and folate intake [lip and nasopharynx excluded]. The authors also evaluated the interaction between smoking and alcohol (results not shown in the publication)

and confirmed that the risk was highest for those with high intakes of both tobacco and alcohol. Low or moderate alcohol intake (0.1-14.9 g/d) was not associated with an increased risk for oral cancer. In a cohort in Karunagappally (Jayalekshmi, 2011) in which 67 cases were never drinkers out of 160 cases of oral cancer identified higher consumption of alcohol (≥70mg/day) was not associated with oral cancer in participants who never chewed tobacco (RR 1.00; 95% CI 0.50-2.00), while there was a non-significant positive association in current tobacco chewers (RR 1.20; 95% CI 0.70-2.20).

In the Trivandrum Oral cancer Screening Trial (TOCSS) (Muwonge, 2008) alcohol drinking was non-significantly positively associated with oral cancer incidence (OR 1.40; 95% CI 0.90-2.20), compared to never-drinking. When compared to never smokers, never pan/nut/tobacco chewers and never drinkers, never smokers, the RR was 1.2 (95% CI, 0.3-6.0) in never smokers, never chewers and ever drinkers, and it was 4.8 (95% CI 2.5-9.3) in ever smokers, ever chewers and ever drinkers.

In the NLCS (Maasland, 2014) alcohol drinkers (>15g/day)/ smokers (≥20 cigarettes/ day) had RR 3.54 (95% CI: 1.66-7.52, 36 cases) while alcohol drinkers (>15 g/day)/ never-smokers had RR 4.16 (95% CI 1.82-9.52, 8 cases) compared to alcohol drinkers (0-15g/day)/ never smokers. Interaction was not significant between categories of alcohol consumption and cigarette smoking (P-interaction= 0.10).

Study quality:

Three studies did not report percentage of lost to follow up (Hippisley-Cox, 2015; Hsu, 2014; Freedman, 2007). Loss to follow-up was low in the other studies. Cancer outcome was confirmed using cancer, registries, death certificates and medical records. Most of the studies did not differentiate oral SCC from adenocarcinomas, except from Maasland *et al.* (2014) and Freedman *et al.* (2007) which included only SCC cases (Maasland, 2014; Freedman, 2007). Furthermore, Shanmugham *et al.* (2010) defines oral cancer as malignant neoplasms of the mouth, oropharynx and hypopharynx (Shanmugham, 2010).

Alcohol intake was assessed by questionnaires or FFQ in most studies. All of the studies included in the dose-response analysis were adjusted for age and smoking.

Table 6. Total alcohol intake and oral cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12 (14 publications)
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in linear dose-response meta-analysis	6

Table 7. Total alcohol (as ethanol) intake and oral cancer risk. Summary of the linear dose-response meta-analysis in CUP

	CUP	
Increment unit used	10g/day	
All studies		
Studies (n)	6	
Cases (total number)	5 617	
RR (95%CI)	1.15 (1.09-1.22)	
Heterogeneity (I^2, p-value)	88.3%, <0.001	
P-value Egger test	0.069	
Stratified analysis		
Sex	**Men**	**Women**
Studies (n)	5	4
RR (95%CI)	1.13 (1.04-1.22)	1.24 (1.07-1.45)
Heterogeneity (I^2, p-value)	91.3%, <0.001	85.3%, <0.001

Table 8. Total alcohol intake and oral cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

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
Hippisley-Cox, 2015 mou08566 England	QResearch database study, UK, Prospective Cohort, Age: 25-84 years, M/W	3 096 1 715/ 4 943 765 15 years	Cancer registry/death certificates/medical records	Medical records	Incidence, oral cancer, Men Women	>9 vs ≤0 units/day	3.71 (2.99-4.59) 4.38 (2.25-8.52)	Age, BMI, cancer diagnosis, smoking status, Townsend social and material deprivation score
Hsu, 2014 mou08580 Taiwan	Taiwan community cohorts, Prospective Cohort, Age: 30-80 years, M, Taiwan residents	97/ 25 611 18.4 years	Cancer registry and death certificates	Structured questionnaire	Incidence, oral cancer	≥80 g/day vs never-drinker	1.54 (0.81-2.92) Ptrend:0.597	Age, cohort, educational level, ethnicity, substance use each other (incl smoking)
						≥1500 g/year vs never-drinker	1.33 (0.67-2.65) Ptrend:0.842	
						>20years vs never-drinker	0.98 (0.52-1.85) Ptrend:0.836	
Maasland, 2014 mou08605 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	110 65 45/ 4 683 17.3 years	Cancer and pathology registries	FFQ	Incidence, oral cavity SCC	per 10 g/day Total Men Women	 1.28 (1.18-1.39) 1.27 (1.17-1.38) 1.58 (1.33-1.87)	Age, sex, cigarette smoking status, duration of smoking, frequency of smoking
						≥30 g/day vs abstainers	6.39 (3.13-13.03) P-trend:<0.001	
Shanmugham, 2010 mou08574	NHS, Prospective Cohort,	147 84 63/	Self-report verified by medical record and pathology	Semi-quantitative FFQ	Incidence, oral cancer Total	>=30 vs 0 g/day	1.92 (1.08-3.40)	Age, follow-up time, current smoking status,

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
USA	Age: 30-55 years, W, nurses	87 621 26 years	report		Folate <350µg/d Folate >= 350µg/d		3.36 (1.57-7.20) 0.98 (0.35-2.70)	folate intake, pack years of smoking
Freedman, 2007 mou08604 USA	NIH-AARP, Prospective Cohort, M/W	236 86/ 492 960 2 203 500 person-years	Cancer registry	FFQ + questionnaire	Incidence, oral cavity SCC, Men Women	>3 vs <1 drinks/day	1.52 (1.01-2.27) 2.81 (1.29-6.11)	Age, BMI, educational level, fruit intake, gender, smoking status and dose, total energy, usual activity throughout the day, vegetable Intake, vigorous physical activity
Boffetta, 1990 mou08603 USA	CPS I, Prospective Cohort, Age: 40-59 years, M	155/ 276 802 12 years	Death certificate and medical records	Questionnaire	Mortality, oral cavity	≥6 drinks/day vs non-drinkers	6.15 (3.73-10.1)	Age, smoking

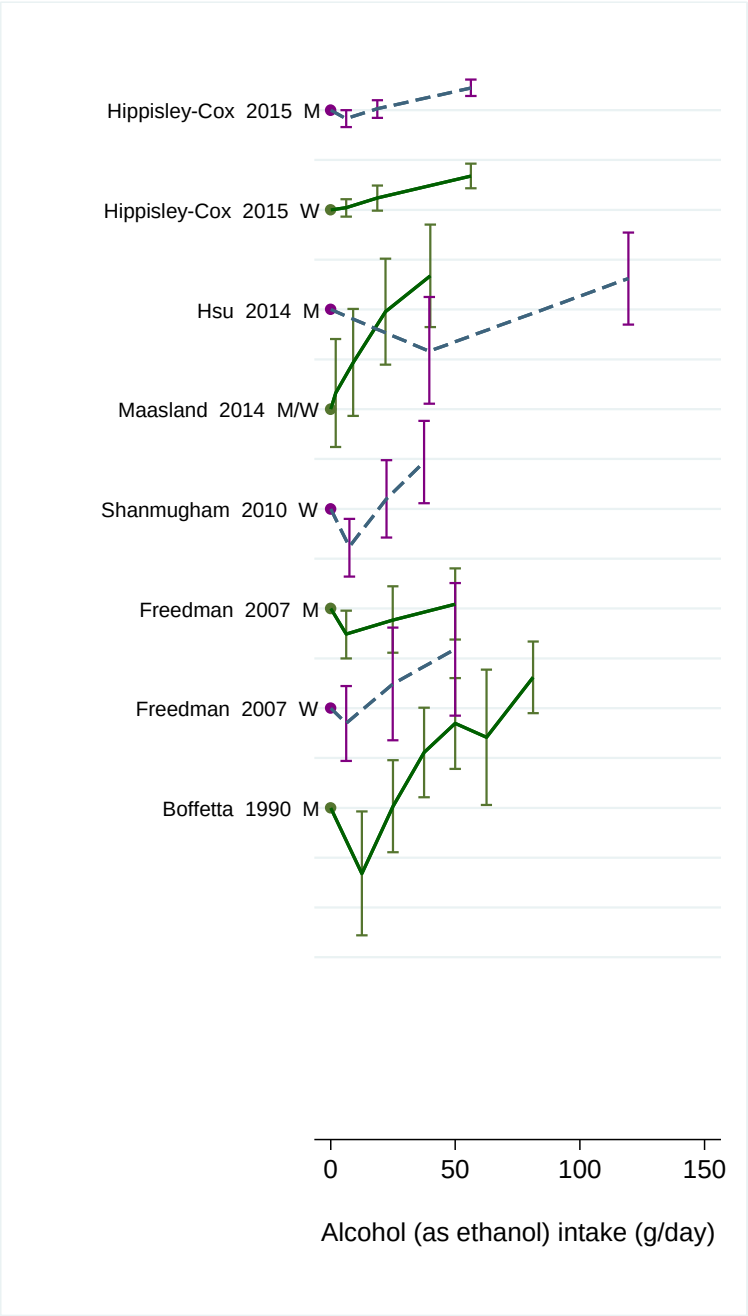
Table 9. Total alcohol intake and oral cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

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	Reason for exclusion
Saieva, 2012 mou08543 Italy	Alcoholics cohort, Italy, Prospective Cohort, Age: 43 years, Alcoholics	14 10 4/ 2 272 9.6 years	Mortality register	CAGE test	Mortality, oral cavity , Alcoholics Men alcoholics Women alcoholics	Observed vs expected deaths	22.2 (13.2-37.6) 18.9 (10.1-35.0) 40.4 (15.1-107.5)	-	Inadequate categorisation Included in the HvsL plot
Jayalekshmi, 2011 mou08575 India	Karunagappally cohort study, Prospective Cohort, Age: 30-84 years, M, adult men	160/ 66 277 13 years	Cancer and mortality registries	Standardized questionnaire	Incidence, oral cancer	Current vs Never-drinkers	1.20 (0.80-1.70)	Attained age, calendar time, educational level, Income	Low alcohol intake range Included in the HvsL plot
					Tobacco chewers, current Tobacco chewers, never	≥70 mg/day vs Never-drinkers	1.20 (0.70-2.20) 1.00 (0.50-2.00)		
Cancela, 2009 mou08602 India	Trivandrum Oral Cancer Screening study, Prospective Cohort, Age: 35-84 years, M	134 91/ 32 347 8.7 years	Cancer registry & house visits	Lifestyle questionnaire	Incidence, oral cancer Mortality, oral cancer	Current vs Never-drinkers	1.49 (1.01-2.21) Ptrend:0.006 1.76 (1.08-2.86) Ptrend:0.008	Age, betel chewing, educational level, fruits Intake, occupation, religion, smoking habits, vegetable Intake, standard of living	Inadequate categorisation
Thygesen, 2009 mou08547 Denmark	Copenhagen alcohol cohort, 1954-1999, Prospective	76 11/ 18 810 304 414 person-	Danish cancer registry	Interview	Incidence, oral cancer Men Women	Alcoholics vs Non-alcoholics	6.90 (5.50-8.70) 10.70 (5.30-19.10)	Age, calendar time	Inadequate categorisation Included in the HvsL plot

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	Reason for exclusion
	Cohort, M/W	years							
Muwonge, 2008 mou08581 India	Trivandrum Oral Cancer Screening study, Nested Case Control, Age: 35- years, M, rural resident	163/ 815 controls 8 years	Cancer, histopathology, mortality and hospital cancer registry, medical departments of hospitals, death records and active follow-up	Structured questionnaire	Incidence, oral cancer	Currently vs Never-drinker	1.40 (0.90-2.20) Ptrend:0.152	Chewing habits, educational level, religion, smoking	Inadequate categorisation Included in the HvsL plot
Thygesen, 2005 mou08589 Denmark	Danish brewery workers cohort, Prospective Cohort, M, Brewery workers	37/ 13 051 422 240 person-years	Brewery workers union	Use of aggregated data	Incidence, mouth cancer	Brewery workers vs general population	2.43 (1.71-3.35)	Age	Inadequate categorisation Included in the HvsL plot
Tønnesen, 1995 mou08562 Denmark	Copenhagen alcohol cohort, Prospective Cohort, Age: 19-75 years, M/W, Danish alcoholics	45 38 7/ 18 307 11 years	Cancer registry/ population register	Hospital notes	Incidence, mouth cancer Men Women	Alcoholics vs General population	7.20 (5.10-9.80) 6.40 (4.40-8.90) 19.40 (7.80-40.00)	Age, sex Age	Superseded by Thygesen 2009
Adami, 1992 mou08561 Sweden	Uppsala Alcoholics, Sweden, Prospective	33 3/ 9 353 7.7 years	Cancer registry	Lifestyle grouping	Incidence, buccal cavity, Men Women	Alcoholics vs Study population	3.90 (2.70-5.50) 7.00 (1.40-20.30)	Age	Inadequate categorisation Included in the HvsL plot

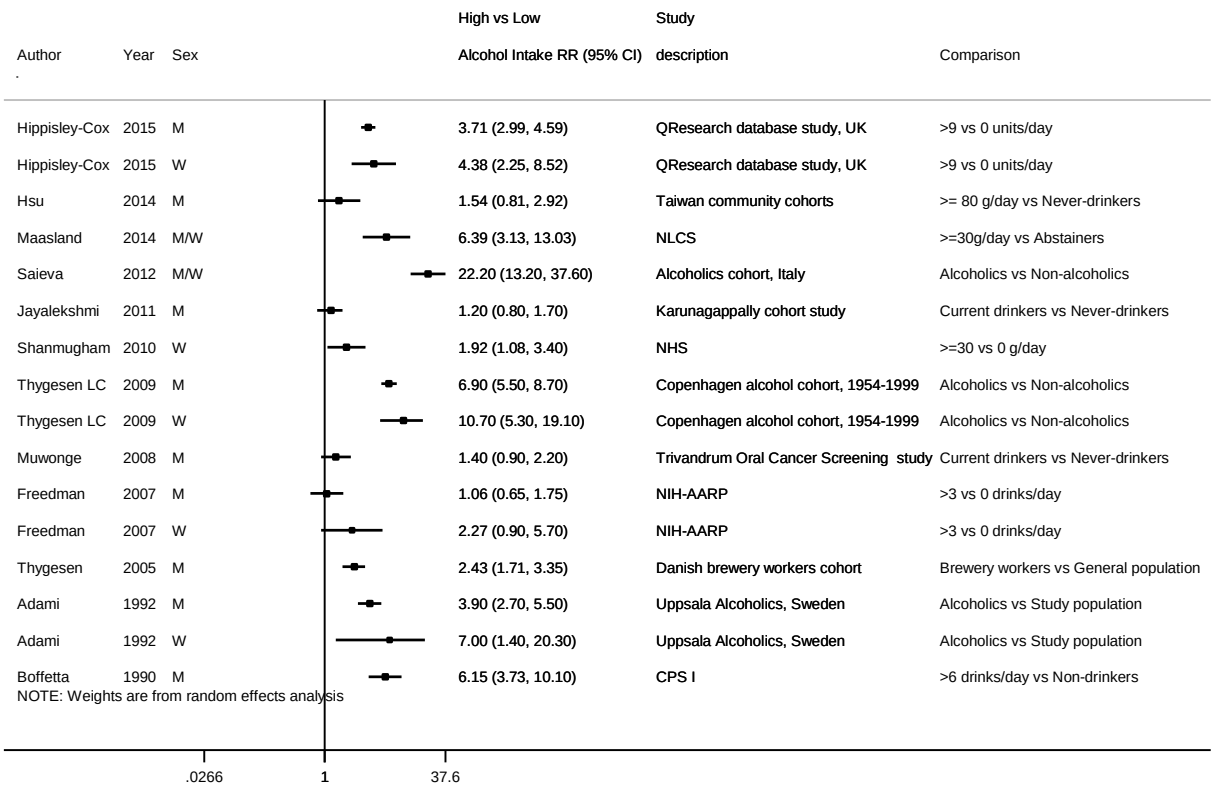
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reason for exclusion
	Cohort, Age: 50 years, M/W, Alcoholics								

Figure 6 RR estimates of oral cancer by levels of alcohol intake



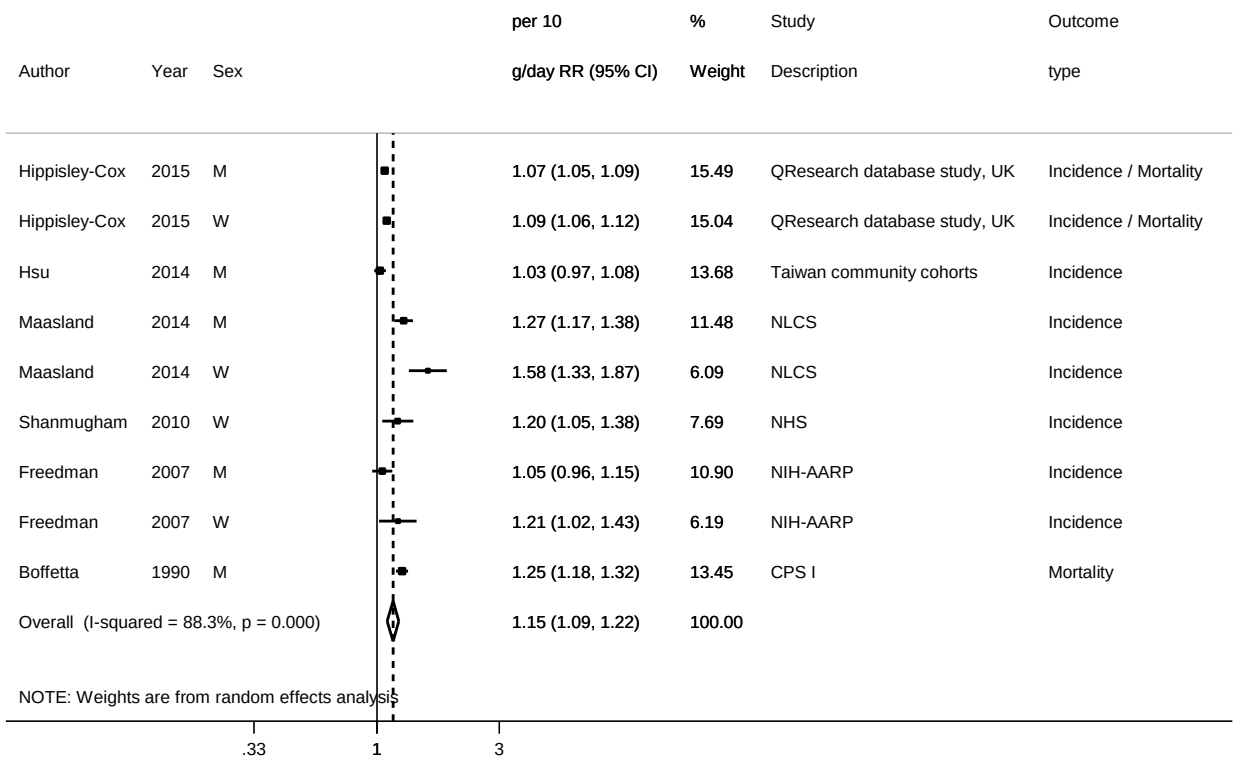
Note: M: men; W: women; M/W: men and women

Figure 7. RR (95% CI) of oral cancer for the highest compared with the lowest level of total alcohol intake



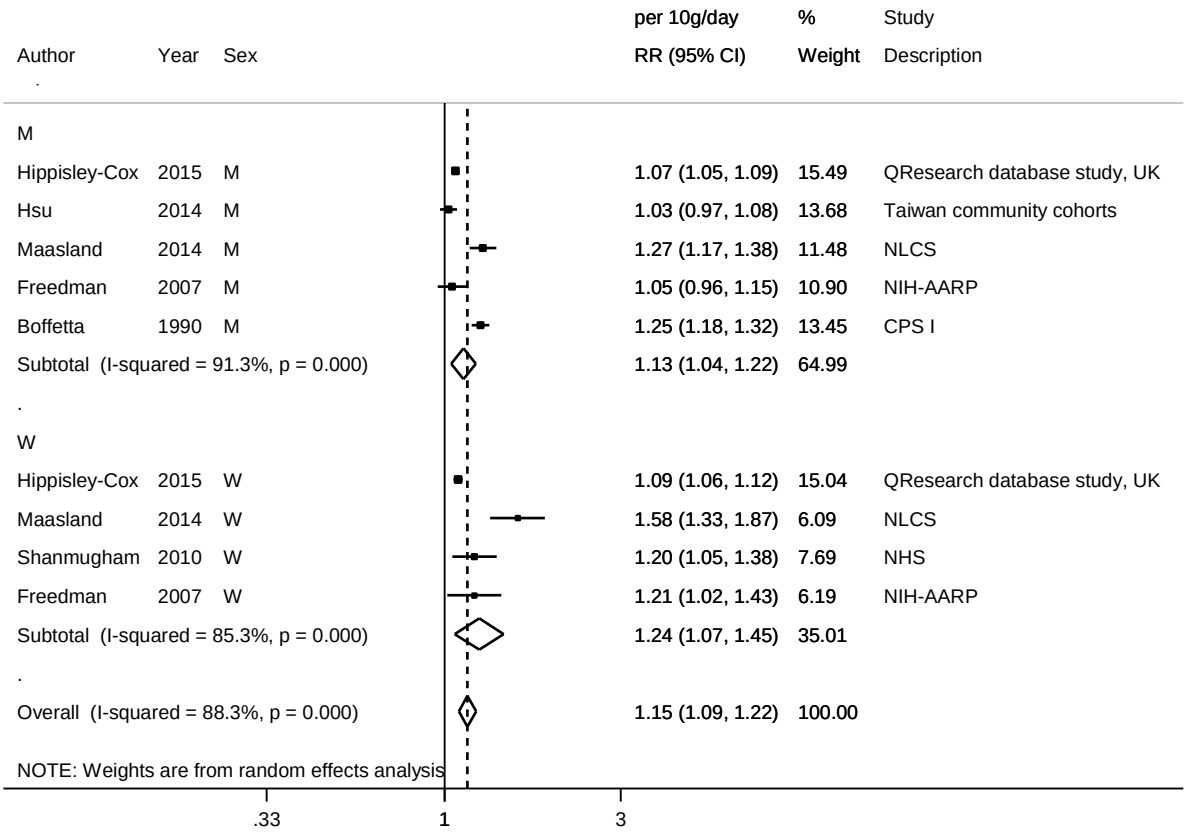
Note: the estimates are SIR in Thygessen, 2009; Thygessen, 2005 and Adami, 1992 and SMR in Saieva 2012. The RRs are recalculated with the Hamling method in Freedman 2007. M: men; W: women; M/W: men and women

Figure 8. Relative risk of oral cancer for 10 g/day increase of total alcohol (as ethanol) intake



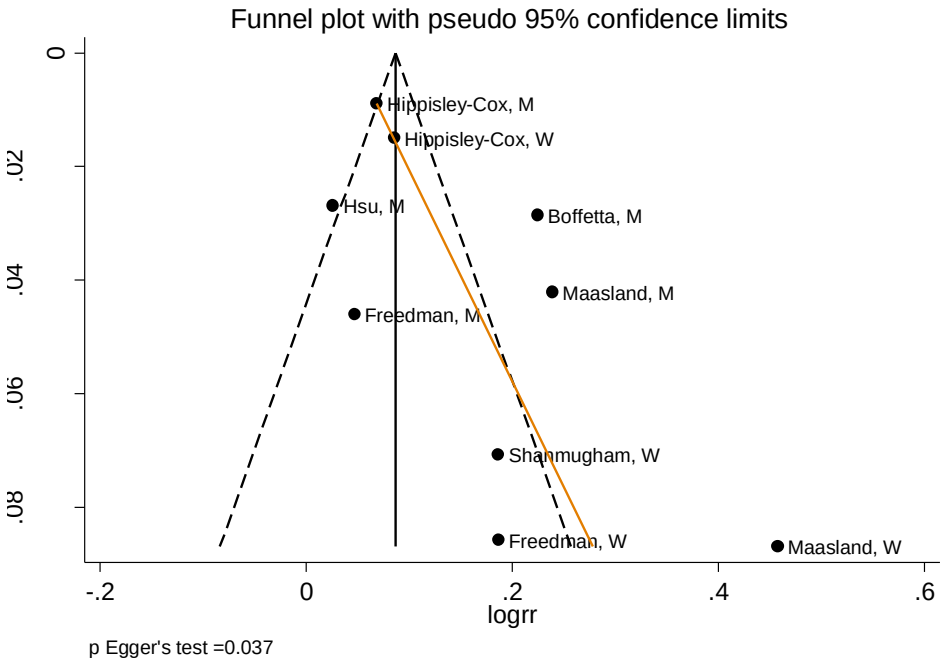
Note: M: men; W: women

Figure 9. Relative risk of oral cancer for 10 g/day increase of total alcohol (as ethanol) intake, by sex



Note: M: men; W: women

Figure 10. Funnel plot of studies included in the dose response meta-analysis of alcohol intake and oral cancer



Note: M: men; W: women

Oral/pharyngeal cancer

Ten cohort studies were identified. Five cohorts (954 cases) were included in the dose-response meta-analysis (Kim, 2010; Allen, 2009; Weikert, 2009; Ide, 2008; Friborg, 2007), from which two are studies in cancer mortality (Kim, 2010; Ide, 2008). A standard conversion unit from drinks to grams was applied in two studies (Ide, 2008; Friborg, 2007).

Five studies were excluded from the dose-response analyses due to lack of the required data (Klatsky, 2015; Jung, 2014; Thygesen, 2009; Thygesen, 2005; Kasum, 2002). All studies reported positive associations. Of the excluded studies, one study was on alcoholics (Thygesen, 2009) and one in brewery workers (Thygesen, 2005).

