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COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Consumption of Alcohol and Oral Cavity and/or Pharyngeal Cancer Risk

1. As part of the strategy proposed to consider the role of alcohol consumption and cancer risk, it was suggested that the COC review the epidemiological data on alcohol consumption and cancer. In 2007 (published IARC 2010), IARC reviewed the epidemiological evidence on the possible association between alcoholic beverage consumption and cancer at 27 anatomical sites (cancers of the oral cavity and the pharynx, larynx, oesophagus, liver, breast stomach, colon and/or rectum, pancreas, lung, urinary bladder, endometrium, ovary, uterine cervix, prostate, kidney, lymphatic and haematopoietic system, testis, brain, thyroid, melanoma and other female cancers (vulva and vagina). They re-affirmed their previous conclusion (IARC, 1988) that cancers of the upper digestive tract (oral cavity, pharynx, larynx, and oesophagus) and the liver are causally related to the consumption of alcoholic beverages. In addition, IARC considered that there was now sufficient evidence to conclude that cancer of the colo-rectum and female breast are causally related to the consumption of alcoholic beverages (IARC, 2010). Following another IARC review in 2009 (IARC 2012), IARC reaffirmed their position for the aforementioned cancers and also reported an association between alcohol consumption and cancer of the pancreas, although they were unable to reach a conclusion on whether this was causal.

Oral Cavity and Pharyngeal Cancer Statistics for the UK

2. Oral cancer represents a group of cancers that includes cancer of the lip, tongue mouth, (and the oropharynx, piriform sinus, hypopharynx and other ill-defined sites of the lip, oral cavity and pharynx – that are considered as part of the pharynx) (CRUK, 2014). Cancers of the nasopharynx are considered as part of other head and neck sites although they are often reported in the literature with oral cancers. Oral cancer is the 16th most common cancer in the UK (2011), accounting for 2% of all new cases. In males, it is the 12th most common cancer (3% of the male total), whilst it is 16th in females (1%). In 2011, approximately 6,767 people (4,510 men and 2,257 women) were diagnosed with oral cancer in the UK. One fifth of oral cancer cases diagnosed in the UK occur in people aged 75 and over. This proportion is lower in males (15%) than females (29%). The 50-74 age group contributes around 7 in 10 male oral cancer cases, and around 6 in 10 female cases. Oral cancer incidence rates in the UK have risen by a third in the last decade. Around 2,100 people died of oral cancer in 2012 in the UK. Around two-thirds of oral cancer deaths in the UK in 2012 were in men. Almost three-quarters (74%) of oral cancer deaths in the UK in 2012 were in people aged 60 and older. Oral cancer mortality rates have increased by around 10% in the last decade.

Oral Cavity and Pharyngeal Cancer Risk Factors

3. More than two-thirds of oral cancers in men and more than half in women in the UK were caused by smoking (CRUK, 2014). More than a third of oral cancers in men and around a sixth in women in the UK were linked to alcohol consumption. Infection with the human papillomavirus (HPV) increases risk of oral cancer, particularly in the oropharynx. Several other infections are also linked with increased (CRUK, 2014).

Mechanism of action of alcoholic beverages and oral cavity and pharyngeal cancers

4. Multiple explanations exist to describe how alcohol causes cancer, however the pathogenic mechanism is not clear largely due to the fact that ethanol has not been verified to be carcinogenic. An article by Ruiz et al (2004) provides an overview of the potential mechanisms for ethanol as a risk factor, both locally or systemically, in the development of oral cancer.

5. Local effects relate to ethanol's ability to:

- increase the penetration of carcinogens across the oral mucosa by either increasing their solubility, or by increasing the permeability of the mucosa by dissolving the lipid component of the epithelium that normally acts as a protective barrier;
- induce changes in mucosal morphology e.g. epithelial atrophy and decreased basal cell size, dysplastic changes with keratosis, increased density of the basal cell layer and a slightly increased number of mitotic figures;
- induce cellular damage by acetaldehyde leading to mutagenic and carcinogenic effects following interference of the synthesis and reparation of DNA; induction of exchanges between sister chromatids; production of gene mutations; inhibition of the enzyme O^6-methylguanitransferase (responsible for repairing injuries to DNA caused by alkylating agents); binding of cellular proteins and DNA resulting in morphological and cellular injury; potentiate the genotoxicity of other mutagenic, clastogenic (ability to disrupt chromosomal material) or carcinogenic agents;
- cause reduced salivary flow that prolongs the contact time of carcinogens with the mucosa, increasing the risk of cancer development.

6. Systemic effects relate to ethanol's ability to:

- affect the liver's ability to metabolise toxic or potentially carcinogenic compounds, resulting in an increased metabolism in extrahepatic tissues - this may play a contributing role in carcinogenesis;
- impair both the innate and acquired immune systems, resulting in increased susceptibility to infection and certain neoplasms;
- cause immunosuppression and subsequent malnutrition, vitamin deficiencies and hepatic cirrhosis, thought to be inversely associated with prevalence of oral cancer

Updated review of Alcohol consumption and oral cavity and pharyngeal Cancer

7. In the evaluation of the carcinogenicity of alcohol (IARC monograph 96, 2010 (Annex A) and IARC monograph 100e, 2012 (Annex B)), IARC state that alcohol causes oral cavity, pharyngeal and laryngeal cancer and classifies it as a group 1 definite carcinogen. Literature for the current review was obtained following a PubMed search and the search terms included alcohol, ethanol, drinking, consumption and oral cavity and pharyngeal cancer. Studies published since January 2008 to December 2014 were included in the retrieval to ensure all studies published on this topic since the last IARC review to date were considered. The current evaluation is restricted to data provided from meta-analyses, pooled analyses, cohort and case-control studies.

8. Each cohort and case-control study was assessed for quality using a modified scoring scheme similar to the Newcastle-Ottawa star scoring scheme. Pooled or meta-analyses were not scored. Information on alcohol consumption was extracted from all the relevant studies. Alcohol consumption categories varied between studies. For comparative purposes and to obtain a uniform variable for alcohol consumption, where possible, we calculated alcohol intake in terms of grams of ethanol/day. Information on adjustment factors used in the individual studies e.g. smoking, body mass index (BMI), obesity and caffeine intake were also extracted from the papers. All studies have been summarised in tables 1 – 6, which also contain further information on possible study limitations and details of the quality scores.