Significant positive association was found between alcohol consumption (as ethanol, per 10g/day increase) and oral/pharyngeal cancer (RR 1.19; 95% CI 1.10-1.30). There was high heterogeneity, mainly explained by a strong association reported in a cohort of Singapore Chinese (Friborg, 2007). The funnel plot shows that there were two outliers (Allen, 2009; Friborg, 2007). Influence analysis revealed that the summary RR did not change substantially when each study was excluded in turn from the meta-analysis.

Interaction with smoking

In one study in cancer mortality (Ide, 2008), 26 out of 52 cases identified were smokers and drinkers. The RR in this men compared to never smokers/never drinkers was 3.3 (95% CI 1.1-9.6) and it was 1.0 (95% CI 0.3-3.3) in drinkers never smokers, but only 8 cases were in this category.

In a study in Singapore Chinese (Friborg, 2007), compared to non-smokers non-drinkers, the relative risk in people who drink more than 7 drinks/week was 4.9 (95% CI 1.3-18.5) in people with less than 39 years of smoking and 18.4 (95% CI 7.5-14.5) in those with >39 years of smoking.

Study quality:

Loss to follow up was low in most studies. Cancer outcome was confirmed using cancer, death and population registries in most studies. In two of the included studies, the outcome was mortality. Most of the studies did not differentiate oral/pharyngeal SCC from adenocarcinomas, except from Weikert *et al*. (2009) who included only SCC cases (Weikert, 2009). Two studies included nasopharyngeal cancer cases in the total outcome of oral/pharyngeal cancer (Kim, 2010; Allen 2009).

Alcohol intake was assessed by questionnaires or FFQ in most studies. In Kim et al. (2010), the amount of alcohol was ‘‘soju’’ intake (Kim, 2010).

All of the studies included in the dose-response analysis were adjusted for age and smoking.

Table 10. Total alcohol intake and oral/pharyngeal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (10 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in linear dose-response meta-analysis	5

Table 11. Total alcohol (as ethanol) intake and oral/pharyngeal cancer risk. Summary of the linear dose-response meta-analysis in CUP

	CUP	
Increment unit used	10g/day	
All studies		
Studies (n)	5	
Cases (total number)	954	
RR (95%CI)	1.19 (1.10-1.30)	
Heterogeneity (I^2, p-value)	82.8%, <0.001	
P-value Egger test	0.040	
Stratified analysis		
Sex	**Men**	**Women**
Studies (n)	3	2
RR (95%CI)	1.09 (1.04-1.15)	1.28 (1.16-1.41)
Heterogeneity (I^2, p-value)	58.8%, 0.088	0.00%, 0.822

Table 12. Total alcohol intake and oral/pharyngeal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size/ Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI)	Adjustment factors
Kim, 2010 mou08542 Korea	KNHIC, Prospective Cohort, Age: 40-69 years, M/W	82/ 1 341 393 5 years	National death certificate	Not stated	Mortality, lip, oral cavity, pharynx	≥90g/d vs non-drinkers g/day	2.17 (0.99-4.76)	Age, ≥3 times/week regular exercise, BMI, diastolic blood pressure, fasting blood sugar, residential (urban/rural), smoking status, systolic blood pressure
Allen, 2009 mou08546 UK	MWS, Prospective Cohort, Age: 55 years, W	557/ 1 280 296 7.2 years	National health service central registers	Questionnaire	Incidence, oral (buccal cavity) and pharynx	≥15drinks/week vs ≤2drinks/week	1.99 (1.59-2.50)	Age, area of residence, BMI, HRT use, physical activity, smoking, use of oral contraceptives
						per 10 g/day	1.29 (1.14-1.45)	
Weikert, 2009 mou08557 Denmark,France, Germany,Greece ,Italy,Netherland s,Norway,Spain, Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	126men/62 women 271 253 2 330 381 person-years	Cancer registry, health Insurance records, active follow up and mortality registry	Self-administered questionnaire	Incidence, squamous cell carcinoma of oral cavity, pharynx Men Women	per 10 g	1.09 (1.06-1.12) 1.26 (1.07-1.49)	BMI, current smoking status, current smoking with <15 cig/d, current smoking with ≥ 15 and <25 cig/d, current smoking with ≥ 15 cig/d, current smoking with ≥25 cig/d, duration of smoking, educational level, former drinkers, former smoking with quitting <10 years, former smoking with quitting ≥10 years, former smoking with unknown quitting time, fruits and vegetables consumption, never drinkers
Ide, 2008 mou08572 Japan	JACC, Prospective Cohort, Age: 40-79 years,	52/ 77 847 12.5 years	Population register	Self-administered questionnaire	Mortality, oral and pharynx	≥46g/day vs non-drinker	3.20 (1.20-8.70)	Age, green and yellow vegetable intake, green tea consumption, salt

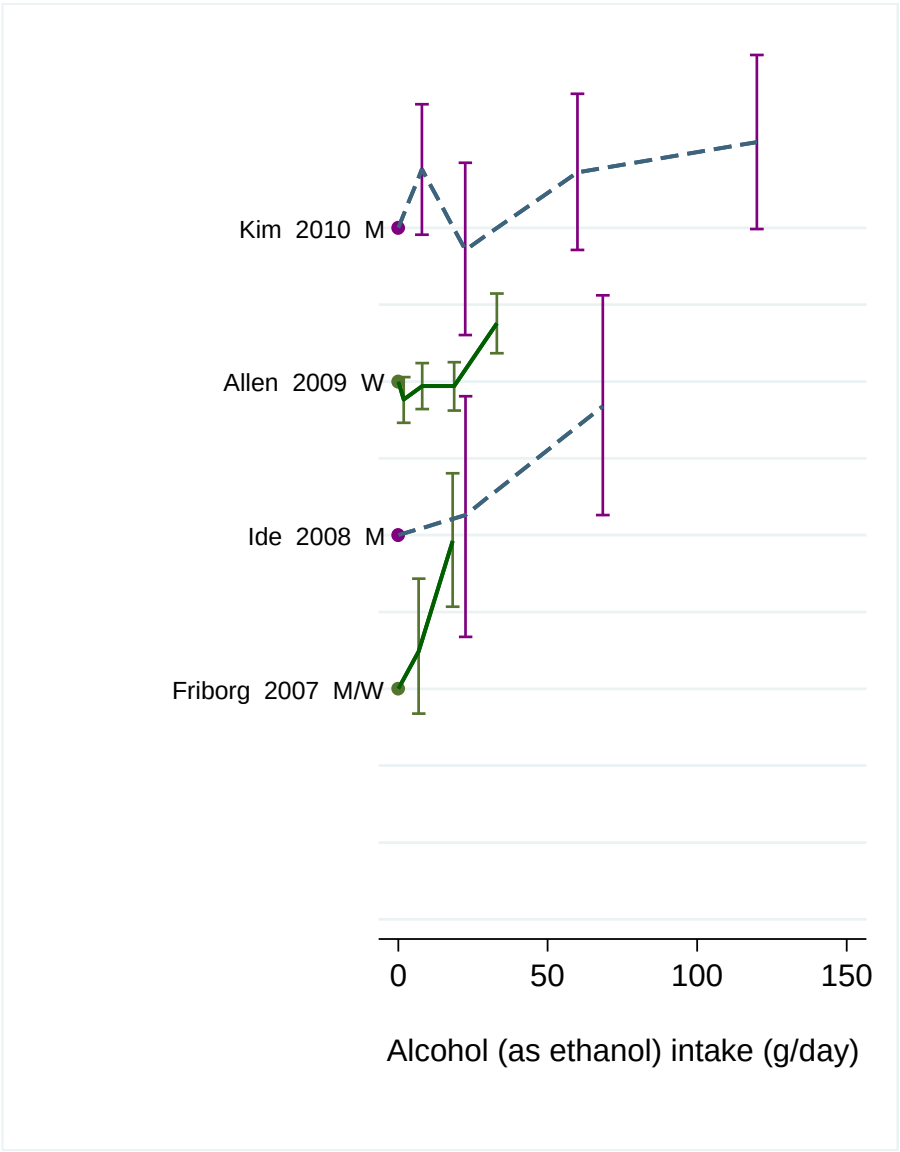
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size/ Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI)	Adjustment factors
	M							preference, smoking status
Friborg, 2007 mou08569 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W, Hokkien and Cantonese dialect	75/ 61 320 12 years	Cancer registry	Semi-quantitative FFQ	Incidence, oral/pharyngeal cancer	>12.5g/day vs non-drinkers	3.80 (2.10-7.00)	Age, sex, dialect group, educational level, family history of NPC, preserved food Intake, veg Intake, year of recruitment, years of smoking

Table 13. Total alcohol intake and oral/pharyngeal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI)	Adjustment factors	Reason for exclusion
Klatsky, 2015 Mou08587 USA	KPMCP, Prospective Cohort, M/W	552/ 124 193 17.8 years	Cancer registry	Questionnaire	Incidence, Oral cavity, lip, pharynx	≥3 vs 0 drinks/day	2.60 (1.40-4.50)	Age, race/ethnicity, BMI, education level, marital status, smoking status, sex	No cases and comparison subjects by category Included in the HvsL plot
Jung, 2014 mou08564 Korea	KCS, Prospective Cohort, Age: 55- years, M	28/ 2 677 20.8 years	National statistics office	Validated FFQ	Mortality, oral/pharyngeal cancer	Daily binge drinkers (≥6drinks) vs non-drinkers	4.90 (1.00-27.00)	Age, BMI, educational level, history of chronic disease, smoking habits, total alcohol drinking	No intake levels Included in the HvsL plot
Thygesen, 2009 mou08547 Denmark	Copenhagen alcohol cohort, 1954-1999, Prospective Cohort, M/W	227men/42 women/ 18 810 304 414 person-years	Danish cancer registry	Interview	Incidence, oral (buccal cavity) and pharynx Men Women	Alcoholics vs General population	4.70 (4.10-5.40) 13.10 (9.50-17.70)	Age, calendar time	Inadequate categorisation Included in the HvsL plot

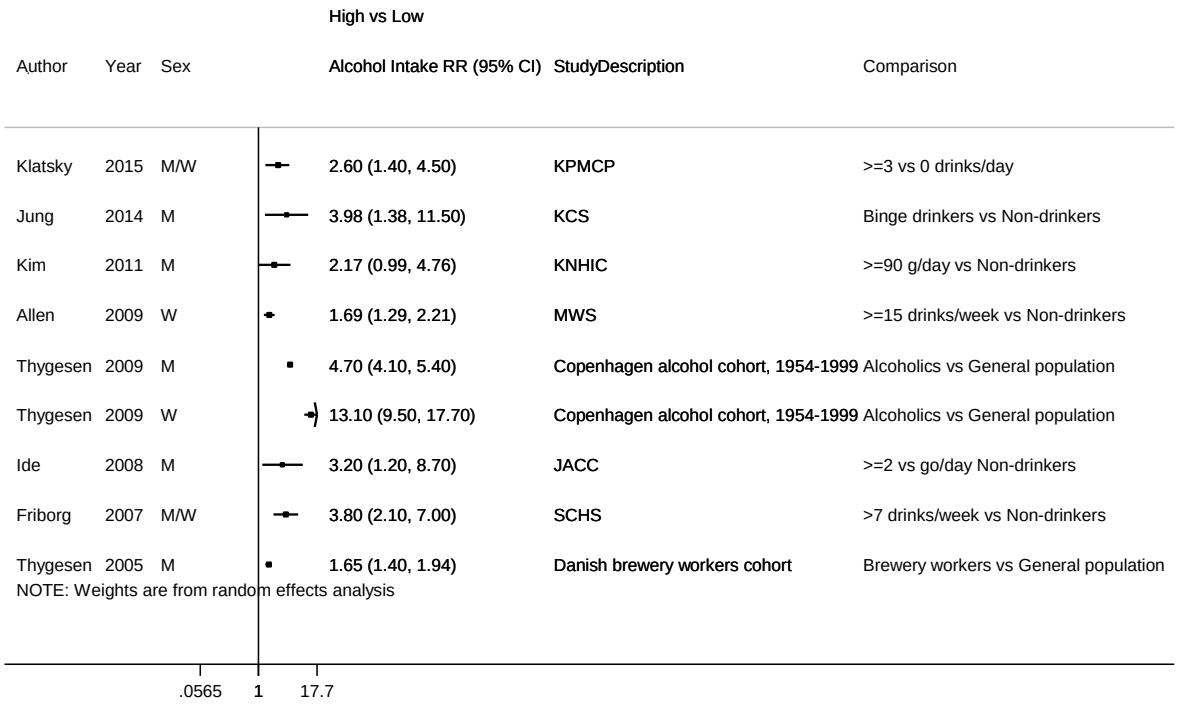
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reason for exclusion
Thygesen, 2005 mou08589 Denmark	Danish brewery workers cohort, Prospective Cohort, M, Brewery workers	148/ 13 051 422 240 person-years	Brewery workers union	Use of aggregated data	Incidence, oral (buccal cavity) and pharynx	Brewery workers vs General population	1.65 (1.40-1.94)	Age	Inadequate categorisation Included in the HvsL plot
Kasum, 2002 Mou03561 USA	IWHS, Prospective Cohort Age: 55-69 years, W, Postmenopausal	53/ 34 351 14 years	Driver's license list	127-item FFQ	Incidence, oral/pharyngeal	≥2 vs 0 drinks/day	1.35	Whole grains, refined grains, yellow/orange vegetables, smoking, age, energy intake	No CI reported in the publication

Figure 11. RR estimates of oral/pharyngeal cancer by levels of alcohol intake



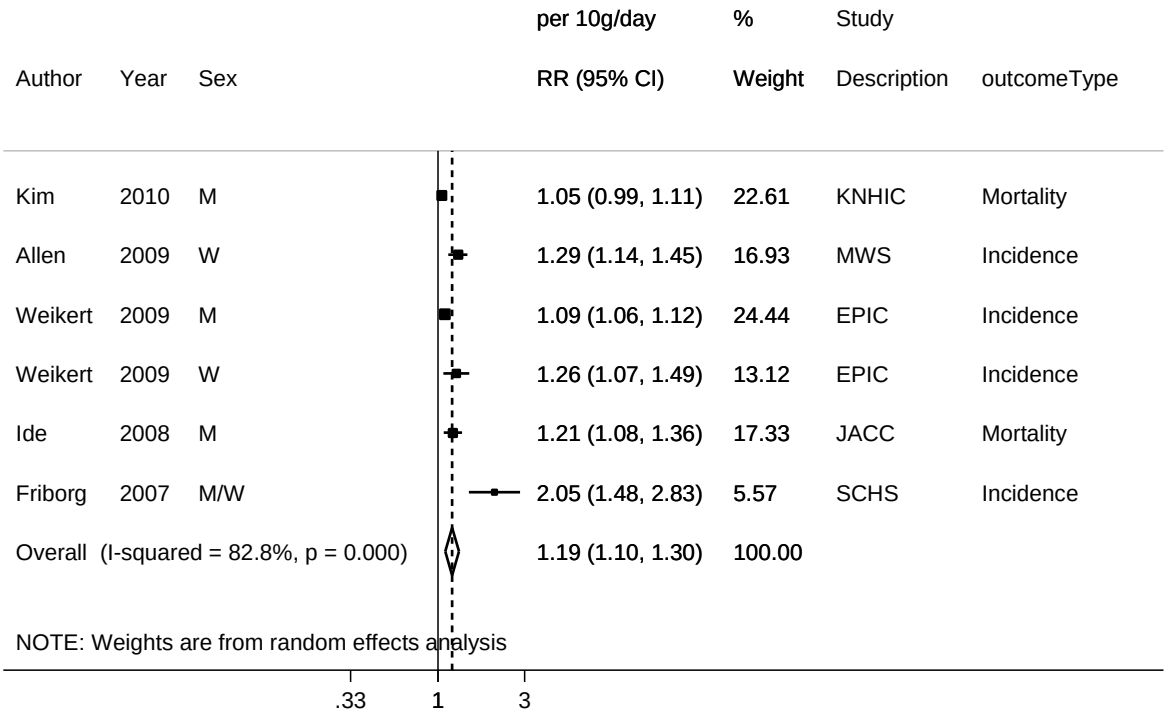
Note: M: men; W: women; M/W: men and women

Figure 12. RR (95% CI) of oral/pharyngeal cancer for the highest compared with the lowest level of total alcohol intake



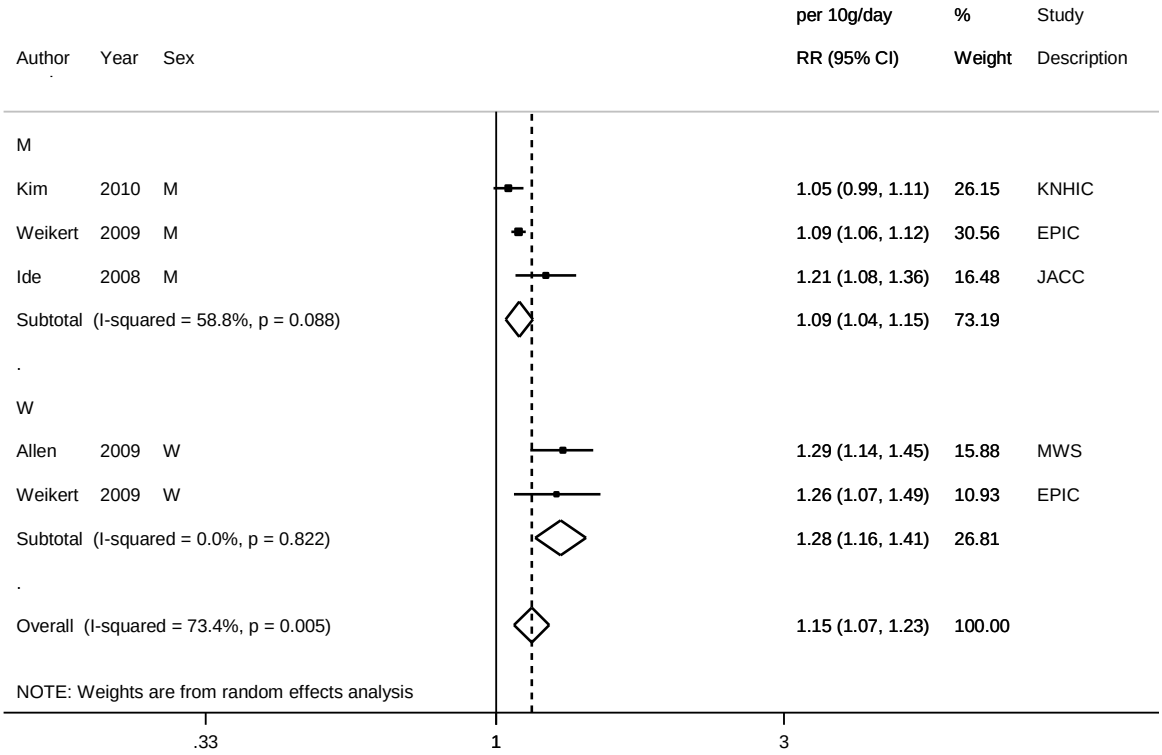
Note: the estimates are SIR in Thygessen, 2009; Thygessen, 2005. The RRs are converted from floating RRs to conventional RRs in Allen 2009. M: men; W: women; M/W: men and women

Figure 13 Relative risk of oral/pharyngeal cancer for 10 g/day increase of total alcohol (as ethanol) intake



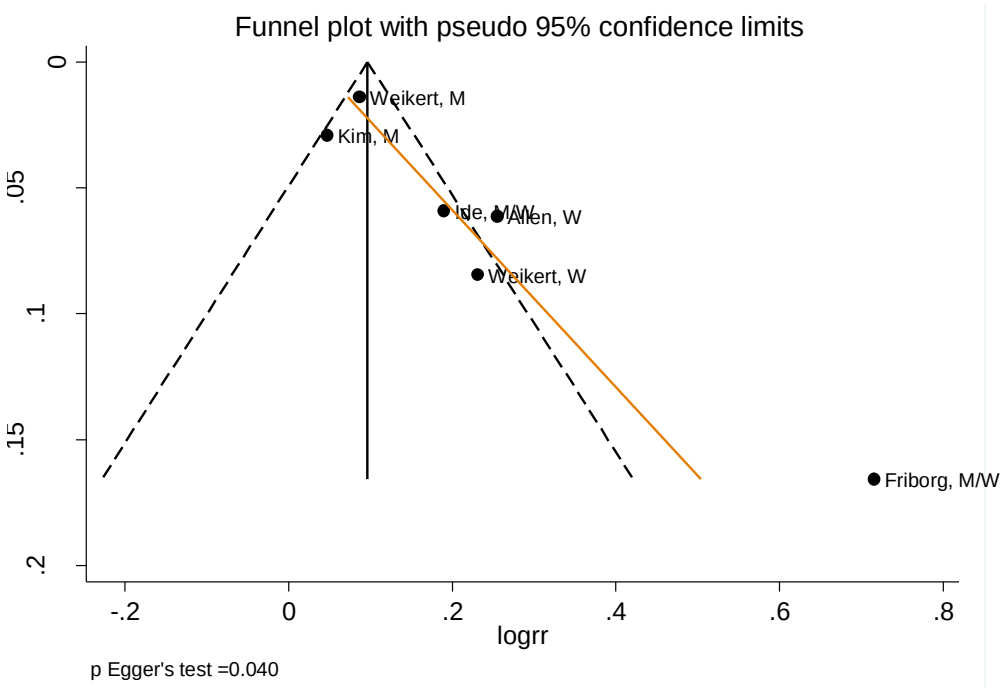
Note: M: men; W: women; M/W: men and women

Figure 14. Relative risk of oral/pharyngeal cancer for 10 g/day increase of total alcohol (as ethanol) intake, by sex



Note: M: men; W: women

Figure 15. Funnel plot of studies included in the dose response meta-analysis of alcohol intake and oral/pharyngeal cancer



Note: M: men; W: women; M/W: men and women

Table 14 Alcohol consumption and oral/pharyngeal cancer risk. Results of a meta-analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Bagnardi, 2015	5 cohorts	993	North America, Europe and Asia	Incidence, Oral cavity and pharyngeal cancer	Light drinking Moderate drinking Heavy drinking	0.86 (0.60-1.23) 1.25 (1.02-1.53) 3.13 (1.59-6.19)	-	68 16 69

Pharyngeal cancer

Nine publications from eight cohorts were identified. Dose response meta-analysis was conducted with four studies. A table with study characteristics, a highest versus lowest graph and a dose-response meta-analysis graph are presented.

A study reporting results from three community cohorts in Taiwan, found an increased significant association between pharyngeal cancer and alcohol consumption for ≥80g/day versus never alcohol consumption (Hsu, 2014). The NLCS study also found positive significant association with pharyngeal cancer for both men and women per 10g/day alcohol consumption; as well as for the comparison ≥30g/day versus abstainers for the total

population (Maasland, 2014). The KNHIC study (Kim, 2010) showed positive non-significant results for the highest versus the lowest analysis, while the NIH-AARP study (Freedman, 2007) found a positive significant association for men but non-significant for women among those who consumed >3 drinks/day versus <1drink/day. The Karunagappally cohort reported results on hypo-pharyngeal cancer cases in men and showed a positive non-significant association for current versus never drinkers (Jayalekshmi, 2013).

Three studies reported results on alcoholics and found significant positive results for the comparison of alcoholics versus non-alcoholics (Saieva, 2012; Thygesen, 2009; Tonnesen, 1995). Lastly, one study on brewery workers (with an average alcohol consumption of 77.7g/day at work) versus general population, showed increased significant results (Thygesen, 2005).

One study was not included in the highest versus lowest graph because was superseded by other publication of the same cohort (Tonnesen, 1995).

Interaction with smoking

In the NLCS cohort (Maasland, 2014), 77 out of 83 cases were smokers. The RR in drinkers (>15g/day)/smokers (≥20cigaretes/day) was 16.12 (95% CI 4.31-60.27, 31 cases) and in drinkers (>15g/day)/never smokers was 10.18 (95% CI 2.03-51.06, 3 cases) compared to alcohol drinkers (0-15g/day)/never smokers. No significant interaction was found between categories of alcohol consumption and cigarette smoking (P-interaction= 0.09).

Jayalekshmi *et al*. (2013) reports that drinkers (≥70mg/day)/current tobacco chewers had a RR of 1.2 (95% CI 0.7-2.2), while drinkers (≥70mg/day)/never tobacco chewers had RR 1.0 (95% CI 0.5-2.0) (Jayalekshmi, 2013).