Meta- and combined analyses of alcohol consumption and oesophageal cancer risk and mortality and secondary events (Table 1)

Alcohol Consumption and oral cavity and pharyngeal Cancer Risk

9. Hashibe et al. (2009) conducted a pooled analysis of 17 ongoing or completed European and American case-control studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. They examined the effect of alcohol alone, tobacco alone and the interaction of both alcohol and tobacco on the risk of head and neck cancers including oral cavity and pharyngeal cancers. The population attributable risk (PAR) was also estimated for each cancer sub-site. NB. Only data relating to the independent effects of exposure to alcohol are summarised here. There were 2,992 oral cavity and 4038 pharyngeal cancer cases and 16152 oral cavity/pharyngeal controls included in the analysis (these figures changed depending on the variable being measured). Most studies used face-to-face interviews to collect information on drinking status, frequency of consumption, duration of consumption and types of alcoholic beverages consumed; a self-reported questionnaire was used in a study in Iowa. Referents were defined as never drinkers and data for drinkers who drank 1-2 drinks/day; ≥ 3 drinks/day were restricted to never smokers in this summary. Heterogeneity among the study ORs was determined via the likelihood ratio test and was consistently detected. Therefore, a two-stage random effects logistic regression model with between-study variability was used to pool data. Odds ratios (OR) and 95% CI were estimated using unconditional logistic regression models (common ORs via maximum likelihood estimation) and were adjusted for age, sex, education, race/ethnicity and study

centre. Risk estimates increased generally with higher alcohol consumption, although this was only significant for pharyngeal cancer: OR= 1.26 (95% CI=0.92-1.73) 1-2 drinks/day and OR= 2.94 (95% CI= 1.73-5.02) ≥ 3 drinks/day. ORs for oral cavity were 0.88 (95% CI= 0.65-1.20) for 1-2 drinks/day and 1.05 (95% CI= 0.62-1.77) for ≥ 3 drinks/day.

10. Lubin et al (2010) also conducted a pooled analysis using data from the INHANCE consortium on the effects of alcohol consumption, tobacco smoking and body mass index (BMI) on head and neck cancers including cancer of the oral cavity (2563 cases), pharynx (i.e. oropharynx and hypopharynx – comprised 3089 cases) and oral cavity or pharynx not otherwise specified (828 cases). The analysis was performed using data from 15 of the 17 case-control studies outlined in Hashibe et al. (2009). Two of the studies were excluded from the analysis: an Iowa study that did not collect data on BMI, and the French study used in the analysis by Gaudet et al. that did not enrol never-smokers. Linear exponential models were fitted for the excess odds ratio (EOR) for cancers of the oral cavity and pharynx in total drink-years and drinks/day. For analysis of alcohol consumption, results were adjusted for sex, education, BMI, smoking and use of other tobacco products. Polytomous regression was used to test for homogeneity of category-specific ORs. The authors observed an increased risk in oral cavity cancer with increasing drink-years compared to the reference category of never drinker (OR=1.04 (95%CI= 0.9-1.3) for 1-49 drink-years; 1.66 (95%CI= 1.2–2.3) for 50–99 drink-years; 2.24 (95%CI= 1.5–3.3) for 100–149 drink-years; 2.81 (95%CI=1.8–4.4) for 150–199 drink years and 3.22 (95%CI= 2.0–5.2) for ≥200 drink years). Similarly, increased risk of pharyngeal cancer was observed with increasing drink-years compared to the reference category of never drinker (OR= 1.30 (95%CI=1.1-1.5) for 1-49 drink-years; 1.50 (95%CI= 1.1–2.0) for 50–99 drink-years; 1.41 (95%CI= 1.0–2.0) for 100–149 drink-years; 1.57 (95%CI= 1.1-2.3) for 150–199 drink years and 1.96 (95%CI= 1.3–3.0) for ≥200 drink years). Adjusting additionally for drink-years (instead of drink-days), they also observed an increase in risk of oral cavity cancer with increasing drinks/day compared to the reference category of < 1 drink/day (OR= 1.26 (95%CI= 1.0–1.6) for 1–2.9 drinks/day; 1.29 (95%CI= 0.9–1.8) for 3.0-4.9 drinks/day and 1.87 (95%CI= 1.2-3.9) for 5-10 drinks/day). Similarly, they observed an increase in risk of pharyngeal cancer with increasing drinks/day compared to the reference category of < 1 drink/day (OR= 1.52 (95%CI= 1.3-1.9) for 1–2.9 drinks/day; 2.30 (95%CI= 1.7–3.1) for 3.0-4.9 drinks/day and 3.67 (95%CI= 2.6–5.3) for 5-10 drinks/day). Across all BMI categories (except for < 18.5), they found that the ORs for oral cavity/pharyngeal cancer by drink-years and drinks/day were greater at lower BMIs.

11. In a further publication, Lubin et al. (2011) examined whether gender modified the ORs for head and neck cancers by BMI, smoking and alcohol consumption. Using the same data-set as previously described by Lubin et al (2010) health outcomes included cancers of the oral cavity (2441 cases: 925f, 1516m), oro-pharynx (2297 cases: 564f, 1733m) and hypo-pharynx (508 cases: 96f, 412m) and 13829 controls (4415f, 9414m). ORs were adjusted for study, age, education, BMI, cigarette per day, years since smoking cessation, use of other tobacco products, DPD in the drink-year analysis and drink-years in the DPD analysis. Excess ORs (EOR) per drink-year within categories of drinks per day and sex were estimated using a linear-exponential excess OR model for total exposure (drink-years) and exposure rate drinks per day (DPD). This complex analysis provided data on the

effect of increasing exposure rate and decreasing exposure duration for fixed total exposure. For both exposure measures i.e. drink-years and DPD, the P test for trend was <0.01, which the authors suggested demonstrated a significant dose response relationship in all sites and for both sexes. However, ORs for oropharyngeal and hypopharyngeal cancers were larger in females, while ORs for oral cavity were similar by sex. For example, in highest drink category for the DPD exposure measure, ORs for: (i) oropharyngeal cancer were 7.63 (95% CI= 2.8-21) in females cf. 2.82 (95% CI= 1.8-4.3) in males; (ii) hypopharyngeal cancer ORs were 19.6 (95% CI= 1.8-217) in females cf. 7.03 (95% CI= 2.6-19) in males; (iii) oral cavity 2.37 (95% CI= 0.8-7.5) in females cf. 1.75 (95% CI= 1.1-2.8) in males. EOR/drink-year estimates by DPD categories generally increased with greater DPD, indicating a strengthening of the associations, and were greater in females for oropharynx (p<0.01) and hypopharynx (p=0.06) and similar by sex for oral cavity (p=0.64) (graphically presented). The authors noted that the enhanced association with alcohol consumption for oropharyngeal cancer in females appeared to result from effect modification by drink-years and not consumption rate (DPD).

12. Tramacere et al 2010 sought to update and quantify the association between alcohol drinking and oral and pharyngeal cancer (OPC) risk (combined) more precisely. A meta-analysis of 45 studies from America (18), Europe (17) and Asia (10), published up to September 2009, was performed using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Forty-three case-control studies and two cohort studies were identified through Pubmed, and all considered at least three levels of alcohol consumption and reported OR or RR and corresponding CIs (or sufficient info to calculate them) for each exposure level. This provided a total of 17278 cases and 80041 controls in case control studies and 192 cases and 2854647 non-cases in cohort studies. The referent category was set to the group with the lowest alcohol consumption per study (non-drinkers, when possible) and occasional drinkers (included as referents in some studies). Drinking groups were stratified into: low alcohol intake = drinkers of ≤ 1 drink/day; and heavy alcohol drinking = drinkers of ≥ 4 drinks/day, with 1 drink = 12.5g ethanol. Heterogeneity was assessed using Chi-squared test (significant heterogeneity defined a p value <0.10). A random effects model was used to compute summary relative risks for cohort and case controls studies. The alcohol level associated with each RR estimate was computed as the midpoint of each exposure category and for the open-ended upper category as 1.2 times its lower bound. Multivariate-adjusted risk estimates were used (when available) that included an allowance for tobacco, social class, selected dietary factors, oral hygiene and other recognised risk factors for OPC, otherwise the authors computed the unadjusted RRs provided from papers. Standard errors were computed for risk estimates from studies that did not report corresponding variances i.e. CIs. The dose-risk relationship was assessed via use of a random-effects meta-regression model in a non-linear DR relationship framework. The authors plotted a RR function and corresponding 95% CI to describe the best-fitting DR-relationship between alcohol consumption (10-100g ethanol/day) and OPC risk (i.e. the quadratic relation, $\ln(RR)=\text{dose} + \text{dose}^2$).

13. Heavy alcohol drinking was significantly associated with an increased risk of OPC in all studies combined (n=31), pooled OR=5.24 (95% CI=4.36-6.30); p for heterogeneity<0.01 (heterogeneity present). This association was particularly pronounced in case-control studies (n=29) where pooled RR=5.33 (95% CI=4.40-

6.47); p for heterogeneity<0.01. Pooled RR in cohort studies (n=2) were substantially elevated 4.25 (95% CI=3.03-5.96); p for heterogeneity=0.55. Light alcohol drinking was also significantly associated with an (albeit slight) increased risk of OPC in all studies combined (n=20), pooled RR=1.21 (95% CI=1.10-1.33); p for heterogeneity=0.71 (no heterogeneity). However, this association was only significant in case control studies (n=19), pooled RR=1.23 (95% CI=1.11-1.34), with a non-significant inverse association reported in the single cohort study, pooled RR=0.78 (95% CI=0.46-1.36). The dose-response analysis showed significant increased risks even at low alcohol intakes: pooled RR estimates for following doses of ethanol (g)/day were: 10: RR = 1.29 (95% CI=1.25-1.32); 25: RR = 1.85 (95% CI=1.74-1.96); 50: RR = 3.24 (95% CI=2.89-3.64); 75: RR = 5.24 (95% CI=4.58-6.40); 100: RR = 8.61 (95% CI=6.91-10.73) and 125: RR = 13.02 (95% CI=9.87-17.18). Finally, sensitivity analysis was conducted to verify the influence on summary estimates of studies that had either used a reference category different from non- or occasional drinkers; reported estimates not adjusted for the main risk factors (i.e. sex, age and smoking); computed SE (by multiplying the crude SE by 1.5). These factors did not substantially change the overall result; removing those studies produced a summary RR of 1.18 (95% CI=1.06-1.32) for light alcohol drinking, and RRs ranging from 4.98 to 5.33 for heavy alcohol drinking.

14. In a related study, Turati et al 2010 extended the findings of Tramacere et al (2010) to provide a more detailed and separate quantification of the association between alcohol consumption and cancers of the oral cavity and pharynx both individually and for their subsites. Thirty case-control studies and one cohort were identified that reported risk estimates for oral cavity and/or pharynx separately; data for subsites were included where a minimum of four studies were available (these included the tongue, oropharynx and the hypopharynx). The authors reported that the nasopharynx was not considered due to apparent epidemiological and histological evidence that it is different from that of other cancers of the oral cavity and pharynx. This provided 7419 cases of oral cavity cancer (22 studies): tongue (558 cases, 6 studies); 4664 cases of pharyngeal cancer (22 studies): oropharynx (1060 cases, 4 studies); hypopharynx (910 cases, 4 studies). With significant heterogeneity detected among studies (wrt strength of association rather than its direction) random-effects models were used to calculate summary measures that considered both within- and between-study variations. For dose-response analysis the authors plotted the RR function and corresponding 95% CIs to describe the best-fitting DR-relationship between alcohol consumption (10-100g ethanol/day) and oral or pharyngeal cancer risk (i.e. two terms fractional-polynomial models, $\log(RR)=(beta1)*dose + (beta^2)*dose^2$).

15. Higher risk estimates for alcohol intake were observed for pharyngeal cancer compared to oral cavity cancer. Heavy alcohol drinking was significantly associated with a substantially increased risk of pharyngeal cancer in all 17 case control studies (there were no cohort studies), pooled RR= 6.62 (95% CI=4.72-9.29); p for heterogeneity< 0.001 (heterogeneity present). Light alcohol drinking was not significantly associated with an increased risk of pharyngeal cancer in all 5 case-control studies (there were no cohort studies), pooled RR=1.23 (95% CI=0.87-1.73); p for heterogeneity=0.152 (no heterogeneity). Heavy alcohol drinking also yielded significantly elevated risk estimates for oral cavity cancer for all studies combined (n=17): 4.64 (95% CI=3.78-5.70); p for heterogeneity = 0.001 (heterogeneity

present). The 16 case-control studies and one cohort study yielded similar significant pooled risk estimates (i.e. 4.70 and 4.41 respectively). Marginally increased risk estimates for oral cavity cancer in light drinkers were observed when all studies were combined (n=9): pooled RR=1.17 (95% CI=1.01-1.35); p for heterogeneity=0.620 (no heterogeneity) and when studies were considered separately, pooled RR for 8 case controls studies was 1.20 (95% CI=1.03-1.40); the single cohort study yielded non-significant results, RR=0.78 (95% CI=0.46-1.33). Heavy alcohol drinking was also associated with significantly increased risks of cancer for studies investigating the different subsites (all were of case-control design, no cohorts): summary RRs for cancer of the tongue (n=5) was: 4.11 (95% CI=2.46-6.87); p for heterogeneity = 0.154 (no heterogeneity); oropharynx (n=4): 7.76 (95% CI=4.77-12.62); p for heterogeneity = 0.008 (heterogeneity present); and hypopharynx (n=4): 9.03(95% CI=4.46-18.27); p for heterogeneity < 0.001 (heterogeneity present). The dose-response analysis showed significant increased risks for all cancers and their subsites at all levels of alcohol intakes (except for cancer of the oropharynx which was significant at doses above 50g ethanol/day). Pooled RR estimates for cancers of the oral cavity ranged from 1.28 to 6.65, pharynx (1.32 to 11.58), tongue (1.05 to 4.15), oropharynx (1.20 to 5.96), and hypopharynx (1.08 to 8.83). Finally, sensitivity analysis performed by removing studies from the analysis that did not consider the two main sites separately confirmed the stronger association of alcohol with pharyngeal rather than oral cancer: pharyngeal cancer: pooled RR = 6.08 (95% CI = 4.06-9.08) while oral cavity cancer pooled RR = 4.44 (95% CI= 3.54-5.57). Excluding other factors from the analysis did not appreciably change the pooled RR.