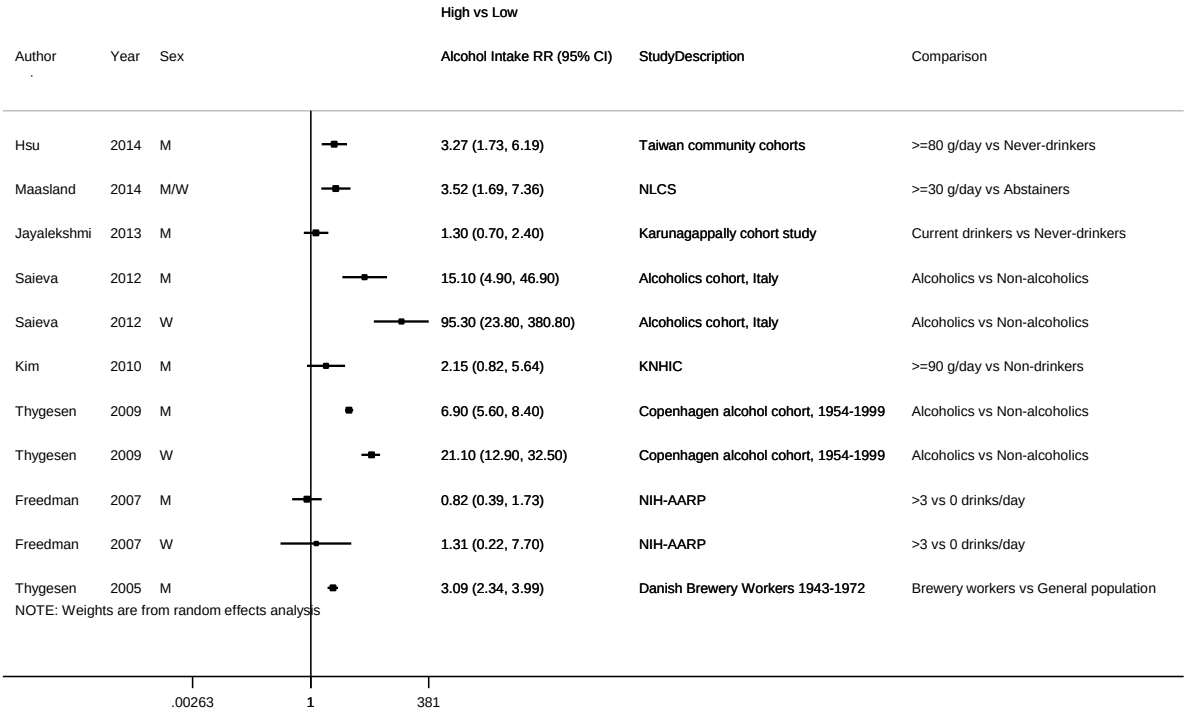
Table 15. Total alcohol intake and pharyngeal cancer risk. Main characteristics of studies identified in the search

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors	Included/ Reason of exclusion
Hsu, 2014 mou08580 Taiwan	Taiwan community cohorts, Prospective Cohort, Age: 30-80 years, M, Taiwan residents	70/ 25 611 18.4 years	Cancer registry and death certificates	Structured questionnaire	Incidence, pharyngeal cancer	≥80 g/day vs never-drinker	3.27 (1.73-6.19) P-trend:0.001	Age, cohort, educational level, ethnicity, substance use each other	Included in the HvsL plot and dose-response meta-analysis
						≥1500 g/year vs never-drinker	2.86 (1.43-5.75) P-trend:0.003		
						>20years vs never-drinker	1.53 (0.74-3.15) Ptrend:0.065		
Maasland, 2014 mou08605 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	83 61 22/ 4 683 17.3 years	Cancer and pathology registries	FFQ	Incidence, oropharynx and hypopharynx, squamous cell	per 10 g/day Total Men Women	1.27 (1.16-1.38) 1.27 (1.16-1.39) 1.31 (0.91-1.87)	Age, sex, cigarette smoking status, duration of smoking, frequency of smoking	Included in the HvsL plot and dose-response meta-analysis
						≥30 g/day vs Abstainers	3.52 (1.69-7.36) P-trend:<0.001		
Kim, 2010 mou08542 Korea	KNHIC, Prospective Cohort, Age: 40-69 years, M	46/ 1 341 393 5 years	National death certificate	Not stated	Mortality, pharynx, men	≥90 vs non-drinkers g/day	2.15 (0.82-5.64) P-trend:0.11	Age, ≥3 times/week regular exercise, BMI, diastolic blood pressure, fasting blood sugar, residential	Included in the HvsL plot and dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors	Included/ Reason of exclusion
								(urban/rural), smoking status, systolic blood pressure	
Freedman, 2007 mou08604 USA	NIH-AARP, Prospective Cohort, M/W	109 34/ 492 960 2 203 500 person-years	Cancer registry	FFQ + questionnaire	Incidence, oropharynx and hypopharynx, squamous cell	>3 vs <1 drinks/day Men Women	2.32 (1.29-4.18) 1.97 (0.42-9.31)	Age, BMI, educational level, fruit intake, gender, smoking status and dose, total energy, usual activity throughout the day, vegetable Intake, vigorous physical activity	Included in the HvsL plot and dose-response meta-analysis
Jayalekshmi, 2013 mou08576 India	Karunagappally cohort study, Prospective Cohort, Age: 30-84 years, M	52/ 65 553 13 years	Cancer and mortality registries	Standardized questionnaire	Incidence, hypopharynx	Current drinkers vs Never-drinkers	1.30 (0.70-2.40)	Attained age, calendar time, educational level, Income	Inadequate categorisation Included in the HvsL plot
Saieva, 2012 mou08543 Italy	Alcoholics cohort, Italy, Prospective Cohort, Age: 43 years, M/W Alcoholics	5 3 2/ 2 272 9.6 years	Mortality register	CAGE test	Mortality, pharynx	Alcoholics vs Non-alcoholics Total Men Women	22.80 (9.50-54.80) 15.10 (4.90-46.90) 95.30 (23.80-380.80)		Inadequate categorisation Included in the HvsL plot
Thygesen,	Copenhagen	95	Danish cancer	Interview	Incidence,	Alcoholics vs	6.90 (5.60-	Age, calendar	Inadequate

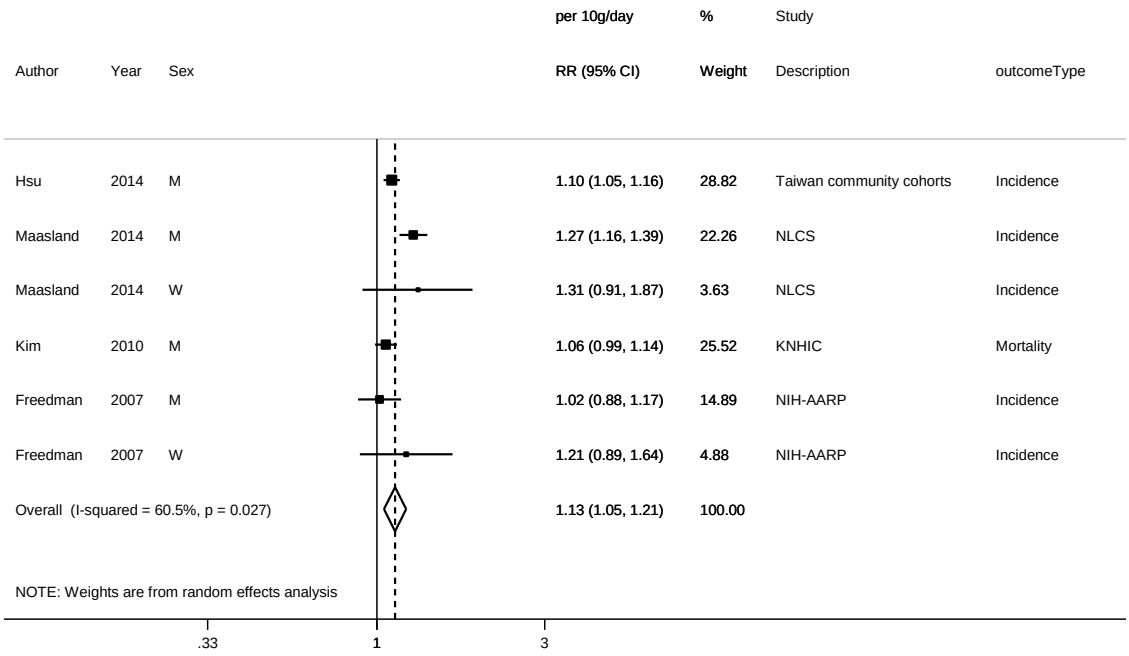
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors	Included/ Reason of exclusion
2009 mou08547 Denmark	alcohol cohort, 1954-1999, Prospective Cohort, M/W	20/ 18 810 304 414 person-years	registry		pharynx	Non-alcoholics Men Women	8.40) 21.10 (12.90-32.50)	time	categorisation Included in the HvsL plot
Thygesen, 2005 mou08589 Denmark	Danish brewery workers cohort, Prospective Cohort, M, Brewery workers	58/ 13 051 422 240 person-years	Brewery workers union	Use of aggregated data	Incidence, pharynx	Brewery workers vs General population	3.09 (2.34-3.99)	Age	Inadequate categorisation Included in the HvsL plot
Tønnesen, 1995 mou08562 Denmark	Copenhagen alcohol cohort, Prospective Cohort, Age: 19-75 years, M/W, Danish alcoholics	53 44 9/ 18 307 11 years	Cancer registry/ population register	Hospital notes	Incidence, pharyngeal cancer	Alcoholics vs General population Total Men Women	7.30 (5.40-9.50) 6.40 (4.60-8.50) 25.00 (11.40-47.50)	Age, sex	Suppressed by Thygesen 2009

Figure 16. RR (95% CI) of pharyngeal cancer for the highest compared with the lowest level of total alcohol intake



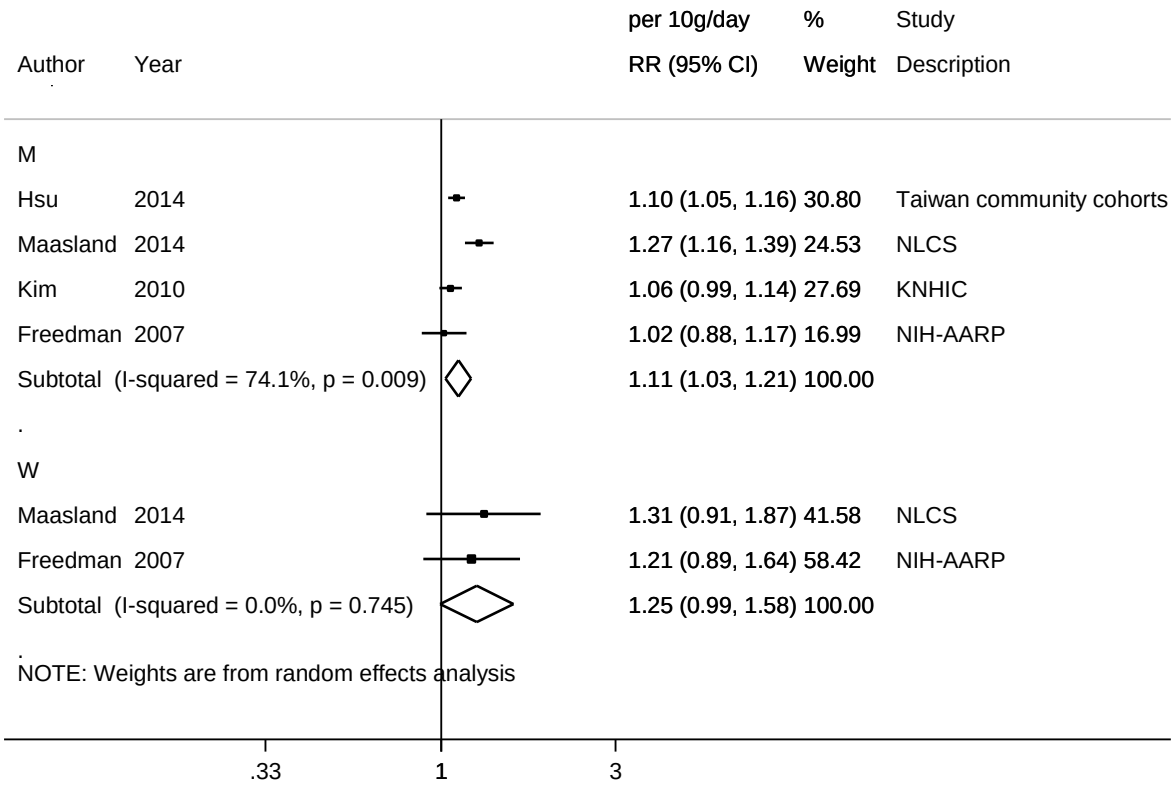
Note: the estimates are SMR in Saieva *et al*. (2012), SIR in Thygesen *et al*. (2009) and Thygesen *et al*. (2005). RRs are recalculated with the Hamling method in Freedman *et al*. (2007). M: men; W: women; M/W: men and women

Figure 17. Relative risk of pharyngeal cancer for 10 g/day increase of total alcohol (as ethanol) intake



Note: M: men; W: women

Figure 18. Relative risk of pharyngeal cancer for 10 g/day increase of total alcohol (as ethanol) intake, by sex



Laryngeal cancer

Thirteen publications from thirteen cohort studies were identified. Most studies reported positive significant associations except in some analyses in women.. Six studies (781 cases) were included in the dose-response meta-analysis (Hsu, 2014; Maasland, 2014; Kim, 2010; Allen, 2009; Weikert, 2009; Freedman, 2007). Significantly positive association was found between alcohol (as ethanol, 10g/day) consumption and laryngeal cancer risk (RR 1.09; 95% CI 1.05-1.13). There was moderate heterogeneity. The funnel plot does not reveal publication biases; however the study Allen *et al.* (2009) (for women) is an outlier. Influence analysis showed that the summary RR did not change substantially when each study was excluded in turn from the meta-analysis.

Studies on alcoholism revealed that alcoholics had significantly increased risk of laryngeal cancer compared to non-alcoholics (Thygesen, 2009; Saieva, 2012; Adami, 1992).

Interaction with smoking

In the NLCS cohort (Maasland, 2014), 190 out of 199 cases were smokers. The RR in drinkers (>15g/day)/smokers (≥20cigaretes/day) was 5.54 (95% CI 2.15-14.27, 53 cases) and in drinkers (>15g/day)/never smokers was 3.05 (95% CI 0.72-12.92, 3 cases) compared to drinkers (0-15g/day)/ never smokers. Interaction between categories of alcohol consumption and cigarette smoking was not found (P-interaction= 0.19).

Study quality:

Loss to follow up was not reported in most studies, except Maasland *et al.* (2014) which had low loss to follow-up (Maasland, 2014). Cancer outcome was confirmed using cancer, death and population registries in most studies. Most of the studies did not differentiate laryngeal SCC from adenocarcinomas, except Weikert *et al.* (2009) and Maasland *et al.* (2014) which included only SCC cases (Maasland, 2014; Weikert, 2009).

Alcoholic drinks intake was assessed by questionnaires or FFQ in most studies. In Kim et al. (2010), the Korea's most popular alcoholic beverage ''soju'' was assessed. Alcohol consumption was converted to ethanol intake (g) using conversion units given in the publications. A standard conversion unit was applied in two studies (Ide, 2008; Friborg, 2007).

All of the studies were adjusted for age and smoking, except one which did not adjust for age (Weikert, 2009).

Table 16. Total alcohol intake and laryngeal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in linear dose-response meta-analysis	6

Table 17. Total alcohol (as ethanol) intake and laryngeal cancer risk. Summary of the linear dose-response meta-analysis in CUP

	CUP	
Increment unit used	10g/day	
All studies		
Studies (n)	6	
Cases (total number)	781	
RR (95%CI)	1.09 (1.05-1.13)	
Heterogeneity (I^2, p-value)	33.4%, 0.151	
P-value Egger test	0.370	
Stratified analysis		
Sex	**Men**	**Women**
Studies (n)	5	4
RR (95%CI)	1.09 (1.05-1.12)	1.22 (1.03-1.45)
Heterogeneity (I^2, p-value)	32.5%, 0.205	19.1%, 0.294

Table 18. Total alcohol intake and laryngeal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)d	Adjustment factors
Hsu, 2014 mou08580 Taiwan	Taiwan community cohorts, Prospective Cohort, Age: 30-80 years, M, Taiwan residents	37/ 25 611 18.4 years	Cancer registry and death certificates	Structured questionnaire	Incidence, laryngeal cancer	≥80g/day vs Never-drinkers	5.92 (2.32-15.10)	Age, ethnicity, education, substance use each other (betel quid, cigarette smoking, alcohol drinking), study cohort
Maasland, 2014 mou08605 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	199 187 12/ 4 683 17.3 years	Cancer and pathology registries	FFQ	Incidence, laryngeal, squamous cell carcinoma	per 10 g/day Total Men Women	1.10 (1.02-1.18) 1.10 (1.03-1.19) 0.85 (0.46-1.59)	Age, sex, cigarette smoking status, duration of smoking, frequency of smoking
Kim, 2010 mou08542 Korea	KNHIC, Prospective Cohort, Age: 40-69 years, M	49/ 1 341 393 5 years	National death certificate	Not stated	Mortality, larynx, men	≥90g/day vs Non-drinkers	2.50 (1.07-5.85)	Age, residential (urban, rural), smoking status, ≥ 3times/week exercise, BMI, systolic and diastolic pressure, fasting blood sugar
Allen, 2009 mou08546 UK	MWS, Prospective Cohort, Age: 55 years, W	99/ 1 280 296 7.2 years	National health service central registers	Questionnaire	Incidence, larynx	per 10 g/day	1.44 (1.10-1.88)	Age, area of residence, BMI, smoking, physical activity, use of oral contraceptives, HRT use
		138				≥15drinks/week vs ≤2drinks/week	2.02 (1.19-3.44)	
Weikert, 2009 mou08557 Denmark,France,Germany,Greece,Italy,Netherlands,Norway	EPIC, Prospective Cohort, Age: 35-70 years, M/W	101men/16 women 271 253 2 330 381 person-years	Cancer registry, health Insurance records, active follow up and mortality registry	Self-administered questionnaire	Incidence, SCC of larynx Men Women	per 10 g	1.08 (1.05-1.12) 1.32 (0.93-1.89)	Duration of smoking, former smoking with quitting ≥10y, former smoking with quitting <10y, former smoking

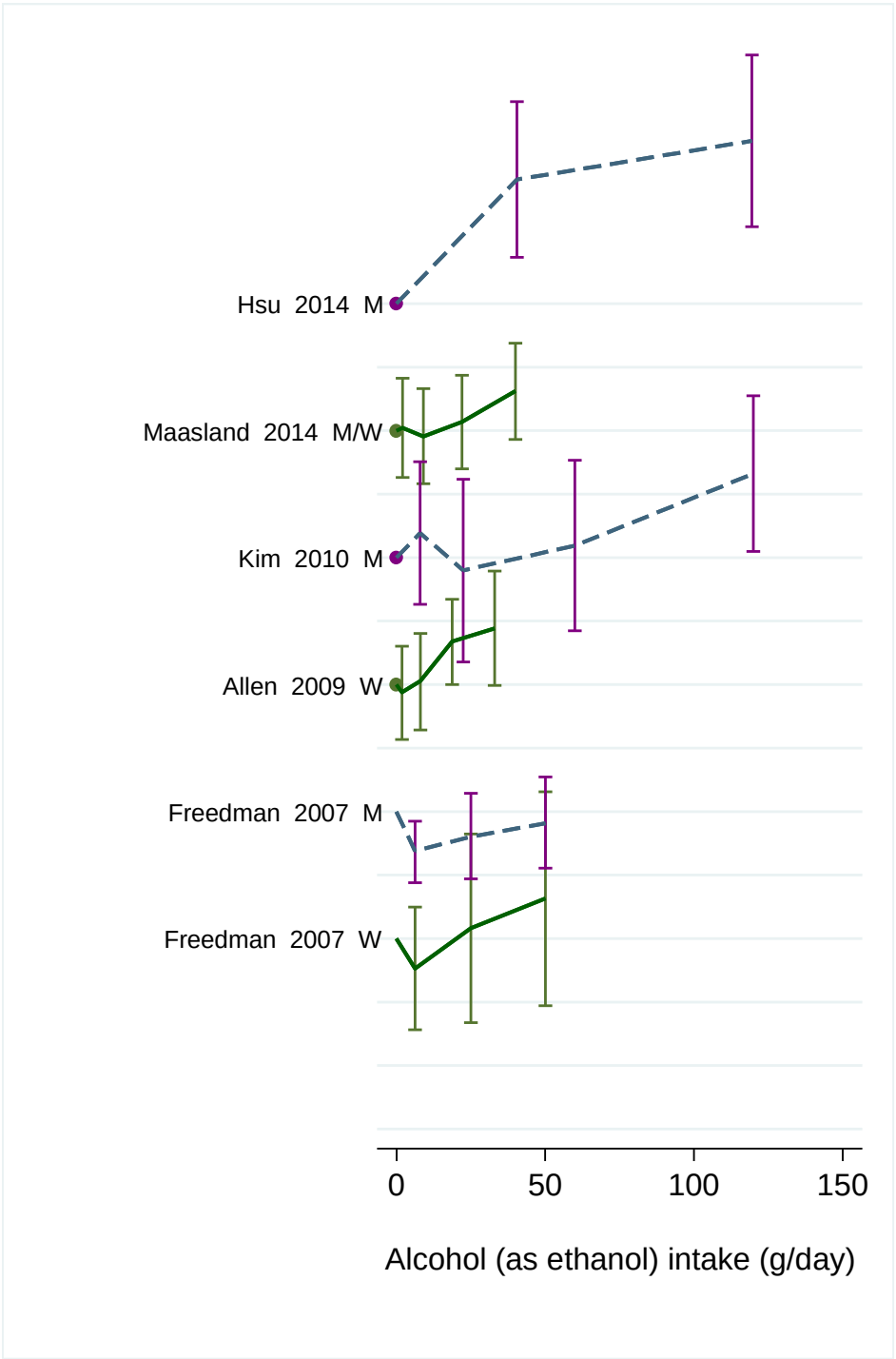
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)d	Adjustment factors
,Spain,Sweden,UK								with unknown quit, current smoking with <15, current smoking with ≥15and ≤25, current smoking with ≥25 cig/d, current smoking with unknown quantity, education, fruit and vegetable intake, BMI, never-drinker, former drinker
Freedman, 2007 mou08604 USA	NIH-AARP, Prospective Cohort, M/W	229 51/ 492 960 2 203 500 person-years	Cancer registry	FFQ and questionnaire	Incidence, Laryngeal squamous cell carcinoma	>3 vs <1 drinks/day Men Women	1.37 (0.91-2.05) 2.15 (0.82-5.65)	Age, BMI, educational level, fruit Intake, gender, smoking status and dose, total energy, usual activity throughout the day, vegetable Intake, vigorous physical activity

Table 19. Total alcohol intake and laryngeal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reason for exclusion
Klatsky, 2015 mou08587 USA	KPMCP, Prospective Cohort, Age: 41 years, M/W	161/ 124 193 17.8 years	Cancer registry	Questionnaire	Incidence, laryngeal cancer	≥3 vs 0 drinks/day	1.90 (1.20-3.00)	Age, race/ethnicity, BMI, Education level, marital status, smoking, sex	Inadequate categorisation, Included in HvsL graph
Jayalekshmi, 2013 mou08576 India	Karunagappally cohort study, Prospective Cohort, Age: 30-84 years, M, adult men	85/ 65 553 13 years	Cancer and mortality registries	Standardized questionnaire	Incidence, laryngeal cancer	Current vs Never-drinkers	2.1 (1.3-3.5)	Attained age, educational level, Income	Inadequate categorisation, Included in HvsL graph
Saieva, 2012 mou08543 Italy	Alcoholics cohort, Italy, Prospective Cohort, Age: 43 years, M/W Alcoholics	9men/1 women 2 272 9.6 years	Mortality register	CAGE test	Mortality, larynx, alcoholics Total Men Women	Alcoholics vs Non-alcoholics	10.70 (5.80-19.90) 10.00 (5.20-19.30) 27.00 (3.80-191.90)		Inadequate categorisation, Included in HvsL graph
Thygesen, 2009 mou08547 Denmark	Copenhagen alcohol cohort, 1954-1999, Prospective Cohort, M/W	121men/4 women 18 810 304 414 person-years	Danish cancer registry	Interview	Incidence, larynx, Men Women	Alcoholics vs General population	4.60 (3.90-5.50) 3.90 (1.00-9.90)	Age, calendar time	Inadequate categorisation, Included in HvsL graph
Thygesen, 2005 mou08589 Denmark	Danish brewery workers cohort, Prospective Cohort,	124/ 13 051 422 240 person-years	Brewery workers union	Use of aggregated data	Incidence, larynx	Brewery workers vs General population	2.68 (2.23-3.19)		Inadequate categorisation, Included in

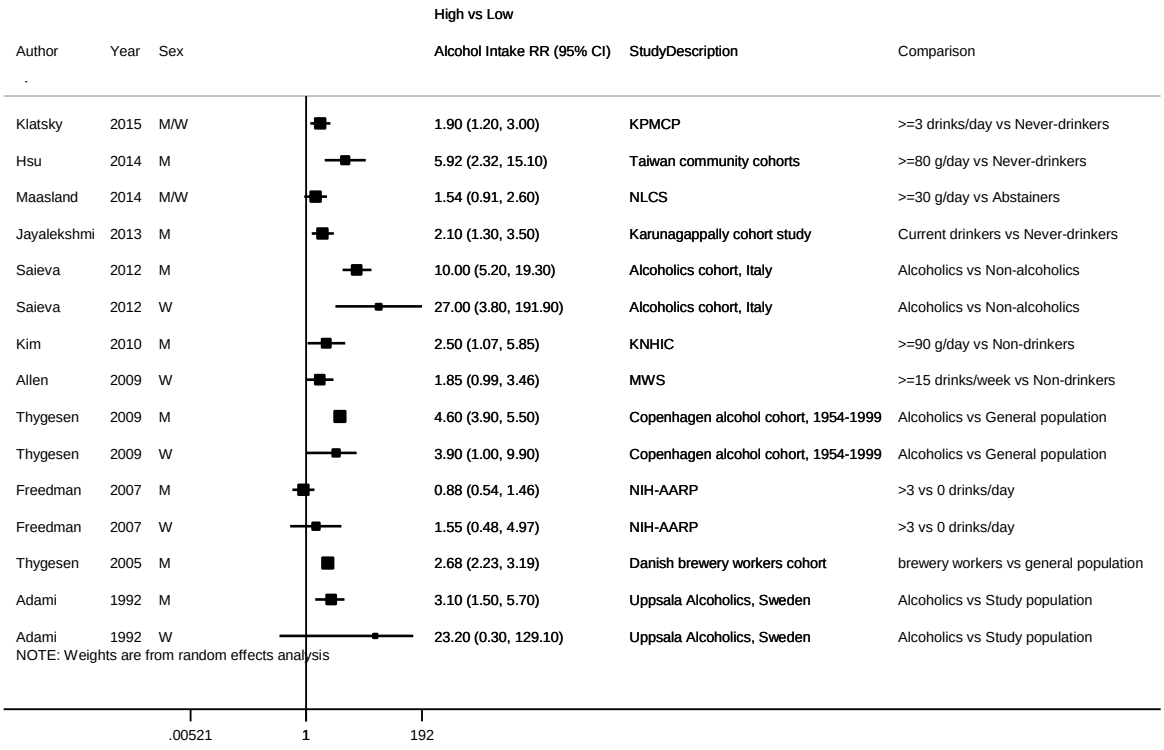
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reason for exclusion
	M, Brewery workers								HvsL graph
Adami, 1992 mou08561 Sweden	Uppsala Alcoholics, Sweden, Prospective Cohort, Age: 50 years, M/W, Alcoholics	13men/1women 9 353 7.7 years	Cancer registry	Lifestyle grouping	Incidence, larynx Men Women	Alcoholics vs Study population	3.10 (1.50-5.70) 23.20 (0.30-129.10)		Inadequate categorisation, Included in HvsL graph
Kasum, 2002 Mou03561 USA	IWHS, Prospective Cohort Age: 55-69 years, W, Postmenopausal	21/ 34 351 14 years	Driver's license list	127-item FFQ	Incidence, larynx	≥2 vs 0 drinks/day	1.77	Whole grains, refined grains, yellow/orange vegetables, smoking, age, energy intake	Does not report CI

Figure 19 RR estimates of laryngeal cancer by levels of alcohol intake



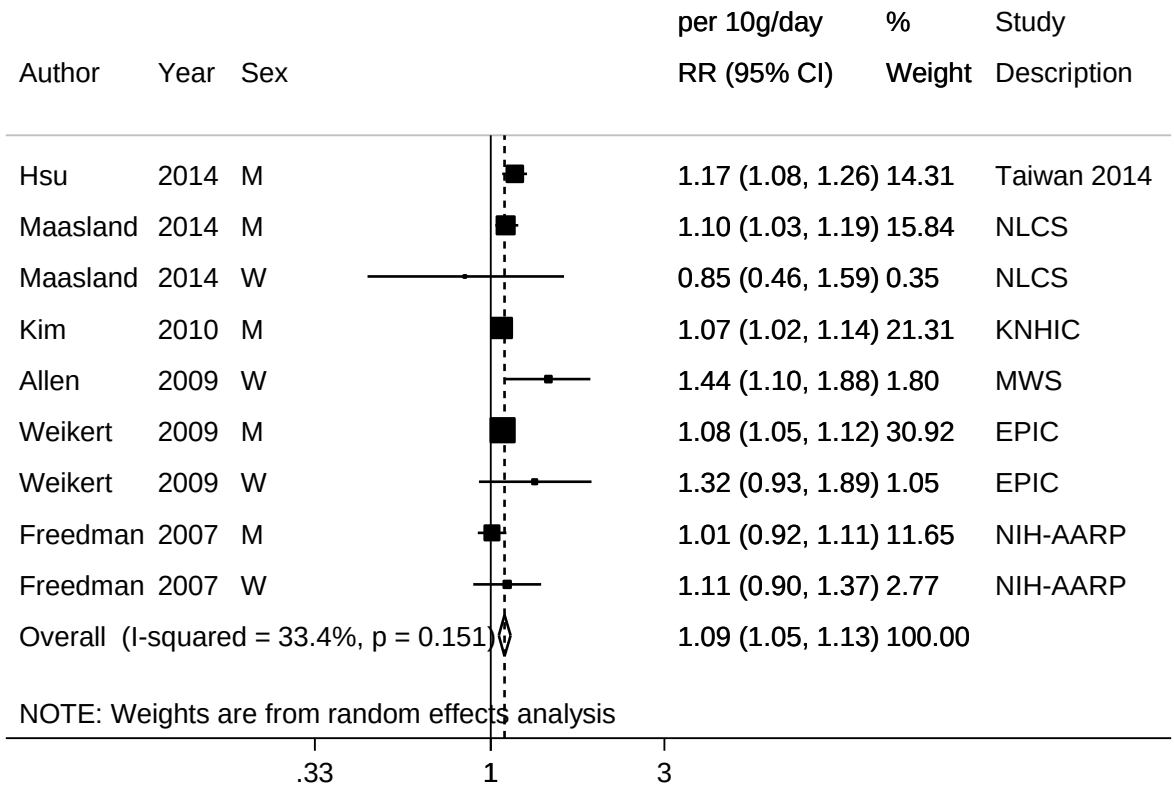
Note: M: men; W: women; M/W: men and women

Figure 20. RR (95% CI) of laryngeal cancer for the highest compared with the lowest level of total alcohol intake



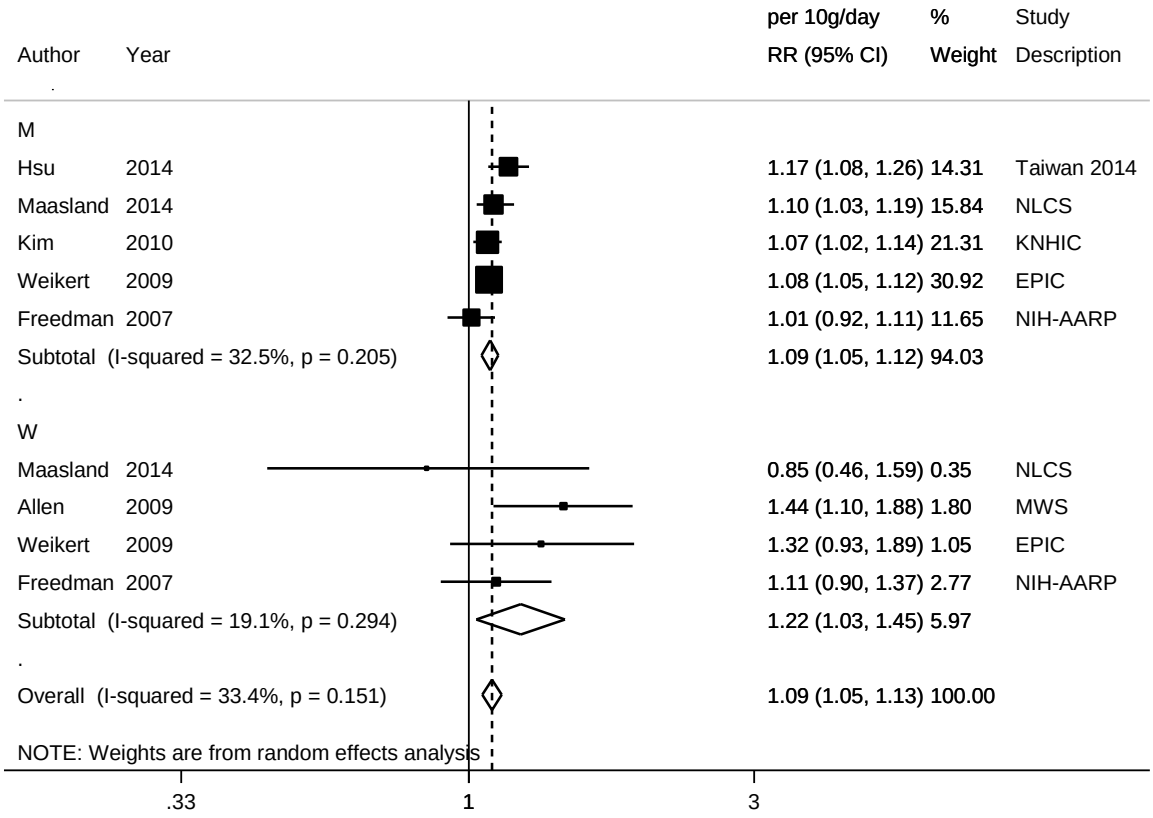
Note: the estimates are SMR in Saieva *et al*. (2012) and SIR in Thygessen *et al*. (2009); Thygessen *et al*. (2005); Adami *et al*. (1992). RRs are recalculated with the Hamling method in Freedman *et al*. (2007). The RRs are converted from floating RRs to conventional RRs in Allen *et al.* (2009). M: men; W: women; M/W: men and women.

Figure 21. Relative risk of laryngeal cancer for 10 g/day increase of total alcohol (as ethanol) intake



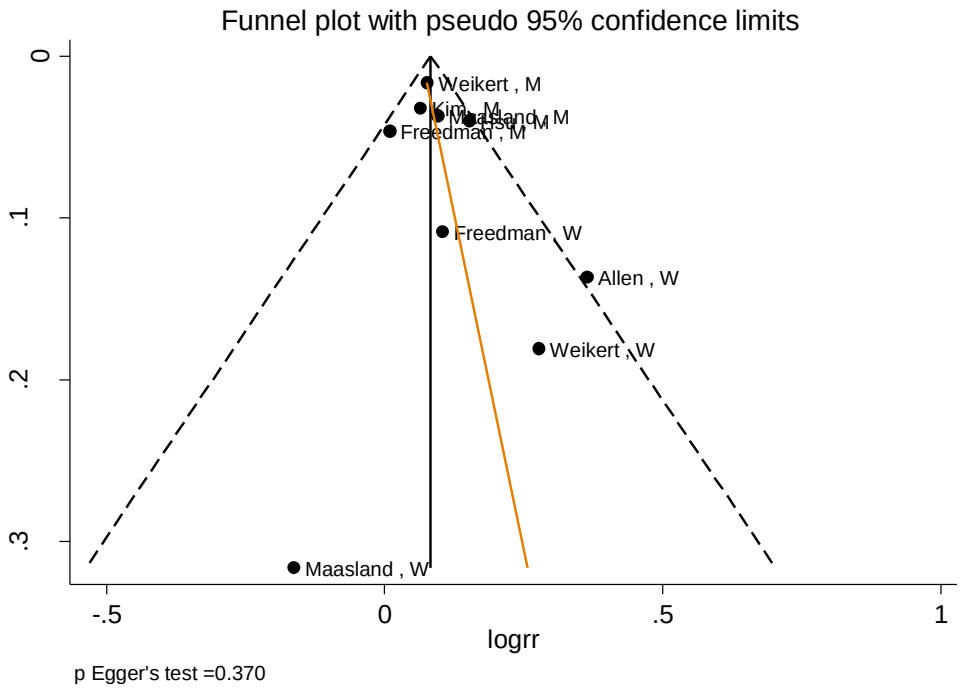
Note: M: men; W: women

Figure 22. Relative risk of laryngeal cancer for 10 g/day increase of total alcohol (as ethanol) intake, by sex



Note: M: men; W: women

Figure 23. Funnel plot of studies included in the dose response meta-analysis of alcohol intake and laryngeal cancer



Note: M: men; W: women

Table 20 Alcohol consumption and laryngeal cancer risk. Results of a meta-analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Bagnardi, 2015	3 cohorts	467	North America, Europe and Asia	Incidence, laryngeal cancer	Light drinking Moderate drinking Heavy drinking	0.81 (0.61-1.07) 1.09 (0.70-1.72) 1.12 (0.75-1.67)	-	21 46 0

Head and Neck cancer

No meta-analysis was conducted.

In a Dutch cohort (Maasland, 2014) the HR of SCC of head and neck cancer for 10 g increment of alcohol intake was RR 1.19; 95% CI 1.12-1.27, RR 1.40; 95% CI 1.18-1.65, in men and women respectively. The HR for the highest compared to the lowest intake was 2.74; 95% CI 1.85-4.06.

In the PLCO study the HR for ≥4 drinks/day compared to none was 2.24; 95% CI, 1.37–3.65 (Hashibe, 2013).

The NIH-AARP (Freedman, 2007) study revealed that consumption of more than three drinks per day had a significant positive association with HN SCC in both men and women compared to consumption of less than one drink per day (HR 1.48; 95% CI 1.15-1.90, HR 2.52; 95% CI 1.46-4.35, respectively)

Interaction with smoking

In the NLCS cohort (Maasland, 2014) 506 out of 550 cases were smokers. The RR in drinkers (≥30g/day)/smokers (≥20cigaretes/day) was 8.28 (95% CI 3.98-17.22, 80 cases) and in drinkers (≥30g/day)/never smokers was 2.97 (95% CI 0.78-11.40, 3 cases) compared to non-drinkers/never smokers (P-interaction= 0.03).

In the PLCO cohort (Hashibe 2013), 139 out of 175 cases were smokers. The RR in drinkers (≥2 drinks/day)/ smokers (≥20 cigarettes/day) was 11.07 (95% CI 5.07-24.14) and in drinkers (≥2 drinks/day)/ never-smokers was 1.37 (95% CI 0.29-6.47). However there were only two cases in the latter category.

UADT cancer

Ten studies from fifteen publications were identified. Nine studies (1 826 cases) were included in the dose-response meta-analysis (Jayasekara, 2015; Klatsky, 2015; Ferrari, 2014; Hsu, 2014; Everatt, 2013; Kasum, 2002; Gronbaek, 1998; Kjaerheim; 1998; Chyou, 1995).

Significant positive association was found between alcohol consumption (as ethanol, per 10g/day increment) and UADT cancer risk (RR 1.18; 95% CI 1.10-1.26). High and significant heterogeneity was observed. Egger's test showed evidence of publication or small

study bias. Influence analysis showed that the summary RR did not change substantially when each study was excluded in turn from the meta-analysis.

Six studies were excluded from the dose-response analyses due to lack of data or were results from overlapping cohorts. All studies showed significant positive associations except a Japanese study in alcoholic men followed with endoscopy in which risk of UADT was not related to higher intake of alcohol (Yokoyama, 2006) in which only two categories of alcohol intake were compared.

Interaction with smoking

Tests for interaction were in general not conducted in the studies due to low number of cases in the groups of non-smokers and non-drinkers.

A study in three male cohorts in Taiwan (Hsu, 2014) reported a relative risk of UADT cancers of 8.88 (95% CI 6.08-12.98) in men who betel quid chewed and smoked but never drank alcohol (39 cases) and 12.04 (95% CI 7.66-18.93) in men who chewed/smoked and also drank alcohol (33 cases), compared to never chewed, never smoked and never drank (30 cases).

A Danish study reported no significant interaction of alcohol and tobacco in the risk of UADT cancers (Gronbaek, 1998). The data was not shown in the publication.

In Japanese men in Hawaii, compared to non-smokers and non-drinkers (3 cases), the RR for UADT cancer in men drinking more than 14 oz/week was 6.5 (1.63-25.0) in non-smokers (6 cases) and 14.35 in smokers of more than 20 cig/day (28 cases). For the same comparison, the RR was 3.2 (95% CI 0.76-13.39) in men not drinking and smoking more than 20 cig/day (Chyou, 1995)

Study quality:

No study reported loss to follow up. Cancer outcome was confirmed using cancer and death registries in most studies. Most of the studies did not differentiate UADT SCC from adenocarcinomas, except from two studies which included only SCC cases (Chyou, 1995; Jayasekara, 2015)

Alcohol intake was assessed by questionnaires or FFQ in all of the studies. The reference category for most studies was the ‘‘non-drinkers’’ category, except from Ferrari et al. (2014) who used as reference category “0.1-4.9g/day” (Ferrari, 2014)

Alcohol consumption was converted to ethanol intake (g) using conversion units given in the publications. A standard conversion unit was applied in three studies (Klatsky, 2015; Kasum, 2002; Gronbaek, 1998; Kjaerheim; 1998; Chyou, 1995).

All of the studies included in the dose-response analysis were adjusted for age and smoking. Four of those studies were further adjusted for BMI (Ferrari, 2014; Everatt, 2013; Klatsky, 2015; Jayasekara, 2015).

Table 21. Total alcohol intake and UADT cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (15 publications)
Studies included in forest plot of highest compared with lowest exposure	10
Studies included in linear dose-response meta-analysis	9

Table 22. Total alcohol (as ethanol) intake and UADT cancer risk. Summary of the linear dose-response meta-analysis in CUP

	CUP	
Increment unit used	10g/day	
All studies		
Studies (n)	9	
Cases (total number)	1 826	
RR (95%CI)	1.18 (1.10-1.26)	
Heterogeneity (I^2, p-value)	95%, <0.001	
P-value Egger test	0.005	
Stratified analysis		
Sex	**Men**	**Women**
Studies (n)	6	3
RR (95%CI)	1.17 (1.08-1.27)	1.19 (0.95-1.49)
Heterogeneity (I^2, p-value)	93.3%, <0.001	74.3%, 0.020

Table 23. Total alcohol intake and UADT cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
Jayasekara, 2015 oes00914 Australia	MCCS, Prospective Cohort, M/W	57 men/41 women 38 159 16.2 years	Cancer registry/death records/national death Index	FFQ	Incidence, SCC UADT Total Men Women	per 10 g/d	1.16 (1.06-1.28) 1.16 (1.05-1.29) 1.10 (0.79-1.52)	Age, sex, BMI, country of origin, educational level, energy intake, fruit consumption, smoking, socio-economic status, vegetable consumption
						≥40g/day vs Lifetime abstainer	2.67 (1.27-5.60)	
Klatsky, 2015 mou08587 USA	KPMCP, Prospective Cohort, Age: 41 years, M/W	552/ 124 193 17.8 years	Cancer registry	Questionnaire	Incidence, UADT	≥3drinks/day vs Never-drinkers	2.50 (1.70-2.80)	Age, sex, BMI, educational level, marital status, race/ethnicity, smoking
Ferrari, 2014 mou08584 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	235men/ 101women 349 730 12.6 years	Active follow up, cancer registry and death certificate	Lifestyle questionnaire	Mortality, UADT Men Women	≥60 vs 0.1-4.9 g/day ≥30 vs 0.1-4.9 g/day	3.29 (1.81-5.96) 5.01 (2.42-10.37)	Age, age first smoked, BMI, duration of smoking, educational level, energy Intake, former drinkers, height, smoking status, study centre, time since quitting smoking Further adjustment for women: Ever use of HT, menopause status, nr of full-term pregnancies
						Smoker/ ≥60g/day vs non-smoker/0.1-4.9 g/day Smoker/ ≥30g/day vs non-smoker/0.1-4.9 g/day	2.43 (1.55-3.80) 2.08 (1.55-2.73)	
Hsu, 2014 oes00913 Taiwan	Taiwan 2014, Prospective Cohort, Age: 30-80 years, M, Taiwan residents	269/ 25 611 18.4 years	Cancer registry and death certificates	Structured questionnaire	Incidence, UADT cancer	≥80g vs never	2.49 (1.72-3.61)	Age, ethnicity, education, substance use each other, study cohort.
						No betel chewer/ smoker/drinker Betel chewer/non-smoker/drinker Betel chewer/smoker/drinker	8.73 (4.46-17.10) 24.78 (6.86-89.55) 23.92 (11.81-48.45)	Age, ethnicity, education, study cohort

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI) P-trend	Adjustment factors
Everatt, 2013 mou08555 Lithuania	KRIS-MIHDPS, Prospective Cohort, Age: 40-59 years, M	95/ 7 150 30 years	Cancer registry and death registry	Questionnaire	Incidence, UADT cancer	≥140.1 vs <10.0 g/week	2.79 (1.23-6.34)	Age, BMI, educational level, smoking, study
						per 90 g/week	1.18 (1.06-1.30)	
						per 10 g	1.10 (1.08-1.13) 1.29 (1.16-1.43)	
						>60g/d alcohol/ ≥15cig./d >18g/d alcohol/ ≥15cig/d	22.86 (12.27-42.60) 17.28 (8.39-35.60)	Age, education, vegetable and fruit intake, BMI
Kasum, 2002 Mou03561 USA	IWHS, Prospective Cohort Age: 55-69 years, W, Postmenopausal	169/ 34 351 14 years	Driver's license list	127-item FFQ	Incidence, UADT cancer	≥2 vs 0 drinks/day	1.34 (0.94-1.91)	Whole grains, refined grains, yellow/orange vegetables, smoking, age, energy intake
Gronbaek, 1998 mou02619 Denmark	Copenhagen Prospective Alcohol Study, Prospective Cohort, Age: 20-98 years, M/W, combined population based series of cohort studies	156/ 28 180 13.5 years	Unknown	Questionnaire	Incidence, UADT cancer	≥69 vs 0 drinks/week	11.70 (4.90-27.80)	Age, sex, educational level, smoking habits
Kjaerheim, 1998 mou03731 Norway	Norway 1968-1992 UADT, Prospective Cohort, M	60/ 10 960 25 years	Population survey	FFQ	Incidence, UADT cancer	4-7 vs 0-1 drinks/week	3.20 (1.60-6.10)	Age, smoking habits, orange consumption, bread consumption
Chyou, 1995	HHP,	91/	Selective	FFQ and 24	Incidence,	≥25 vs 0 oz/month	4.67 (2.62-8.32)	Age, smoking habits

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors
oes00128 USA	Prospective Cohort, M	7 995 25 years	service roll	hour recall	SCC UADT			

Table 24. Total alcohol intake and UADT cancer risk. Main characteristics of studies excluded in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) P-trend	Adjustment factors	Reason for exclusion
Weikert, 2009 oes00869 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	282/ 271 253 2 330 381 person-years	Cancer registry, health Insurance records, active follow up and mortality registry	Self-administered questionnaire	Incidence, SCC UADT cancer Men Women	≥96 vs 0.1-6 g/day >30 vs 0.1-6 g/day	4.63 (2.52-8.48) 6.05 (2.98-12.30)	BMI, current smoking status, current smoking with <15 cig/d, current smoking with >= 15 and <25 cig/d, current smoking with >=25 cig/d, duration of smoking, educational level, former drinkers, former smoking with quitting <10 years, former smoking with quitting >= 10 years, former smoking with unknown quitting time, fruits and vegetables Intake, never drinkers	Superseded by Ferrari 2014 mou08584
						per 10 g	1.10 (1.08-1.13) 1.29 (1.16-1.43)		
						>60g/d alcohol/ ≥15cig./d >18g/d alcohol/ ≥15cig/d	22.86 (12.27-42.60) 17.28 (8.39-35.60)	Age, education, vegetable and fruit intake, BMI	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95% CI) P-trend	Adjustment factors	Reason for exclusion
Thygesen, 2007 oes00911 Denmark	CCHS, Prospective Cohort, M/W	105/ 11 135	Danish cancer registry and central person register	Reported type-specific average number of drinks per week	Incidence, UADT cancer	≤69 vs <1 drinks/week	3.30 (1.20-9.60)	Age, sex, average income, BMI, educational level, smoking	Same cohort as Gronbaek 1998 mou02619
Yokoyama, 2006 oes00860 Japan	JAMS, Prospective Cohort, Age: 40-79 years, M, Alcoholics	33model 1/ 47 model 2 805 31 months	Endoscopic diagnosis	Questionnaire	Incidence, SCC UADT cancer	≥100 vs ≤99 g/day Model 1	1.63 (0.78-3.40)	Age, flushing response, mean corpuscular volume	Inadequate categorisation. Included in HvsL graph
						Model 2	1.09 (0.60-1.99)	Age, adh1b genotype, aldh2 genotype	
Boeing, 2002 mou00790 UK, Denmark, Germany, Italy, Spain, Netherlands, Sweden	EPIC, Prospective Cohort, M/W	124/ 417 542	Unknown	Unknown	Incidence, UADT cancer	≥60 vs 0 g/day	9.22 (2.75-30.93)	Sex, BMI, educational level, energy Intake, follow-up time, other nutrients, foods or supplements, smoking habits	Superseded by Ferrari 2014 mou08584
Zheng, 1995 oes00047 USA	IWHS, Prospective Cohort, Age: 55-669 years, W, Postmenopausal	33/ 34 691 7 years	Driving license/private health care list	FFQ	Risk, UADT cancer	≥3.4 vs 0 g/day	1.40 (0.60-3.10)	Age, educational level, smoking habits	Superseded by Kasum 2002 mou03561
Kato, 1992 mou03565 USA	HHP, Prospective Cohort, M	70/ 6 701 15 years	Selective service roll	Interview	Incidence, UADT cancer	≥30 vs 0 ml/day Ex- & current smokers/≥30ml/day vs never-smoker/0 ml/day	5.40 (2.80-10.40)	Age, smoking habits	Superseded by Chyou 1995 oes00128
							17.3 (6.7-44.2)	Age	