16. Bagnardi et al (2013) carried out a meta-analysis of light alcohol drinking and cancer, including oral cavity and pharyngeal cancer (as a composite site). They included 222 unique papers published before December 2010, 23 of which reported estimates for oral cavity/pharyngeal cancers (3 cohort studies and 20 were case-control studies from Europe, North America and Asia). Cancer incidence was evaluated in 21 of these studies (two studies evaluated cancer mortality). Since the included studies usually reported alcohol exposure in intervals, the authors considered light drinking as every interval whose midpoint was <12.5 g/day (1 drink/day) of alcohol. Where studies reported two or more adjusted risk estimates for light drinking, they combined them into a single estimate. The reference category included non-drinkers (15% of estimates also included occasional drinkers). The reference category contained 2783 cases while the light drinker category contained 2036 cases. Although, heterogeneity between study estimates was low for oral cavity and pharynx (I^2<50%), the authors used a random effects model to compute pooled relative risks and corresponding CIs that were translated into log(RR). Meta-regression was conducted to investigate potential sources of between-study heterogeneity i.e. study design, geographical area and sex (using chi-square statistic to test for differences of summary estimates among subgroups). The pooled estimates indicated a significant association between light drinking and oral cavity/pharyngeal cancer (RR= 1.17 (95%CI= 1.06–1.29). Results of the meta-regression analyses revealed no significant sources of heterogeneity (p values>0.05 for all factors). Relative risks were slightly higher in men compared to women (RR= 1.20 (95%CI= 1.06–1.36) for men and 1.09 (95%CI= 0.89–1.34)). When stratified by study type, the RRs were 1.01 (95%CI= 0.70-1.45) for cohort studies and 1.22 (95% CI=1.11–1.35) for case-control studies. When stratified by geographical area the RRs were 1.44 (95%CI= 0.87–2.34), 1.15 (95%CI=1.01-1.30), 1.34 (95%CI=1.06–

1.68) for European, North American and Asian populations, respectively. Sensitivity analysis was also performed to study the effects on the pooled RRs of estimates either adjusted for main risk factors or estimates that did not consider occasional drinkers in the reference category. The results did not change appreciably from those of the overall analysis (RR=1.11 and 1.21 respectively). The authors also estimated the proportion and number of cancer deaths attributable to light alcohol drinking and drinking at any dose using methods described in Gmel et al. A total of 3521 male deaths and 1359 female deaths from oropharyngeal cancer were attributable to light drinking.

17. Bagnardi et al. (2015) updated and expanded the above study by conducting a meta-analysis of data on alcohol drinking (light, moderate and heavy drinking) and cancer risk using data from 572 studies published between 1956 and 2012. Fifty-two studies investigated the risk of oral cavity and pharyngeal cancer as a group (5 cohort and 47 case-control studies). Cancer incidence was examined in 49 studies and cancer mortality in three studies. Criteria set for inclusion in the meta-analysis were a) original case-control, nested case-control or cohort studies; b) studies that reported findings as odds ratios (ORs), relative risks (RRs) or hazard ratio (HRs) for at least two levels of alcohol consumption versus non-drinkers or occasional drinkers; c) studies that reported confidence intervals (CI) or standard errors of the risk estimates or sufficient data to calculate them. Criteria set for exclusion from the meta-analysis were studies reporting on specific alcohol beverage only as the non-drinkers in those studies could be drinkers of another alcoholic beverage type. For the purposes of the analysis and to have unity in the expression of consumption, grams per day was used as a standard measure of ethanol intake using the following equivalencies 0.8g/ml, 28g/ounce and 12.5 g/drink. For studies where the levels of consumption were reported in a range, the exposure was assigned as the midpoint of the range for the reported categories of alcohol intake. Light, moderate and heavy drinking was defined as every interval whose midpoint was ≤12.5g, ≤50g and > 50g per day of alcohol respectively. The reference category comprised of non-drinkers and occasional drinkers (in 20 studies). Statistical heterogeneity among studies was assessed using I^2. Random effects models were used to calculate pooled RRs for oral cavity/pharyngeal cancer in light drinkers versus non-drinkers, moderate drinkers versus non-drinkers and heavy drinkers versus non-drinkers. Subgroup meta-regression analyses were also performed to investigate potential sources of between-study heterogeneity i.e. study design type, gender and geographical area. Oral cavity/pharyngeal cancer was among those sites where 10 or more studies were available. The authors also tested the overall difference of summary estimates among study design groups. F-statistics associated with each group was taken as a global test of heterogeneity of pooled estimates between strata. Finally, dose-risk analysis was performed using a random effect meta-regression model based on a non-linear dose-response relationship framework.

18. Bagnardi et al. (2015) observed a clear dose-response and reported RRs of 1.13 (95%CI=1.00-1.26) for light drinkers, 1.83 (95%CI= 1.62–2.07) for moderate drinkers and 5.13 (95%CI= 4.31–6.10) for heavy drinkers compared to the reference category. This relationship was graphically verified in dose-response models. Case-control studies reported a stronger association with alcohol on oral cavity and pharyngeal cancer compared to cohort studies (p test for heterogeneity=0.007). Pooled risk estimates in heavy drinkers from case controls studies were approx. 1.7-

fold higher than that reported in cohort studies (5.34 vs 3.13 respectively). When results were stratified according to gender, similar RRs were observed in men and women (P test for heterogeneity=0.165). The effect of light drinking on risk of oral cavity and pharynx cancer was statistically significant only in studies carried out in Asian populations (pooled RR=1.33 (95% CI=1.06-1.68); n=7; I^2= 21; P test for heterogeneity = 0.375). Sensitivity analysis using studies that either reported adjusted estimates only, or studies did not include occasional drinkers in the reference category yielded similar estimates to those obtained in the main analysis. The authors note that publication bias and the differentiation between hospital-based and population-based controls) were extensively investigated by their research group in a series of meta-analytical studies on the association between alcohol and single cancers (See Tramacere et al 2010 and Turati et al 2010 for some of the results).

19. Chen et al (2009) used a World Cancer Research Fund (WCRF) standardised protocol to systematically review and pool 11 case-control studies published between 1976 and 2001 that investigated the association between alcohol consumption and the risk of nasopharyngeal carcinoma (NPC). The study was conducted as part of a WCRF and American Institute for Cancer Research (AICR)-funded project entitled "Food, Nutrition, Physical Activity and Prevention of Cancer: a Global Perspective" and provided data from the US (n=4), and Asia (n=7) for 7123 subjects: 2866 cases and 4257 controls. The quality of the studies were assessed using a modified criteria taken from a study by Longnecker et al used to evaluate studies on breast cancer and alcohol intake. Most studies were considered to be of poor quality due to lack of information on: data collection i.e. standardised approach, use of blinded interviewers, health status assessment timeframe, exposure assessment method, definition of alcoholic drink, use of histologically confirmed cases, response rates, adjustments. All 11 studies provided data on total alcohol intake (drinks/week) whereby one drink = 13.7g ethanol. The referent category comprised the lowest reported alcohol intake category, and the drinking group comprised the highest reported alcohol intake category. However, classification of alcohol drinking in highest category varied across studies, which the authors considered may impact on the risk estimates. Statistical heterogeneity was assessed using Der Simonian and Laird's Q statistic and I^2 statistic (I^2>50% was considered a meaningful level of heterogeneity) and the findings suggested there was no evidence of statistical heterogeneity: P for heterogeneity of Q test = 0.28; I^2 statistic=17.1%. A meta-regression analysis was conducted to explore potential sources of statistical heterogeneity and included the following variables: country of study; number of cases, sources of controls, statistical adjustment for smoking, and or salted fish; histological confirmation of cases (yes/no). A random effects model (using inverse variance weights) was used to estimate pooled ORs and 95% CI. A number of stratified analyses were performed to address potential effect modifications in relation to whether dichotomous or categorical drinking variables were provided (for dose-response calculations), and the duration of alcohol intake and type-specific alcohol intake for beer (n=3), spirits (n=3), wine (n=2) and Chinese rice wine (n=1) to address the heterogeneity associated with heavy drinking category classifications.

20. Comparing the highest category of total alcohol intake to the lowest category across all 11 case control studies the risk of NPC increased by 33%: pooled OR= 1.33 (95% CI=1.09-1.62). Meta-regression analysis found that 'study population' and 'statistical adjustment for smoking' had a statistically significant influence on

heterogeneity. When the analysis was restricted to studies that controlled for smoking in their original analyses the pooled OR was slightly attenuated and borderline significant OR= 1.26 (95% CI=0.99-1.62) n=6; this contrasts with the significant and strengthened association in studies that did not control for smoking OR=1.47(95% CI=1.02-2.12) n=5. Alcohol intake was associated with an increased risk in both US and Chinese populations, but the association was stronger and statistically significant in US studies: pooled OR=1.21 (95% CI=0.98-1.62) for Chinese populations (n=7); OR=1.50 (95% CI=1.08-2.10) US populations (n= 4). A similar finding was apparent for drinking variables: a stronger and significant association was apparent in studies providing ≥ 3 drinking categories (i.e. intervals of drinks/week or duration in years), pooled OR = 1.45(95% CI=1.12-1.87), n=7, compared to risk estimate produced when limited to studies providing a simple dichotomous comparison (i.e. ever/never categories), pooled OR= 1.15(95% CI=0.82-1.62) (n=4). Consequently, dose-response analyses were conducted in studies that reported ≥3 categories of exposure (n=6). Using a pooled DR curve (produced from a quadratic model that used generalised least squares for trend estimation) the authors identified a J-shaped relationship with the lowest NPC risk observed at approximately 15 drinks/wk (OR=0.82) compared to non-drinkers and an increased risk above 28-30 drinks/wk (4 drinks/day) (OR=1.12); P value for quadratic term = 0.005. The effect of duration of alcohol intake was assessed in two studies of Chinese populations (for up to 15 or 30 years) and observed no significant increased risk of NPC. Similarly, no significant positive associations were found when the data was stratified according to alcohol type, although a significant inverse association with NPC risk was reported in one study of Chinese rice wine drinkers: OR= 0.56 (95% CI=0.35-0.90). There was no suggestion of the presence of publication bias, and sensitivity analysis conducted to examine the influence of each individual study did not substantially change the overall risk estimate (pooled ORs ranged from 1.25 to 1.40)

21. Li et al. (2011) carried out a systematic review on 5 cohort and 115 case-control studies to understand the effect of alcohol consumption on the risk of developing various cancers in the Chinese population. Four case control studies were identified that investigated the risk of nasopharyngeal cancer (NPC) and three case control studies investigated oral cancer (OC) risk. These studies were included in a subsequent meta-analysis with a sample size that consisted of 1698 cases and 1874 controls for nasopharyngeal cancer, and 347 cases and 539 controls for oral cancer. Newcastle Ottawa Scale was used to assess the methodological quality of the studies, which was reported to be generally good (median overall score of 7, range 5-9). The types of alcohol consumed included beer, yellow rice wine, red wine and spirits. The authors noted the complexity of the definition of drinker and non-drinker. Participants who described drinking the smallest amount and those who never drank were classified as “non-drinkers” and the rest of subjects were classified as the “drinkers” category. Exposure was often reported as a categorical data with a range so the authors assigned the mid-point of the range as the average length of exposure. The highest consumption category, was assigned with a value equal to half of the width of the previous interval above the uppermost cut-off point. Significant heterogeneity ($p \leq 0.10$, $I^2 > 50\%$) was found between the studies investigating NPC (i.e. Q(p)=0.08; I^2=55) and therefore the meta-analysis was performed using the random effects model to calculate pooled odd ratios (ORs) and confidence intervals tested at 99%. For OC, studies did not demonstrate significant

heterogeneity (i.e. Q(p)=0.33; I^2=9) and so a fixed effects model was used. Comparing non-drinkers with drinkers, the authors reported that alcohol consumption was associated with an increased risk of NPC, [OR= 1.21 (99%CI=1.00–1.46); n= 1127 non-drinking / 571 drinking cases, 1338/536 controls; p=0.009], and OC [OR= 1.71 (99%CI=1.20-2.44); n= 170 /172 cases, 388/243 controls]; p= 0.0001. Studies reporting on these sites were not included in a subgroup analysis exploring possible reasons for heterogeneity or a sensitivity analysis evaluating the stability of the alcohol and cancer relationship. The authors reported that there was no significant dose-response relationship between alcohol consumption and any cancer (after pooling the data and finding that no data indicated a monotonic increasing function relating alcohol consumption with any cancer site).

22. Petti et al (2013) performed a meta-analysis of 14 observational studies conducted in SE Asian (non-immigrant) native adults to explore and assess the interactive effects of tobacco smoking, alcohol drinking and betel-quid chewing on oral cancer risk. The independent effects of alcohol are summarised here for the purpose of this review. All 14 case-control studies included 5192 cases that were histologically and clinically confirmed to have squamous cell carcinoma of the mouth and/or oropharynx, and 48041 controls selected from either the same hospitals as cases, or from the underlying study population who were free of cancer and not affected by oral precancerous lesions or other diseases promoted by risk factors under investigation. Three independent reviewers extracted the data and also assessed the quality of the studies on the basis of their study design using the following scoring system: high quality (scored 1); moderate (0.5); low (0.25). All studies included in the analyses were scored 0.5 (moderate quality). The authors classified exposures into broad categories i.e. ever or never usage. The referent category were defined as never users of the alcohol, cigarettes, and betel quid, and the drinking category comprised of current daily users (for at least five years), stratified according to their whether or not they also smoked cigarettes and/or chewed betel-quid. NB. Risk estimates reported here were restricted to non-smoking, non-betel quid chewing drinkers. Cochran's Q test did not detect any significant between-study heterogeneity (chi-squared test=0.008) and so the authors used a fixed-effect model to pool ORs with 95% CIs adjusted for publication bias (funnel plots showed that the drinking category yielded an asymmetric plot which was suggestive of high level of publication bias).