Figure 24. RR estimates of UADT cancer by levels of alcohol intake

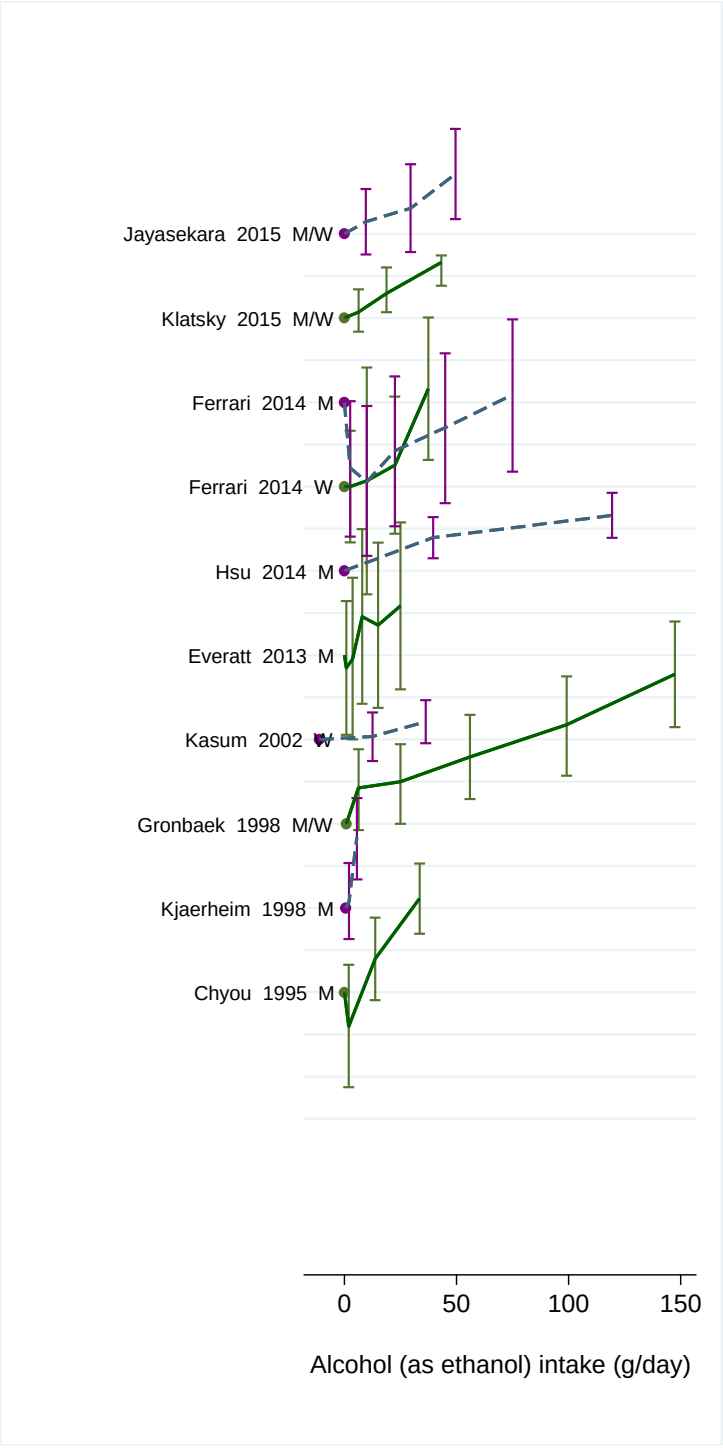
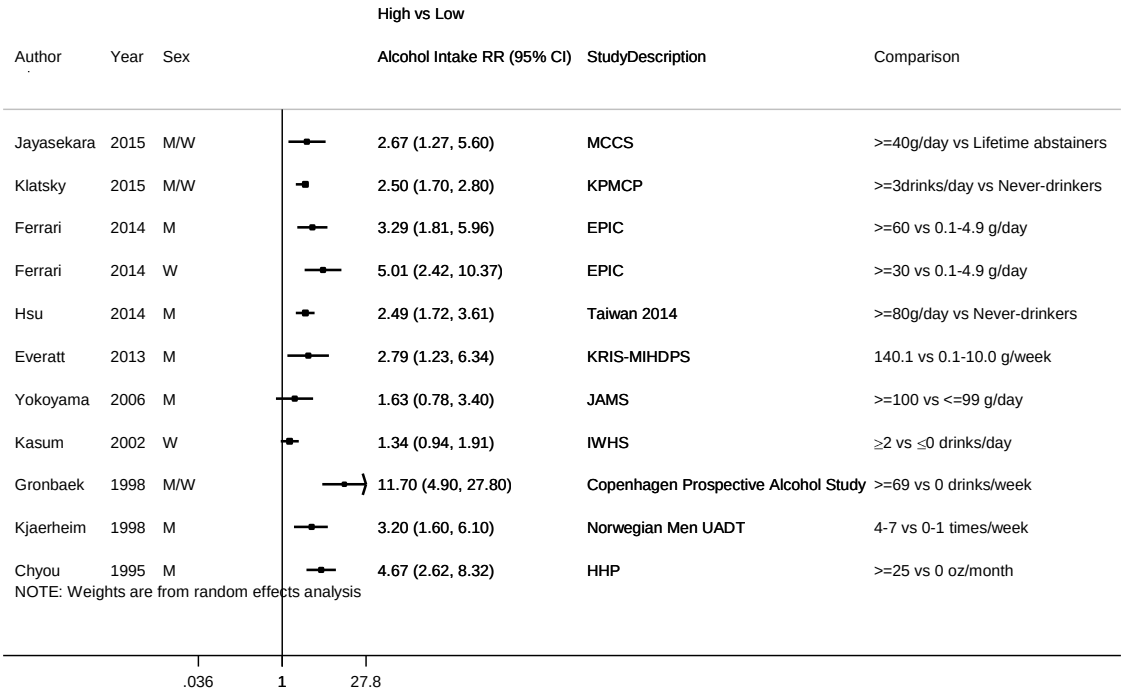
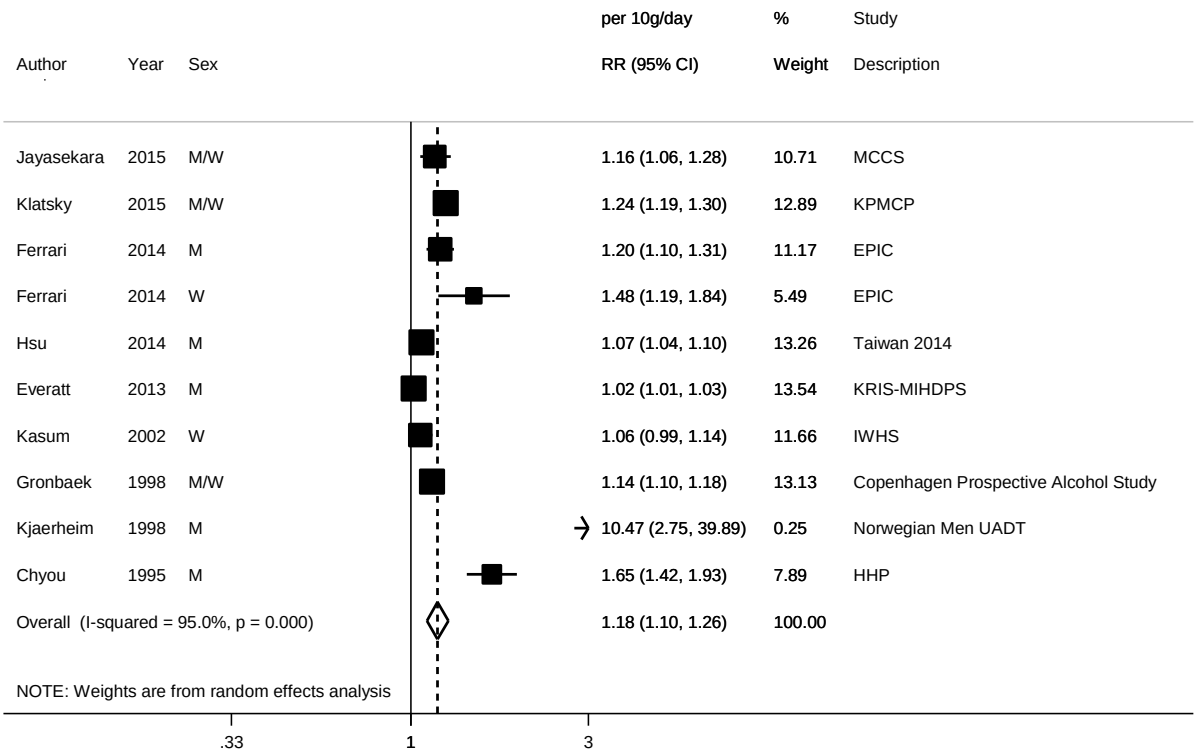


Figure 25. RR (95% CI) of UADT cancer for the highest compared with the lowest level of total alcohol intake



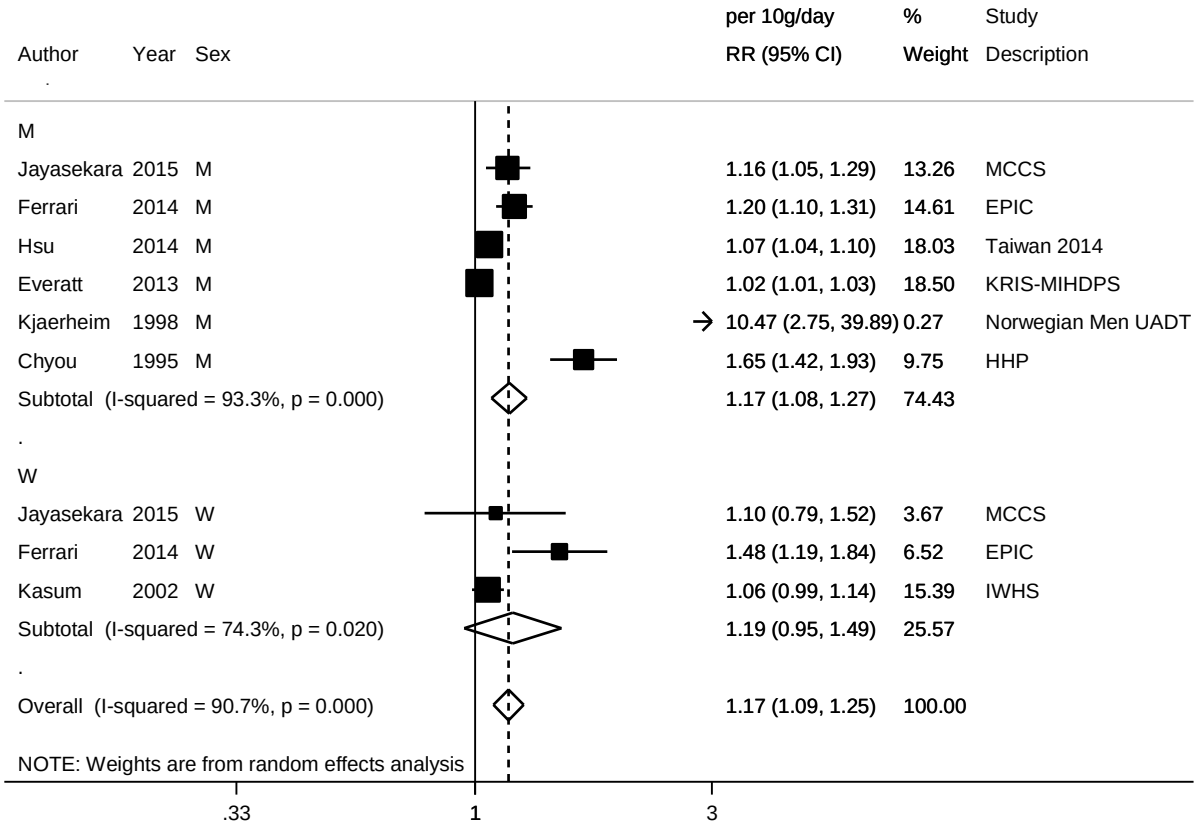
Note: M: men; W: women; M/W: men and women

Figure 26. Relative risk of UADT cancer for 10 g/day increase of total alcohol (as ethanol) intake



Note: M: men; W: women; M/W: men and women

Figure 27. Relative risk of UADT cancer for 10 g/day increase of total alcohol (as ethanol) intake, by sex



Note: M: men; W: women; M/W: men and women

Figure 28. Funnel plot of studies included in the dose response meta-analysis of alcohol intake and UADT cancer

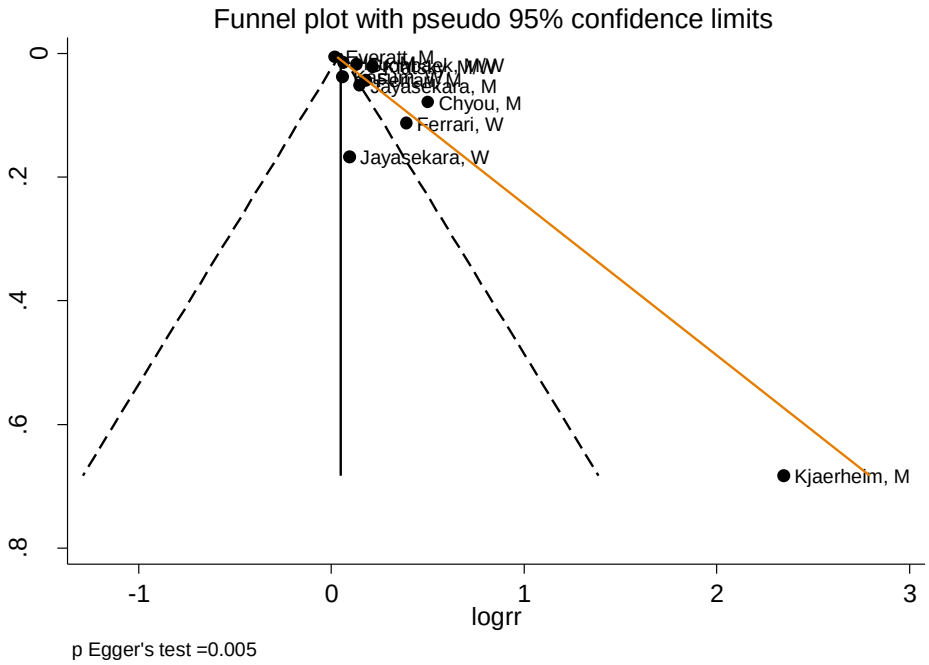


Table 25 Alcohol consumption and UADT cancer risk. Results of a meta-analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Jayasekara, 2016	3 cohorts	595	Europe and Australia	Incidence, UADT cancer	Highest versus lowest	2.83 (1.73-4.62)	-	0

Pooled analysis of case-control studies

The INHANCE consortium (Lubin, 2011) analysed individual-level pooled data from 15 case–control studies (2 441 oral cavity cancer cases, 2 297 oropharyngeal cancer cases, 508 hypopharyngeal cancer cases and 1 740 laryngeal cancer cases). Depending on analysis controls numbered from 7 604 to 13 829. ORs were adjusted for age, sex, education, BMI, pack-years, cigarettes per day, years since smoking cessation, use of other tobacco products and drink-years.

Consumption of 5 to 10 drinks per day compared to 0.01 to 0.9 drinks per day had a positive significant association with oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancer in men (OR 1.75; 95% CI 1.10-2.80; OR 2.82; 95% CI 1.80-4.30; OR 7.03; 95% CI 2.60-19.0; OR 1.89; 95% CI 1.10-3.10, respectively). P-trend for all comparisons was <0.01. Comparisons in women showed a positive significant association with oropharyngeal cancer and hypopharyngeal cancer (OR 7.63; 95% CI 2.80-21.0, p-trend<0.01; OR 19.6; 95% CI 1.80-217.0, p-trend<0.01, respectively), while a positive non-significant association was found for oral cavity cancer (OR 2.37; 95% CI 0.80-7.50, p-trend<0.01). An inverse non-significant association was found for laryngeal cancer (OR 0.52; 95% CI 0.10-2.70, p-trend=0.88).

3.7.1.1 Beers

Cohort studies

Summary

Three studies (on UADT cancer) were identified in the 2005 SLR and three studies (on oral cavity, oro/hypopharyngeal, laryngeal, HN and UADT cancer) were identified in CUP.

Dose-response meta-analysis was conducted for oral cancer, oro/hypopharyngeal, laryngeal and HN cancer (see figure 29).

Oral cavity cancer

The NLCS (Maasland, 2014) reported no association with oral cavity SCC with consumption of two or more drinks of beer per day compared to no consumption of beer (RR 0.99; 95% CI 0.34-2.82). Analysis was adjusted for total ethanol intake.

In the NIH-AARP study (Freedman, 2007) showed that consumption of more than three drinks of beer per day had a positive significant association oral cavity SCC in both men and women (HR 1.78; 95% CI 1.08-2.94; HR 5.96; 95% CI 1.94-18.30, respectively). Analysis was adjusted for categories of wine and liquor intake.

Oro/hypopharyngeal cancer

The NLCS (Maasland, 2014) reported a positive significant association with oro/hypopharyngeal SCC with consumption of two or more drinks of beer per day compared to no consumption of beer (RR 2.48; 95% CI 1.03-5.98). Analysis was adjusted for total ethanol intake.

In the NIH-AARP study (Freedman, 2007) showed that consumption of more than three drinks of beer per day had a positive significant association with oro/hypopharyngeal SCC in men (HR 3.12; 95% CI 1.54-6.31), compared to consumption of less than one drink of beer per day. In women, consumption of one to three drinks of beer per day showed a positive non-significant association with oro/hypopharyngeal SCC (HR 1.14; 95% CI 0.15-8.86). However, only one case was reported in this category. Analysis was adjusted for categories of wine and liquor intake.

Laryngeal cancer

The NLCS (Maasland, 2014) reported a positive non-significant association with laryngeal SCC with consumption of two or more drinks of beer per day compared to no consumption of beer (RR 1.30; 95% CI 0.69-2.46). Analysis was adjusted for total ethanol intake.

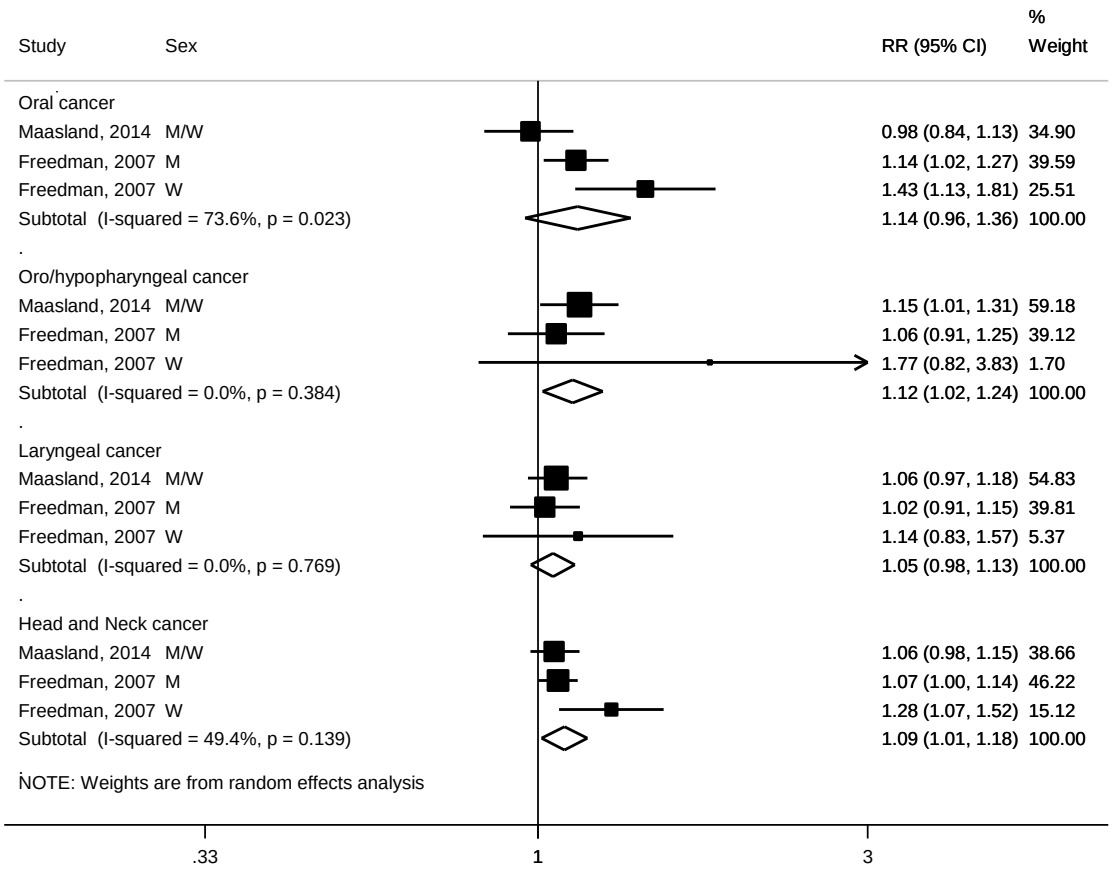
In the NIH-AARP study (Freedman, 2007) showed that consumption of more than three drinks of beer per day had a positive non-significant association with laryngeal SCC in both men and women (HR 1.14; 95% CI 0.65-1.98; HR 3.76; 95% CI 0.78-18.23, respectively). Analysis was adjusted for categories of wine and liquor intake.

Head and Neck cancer

The NLCS (Maasland, 2014) reported a positive non-significant association with HN SCC with consumption of two or more drinks of beer per day compared to no consumption of beer (RR 1.39; 95% CI 0.83-2.34). Analysis was adjusted for total ethanol intake.

In the NIH-AARP study (Freedman, 2007) showed that consumption of more than three drinks of beer per day had a positive significant association with HN SCC in both men and women, compared to consumption of less than 1 drink of beer per day (HR 1.61; 95% CI 1.16-2.22; HR 3.40; 95% CI 1.40-8.24, respectively). Analysis was adjusted for categories of wine and liquor intake.

Figure 29. Relative risk of HNC and subsites for 10 g/day increase of beer intake (as ethanol)



Note: M: men; W: women; M/W: men and women

UADT cancer

In a large multi-ethnic cohort in Northern California (Klatsky, 2015) beer intake was not significantly associated with increased risk for UADT cancer (HR 2.90; 95% CI 1.00-4.30), comparing consumption of 3 or more drinks/ day to less than 1 drink/ day. The analysis was adjusted for alcohol intake among drinkers of more than one drink per month.

In a cohort of Hawaii Japanese-American men (Chyou, 1995) consumption of 361oz per month or more of beer was associated with significant increased risk for UADT cancer, compared to non-drinking alcohol (RR 3.66; 95% CI 2.01-6.69). Adjustments did not include alcohol intake.

A Danish population based study investigating the relation between different types of alcoholic drinks and UADT cancer (Gronbaek, 1998) showed that intake of 7 or more beers per week compared with none increased significantly the risk of UADT cancer (RR 2.90; 95% CI 1.80-4.80). Adjustments did include alcohol intake.

A prospective cohort of 10,900 Norwegian men (Kjaerheim, 1998) found a significant increased risk of UADT cancer when comparing drinking beer 4 to 7 times/week to never/infrequent drinking (RR 4.40; 95% CI 2.40-8.30). Analyses were not adjusted for alcohol intake.

3.7.1.2 Wines

Cohort studies

Summary

Two studies (on UADT cancer) were identified in the 2005 SLR and four studies (on oral, oro/hypopharyngeal, laryngeal, HN and UADT cancer) were identified in CUP.

Dose-response meta-analysis was conducted for oral cancer, oro/hypopharyngeal, laryngeal and HN cancer (see figure 30).

Oral cancer

The NLCS (Maasland, 2014) reported an inverse non-significant association with oral cavity SCC with consumption of two or more drinks of wine per day compared to no consumption of wine (RR 0.93; 95% CI 0.34-2.57). Analysis was adjusted for total ethanol intake.

The MWS (Allen, 2009) showed that increment of 10g per day of alcohol intake among women who drank wine exclusively was not related to oral cancer (RR 1.07; 95% CI 0.85-1.33). Adjustments did not include alcohol intake.

In the NIH-AARP study (Freedman, 2007) showed that consumption of one to three drinks of wine per day was not related to oral cavity SCC in men, while in women a positive non-significant association was observed, compared to consumption of less than one drink of wine per day (HR 0.97; 95% CI 0.55-1.70; HR 2.07; 95% CI 0.99-4.34, respectively). Analysis was adjusted for categories of beer and liquor intake.

Oro/hypopharyngeal cancer

The NLCS (Maasland, 2014) reported an inverse non-significant association with oro/hypopharyngeal SCC with consumption of two or more drinks of wine per day compared to no consumption of wine (RR 0.52; 95% CI 0.15-1.81). Analysis was adjusted for total ethanol intake.

In the NIH-AARP study (Freedman, 2007) showed that consumption of more than three drinks of wine per day had a positive non-significant association with oro/hypopharyngeal SCC in men (HR 2.59; 95% CI 0.35-19.05). Only one case was reported in this category. In women a positive non-significant association was observed with consumption of one to three drinks of wine per day compared to consumption of less than one drink of wine per day (HR 2.28; 95% CI 0.74-7.09). Analysis was adjusted for categories of beer and liquor intake.

Laryngeal cancer

The NLCS (Maasland, 2014) reported an inverse significant association with laryngeal SCC with consumption of two or more drinks of wine per day compared to no consumption of wine (RR 0.39; 95% CI 0.15-0.99). Analysis was adjusted for total ethanol intake.

The MWS (Allen, 2009) showed that increment of 10g per day of alcohol intake among women who drank wine exclusively had a non-significant increased risk for laryngeal cancer (RR 1.33; 95% CI 0.78-2.25). Adjustments did not include alcohol intake.

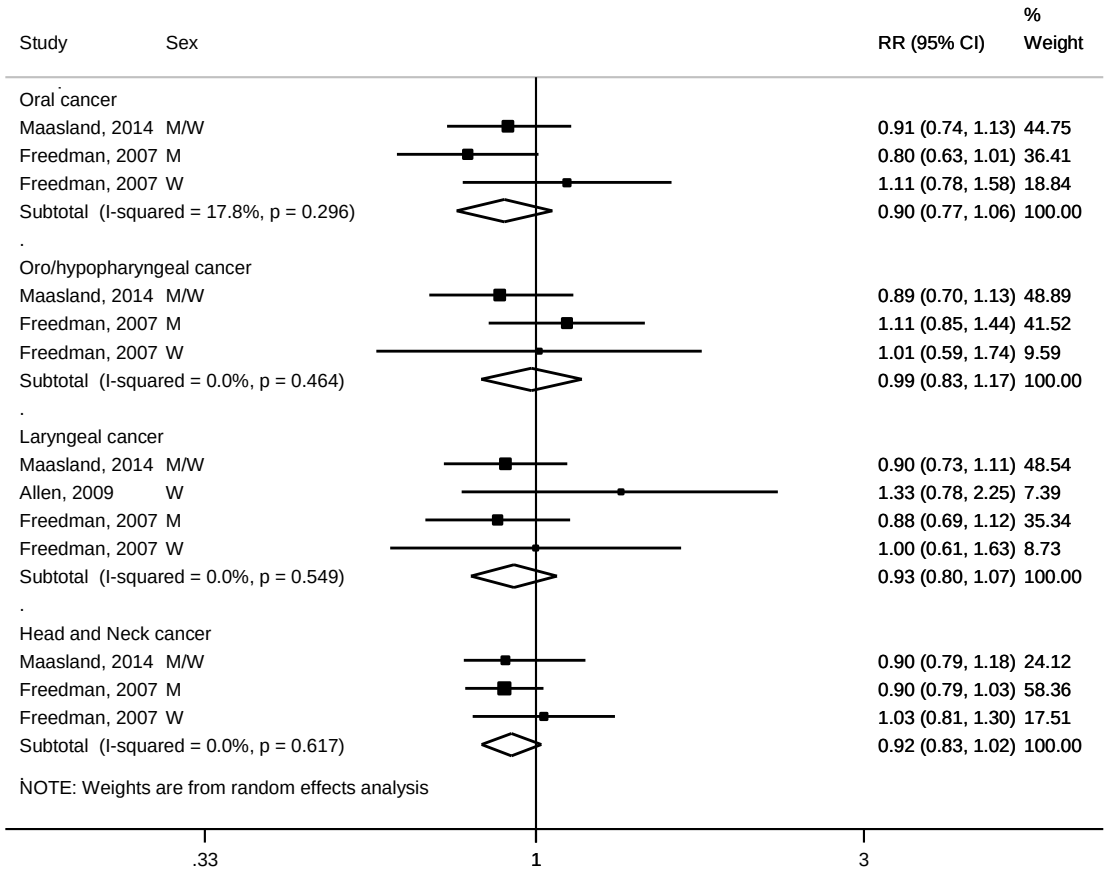
In the NIH-AARP study (Freedman, 2007) showed that consumption of one to three drinks of wine per day was not related to laryngeal SCC in men, whereas in women a positive non-significant association was found (HR 1.03; 95% CI 0.58-1.84; HR 1.56; 95% CI 0.53-4.59, respectively). Analysis was adjusted for categories of beer and liquor intake.