23. Point estimates for oral cancer ORs for the drinkers category ranged from 0.5 to 35.6 in the 14 studies evaluated. However, pooled OR was 2.2 (95% CI=1.6-3.0). Differences between studies were assessed with regard to age, gender and country (as a surrogate marker for ethnicity); only the result for the latter variable was presented. Pooled oral cancer OR estimates were higher in Indian studies (n=7), pooled OR = 2.69 (95% CI=1.73-4.18) cf. Taiwanese studies (n=7), pooled OR = 1.8 (95% CI=1.17-2.77).

Summary of meta-analysis and combined analysis studies

24. Six meta-/ pooled-analyses provided data on the risk of cancer of the oral cavity (as a whole) and alcohol consumption. Five out of the six studies reported significant positive associations in light or heavy drinkers (consuming up to 100 g/day) with pooled risk estimates ranging from 1.2 to 6.7 (Lubin et al., 2010; Turati et al 2010; Li et al., 2011; Lubin et al., 2011; Petti et al., 2013). A significant dose-

response relationship was also reported for cancer of the tongue. Hashibe et al (2009) did not observe any significant increased risk of cancer of the oral cavity even at the highest category of more than 3 drinks a day in their pooled analysis of 17 case-control studies participating in the INHANCE consortium. It is unclear whether the missing data for alcohol frequency categories leading to reduced number of cases and controls may have contributed to this. Using same dataset, Lubin et al (2011) provided data showing that gender appeared to significantly modify the risk of cancer of the oral cavity, with significant associations (less than 2-fold increased risk) apparent in men only who consumed between 5 to 10 drinks per day and had a cumulative exposure of 50 or more drink-years.

25. Three meta-/ pooled-analyses provided data on the risk of cancer of the pharynx and alcohol consumption and all reported significant positive associations in drinkers who consumed between 1 and 10 drinks per day - risk estimates ranged from 1.5 to 6.6 (Hashibe et al., 2009; Lubin et al., 2010; Turati et al., 2010). Highest pooled risk estimates (RR=11.6) were reported in subjects consuming up to 100g/day (Turati et al., 2010). No significant association was observed with light drinking (≤ 1 drink/day). Studies providing data for cancer in subtypes of the pharynx i.e. oropharynx and hypopharynx generally all reported significant positive associations in drinkers. Two studies provided pooled risk estimates from studies investigating alcohol consumption and cancer of the oropharynx (Turati et al 2010; Lubin et al 2011). Both studies reported significant dose-related increases in terms of both quantity (1-10 drinks/day) and cumulative exposure (1 to 199 drink/years), and these risks were stronger in women compared to men (highest estimates were approx. 8-fold and 3-fold respectively). The same two studies provided pooled risk estimates from studies investigating alcohol consumption and cancer of the hypopharynx (Turati et al 2010; Lubin et al 2011). Both studies reported significant dose-related increases which were stronger in women compared to men (highest estimates were 19.6 and 7.0 respectively). No significant association with cumulative exposure (1-200 drink-years) was observed for either sex. Two studies provided pooled risk estimates from studies investigating alcohol consumption and cancer of the nasopharynx (Chen et al., 2009; Li et al 2011). Significant associations were reported although pooled risk estimates were only marginally increased by 21% in ever drinkers compared to never drinkers (Li et al., 2011). A significant J-shaped pooled dose response curve was reported by Chen et al when six studies providing ≥3 categories of exposure were pooled. Subanalysis according to alcohol beverage type showed Chinese rice wine produced an inverse association.

26. Three studies provided pooled risk estimates from studies investigating alcohol consumption and cancer of the oral cavity and pharynx combined (Tramacere et al 2010; Bagnardi et al.,2013; Bagnardi et al., 2015). All reported significantly increased risks of OPC at light and heavy levels of alcohol drinking. Dose response analyses showed that the lowest OR of 1.1 arose in subjects in the ≤ 12.5g ethanol per day drinking category (Bagnardi et al 2015), whilst a 10-fold higher OR was given for subjects who drank up to 125g per day (OR=13) (Tramacere et al 2010).

Cohort studies

27. The cohort studies have been divided into two categories: a) those examining oral cavity and pharyngeal cancer incidence (5 studies) and b) those examining oral

cavity and pharyngeal cancer mortality (2 studies). Within each section, the studies are reported by geographical region (UK, European, US and others regions) and within each region in order of their Newcastle-Ottawa (NO) score, beginning with the highest scoring studies.

Cohort studies examining alcohol consumption and oral cavity and pharyngeal cancer risk (Table 2)

28. Maasland et al. (2014) investigated the effects of alcohol and tobacco consumption, both independently and jointly, on the risk of head and neck cancer (HNC), which included cancers of the oral cavity and pharynx. The study was conducted within in a large prospective Netherlands cohort study (NLCS) of 120,852 participants, aged 55-69 years from 204 Dutch population registries. All subjects were eligible if they were cancer-free at baseline (skin cancer allowed) and provided information on alcohol consumption obtained using a self-completed food frequency questionnaire (FFQ). Details were provided on habitual intake of alcoholic beverage type during the year preceding the study, the frequency of consumption and the number of glasses consumed per occasion. Standard glass sizes were defined as 200ml for beer (8 g ethanol), 105 ml for wine (10 g ethanol) and 45 ml of liquor/spirits (13 g ethanol). Information was also obtained on drinking habits five years prior to baseline questionnaire. Abstainers (referents) were participants who never drank alcohol or drank less than once a month. After 17.3 years of follow-up, 395 incident HNC cases and 4288 subcohort members were available for the analysis identified by annual record linkage to the Netherlands Cancer Registry and nationwide network pathology registry. This included 110 (65m, 45f) cases of oral cavity cancer (OC), 83 (61m, 22f) cases of oro-hypopharyngeal cancer (OHPC), and 3 cases of oral cavity/pharynx that were unspecified or overlapping. Relative Risks (RR) and 95% CI were estimated using Cox proportional hazard models and adjusted for age (years), sex, cigarette smoking. Exposure was assessed in terms of grams of ethanol per day and also as a continuous variable (either 10g ethanol/ day or 1 glass/day increments). The authors performed a sub-analysis of the different types of alcoholic beverages to examine whether other components of the beverage may have an effect on the cancer risk. These were adjusted for continuous ethanol intake (g/day).

29. Compared to abstinence, alcohol consumption of ≥ 30 g/day was associated with a statistically significantly increased risk for both cancer subtypes. A strong dose-response relationship was found between categories of increasing alcohol consumption and the risk of these cancer subtypes. Risk estimates for oral cavity cancer were: >0 to<5 g/day: RR= 1.25 (95% CI=0.59-2.65) n=17; 5 to <15 g/day: RR= 1.91 (95% CI=0.91-4.03) n=19; 15<30 g/day: RR= 3.88 (95% CI=1.86-8.12) n=30; ≥30 g/day: RR= 6.39 (95% CI=3.13-13.03) n=32; p for trend = <0.001. Continuous exposure (10g/day increments): RR= 1.28 (95% CI=1.18-1.39) n=110. Risk estimates for oro-hypopharyngeal cancer were: >0 to <5 g/day: RR= 1.06 (95% CI=0.47-2.40) n=14; 5 to <15 g/day: RR= 0.90 (95% CI=0.38-2.13) n=12; 15-30 g/day: RR= 0.99 (95% CI=0.41-2.38) n=13; ≥ 30 g/day: RR= 3.52 (95% CI=1.69-7.36) n=33; p for trend = <0.001. Continuous exposure (10g/day increments): RR= 1.27 (95% CI=1.16-1.38) n=83. Similar findings with albeit slightly increased risk estimates were obtained in sensitivity analysis conducted in subjects with stable alcohol consumption (i.e. who did not change their continuous habits in the 5 years before baseline) p for trend <0.001 for both cancer subtypes. Sub-analysis of alcohol

type-specific effects revealed that beer consumption was associated with a significantly increased risk of OHPC: no beer: RR=1.0 n=36; >0 to <1 (glasses/day): RR= 0.98 (95% CI=0.54-1.76) n=24; 1 to <2: RR= 1.04 (95% CI=0.41-2.66) n=6; ≥ 2: RR= 2.48 (95% CI=1.03-5.98) n=17; p for trend = 0.03; Continuous exposure (1 glass/day increments): RR= 1.19 (95% CI=1.01-1.40) n=83. Liquor consumption was also associated with a significantly increased risk of OC: no liquor: RR=1.0, n=40; >0 to <1(glasses/day): RR= 1.10 (95% CI=0.67-1.80) n=31; 1 to <2: RR= 1.65 (95% CI=0.87-3.15) n=18; ≥ 2: RR= 2.26 (95% CI=1.02-4.99) n=20; p for trend = 0.03; Continuous exposure (1glass/day increments) : RR= 1.18 (95% CI=0.89-1.56) n=109. Other permutations of cancer subtypes and type of alcohol beverage did not produce significant findings. A significant interaction was found between sex and continuous alcohol consumption in oral cavity cancer with women having higher RRs than men; OC: RR=1.58 (95% CI=1.33-1.87) in women cf. RR=1.27 (95% CI=1.17-1.38) in men (P for interaction=0.004). For OHPC, P for interaction=0.68.

30. Shanmugham et al (2010) sought to quantify the effect of alcohol on the risk of oral cancer in different strata of folate intake. This summary details the independent effects of alcohol consumption. Data was obtained from an ongoing prospective cohort study of 87,621 registered female nurses with a mean age of 47 years that provided complete information from the US Nurses' Health Study. Between 1980 and 2006, participants completed a baseline self-reported questionnaire and FFQ, and follow-up questionnaires mailed every 2-4 years to update information on risk factors and the onset of newly diagnosed diseases and data on alcohol intake. Each follow-up cycle has achieved overall response rates of 90% or higher. Subjects were followed up to date of diagnosis of oral cancer/ death/ end of follow-up (Dec 2006) whichever came first. Self-reports of cancer diagnosis/death were followed by reviews of medical and pathology reports and adjudicated by study physicians who were blinded to risk factor information. The International Classification of Diseases (9th revision) was used to categorise the oral cancers according to site/region. Cancers of the lip and nasopharynx were excluded from the analyses. 147 confirmed cases of oral cancer were included in the analyses.

31. The cumulative average updating method was used to estimate long term alcohol exposure (thought to reduce within-person variation) and total alcohol intake was calculated as the sum of all alcoholic beverages (beer, liquor, wine); ethanol content estimated as 13.1g/ 12oz bottle or can of beer; 11g per 4-ounce glass of wine, and 14g per standard drink or shot of liquor. Referents were non-drinkers, while drinkers were grouped into 3 categories: 0.1-14.9 g/day; 15-29.9 g/day; and ≥30 g/day (i.e. approx 2 drinks/day – the authors noted that these participants were more likely to report current cigarette smoking). RR and 95% CI were calculated via multivariate Cox proportional regression analyses (with time-varying covariates) and adjusted for either age only or age plus follow-up time, pack-years of smoking, smoking status, and folate intake. Compared to non-drinkers (n=43), cumulative average alcohol intake (age-adjusted) was significantly associated with oral cancer among women who consumed ≥30 g/day (n=19), RR=2.70 (95% CI=1.57-4.65); p≤0.001. An inverse association was observed at the lowest level of intake: 0.1-14.9g/day: RR=0.57 (95% CI=0.39-0.84) n=64, p≤0.01; and a non-significant increased risk at moderate intake levels, 15-29.9g/day: RR=1.29 (95% CI=0.76-2.18) n=21. Similar associations were observed for multivariate adjusted risk estimates

albeit with slightly reduced values: 0.1-14.9 g/day: RR=0.59 (95% CI=0.39-0.87) p≤0.01;15-29.9: RR=1.15(95% CI=0.67-1.97); ≥30: RR=1.92 (95% CI=1.08-3.40); n=19; p≤0.001. The authors also observed a significant interaction between alcohol and folate intake (p= 0.02). The cancer risk for subjects with high alcohol drinking (>30 g/day) and low folate intake (<350 µg/day) was significantly elevated (RR: 3.36; 95% CI: 1.57-7.20) as compared to non-drinkers with low folate. The risk associated with high alcohol (>30 g/day) was reduced to 0.98 (0.35-2.70) in the high folate (>350 µg/day) group, as compared to non-drinkers with high folate.

32. Jayalekshmi et al. (2013) examined the association of alcohol drinking and tobacco use with hypopharyngeal and laryngeal cancer risk in a cohort of 65,553 men from the Karunagappally area in India. Subjects were selected from a 1991 Consensus, and were all healthy local non-factory workers aged between 30-84 years old. Trained personnel collected baseline information including alcohol consumption status via a standardised interview questionnaire between Jan 1990 and Dec 1997. Subjects were followed-up from Jan 1997 to Dec 2009 and 52 cases of hypo-pharyngeal cancers were identified by the Karunagappally Cancer registry. Cases underwent further follow-up at cancer centres, hospitals and pathology laboratories. RR and 95% CI were obtained from Poisson regression analysis of grouped survival data and stratified by attained age, income and education. Compared to referent never drinkers (23 cases) alcohol consumption was not significantly related to the risks of hypopharyngeal cancer in either former (n=9) or current drinkers (n=20), RR = 1.2 (95%CI=0.6-2.6; and RR= 1.3 (95%CI=0.7-2.4) respectively P>0.5.