Head and Neck cancer

The NLCS (Maasland, 2014) reported an inverse non-significant association with HN SCC with consumption of two or more drinks of wine per day compared to no consumption of wine (RR 0.56; 95% CI 0.29-1.07). Analysis was adjusted for total ethanol intake.

In the NIH-AARP study (Freedman, 2007) showed that consumption of one to three drinks of wine per day had a positive non-significant association with HN SCC in men, while in women a positive significant association was observed (HR 1.16; 95% CI 0.83-1.62; HR 1.97; 95% CI 1.17-3.31, respectively). Compared to consumption of less than one drink of wine per day, inverse non-significant association was found with consumption of more than three drinks of wine in men (HR 0.43; 95% CI 0.06-3.05). One case was reported in the latter category. Analysis was adjusted for categories of beer and liquor intake.

Figure 30. Relative risk of HNC and subsites for 10 g/day increase of wine intake (as ethanol)



Note: M: men; W: women; M/W: men and women

UADT cancer

Three studies investigated wine consumption in relation to UADT cancer. Dose response meta-analysis was not conducted due to lack of sufficient studies.

In a large multi-ethnic cohort in Northern California (Klatsky, 2015) it was found that consumption of three or more drinks of wine per day had a significant increased risk for UADT cancer (HR 2.10; 95% CI 1.10-4.20) compared to participants who consumed less than one drink per day. Analysis was adjusted for alcohol intake among drinkers of more than one drink per month.

A cohort of Hawaii Japanese-American men (Chyou, 1995) showed that consumption of more than 4oz per month of wine had a significant increased risk for UADT cancer, compared to alcohol non-drinkers (RR 3.80; 95% CI 1.76-8.18). Adjustments did not include alcohol intake.

A Danish population based study (Gronbaek, 1998) revealed that intake of seven or more drinks of wine per week decreased significantly the risk for UADT cancer (RR 0.40; 95% CI 0.20-0.80). Adjustments did not include alcohol intake.

3.7.1.3 Spirits

Cohort studies

Summary

Two studies (on UADT cancer) were identified in the 2005 SLR and no studies were identified in CUP.

UADT cancer

A Danish population based study investigating the relation between different types of alcoholic drinks and UADT cancer (Gronbaek, 1998) showed that intake of seven or more drinks of spirits per week increased significantly the risk (RR 1.50; 95% CI 1.20-1.90). Adjustments did not include alcohol intake.

A prospective cohort of 10,900 Norwegian men (Kjaerheim, 1998) found a significant positive association in frequent alcohol drinkers (4-7 times/week) of spirits compared to never/infrequent drinkers (RR 2.70; 95% CI 1.10-7.00). Analyses were not adjusted for alcohol intake.

3.7.1.4 Other alcoholic drinks

No studies were identified in the 2005 SLR and five studies (on oral, oro/hypopharyngeal, laryngeal, HN and UADT cancer) were identified in the CUP 2005.

Dose-response meta-analysis was conducted for oral cancer, oro/hypopharyngeal, laryngeal and HN cancer and liquor consumption (as ethanol) (see figure 31).

Oral cancer

The NLCS (Maasland, 2014) reported a positive significant association with oral cavity SCC with consumption of two or more drinks of liquor per day compared to no consumption of liquor (RR 2.26; 95% CI 1.02-4.99). Analysis was adjusted for total ethanol intake.

The MWS (Allen, 2009) showed that increment of 10g per day of alcohol intake from other "other alcoholic drinks" (defined as consumption of beer and/or spirits exclusively or a mixture of wine, beer and/or spirits) had a significant increased risk for oral cancer (RR 1.38; 95% CI 1.20-1.60). Adjustments did not include alcohol intake.

In the NIH-AARP study (Freedman, 2007) showed that consumption of more than three drinks of liquor per day had a positive borderline association with oral cavity SCC in men and a positive non-significant association in women (HR 1.65; 95% CI 1.00-2.72; HR 2.45; 95% CI 0.99-6.05, respectively). Analysis was adjusted for categories of beer and wine intake.

The TOCSS (Muwonge, 2008) showed a non-significant increased risk of oral cancer with drinking of liquor such as toddy, arrack or foreign liquor compared to never-drinkers (OR 2.50; 95% CI 0.60-10.90; OR 2.00; 95% CI 0.90-4.40; OR 2.10; 95% CI 0.60-5.20, respectively). Analyses were not adjusted for alcohol intake. The study was not included in the meta-analysis, since the exposure was not comparable.

Oro/hypopharyngeal cancer

The NLCS (Maasland, 2014) reported an inverse non-significant association with oro/hypopharyngeal SCC with consumption of two or more drinks of liquor per day compared to no consumption of liquor (RR 0.83; 95% CI 0.33-2.13). Analysis was adjusted for total ethanol intake.

In the NIH-AARP study (Freedman, 2007) showed that consumption of more than three drinks of liquor per day had a positive significant association with oro/hypopharyngeal SCC in men and a positive non-significant association in women (HR 2.52; 95% CI 1.28-4.99; HR 3.28; 95% CI 0.66-16.27, respectively). Two cases were reported in this category for women. Analysis was adjusted for categories of beer and wine intake.

Laryngeal cancer

The NLCS (Maasland, 2014) reported no association with laryngeal SCC with consumption of two or more drinks of liquor per day compared to no consumption of liquor (RR 0.95; 95% CI 0.47-1.93). Analysis was adjusted for total ethanol intake.

The MWS (Allen, 2009) showed that increment of 10g per day of alcohol intake from "other alcoholic drinks" (defined as consumption of beer and/or spirits exclusively or a mixture of wine, beer and/or spirits) had a significant increased risk for oral cancer (RR 1.39; 95% CI 1.10-1.90). Adjustments did not include alcohol intake.

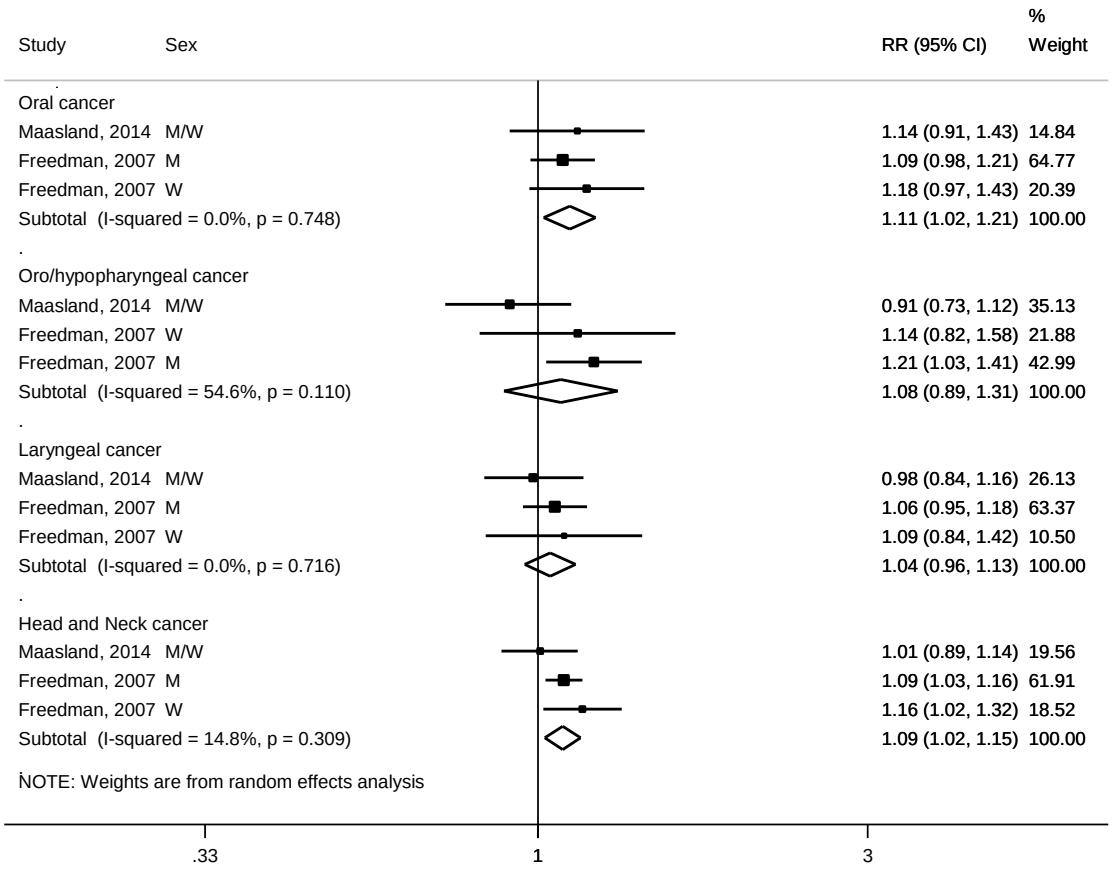
In the NIH-AARP study (Freedman, 2007) showed that consumption of more than three drinks of liquor per day had a positive significant association with laryngeal SCC in men and a positive non-significant association in women (HR 1.99; 95% CI 1.24-3.21; HR 1.31; 95% CI 0.38-4.57, respectively). Three cases were reported in this category for women. Analysis was adjusted for categories of beer and wine intake.

Head and Neck cancer

The NLCS (Maasland, 2014) reported a positive non-significant association with HN SCC with consumption of two or more drinks of liquor per day compared to no consumption of liquor (RR 1.18; 95% CI 0.71-1.95). Analysis was adjusted for total ethanol intake.

In the NIH-AARP study (Freedman, 2007) showed that consumption of more than three drinks of liquor per day had a positive significant association with HN SCC in both men and women (HR 1.85; 95% CI 1.37-2.50; HR 2.25; 95% CI 1.19-4.26, respectively). Analysis was adjusted for categories of beer and wine intake.

Figure 31. Relative risk of HNC and subsites for 10 g/day increase of liquor intake (as ethanol)



Note: M: men; W: women; M/W: men and women

UADT cancer

In large multi-ethnic cohort in Northern California (Klatsky, 2015) it was found that consumption of three or more drinks of liquor per day had a significant increased risk for UADT cancer (HR 2.90; 95% CI 1.50-5.50) compared to participants who consumed less than one drink per day. Analysis was adjusted for alcohol intake among drinkers of more than one drink per month.

4 Food production, preservation, processing and preparation

4.3 Processing

Cohort studies

Summary

One study (on UADT cancer) was identified in the 2005 SLR and no study was identified in CUP. Meta-analyses were not conducted.

Processed fish

In a cohort study of 10,900 Norwegian men (Kjaerheim, 1998), no association was found between consumption of processed fish 6 times per month or more and UADT cancer (RR 1.10; 95% CI 0.50-2.70).

4.4.2 Cooked food

Acrylamide

Cohort studies

Summary

No study was identified in the 2005 SLR. One study regarding the association between acrylamide intake and HN, oral cavity, oro/hypopharyngeal and laryngeal cancer, was identified in CUP. Meta-analyses were not conducted.

Oral cavity cancer

In the NLCS (Schouten, 2009), an inverse non-significant association was found between acrylamide intake and oral cavity cancer (HR per 10µg increment: 0.90; 95% CI 0.73-1.10; 37.2µg/day vs 10.1µg/day: HR 0.72; 95% CI 0.36-1.42; p-trend 0.49). In stratified analyses by sex similar results were found in both men (HR per 10µg increment: 0.85; 95% CI 0.65-1.12; 37.2µg/day vs 10.1µg/day: HR 0.68; 95% CI 0.33-1.43; p-trend 0.26) and women (HR per 10µg increment: 0.94; 95% CI 0.70-1.27). Analyses on continuous intake in non-smokers revealed an increased non-significant association in total participants (HR per 10µg increment: 1.06; 95% CI 0.84-1.33), while in women a significant positive association was found (HR 1.28; 95% CI 1.01-1.62)

Oro/hypopharyngeal cancer

In the NLCS (Schouten, 2009), the HRs were decreased for oro/hypopharyngeal cancer and acrylamide intake, although they did not reach statistical significance. (HR per 10µg increment 0.74; 95% CI 0.53-1.03; HR for 37.2µg/day vs 12.0µg/day: 0.61; 95% CI 0.33-1.12; p-trend 0.17). In men the HR per 10µg acrylamide intake increment was 0.65 (0.42-

1.00) (and HR for 32.5µg/day vs 12.0µg/day: 0.50; 95% CI 0.24-1.04; p-trend 0.15) and in women 0.94 (0.61-1.43).

Laryngeal cancer

Results from the NLCS (Schouten, 2009) showed that the associations between laryngeal cancer and acrylamide intake were close to or higher than one for analyses on total participants (HR per 10µg increment: 1.05; 95% CI 0.91-1.21; 37.2µg/day vs 10.1µg/day: HR 0.93; 95% CI 0.54-1.58; p-trend 0.85) and on men only (HR per 10µg increment: 1.06; 95% CI 0.91-1.23; 37.2µg/day vs 10.1µg/day: HR 0.95; 95% CI 0.55-1.65; p-trend 0.86). Inverse non-significant associations were found in non-smokers per 10µg increment (HR 0.82; 95% CI 0.53-1.29 for total participants; HR 0.85; 95% CI 0.54-1.34 for men).

Head and Neck cancer

The NLCS (Schouten, 2009) showed that acrylamide intake had an inverse non-significant association with HNC for the total population and among men (HR for 37.2µg/day vs 10.1µg/day: 0.74; 95% CI 0.50-1.09; p-trend 0.40; HR 0.74; 95% CI 0.47-1.15; p-trend 0.35, respectively), while among women no association was found (HR 1.01; 95% CI 0.53-1.93, p-trend 0.998). HRs for continuous acrylamide intake (per 10µg increment) were decreased but did not reach statistical significance in total population as well as among men and women separately (total population: HR 0.95; 95% CI 0.84-1.07; men: HR 0.96; 95% CI 0.84-1.10; women: HR 0.91; 95% CI 0.71-1.15). Stratified analyses by smoking showed a significantly inverse association for the highest versus the lowest acrylamide intake in men (HR 0.45; 95% CI 0.21-0.94; p-trend 0.03). The HRs did not reach statistical significance for the highest versus lowest analysis in the total population (HR 0.68; 95% CI 0.37-1.25; p-trend 0.07) as well as for the continuous intake (total population: HR 0.89; 95% ci 0.71-1.12; men: HR 0.82; 95% CI 0.59-1.14; women: HR 1.08; 95% CI 0.83-1.42).

5 Dietary constituents

5.5 Vitamins

5.5.1.1 Retinol

Cohort studies

Summary

Two studies on oral and UADT cancer were identified in 2005 SLR and no study was identified in CUP.

Oral cancer

A nested case-control study of adults in Washington County (Zheng, 1993) showed that high levels of serum retinol were positively but not significantly related to oral cancer (RO 2.51; p-trend 0.14).

UADT cancer

The IWHS (Zheng, 1995) showed no association of higher intake of dietary retinol intake and UADT cancer (RR 0.90; 95% CI 0.40-2.20).

5.5.1.2 Beta-carotene, supplement

Randomised controlled trials

No randomised controlled trial was identified in the 2005 SLR and one randomised controlled trial was identified in CUP: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study (Wright, 2007). Wright *et al.* (2007) examined whether daily supplementation with 50 mg dl alpha-Tocopheryl acetate and/or 20 mg beta-Carotene reduced the incidence of or mortality from oral/pharyngeal, and laryngeal cancers in the ATBC study, a double-blind, placebo-controlled primary prevention trial conducted in Finland. A total of 29 133 male smokers, aged 50–69 years and free of cancer at baseline, were randomized in a 2 x 2 factorial design to the supplementation regimen for 5–8 years (median, 6.1 years). Incident cancers of the oral cavity and pharynx (65 cases) and larynx (56 cases) were identified through the Finnish Cancer Registry.

Oral/pharyngeal cancer

There was no effect of alpha-Tocopherol and/or 20 mg beta-Carotene on the incidence or mortality of oral/pharyngeal cancers.

Compared to the placebo group (18 cases), the relative risks for oral/pharyngeal cancer incidence were 0.84 (0.42–1.66) for alpha-Tocopherol supplementation (15 cases), 0.84 (0.42–1.66) for beta-Carotene (17 cases) and 0.95 (0.49–1.84) for both (15 cases), and for mortality, the relative risks were 2.51 (0.49–12.92) for alpha-Tocopherol supplementation (5

cases) , 2.01 (0.37–10.95) (6 cases) for beta-Carotene and 3.01 (0.61–14.93) for both (2 cases) (Wright, 2007).

Laryngeal cancer

There was no effect of alpha-Tocopherol and/or 20 mg beta-Carotene on the incidence or mortality of laryngeal cancers.

Compared to the placebo group (17 cases), the relative risks for oral/pharyngeal cancer incidence were 1.00 (0.51–1.97) for alpha-Tocopherol supplementation (17 cases), 0.71 (0.34–1.48) for beta-Carotene (10 cases) and 0.59 (0.27–1.29) for both (12 cases), and for mortality, the relative risks were 0.67 (0.11–4.00) for alpha-Tocopherol supplementation (2 cases) , 1.00 (0.20–4.96) (2 cases) for beta-Carotene and 0.67 (0.11–4.00) for both (3 cases). There was a suggestion of beta-Carotene supplementation decreasing the risk of laryngeal cancer (RR 0.65 (CI 0.38–1.11)). Subgroup analyses also suggested that the beta-Carotene supplement may have been more protective against stage I laryngeal cancers (RR 0.28 (0.10–0.75); P-interaction= 0.04), those localized to the glottis (RR: 0.46 (0.22–0.96)), and in participants who entered the trial with high serum beta-Carotene concentrations (RR: 0.41 (0.17–0.99) P-interaction> 0.05). There was no modification of the beta-Carotene effect by smoking intensity, alcohol intake, or serum alpha-Tocopherol (Wright, 2007).

Cohort studies

No cohort study was identified.

Pooled analyses of case-control studies

The International Head and Neck Cancer Epidemiology consortium (INHANCE) analysed individual-level pooled data from 12 case–control studies (7 002 HNC cases and 8 383 controls). There were a total of 2 028 oral cavity cancers, 2 465 pharyngeal cancers, 874 unspecified oral/pharynx cancer, 1 329 laryngeal cancer and 306 overlapping HNC cases. ORs were adjusted for age, sex, race/ethnicity, study centre, education level, pack-years of smoking, frequency of alcohol drinking and fruit/vegetable intake. No association with head and neck cancer risk was observed when comparing ever use of beta-Carotene supplements with never use (OR=1.35; 95% CI 0.62-2.81, 50 cases and 92 controls reported ever use) (Li, 2012).

5.5.1.2 Provitamin A carotenoids (serum levels)

Cohort studies

Summary

Two studies on oral/pharyngeal and UADT cancer were identified in the 2005 SLR and no study was identified in CUP.

Oral/pharyngeal cancer

A nested case-control study including 28 individuals who developed oral and pharyngeal cancer during 1975 to 1990 and 112 matched controls. In a cohort of adults in Washington County (Zheng, 1993) reported that high serum level of total carotenoids were marginally related to lower risk of oral/pharyngeal cancers (OR for tertile 3 vs tertile 1=0.33; p-trend= 0.05). The OR for the same comparison of serum levels of beta-Carotene, alpha-Carotene and Cryptoxanthin were 0.50; p-trend 0.17; 0.37; p-trend 0.06, and 0.33; p-trend 0.07, respectively).

UADT cancer

In a nested case-control study among American men of Japanese ancestry (Nomura, 1997), 28 oesophageal, 23 laryngeal, and 16 oral/pharyngeal cancer cases identified during 20 years and were matched to 138 controls. Mean serum levels of total carotenoids were lower in cases than in controls (82.9 µg/dl and 96.7 µg/dl, respectively, P-dif= 0.004) as similar difference was observed for alpha-Carotene, beta-Carotene and beta-Cryptoxanthin. Lower mean values, although not significantly, were also observed in cases of oral/pharyngeal cancer (p= 0.20, 18 cases) and laryngeal cancer (p= 0.07, 23 cases) compared to controls.

5.5.1.2 Dietary carotenoids

Cohort studies

Summary

One study on UADT cancer was identified in the 2005 SLR and no study was identified in CUP.

UADT cancer

In the IWHS (Zheng, 1995), no association was observed between carotene intake and oral/pharyngeal/oesophageal cancers (RR for >9.27 UI vs 8.62 UI=0.70; 95% CI 0.30-1.80; p-trend=0.44).

Pooled analysis of case-control studies

The relationship of dietary carotenoids and head and neck cancer was investigated in the INHANCE consortium of case-control studies. The pooled analysis from 10 case-control

studies included 4 144 cases with oral and pharyngeal cancer, 1 545 with laryngeal cancer and 12 248 controls (Leoncini, 2015).

Oral/pharyngeal cancer

Oral and pharyngeal cancer risk was inversely related to dietary intake of total carotenoids (pooled OR for the highest compared to the lowest quintile 0.61; 95% CI 0.53-0.71 p-trend< 0.001), beta-carotene equivalents (OR for same comparison levels 0.52; 95% CI 0.40-0.67, p-trend< 0.001) and beta-cryptoxanthin (OR 0.62; 95% CI 0.52-0.74; p-trend< 0.001). When oral and pharyngeal cancers were evaluated separately, the inverse association with carotenoids persisted (data not shown in the publication).

Substantial heterogeneity was detected across strata of alcohol consumption for total carotenoids (p< 0.01), with a stronger inverse association for heavy drinkers. The ORs for the fifth quintile compared to the first one were 0.79 (95 %CI 0.64–0.97) for never or light drinkers, 0.54 (95 % CI 0.42–0.70) for moderate drinkers, and 0.40 (95 % CI 0.29–0.56) for heavy drinkers. There was no statistical evidence of heterogeneity of the association with total carotenoids across strata by smoking status.

No heterogeneity across strata of alcohol consumption or smoking status was observed for beta-carotene equivalents.

Laryngeal cancer

Laryngeal cancer risk was inversely related to dietary intake of total carotenoids (pooled OR for the highest compared to the lowest quintile 0.61; 95% CI 0.50-0.76 p-trend <0.001), beta-carotene equivalents (OR for same comparison levels 0.55; 95% CI 0.43-0.71, p-trend< 0.001) and beta-cryptoxanthin (OR 0.73; 95% CI 0.59-0.89; p-trend< 0.001).

Substantial heterogeneity was detected across strata of alcohol consumption for total carotenoids (p=0.46), with a stronger inverse association for moderate and heavy drinkers. The ORs for the fifth quintile compared to the first one were 0.92 (95 %CI 0.64–1.31 for never or light drinkers, 0.58 (95 % CI 0.41–0.81) for moderate drinkers, and 0.42 (95 % CI 0.27–0.65) for heavy drinkers. There was no statistical evidence of heterogeneity of the association with total carotenoids across strata by smoking status.

No heterogeneity across strata of alcohol consumption or smoking status was observed for beta-carotene equivalents.

5.5.2 Non-provitamin A carotenoids

Cohort studies

Summary

One study on oral/pharyngeal cancer was identified in 2005 SLR and no studies were identified in CUP.

Serum levels of non-provitamin A carotenoids

Oral/pharyngeal cancer

A nested case-control study within adults in Washington County (Zheng, 1993) including 28 individuals who developed oral and pharyngeal cancer and 112 matched controls reported OR 0.61; p-trend 0.37 and OR 0.65; p-trend 0.46 for the comparison of the highest and the lowest tertiles of serum levels of lutein and lycopene, respectively.

Pooled analysis of case-control studies

The relationship of dietary carotenoids and head and neck cancer was investigated in the INHANCE consortium of case-control studies. The pooled analysis from 10 case-control studies included 4 144 cases with oral and pharyngeal cancer, 1 545 with laryngeal cancer and 12 248 controls (Leoncini, 2015).

Lycopene

Oral/pharyngeal cancer

Oral and pharyngeal cancer risk was inversely related to dietary intake of lycopene (pooled OR for the highest compared to the lowest quintile 0.82; 95% CI 0.71-0.94 p-trend= 0.043) and lutein plus zeaxanthin (OR 0.66; 95% CI 0.54-0.80; p<0.001). When oral and pharyngeal cancers were evaluated separately, the inverse association of carotenoids persisted (data not shown in the publication).

Heterogeneity was detected across strata of alcohol consumption for lycopene (p= 0.05), for which the association was observed only in alcohol drinkers. The ORs for the fifth quintile compared to the first one were 0.95 (95% CI 0.77–1.17) for never or light drinkers, 0.79 (95% CI 0.63–0.99) for moderate drinkers, and 0.68 (95% CI 0.48–0.95) for heavy drinkers. There was no statistical evidence of heterogeneity of the association with beta-carotenes across strata of smoking status.

Laryngeal cancer

Laryngeal cancer risk was inversely but not significantly related to dietary intake of lycopene (pooled OR for the highest compared to the lowest quintile 0.83; 95% CI 0.68-1.02, p-trend =0.25) but a significant association was observed for lutein plus zeaxanthin (OR 0.68; 95% CI 0.55-0.84; p<0.001).

The relationship with lycopene did not vary across strata of several covariates. The association of lutein plus zeaxanthin was not modify by smoking status, but it was stronger in younger adults (<55 years) than in older (>55 years) (P-heterogeneity= 0.036).

5.5.3 Folates and associated compounds

Cohort studies

Summary

No cohort study was identified in 2005 SLR and CUP. The pooled analysis of case-control studies (INHANCE) investigated total folate intake and folate intake from natural sources only and risk of oral cavity and pharyngeal cancer (Galeone, 2015).

Pooled analysis of case-control studies

In the INHANCE consortium, total folate intake (10 studies, 13 249 controls) was significantly related to decreased risk of oral and pharyngeal cancer (5 127 cases) and oral cavity cancer (1 613 cases) (HvsL OR 0.65; 95% CI 0.43-0.99, p-trend= 0.04; OR 0.57; 95% CI 0.43-0.75, p-trend<0.01, respectively), whereas a non-significant inverse association was found for oro/hypopharyngeal cancer (2 571 cases) (OR 0.74; 95% CI 0.42-1.30, p-trend=0.28). Highest versus lowest analyses for folate intake from natural sources revealed (8 studies, 11 805 controls) an inverse non-significant association for oral and pharyngeal (3 910 cases) and oro/hypopharyngeal cancer (2 035 cases) (OR 0.72; 95% CI 0.46-1.14, p-trend=0.08; OR 0.79; 95% CI 0.44-1.43, p-trend=0.19, respectively). Inverse significant association was found for oral cavity cancer (1 152 cases) (OR 0.64; 95% CI 0.45-0.91, p-trend<0.01). There was significant heterogeneity between studies (p< 0.1) for oral and pharyngeal and oro/hypopharyngeal cancer. Total folate intake was inversely related to oral and pharyngeal cancer among heavy drinkers (431 cases) and heavy tobacco users (696 cases). The pooled ORs for the highest versus lowest comparisons were 0.59 (95% CI 0.39-0.90, p-heterogeneity between studies<0.01) and 0.55 (95% CI 0.43-0.71, p-heterogeneity between studies=0.47). Analyses were adjusted for age, gender, race/ethnicity, education, study, cigarette smoking, alcohol intake and total energy intake (as appropriate).

5.5.10 Vitamin D (and calcium)

Cohort studies

Summary

No cohort study was identified in 2005 SLR. Three cohort studies (on oral cavity, pharynx, larynx and HNC) were identified in CUP.

<u>Oral cavity</u>

In a nested case-control study among participants of the ATBC study (Arem, 2011), the OR of oral cavity cancer (134 cases) were 1.35 (95% CI 0.53–3.43) for >=75 nmol/L and 0.88; 95% CI 0.39-1.98 for <25 nmol/L compared to serum levels of 50-<75 nmol/L.

Pharynx

In a nested case-control study among participants of the ATBC study (Arem, 2011), the OR of pharyngeal cancer (48 cases) were 3.61; 95% CI 0.28-45.93 for >=75 nmol/L and and 1.07; 95% CI 0.20-5.64 for <25 nmol/L compared to serum levels of 50-<75 nmol/L.

Larynx

In a nested case-control study among participants of the ATBC study (Arem, 2011), the OR of laryngeal cancer (158 cases) were 2.50; 95% CI 0.61-10.25 for >=75 nmol/L and and 0.92; 95% CI 0.40-2.13 for <25 nmol/L compared to serum levels of 50-<75 nmol/L.

Head and Neck cancer

In a cohort including the population-based studies Monica10, Inter99 and Health2006 (Skaaby, 2014) high serum levels of vitamin D were not associated with HNC risk (HR per 10 nmol/l =0.97; 95% CI, 0.84–1.12).

In a population-based cohort from the Copenhagen City Heart study (Afzal, 2013), decreasing 25(OH)D concentrations were associated with increasing cumulative incidence of HNC. The hazard ratio for 50% reduction in plasma 25(OH)D was 1.44; 95% CI 1.19-1.73.

In a nested case-control study among participants of the ATBC study (Arem, 2011), the OR of head and neck cancer (348 cases) were 1.35; 95% CI 0.53-3.43 for >=75 nmol/L and 0.96; 95% CI 0.58-1.59 for <25 nmol/L compared to serum levels of 50-<75 nmol/L.

5.5.11 Vitamin E

Supplements

Randomised controlled trial

Summary

No randomised controlled trial was identified in the 2005 SLR and one randomised controlled trial was identified in CUP: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study (Wright, 2007). Wright et al, 2007 examined whether daily supplementation with 50 mg dl alpha-tocopheryl acetate and/or 20 mg beta-carotene reduced the incidence of or mortality from oral/pharyngeal, and laryngeal cancers in the ATBC study, a double-blind, placebo-controlled primary prevention trial conducted in Finland. A total of 29 133 male smokers, aged 50–69 years and free of cancer at baseline, were randomized in a 2 x 2 factorial design to the supplementation regimen for 5–8 years (median, 6.1 years). Incident cancers of the oral cavity and pharynx (n = 65) and larynx (n = 56) were identified through the Finnish Cancer Registry. Alpha-tocopherol supplementation (AT) did not have any significant effect on the incidence and mortality from cancers of the mouth larynx and pharynx.

Oral/pharyngeal cancer

In the ATBC study, the RR in the group with AT supplementation compared to no AT were 0.97; 95% CI 0.60-1.58 and RR 1.84; 95% CI 0.68-4.97,

Laryngeal cancer

In the ATBC study the RR in the group with AT supplementation compared to no AT were RR 0.93; 95% CI 0.55-1.58 and RR 0.67; 95% CI 0.19-2.37) for incidence and mortality of laryngeal cancer respectively (Wright, 2007).

Blood levels

Cohort studies

Summary

Three cohort studies (on oral and UADT cancer) were identified in 2005 SLR and no study was identified in CUP. Dose-response meta-analysis was not conducted.

Oral cancer

In a nested case-control study within adults in Washington County (Zheng, 1993) serum levels of alpha-Tocopherol were inversely associated with risk of oral cancer (RO for highest compared to lowest 0.31; p-trend 0.07), while serum levels of gamma-Tocopherol were positively associated (RO for highest vs lowest 4.04; p-trend 0.05). Serum levels of total tocopherol were not significantly associated with oral cancer (RO 0.89; p-trend 0.75).

UADT cancer

A nested case-control study among Japanese American men (Nomura, 1997), revealed that serum levels of gamma-Tocopherol were not significantly inversely associated with UDAT cancer (OR for highest vs lowest 0.69; 95% CI 0.26-1.87).

Diet

UADT cancer

In the IWHS (Zheng, 1995) there was a non-significant inverse association between higher intake of vitamin E and UADT cancer (RR 0.80; 95% CI 0.30-2.00).

5.6 Minerals

5.6.3 Calcium (and Vitamin D)

Supplement

Randomised controlled trial

Summary

No randomised controlled trial was identified in the 2005 SLR and one randomised controlled trial was identified in CUP.

The WHI trial examined the association between supplementation of calcium (1000mg) and vitamin D3 (400IU) and cancer mortality and incidence in postmenopausal women (Brunner, 2011). There was no significant effect of Ca and Vit D3 supplementation on oral cancer (HR 1.43; 95% CI 0.51-4.02), cancer of the lip/oral cavity/pharyngeal cancer (HR 1.33; 95% CI 0.61-2.89) or pharyngeal cancer (HR 1.45; 95% CI 0.24-8.69).

Cohort studies

Summary

No study was identified in the 2005 SLR and one study on HNC was identified in CUP.

In the NHI-AARP Diet and Health study (Park, 2009) supplementary calcium intake was not associated with HNC in men and women (RR 1.18; 95% CI 0.81-1.73; RR 1.05; 95% CI 0.72-1.53).

Dietary calcium

Cohort studies

Summary

One study on UADT cancer was identified in the 2005 SLR and one study on HNC was identified in CUP.

Head and Neck cancer

In the NHI-AARP Diet and Health study (Park, 2009) the HR for the comparison of the highest to the lowest intake of dietary calcium was 0.78; 95% CI 0.64-0.96 in men and 1.03; 95% CI 0.72-1.47 in women.

Highest intake of total calcium (intake of calcium form food and supplements combined) was not associated with HNC in men (RR 0.99; 95% CI 0.81-1.21), while in women a non-significant increased risk for HNC was suggested (RR 1.30; 95% CI 0.91-1.86).

UADT cancer

In a Japanese-American cohort (Chyou, 1995) a non-significant inverse association for UADT cancer was found when comparing consumption of more than 555mg per day of total calcium less than 335mg per day (RR 0.67; 95% CI 0.38-1.17).

6 Physical activity

6.1.1.2 Recreational physical activity

Cohort studies

Summary

No study was identified in the 2005 SLR. Five publications from three cohort studies on the relationship of non-occupational physical activity with risk of cancers of oral cavity, pharynx and larynx (Leitzmann, 2008); HN (Hashibe 2013; Leitzmann, 2008; Yun 2008) and UADT (Arem, 2014; Wannamethee, 2001) had been identified in CUP.

In the NIH-AARP Diet and Health Study, the questionnaire assessed frequency each week spent at activities that lasted 20 min or more and caused either increases in breathing or heart rate or working up a sweat. Participants were men and women aged 55-70 years at baseline (Leitzmann, 2008; Arem, 2014). The analyses included as covariates age, gender, body mass index, a combination of smoking status, time since quitting for former smokers and smoking intensity for former and current smokers, race/ethnicity, education, marital status, family history of cancer, intakes of fruit and vegetables combined red meat, and alcohol.

In the PLCO trial hours of vigorous physical activity at age 40 years and at baseline were assessed only in the intervention group and 177 cases with data on physical activity were identified during follow-up, ten years after screening ended (Hashibe 2013). The analyses were adjusted by age, sex, education, race, alcohol drinking, and tobacco pack-years.

In the British Regional Heart Study (BRHS) men aged 40-59 years were asked their pattern of non-occupational physical activity, including regular walking or cycling, sporting (vigorous) activity and recreational activity - gardening, pleasure walking and Do-it-Yourself jobs (Wannamethee, 2001). The analyses were adjusted for age, cigarette smoking, BMI, alcohol intake and social class.

In the large, population-based Korean male cohort, leisure time physical activity refereed to vigorous, sweat producing activity (Yun ,2008) The analyses were adjusted by age, dietary preference, smoking status, alcohol drinking, body mass index, and employment.

Oral cavity

In the NIH-AARP physical activity (five or more times per week compared with none) was not related to cancers of the oral cavity (RR 0.98; 95% CI 0.75-1.29, p-trend 0.956, 525 cases) (Leitzmann, 2008).

Pharyngeal cancer

In the NIH-AARP physical activity (five or more times per week compared with none) was inversely but not significantly related to cancers of the pharynx (RR 0.70; 95% CI 0.45-1.08, p-trend 0.180, 236 cases) (Leitzmann, 2008).

Laryngeal cancer

In the NIH-AARP, physical activity (five or more times per week compared with none) was inversely but not significantly related to cancers of the larynx (RR 0.82; 95% CI 0.59-1.13, p-trend 0.225, 406 cases) (Leitzmann, 2008)

Head and Neck cancer

In the PLCO study, individuals spending 3 or more hours per week on vigorous activity had a significant reduction in head and neck cancer risk compared to those with less than one hour/week of vigorous activity (RR 0.58; 95% CI 0.35–0.96 p-trend 0.03). The RR for the same comparison for vigorous activity at age 40 was 0.69 0.42–1.14 p-trend 0.15) (Hashibe 2013).

In the NIH-AARP, physical activity (five or more times per week compared with none) was not significantly related to cancers of the head and neck (RR 0.89; 95% CI 0.74-1.06, p-trend 0.272, 1249 cases) (Leitzmann, 2008).

In the population-based Korean male cohort (Yun, 2008), leisure-time physical activity was not related to head and neck cancer risk (685 cases). The RR comparing moderate-high to low physical activity was 0.96; 95% CI 0.83-1.12. No significant associations were found in never/former smokers and current smokers (RR 1.17; 95% CI 0.91-1.51; RR 0.87; 95% CI 0.71-1.05, respectively for the same comparison).

UADT cancer

In the BRHS study (Wannamethee, 2001), physical activity was inversely related to risk of oral/oesophageal cancers (65 cases). The RR were 0.31 (0.10, 0.99) for moderate-vigorous physical activity and 0.46 (0.11, 1.90) for vigorous activity compared to none to moderate activity (P trend 0.05). Also, the HR was 0.56 (0.32, 0.96) for sporting activity more than once /month compared to less than that. Regular walking was not related to risk of UADT (RR more than 60 min/day vs less than 20 min/day= 0.97; 95% CI 0.39, 2.42).

Pooled analysis of case-control studies

In the INHANCE pooled analysis of four case-control studies, including 2 289 HNC cases and 5 580 controls, recreational physical activity was associated with lower risk of head and neck cancer (Nicolotti, 2011). The pooled ORs for high compared to none or very low recreational physical activity levels were 0.53, 95% CI: 0.32- 0.88 for oral cavity and 0.58, 95% CI: 0.38- 0.89 for pharynx. Significant inverse associations were also observed when comparing moderate to low-none activity. However, a positive association with larynx cancer was found for high compared to low-none activity (OR 1.73, 95% CI: 1.04- 2.88). The positive association may be due to residual confounding by tobacco as a higher proportion of laryngeal cancers with high physical activity levels are cigarette smokers (indicated by the authors of the publication but data not shown).

8 Anthropometry

8.1.1 BMI

Cohort studies

Summary

No study was identified in 2005 SLR and seven studies (on oral, oropharyngeal, oro/ hypopharyngeal, laryngeal, oral cavity/ hypo-pharyngeal/ laryngeal, oral/ pharyngeal/ laryngeal, HN and UADT cancer) were identified in CUP. In addition, the National Cancer Institute (NCI) Cohort Consortium (Gaudet, 2015) analysed individual-level pooled data from 20 cohort studies on HNC with a total of 1 941 300 participants including 3 760 cases. HRs were adjusted for age, sex, genetic ancestry, cohort, education, alcohol drinking status and smoking status (as appropriate). Furthermore, the pooled analysis of individual participant data from 39 cohort studies (within the Asia-Pacific Cohort Studies Collaboration (APCSC)), with a total of 424 519 participants and 4 872 cases, investigated BMI and cancer mortality (Paar, 2010). Models were stratified by study and sex and were adjusted for age and smoking.

Oral cancer

The NCI cohort consortium (Gaudet, 2015), revealed that per 5kg/m^2 increment of BMI there was a non-significant association with oral cavity cancer in never smokers (HR 1.10; 95% CI 0.97-1.25, p-trend=0.14).

A population-based cohort using data from the UK Clinical Practice Research Datalink (CPRD) (Bhaskaran, 2014), showed a significant inverse association of BMI with oral cavity cancer in the total population (HR for 5kg/m^2 increase 0.81; 99% CI 0.74-0.89). However, analysis in never smokers showed no association (HR 1.07; 99% CI 0.91-1.26).

The NIH-AARP Diet and Health study (Etemadi, 2014) showed a non-significant inverse association of SCC of oral cavity when comparing obese to “normal” BMI participants (HR 0.76; 95% CI 0.52-1.11). No significant association was found when comparing underweight with normal weight participants (HR 0.88; 95% CI 0.22-3.57). Stratified analysis by smoking status found significant inverse association among current smokers (0.70 (0.50-0.98)) but non-significant for never and former smokers (0.95 (0.69-1.32), 0.91 (0.72-1.16), respectively). This study was included in the NCI Pooling Project; Gaudet, 2015.

Table 26. BMI and oral cavity cancer risk. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Gaudet, 2015	20 cohorts	298	North America, Europe and Asia	Incidence, Oral cavity cancer	Per 5 kg/m^2 Never smokers	1.10 (0.97-1.25)	0.14	0.01

Oropharyngeal cancer

The NCI cohort consortium (Gaudet, 2015), showed a positive significant association per 5kg/m^2 increment of BMI with oral/pharyngeal NOS cancer in never smokers (HR 1.36; 95% CI 1.11-1.66, p-trend=0.003).

Incidence analyses in the CPS-II Nutrition Cohort showed no significant associations between BMI and oropharyngeal cancer (Gaudet, 2012). More specifically, no association was reported when comparing underweight (<22.5kg/m^2) and obese participants (BMI ≥30.0kg/m^2) to normal weight participants (HR 0.99; 95% CI 0.45-2.16; HR 0.89; 95% CI 0.38-2.09, p-trend= 0.74). Analyses were adjusted for sex, education level, alcohol intake and cigarette smoking at baseline and age at enrolment. Regarding mortality analyses, no association was found between oropharyngeal cancer and obese participants compared to normal weight participants (HR 1.00; 95% CI 0.57-1.74). Underweight participants showed a non-significantly increased risk for oropharyngeal mortality compared to normal weight participants (HR 1.35; 95% CI 0.91-2.02). HRs were additionally adjusted for joint smoking variable of status at baseline, years since last cigarette and cigarettes per day (This study was included in the NCI Pooling Project; Gaudet, 2015).

Table 27. BMI and oral/pharyngeal cancer risk. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Gaudet, 2015	20 cohorts	93	North America, Europe and Asia	Incidence, Oral/pharyngeal NOS cancer	Per 5 kg/m^2 Never smokers	1.36 (1.11-1.66)	0.003	0.01

Oro/hypopharyngeal cancer

In the NCI cohort consortium (Gaudet, 2015), no association was found for oropharyngeal cancer and hypopharyngeal cancer per 5 kg/m^2 increment of BMI in never smokers (HR 0.98; 95% CI 0.84-1.14, p-trend=0.77; HR 0.96; 95% CI 0.55-1.67, p-trend=0.88, respectively).

Inverse non-significant association of BMI with oro/hypopharyngeal SCC was observed when comparing obese with normal weight in the NIH-AARP Diet and Health study (Etemadi, 2014) (HR 0.61; 95% CI 0.31-1.18). An increased risk was observed in underweight participants compared to normal weight (HR 4.20; 95% CI 1.28-13.81). Analyses were adjusted for age, sex, marital status, cigarette smoking, education, ethnicity, alcohol consumption, physical activity, and fruit and vegetable intake and BMI. Stratified analysis by smoking status showed that there was a significant inverse association only observed among current smokers (HR for 5 kg/m^2 increment 0.44; 95% CI 0.26-0.76) but not in never or former smokers (HR 0.63; 95% CI 0.29-1.36; HR 0.92; 95% CI 0.63-1.34, respectively) (This study was included in the NCI Pooling Project; Gaudet, 2015).

Table 28. BMI and oro/hypopharyngeal cancer risk. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Gaudet, 2015	20 cohorts	241 22	North America, Europe and Asia	Incidence, Oropharyngeal Hypopharyngeal cancer	Per 5 kg/m^2 Never smokers	0.98 (0.84-1.14) 0.96 (0.55-1.67)	0.77 0.88	0.01

Laryngeal cancer

The NCI cohort consortium (Gaudet, 2015) revealed a positive significant association for laryngeal cancer per 5 kg/m^2 increment of BMI in never smokers (HR 1.42; 95% CI 1.19-1.70, p-trend=0.0001).

In a cohort of Swedish men (Samanic, 2006), BMI was not related to laryngeal cancer (RR for obese compared to normal weight 0.94; 95% CI 0.57-1.56). Analyses were adjusted for age, calendar year and smoking status.

No association of BMI with laryngeal cancer was observed when comparing obese with normal weight in the NIH-AARP Diet and Health study (Etemadi, 2014) (HR 1.04; 95% CI 0.70-1.55). Analyses were adjusted for age, sex, marital status, cigarette smoking, education, ethnicity, alcohol consumption, physical activity, and fruit and vegetable intake and BMI. In stratified analysis by smoking status the HR for 5 kg/m^2 increment were 0.90; 95% CI 0.67-1.21 among current smokers, 1.54; 95% CI 0.86-2.75 in never smokers and 1.02; 95% CI 0.67-1.21 in former smokers, respectively (This study was included in the NCI Pooling Project; Gaudet, 2015).

Table 29. BMI and laryngeal cancer risk. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Gaudet, 2015	20 cohorts	142	North America, Europe and Asia	Incidence, Laryngeal cancer	Per 5 kg/m^2 Never smokers	1.42 (1.19-1.70)	0.0001	0.01

Oropharyngolaryngeal cancer

In the APCSC pooling project (Parr, 2010), the pooled HR per five unit increment of BMI was 0.66 (0.46-0.95). There was a decreased non-significant risk for both the highest BMI category and underweight category compared to the normal BMI category (HR 0.56; CI 95% 0.23-1.41; HR 0.86; 95% CI 0.34-2.19, respectively, p-trend= 0.09).

In the CPS-II Cohort (Gaudet, 2012), incidence analyses showed that BMI was not significantly associated to oral cavity/hypo-pharyngeal/laryngeal cancer. HRs for underweight (<22.5kg/m^2) and obese (≥30.0kg/m^2) participants compared to normal weight participants were 1.06 (0.73-1.55) and 1.11 (0.74-1.64) respectively, with p-trend 0.34. Analyses were adjusted for sex, education level, alcohol intake and cigarette smoking status at baseline and age at enrolment. Mortality analyses revealed an inverse significant association between BMI and oral cavity/hypo-pharyngeal/laryngeal cancer for obese and overweight participants compared to normal weight participants (HR 0.74; 95% CI 0.59-0.95; HR 0.75; 95% CI 0.64-0.86, respectively). A positive significant association was found for underweight participants compared to normal weight participants (HR 1.28; 95% CI 1.10-1.50). HRs were additionally adjusted for joint smoking variable of status at baseline, years since last cigarette and cigarettes per day.

In a cohort of alcoholic Japanese men (Yokoyama, 2006) BMI was non-significantly inversely associated with oropharyngolaryngeal (HR for BMI ≥23.2 kg/m^2 compared to ≤18.9 kg/m^2= 0.31; 95% CI 0.08-1.11). Analyses were adjusted for age.

Table 30. BMI and oropharyngeal/laryngeal cancer risk. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Parr, 2010	39 cohorts	159	Asia and Australia/ New Zealand	Mortality, Oropharyngeal-laryngeal cancer	Per 5 units*	0.66 (0.46-0.95)		Not reported
					30.0-60.0 vs 18.5-24.9 kg/m^2	0.56 (0.23-1.41)	0.09	
					12.0-18.4 vs 18.5-24.9 kg/m^2	0.86 (0.34-2.19)		

*Trend≥18.5 kg/m^2.

Head and Neck cancer

In the NCI cohort consortium (Gaudet, 2015), per 5kg/m^2 increment of BMI an inverse significant association was found with HNC (HR 0.94; 95% CI 0.90-0.98). Similarly, comparisons of obese (≥30kg/m^2) compared to normal weight participants (21-<23kg/m^2) revealed an inverse significant association with HNC (HR 0.85; 95% CI 0.76-0.96, p-trend=0.003), while underweight participants (15-<21kg/m^2) showed a positive significant association (HR 1.28; 95% CI 1.11-1.46). P-trend was calculated excluding underweight category. Stratified analysis by smoking status showed that per 5kg/m^2 increment there was a positive significant association in never smokers (HR 1.15; 95% CI 1.06-1.24), an inverse significant association in current smokers (HR 0.76; 95% CI 0.71-0.82) and no association in former smokers (HR 0.99; 95% CI 0.93-1.06). Similar results were found for the highest versus normal weight comparisons (HR 1.40; 95% CI 1.08-1.81, p-trend=0.0006; HR 0.58; 95% CI 0.47-0.72, p-trend<0.0001; HR 0.96; 95% CI 0.79-1.18, p-trend=0.79, respectively).

Inverse non-significant association of BMI with HN SCC was observed when comparing obese with normal weight in the NIH-AARP Diet and Health study (Etemadi, 2014) (HR 0.85; 95% CI 0.67-1.08). A non-significant increased risk was observed in underweight participants compared to normal weight (HR 1.70; 95% CI 0.84-3.46). Analyses were adjusted for age, sex, marital status, cigarette smoking, education, ethnicity, alcohol consumption, physical activity, and fruit and vegetable intake. Stratified analysis by smoking status showed that there was a significant inverse association only observed among current smokers (HR for 5 kg/m^2 increment 0.76; 95% CI 0.63-0.93) but not in never or former smokers (HR 0.98; 95% CI 0.76-1.26; HR 0.94; 95% CI 0.80-1.10, respectively) (This study was included in the NCI Pooling Project; Gaudet, 2015).

Inverse non-significant association of BMI with HNC was observed when comparing obese with normal weight in the PLCO cohort (Hashibe, 2013) (RR 0.72; 95% CI 0.47-1.10). A non-significant increased risk was observed in underweight participants compared to normal weight (RR 1.23; 95% CI 0.17-8.93). However there was only one case in the latter category. Analyses were adjusted for age, sex, race, education, drinking frequency and tobacco pack-years. Stratified analyses by smoking were not reported (This study was included in the NCI Pooling Project; Gaudet, 2015).

No association was found between BMI and HNC in CPS-II Nutrition Cohort (Gaudet, 2012) in incidence analyses (HR for obese compared to normal weight participants 1.06; 95% CI 0.74-1.52; HR for underweight compared to normal weight participants 1.05; 95% CI 0.75-1.47, p-trend= 0.90). Stratified analyses, showed that in never smokers there was no association between HNC and obese and underweight participants compared to normal weight participants (HR 0.89; 95% CI 0.39-2.06; HR 0.97; 95% CI 0.49-1.96, respectively), while in overweight participants a positive non-significant association was found (HR 1.32; 95% CI 0.76-2.30). P trend was 0.84. In ever smokers no association was found for obese and overweight participants compared to normal weight participants (HR 1.00; 95% CI 0.67-1.49; HR 0.91; 95% CI 0.67-1.23, respectively), while in underweight participants a positive non-significant association was found (HR 1.21; 95% CI 0.82-1.79, p-trend=0.40). All analyses

were adjusted for sex, education level, alcohol intake and cigarette smoking status at baseline and age at enrolment. In mortality analyses HNC was inversely and significantly associate with BMI in obese and overweight participants compared to normal weight participants (HR 0.78; 95% CI 0.63-0.97; HR 0.76; 95% CI 0.67-0.87, respectively). In underweight participants a positive and significant association was found (HR 1.28; 95% CI 1.11-1.47). Stratified analyses by smoking showed that in never smokers there was not a significant association between HNC and BMI (HR for obese 1.15; 95% CI 0.68-1.93; HR for overweight 1.07; 95% CI 0.74-1.56; HR for underweight 0.90; 95% CI 0.58-1.39, p-trend= 0.33). However among ever smokers an inverse significant association was found for obese and overweight participants (HR 0.68; 95% CI 0.53-0.89; HR 0.65; 95% CI 0.55-0.76, respectively). In underweight participants a positive significant association was found (HR 1.42; 95% CI 1.20-1.67). HRs were additionally adjusted for joint smoking variable of status at baseline, years since last cigarette and cigarettes per day (This study was included in the NCI Pooling Project; Gaudet, 2015).

Table 31. BMI and HN cancer risk. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Gaudet, 2015	20 cohorts	3 760	North America, Europe and Asia	Incidence, Head and Neck cancer	Per 5 kg/m^2			Not reported
					Total	0.94 (0.90-0.98)		
					Never smokers	1.15 (1.06-1.24)		
					Former smokers	0.99 (0.93-1.06)		
					Current smokers	0.76 (0.71-0.82)		
					≥30.0 vs 21-<23 kg/m^2			
					Total	0.85 (0.76-0.96)	0.003	
					Never smokers	1.40 (1.08-1.81)	0.0006	
					Former smokers	0.96 (0.79-1.18)	0.79	
					Current smokers	0.58 (0.47-0.72)	<0.0001	
					15.0-<21.0 vs 21.0-<23.0 kg/m^2			
					Total	1.28 (1.11-1.46)		
					Never smokers	1.17 (0.85-1.61)		
					Former smokers	1.24 (0.94-1.63)		
					Current smokers	1.30 (1.08-1.57)		

UADT cancer

The APCSC pooling project (Paar, 2010) revealed that, an increment of five units of BMI was inversely and significantly related to UADT cancer mortality, in participants with BMI greater than 18.5kg/m^2 (HR 0.78; 95% CI 0.62-0.98). However, the inverse association was not significant for the highest compared to normal BMI category (HR 0.69; 95% CI 0.38-1.24, p-trend= 0.07). For participants in the underweight category a non-significant positive

association was found with UADT cancer mortality, compared to the normal BMI category (HR 1.12; 95% CI 0.70-1.81).

In a cohort of alcoholic Japanese men (Yokoyama, 2006) a significant inverse association was observed when comparing the highest category of BMI (≥23.2 kg/m^2) to the lowest category (≤18.9 kg/m^2), (RR 0.28; 95% CI 0.09-0.85). Analyses were adjusted for age.

In a prospective cohort study in China (Chen, 2012) the hazard ratio of mortality for UADT cancer for 5 kg/m^2 of was 1·06 (95% CI 0·83−1·37) in men in the lower range of BMI (15 to <23.5kg/m^2) and 0·87 (95% CI 0·51−1·50) in men in the higher range of BMI (23.5 to <35kg/m^2). Analyses were adjusted for smoking.

Table 32. BMI and UADT cancer risk. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Parr, 2010	39 cohorts	388	Asia and Australia/ New Zealand	Mortality, UADT cancer	Per 5 units*	0.78 (0.62-0.98)		Not reported
					30.0-60.0 vs 18.5-24.9 kg/m^2	0.69 (0.38-1.24)	0.07	
					12.0-18.4 vs 18.5-24.9 kg/m^2	1.12 (0.70-1.81)		

*Trend≥18.5 kg/m^2.

Pooled analysis of case-control studies

The INHANCE consortium (Lubin, 2011) analysed individual-level pooled data from 15 case–control studies (2 441 oral cavity cancer cases, 2 297 oropharyngeal cancer cases, 508 hypopharyngeal cancer cases and 1 740 laryngeal cancer cases). Depending on analysis controls numbered from 7 604 to 13 829. ORs were adjusted for age, sex, education, type of tobacco product used, pack-years of smoking, cigarettes per day, years since cessation of smoking, drink-years and drinks per day.

No significant associations were found for oral cavity when comparing participants with BMI≥ 35.0 kg/m^2 with normal weight participants in both men and women (OR 0.65; 95% CI 0.4-1.10, p-trend <0.01; OR 0.92; 95% CI 0.50-1.60, p-trend< 0.01). Oropharyngeal and hypopharyngeal cancers were inversely and significantly related to BMI for both sexes (men: OR for BMI≥ 35.0 kg/m^2 vs BMI<18.5 kg/m^2 0.48; 95% CI 0.30-0.70; women: OR for BMI≥ 35.0 kg/m^2 vs BMI<18.5 kg/m^2 0.35; 95% CI 0.20-0.70; men: OR for BMI≥ 30.0-34.9 kg/m^2 vs BMI<18.5 kg/m^2 0.24; 95% CI 0.10-0.50; women: OR for BMI≥ 30.0-34.9 kg/m^2 vs BMI<18.5 kg/m^2 0.24; 95% CI 0.10-0.80, respectively). P-trend was <0.01 for all comparisons expect for hypopharyngeal cancer in men (p-trend=0.10). Laryngeal cancer revealed non-significant inverse association with BMI in men, while a significant inverse association was found in women (men: OR for BMI≥ 35.0 kg/m^2 vs BMI<18.5 kg/m^2 0.77; 95% CI 0.40-1.40; women: OR for BMI≥ 35.0 kg/m^2 vs BMI<18.5 kg/m^2 0.27; 95% CI 0.10-0.80, respectively). P-trend was <0.01 for both comparisons. Comparing underweight participants with normal weight participants showed a positive significant association for oral

cavity and oropharyngeal cancer in both men and women (men: OR 3.33; 95% CI 1.90-5.70; women: OR 2.54; 95% CI 1.70-3.80; men: OR 2.38; 95% CI 1.40-4.20; women: OR 3.09; 95% CI 1.80-5.20). Regarding hypopharyngeal cancer a positive significant association was found in men (OR 7.54; 95% CI 2.70-21.0), whereas in women a borderline positive association (OR 3.91; 95% CI 1.00-16.0). Comparisons for laryngeal cancer showed a borderline positive association in men (OR 1.77; 95% CI 1.00-3.30) and a non-significant positive association in women (OR 1.79; 95% CI 0.70-4.90).

8.2.1 Waist circumference

Cohort studies

Summary

No studies were identified in 2005 SLR. One study (NIH-AARP) on oral cavity, oro/hypo-pharyngeal, laryngeal and HN cancer was identified in CUP. In addition, the NCI Cohort Consortium (Gaudet, 2015) was found which analysed individual-level pooled data from 20 cohort studies regarding anthropometry and HNC and its cancer subsites with a total of 1 941 300 participants including 3 760 cases. HRs were adjusted for age, sex, genetic ancestry, cohort, education, alcohol drinking status and smoking status (as appropriate).

Per 5cm increment of WC controlling for BMI an increased association was found for HNC (HR 1.04; CI 1.03-1.05), while highest (WC for men ≥110cm; WC for women ≥90cm) versus lowest (WC form men <90cm; WC for women <70cm) analysis showed a borderline association (HR 1.02; 95% CI 1.00-1.04, p-trend= 0.10). Stratified analyses by smoking status showed positive significant associations per 5cm increment controlling for BMI (never smokers: HR 1.06; 95% CI 1.01-1.14; former smokers: HR 1.06; 95% CI 1.01-1.11; HR 1.04; 95% CI 1.02-1.05). Analyses by cancer site in never smokers showed that per 5cm increment had a positive significant association with oral cavity cancer (HR 1.09; 95% CI 1.03-1.16) while no association was found for hypopharyngeal, oropharyngeal, oral/pharyngeal NOS and laryngeal cancer (HR 0.91; 95% CI 0.70-1.20; HR 0.99; 95% CI 0.92-1.08; HR 1.07; 95% CI 0.95-1.21; HR 1.10; 95% CI 0.99-1.22, respectively).

Significant positive association was observed when comparing participants in the highest with those in the lowest quintile of waist circumference (WC) for cancers of the oral cavity (HR 2.00; 95% CI 1.24-3.23) and head and neck cancers (HR 1.42; 95% CI 1.04-1.93) but no significant association with laryngeal cancer (HR 0.98; 95% CI 0.58-1.66) and oro/hypo-pharyngeal cancer (HR 1.53; 95% CI 0.72-3.25) was observed. Only cancers with squamous histology were included in the analysis. All analyses were adjusted for age, sex, marital status, cigarette smoking, education, ethnicity, alcohol consumption, physical activity, and fruit and vegetable intake and BMI (Etemadi, 2014) (This study was included in the NCI Pooling Project; Gaudet, 2015).

Table 33. Waist circumference, HN cancer risk and its subsites. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Gaudet, 2015	20 cohorts	3 760	North America, Europe and Asia	Incidence, Head and Neck cancer	Per 5 cm* Total Never smokers Former smokers Current smokers	 1.04 (1.03-1.05) 1.07 (1.01-1.14) 1.06 (1.01-1.11) 1.04 (1.02-1.05)	 <0.0001 0.022 0.01 <0.0001	Not reported
					M≥110, W ≥90 vs M<90, W<70 cm Total Never smokers Former smokers Current smokers	 1.08 (0.93-1.25) 1.51 (1.09-2.08) 1.21 (0.94-1.55) 0.80 (0.62-1.04)	 0.10 0.007 0.06 0.18	
		179		Incidence, Oral cavity cancer	Per 5cm in never smokers	1.09 (1.03-1.16)	0.006	0.25
		13		Incidence, Hypopharyngeal cancer	Per 5cm in never smokers	0.91 (0.70-1.20)	0.51	
		145		Incidence, Oropharyngeal cancer	Per 5cm in never smokers	0.99 (0.92-1.08)	0.86	
		56		Incidence Oral/pharynx NOS	Per 5cm in never smokers	1.07 (0.95-1.21)	0.26	
		85		Incidence, Laryngeal cancer	Per 5cm in never smokers	1.10 (0.99-1.22)	0.08	

* Controlling for BMI

8.2.2 Hip circumference

Cohort studies

Summary

No studies were identified in 2005 SLR. One study (NIH-AARP) on oral cavity, oro/hypo-pharyngeal, laryngeal and HN cancer was identified in CUP. In addition, the NCI Cohort Consortium (Gaudet, 2015) was found which analysed individual-level pooled data from 20 cohort studies regarding anthropometry and HNC and its cancer subsites with a total of 1 941 300 participants including 3 760 cases. HRs were adjusted for age, sex, genetic ancestry, cohort, education, alcohol drinking status and smoking status (as appropriate).

The NCI pooling project revealed that per 5 cm increment of HC controlling for BMI no association was found with total HNC (HR 0.99; 95% CI 0.95-1.02) as well as among never

smokers and former smokers (HR 1.03; 95% CI 0.99-1.07; HR 0.99; 95% CI 0.94-1.05, respectively), while an inverse significant association was found for current smokers (HR 0.93; 95% CI 0.88-0.99). Highest (HC for men ≥115cm; HC for women ≥110cm) versus lowest (HC for men <95cm; HC for women <90cm) analysis for total HNC revealed an inverse significant association (HR 0.77; 95% CI 0.63-0.95, p-trend=0.02). Analyses by cancer site in never smokers showed a borderline association with oral cancer (HR 1.03; 95% CI 1.00-1.07), while no association was found for hypopharyngeal, oropharyngeal, oral/pharyngeal NOS and laryngeal cancer (HR 0.79; 95% CI 0.58-1.08; HR 1.03; 95% CI 0.93-1.14; HR 1.01; 95% CI 0.84-1.20; HR 1.06; 95% CI 0.93-1.22, respectively).

Non-significant positive association was observed when comparing participants in the highest with those in the lowest quintile of hip circumference (HC) for cancers of the oral cavity (HR 1.17; 95% CI 0.76-1.80). No association was observed with oro/hypopharyngeal SCC (HR 0.98; 95% CI 0.49-1.96), laryngeal cancer (HR 0.97; 95% CI 0.61-1.54) and head and neck cancers (HR 1.06; 95% CI 0.80-1.93). All analyses were adjusted for age, sex, marital status, cigarette smoking, education, ethnicity, alcohol consumption, physical activity, and fruit and vegetable intake and BMI (Etemadi, 2014) (This study was included in the NCI Pooling Project; Gaudet, 2015).

Table 34. Hip circumference, HN cancer risk and its subsites. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Gaudet, 2015	20 cohorts	3 760	North America, Europe and Asia	Incidence, Head and Neck cancer	Per 5 cm* Total Never smokers Former smokers Current smokers	 0.99 (0.95-1.02) 1.03 (0.99-1.07) 0.99 (0.94-1.05) 0.93 (0.88-0.99)	 0.42 0.18 0.77 0.02	Not reported
					M≥115, W ≥110 vs M<95, W<90 cm Total Never smokers Former smokers Current smokers	 0.77 (0.63-0.95) 1.10 (0.73-1.63) 1.01 (0.70-1.45) 0.46 (0.31-0.69)	 0.02 0.04 0.90 <0.0001	
		179		Incidence, Oral cavity cancer	Per 5cm in never smokers	1.03 (1.00-1.07)	0.04	0.56
		13		Incidence, Hypopharyngeal cancer	Per 5cm in never smokers	0.79 (0.58-1.08)	0.13	
		145		Incidence, Oropharyngeal cancer	Per 5cm in never smokers	1.03 (0.93-1.14)	0.55	
		56		Incidence Oral/pharynx NOS	Per 5cm in never smokers	1.01 (0.84-1.20)	0.92	
		85		Incidence, Laryngeal cancer	Per 5cm in never smokers	1.06 (0.93-1.22)	0.39	

* Controlling for BMI

8.2.3 Waist to hip ratio

Cohort studies

Summary

No studies were identified in 2005 SLR. One study (NIH-AARP) on oral cavity, oro/hypo-pharyngeal, laryngeal and HN cancer was identified in CUP. In addition, the NCI Cohort Consortium (Gaudet, 2015) was found which analysed individual-level pooled data from 20 cohort studies regarding anthropometry and HNC and its cancer subsites with a total of 1 941 300 participants including 3 760 cases. HRs were adjusted for age, sex, genetic ancestry, cohort, education, alcohol drinking status and smoking status (as appropriate).

The NCI pooling project showed that per 0.1 increment of WHR controlling for BMI a positive significant association was found with total HNC (HR 1.07; 95% CI 1.05-1.09) as

well as for the highest (WHR for men ≥1.00; WHR for women ≥0.85) versus lowest (WHR for men <0.90; WHR for women <0.75) comparison (HR 1.30; 95% CI 1.12-1.50, p-trend<0.0001). Among former smokers (HR 1.10; 95% CI 1.01-1.21) and current smokers (HR 1.08; 95% CI 1.04-1.12) similar results were found per 0.1 unit increment after controlling for BMI, while among never smokers no association was found (HR 1.06; 95% CI 0.93-1.11). Analyses by cancer site in never smokers showed that per 0.1 unit increment a positive significant association was found for oral cavity cancer (HR 1.17; 95% CI 1.02-1.34), no significant association was found for hypopharyngeal, oral/pharyngeal NOS and laryngeal cancer (HR 1.14; 95% CI 0.72-1.81; HR 1.17; 95% CI 0.86-1.60; HR 1.15; 95% CI 0.91-1.43, respectively) and an inverse significant association was found for oropharyngeal cancer (HR 0.73; 95% CI 0.54-0.99).

In the NIH-AARP (Etemadi, 2014), a significant positive association of cancers of the oral cavity with waist to hip ratio (WHR) was observed when comparing the highest with the lowest quintile of waist to hip ratio (HR 1.58; 95% CI 1.10-2.28). The association was significant among former smokers (HR for 0.1 unit increase 1.57; 95% CI 1.22-2.01) and positive but not significant in never or current smokers (HR 1.31; 95% CI 0.89-1.92; HR 1.25; 95% CI 0.89-1.75, respectively). Similar although non-significant results were observed for head and neck cancer. The HR for the highest compared to the lowest quintile of waist to hip ratio was 1.13; 95% CI 0.89-1.43. The association was significant among current smokers (HR for 0.1 unit increase 1.25; 95% CI 1.02-1.54) and positive but not significant in never or former smokers (HR 1.08; 95% CI 0.79-1.47; HR 1.14; 95% CI 0.95-1.37, respectively).

In contrast, inverse non-significant association with oro/hypopharyngeal SCC was observed (HR for highest vs lowest quintile =0.77; 95% CI 0.43-1.37). However, the association was positive among current smokers (HR for 0.1 unit increment 1.96; 95% CI 1.22-3.16), while the inverse association was restricted to never and former smokers a significant inverse association was observed (HR 0.38; 95% CI 0.16-0.94; HR 0.58; 95% CI 0.36-0.91, respectively). Waist to hip ratio was not related to laryngeal cancer (HR for highest vs lowest 1.01; 95% CI 0.67-1.52). The HR per 0.1U increase in WHR was 0.90; 95% CI 0.42-1.93 in never smokers; HR 1.09; 95% CI 0.80-1.51 in former smokers and 1.16; 95% CI 0.84-1.59, in current smokers.

Table 35. Waist to hip ratio, HN cancer risk and its subsites. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Gaudet, 2015	20 cohorts	3 760	North America, Europe and Asia	Incidence, Head and Neck cancer	Per 0.1unit*			Not reported
					Total	1.07 (1.05-1.09)	<0.0001	
					Never smokers	1.06 (0.93-1.11)	0.36	
					Former smokers	1.10 (1.01-1.21)	0.03	
					Current smokers	1.08 (1.04-1.12)	0.0001	
					M≥1.00, W ≥0.85 vs M<0.90, W<0.75			
					Total	1.30 (1.12-1.50)	<0.0001	
					Never smokers	1.23 (0.89-1.69)	0.2013	
					Former smokers	1.25 (0.98-1.59)	0.0351	
					Current smokers	1.38 (1.09-1.75)	0.0017	
		179		Incidence, Oral cavity cancer	Per 0.1 unit in never smokers	1.17 (1.02-1.34)	0.02	0.09
		13		Incidence, Hypopharyngeal cancer	Per 0.1 unit in never smokers	1.14 (0.72-1.81)	0.58	
		145		Incidence, Oropharyngeal cancer	Per 0.1 unit in never smokers	0.73 (0.54-0.99)	0.04	
		56		Incidence Oral/pharynx NOS	Per 0.1 unit in never smokers	1.17 (0.86-1.60)	0.32	
		85		Incidence, Laryngeal cancer	Per 0.1 unit in never smokers	1.15 (0.91-1.43)	0.24	

* Controlling for BMI

8.3.1 Height (and proxy measures)

Cohort studies

Summary

No studies were identified in 2005 SLR. Four publications from three cohort studies on oral cavity, mouth and pharynx, oro/hypopharyngeal, laryngeal and HN cancer (NIH-AARP, PLCO and MWS) were identified in CUP. In addition, the NCI Cohort Consortium (Gaudet, 2015) was found which analysed individual-level pooled data from 20 cohort studies regarding anthropometry and HNC and its cancer subsites with a total of 1 941 300 participants including 3 760 cases. HRs were adjusted for age, sex, genetic ancestry, cohort, education, alcohol drinking status and smoking status (as appropriate). Furthermore the INHANCE consortium pooling consortium was found (Leoncini, 2014).

The NCI pooling project (Gaudet, 2015) revealed that per 5cm increment in height a borderline association was found with total HNC (HR 1.02; 95% CI 1.00-1.05), while highest (for men ≥180cm; for women ≥170cm) versus lowest (for men <170cm; for women <160cm) analysis showed no significant association (HR 1.09; 95% CI 0.98-1.21, p-trend=0.07). Among never smokers and former smokers there was a positive significant association per 5 cm increment with HNC (HR 1.08; 95% CI 1.02-1.13; HR 1.05; 95% CI 1.01-1.09, respectively) and among current smokers an inverse significant association (HR 0.95; 95% CI 0.91-0.99). Analyses by cancer site among never smokers revealed no association for oral cavity, hypopharyngeal, oral/pharyngeal NOS and laryngeal cancer (HR 1.06; 95% CI 0.97-1.16; HR 1.01; 95% CI 0.74-1.37; HR 1.03; 95% CI 0.88-1.20; HR 1.02; 95% CI 0.90-1.15, respectively) per 5 cm height increment. A positive significant association was found for oropharyngeal cancer (HR 1.16; 95% CI 1.06-1.26).

In the NIH-AARP Diet and Health study (Etemadi, 2014) participants in the highest quintile of height compared to participants in the lowest quintile had a non-significant higher risk of SCC of the oral cavity (HR 1.31; 95% CI 0.92-1.86) and a significant increased risk of head and neck cancers (HR 1.34; 95% CI 1.06-1.69). Analyses were adjusted for age, sex, marital status, cigarette smoking, education, ethnicity, alcohol consumption, physical activity, and fruit and vegetable intake and BMI. No dose-response association with oral cancer was observed in another analysis in the same cohort. The risk increase for an increment of 10 cm in height was 1.08; 95% CI 0.98-1.18 in men and 0.97; 95% CI 0.82-1.16 in women (Kabat, 2014). Higher height was related to increased risk of SCC of oro/hypopharynx (HR for the highest compared to the lowest quintile 2.28; 95% CI 1.26-4.15), not related to cancer of the larynx (HR= 1.04; 95% CI 0.68-1.57) (Etemadi, 2014). All analyses were adjusted for age, sex, marital status, cigarette smoking, education, ethnicity, alcohol consumption, physical activity, and fruit and vegetable intake and BMI (This study was included in the NCI pooling project; Gaudet, 2015).

In the PLCO cohort (Hashibe, 2013) participants in the highest quintile of height had a non-significant decreased risk of HNC compared to participants in the lowest quintile (RR 0.81;

95% CI 0.40-1.63). Analyses were adjusted for age, sex, race, education, drinking frequency, and tobacco pack-years (This study was included in the NCI pooling project; Gaudet, 2015).

The MWS (Green, 2011) found no association per 10cm increase of height for mouth and pharynx cancer (RR 0.94; 95% CI 0.82-1.08; cases: 1095). Similarly, no association was found among never smokers and current smokers (RR 0.94; 95% CI 0.73-1.21, cases: 351; RR 0.89; 95% CI 0.71-1.11, cases: 443). RRs were adjusted for age, region, socioeconomic status, smoking, alcohol intake, BMI, strenuous exercise, age at menarche, parity and age at first birth (as appropriate).

Table 36. Height, HN cancer risk and its subsites. Results of a pooled analysis published after the 2005 SLR

Author Year	Number of studies	Cases	Country, area	Outcome	Comparison	HR (95% CI)	P-trend	Heterogeneity (I^2, p value)
Pooled analysis								
Gaudet, 2015	20 cohorts	3 760	North America, Europe and Asia	Incidence, Head and Neck cancer	Per 5cm Total Never smokers Former smokers Current smokers	 1.02 (1.00-1.05) 1.08 (1.02-1.13) 1.05 (1.01-1.09) 0.95 (0.91-0.99)	0.07 0.005 0.008 0.01	Not reported
					M≥180, W ≥170 vs M<170, W<160 Total Never smokers Former smokers Current smokers	 1.09 (0.98-1.21) 1.32 (1.05-1.66) 1.20 (1.01-1.43) 0.83 (0.70-0.98)		
		298		Incidence, Oral cavity cancer	Per 5cm in never smokers	1.06 (0.97-1.16)	0.18	0.38
		22		Incidence, Hypopharyngeal cancer	Per 5cm in never smokers	1.01 (0.74-1.37)	0.97	
		241		Incidence, Oropharyngeal cancer	Per 5cm in never smokers	1.16 (1.06-1.26)	0.0013	
		93		Incidence Oral/pharynx NOS	Per 5cm in never smokers	1.03 (0.88-1.20)	0.73	
		142		Incidence, Laryngeal cancer	Per 5cm in never smokers	1.02 (0.90-1.15)	0.78	

Pooled analysis of case-control studies

In the INHANCE consortium (Leoncini, 2014) of 24 case-control studies (17 666 cases and 28 198 controls) the risk of head and neck cancer was inversely and significantly related to higher adult height for both men and women (pooled OR per 10cm increment 0.91; 95% CI 0.86-0.95, p-heterogeneity=0.214; 0.86; 95% CI 0.79-0.93, p-heterogeneity=0.918, respectively). ORs were adjusted by education level, smoking status, cigarette duration, cigarette intensity and alcohol intensity.

Stratified analyses among men showed that ever drinkers had a significantly decreased risk for HNC (OR per 10cm increment 0.91; 95% CI 0.87-0.94) while for never drinkers a borderline inverse association was found (OR 0.89; 95% CI 0.79-1.00). Current and former men smokers showed an inverse significant association with HNC per 10cm of height increment (OR 0.84; 95% CI 0.79-0.89; OR 0.89; 95% CI 0.84-0.95) while no association was found for never smokers (OR 0.99; 95% CI 0.87-1.12). Similar results were reported among women (ever drinkers: OR 0.86; 95% CI 0.78-0.94; never drinkers: OR 0.91; 95% CI 0.81-1.03; current smokers: OR 0.81; 95% CI 0.71-0.92; former smokers: OR 0.74; 95% CI 0.62-0.89; never smokers: OR 0.90; 95% CI 0.79-1.02).

Analyses by cancer site in men revealed a significantly inverse risk for oral cavity (OR 0.87; 95% CI 0.81-0.92), oropharyngeal (OR 0.92; 95% CI 0.86-0.97), hypopharyngeal (OR 0.80; 95% CI 0.73-0.88) and laryngeal cancer (OR 0.93; 95% CI 0.87-0.99). In women inverse significant associations were found for oral cavity, oropharyngeal and hypopharyngeal cancer (OR 0.88; 95% CI 0.79-0.97; OR 0.79; 95% CI 0.70-0.90; OR 0.74; 95% CI 0.58-0.95, respectively), while no association was found for laryngeal cancer (OR 0.94; 95% CI 0.80-1.11). ORs were further adjusted for study centre.

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