33. Hsu et al (2014) evaluated the association between alcohol, betel and cigarette consumption and the risk of distinct cancers of the upper aerodigestive tract (UADT) in 25,000 men sourced from three community-based long term prospective cohort studies in Taiwan: these comprised of the Six Township Hypertension Intervention Project cohort (SCHIP-3900 males), Multiple Risk Factors for Multiple diseases cohort (MRMD-9699m) and the Community-based Cancer Screening Project cohort (CBCSP-12020m). All subjects were recruited between 1982 and 1992 with a mean age that ranged from 48.1 to 52 years. Each participant was interviewed by well-trained research nurses that used structured questionnaires, and provided information on history of alcohol, betel and cigarette consumption. Subjects were followed up for a mean duration of 18.4 years up to December 2009. A total of 97 cases of oral cavity cancer and 70 cases of pharyngeal cancers were identified via the National Cancer registry and confirmed by pathology. Subjects vital status was also ascertained via national death certification records. Several exposure variables were used to assess alcohol consumption: drinking status i.e. never (referent category) and ever (participants with an 'alcohol drinking habit' who regularly drunk alcohol for at least six months); quantity of alcohol (g/day); duration (years) and cumulative exposure to alcohol drinking (g-years). Cox proportional hazards models were used to calculate HRs and 95% CIs and adjusted for age, ethnicity, education, smoking, betel quid chewing, and study cohort. Cumulative lifetime risk (CR) between ages of 30 and 80 years was also estimated via Nelson-Aalen method.

34. Compared to never drinkers, ever alcohol drinking was significantly associated with the risk of pharyngeal cancer, HR= 1.72 (95% CI: 1.03-2.90) but not

oral cancer 0.86 (95% CI: 0.52-1.42) after adjustment for the aforementioned potential confounders. This association cf. never drinkers was also corroborated in dose-response analyses as the authors observed a significant dose response relationship with pharyngeal cancers for both increasing quantity of alcohol consumed (g/day) [for pharyngeal cancers: <80: HR= 1.17 (95% CI: 0.56-2.45), ≥80: HR= 3.27 (95% CI: 1.73-6.19) p for trend=0.001; for oral cancers: <80: HR= 0.56 (95% CI: 0.27-1.19) and ≥80: HR= 1.54 (95% CI: 0.81-2.92) p for trend=0.597] and cumulative consumption of alcohol (g-years) [for pharyngeal cancers: <1500: HR= 1.58 (95% CI: 0.81-3.07), ≥1500: HR= 2.86 (95% CI: 1.43-5.75) p for trend= 0.003; for oral cancers: <1500: HR= 0.66 (95% CI: 0.32-1.34), ≥1500: HR= 1.33 (95% CI: 0.67-2.65) p for trend= 0.842]. However, the authors note that the quantity of alcohol drinking was associated with an increased oral cancer risk (HR=2.43 for ≥80 g/day ethanol vs. never drinker) when betel quid chewing was not included in the adjusted confounders. The authors suggest this shows that betel quid chewing is an important risk factor for oral cancer given that a high proportion of chewers are also alcohol drinkers in Taiwan. Finally, increasing quantity and cumulative exposure of alcohol was associated with an increased cumulative risk of oral and pharyngeal cancer. This was significant for heavy drinkers who drank for ≥80g/day with cumulative exposure of ≥1500 gram-years compared to never drinkers: for oral cancer ≥80g/day: CR (%)=2.22 (1.33-3.72) and ≥1500 gram-years: CR (%)=1.78 (1.00-3.18); for pharyngeal cancer ≥80g/day: CR (%)=3.44 (2.05-5.77) and ≥1500 gram-years: CR (%)=2.96 (1.57-5.59).

35. Lin et al (2011) investigated the relationship between smoking, alcohol consumption and betel-quid chewing and oral cancer development in a prospective hospital-based cohort study of 10657 male patients aged between 18-96 years who visited a tertiary referral hospital centre in central Taiwan between 2005 and 2008. This summary details the independent effects of alcohol consumption. Patients were asked to describe their personal habits during the past six months, which included tobacco use, alcohol consumption and betel quid chewing. Patients then received visual inspection of the oral cavity to detect for the presence of abnormal lesions defined as: a non-healing ulcer for > 2 weeks, a persistent white or red lesion, a lesion that bleeds easily, or an irregular surface lesion inside the oral cavity. Authors do not report whether this was done by a clinician. Patients with positive findings were eligible for a follow-up punch biopsy to diagnose the presence or absence of oral cancer. Authors do not specify the length of the follow-up period. For exposure assessment patients were stratified into those answering yes to having an habitual drinking habit (n=1569) or those answering no (n=9088). The referent group was described as having no personal habits of drinking alcohol, smoking or chewing betel quid (n=7775). A total of 170 of the 514 patients with abnormal lesions were lost to follow-up and no further pathological report could be obtained – these were excluded from the analyses to avoid confounding. Punch biopsy was conducted in the remaining 344 patients with abnormal lesions and 230 were proven to have oral cancer. A total of 10257 patients did not have pathologically proven cancer. ORs & 95% CI were estimated using multivariate logistic regression. The authors did not adjust for any potential confounders as the authors considered that the relevant risk factors for developing oral cavity cancer were being investigated. Comparing subjects with no personal habits (n=7775) with those who only consumed alcohol as their personal habit (n=464), there was no significant increased risk of developing oral cancer OR=1.33 (95% CI=0.48-3.74); p=0.584. Significant positive associations

(p<0.001) were observed in drinking subjects who also either smoked OR=9.88 (6.05-16.12), or chewed betel quid OR=21.84 (8.04-59.36) or smoked and chewed betel quid OR= 46.87 (31.84-69.0)

Summary of cohort studies on oral cavity and pharyngeal cancer risk

36. Four studies investigated the risk of cancer of the oral cavity (as a whole) and alcohol drinking (Shanmugham et al., 2010; Lin et al., 2011; Hsu et al., 2014; Maasland et al., 2014). There was no consistent evidence of an association. A significant dose-response relationship was observed in a Dutch study of older drinkers aged between 55-69y who consumed between 15 and ≥ 30 g/day (RR were 3.9 and 6.4 respectively) (Maasland et al., 2014). Lower risk estimates were reported in female nurses drawn from the Nurses' Health Study and an inverse association was apparent in subjects who consumed up to 15 g/day (Shanmugham et al., 2010). The remaining two studies conducted in Taiwanese men did not observe any significant association although one was a possible cancer screening study that did not adjust for any confounders (Lin et al 2011) and the other was subject to possible selection bias as the authors did not report loss to follow-up (Hsu et al 2014). Hsu et al (2014) was the only cohort study to investigate the risk of cancer of the pharynx (as a whole) from alcohol drinking and observed a significant positive association for all drinking measures used (highest RR of 3.3 was associated with drinking ≥80 g/day).

37. Maasland et al (2014) reported a significant positive association between alcohol consumption (≥ 30 g/day) and cancer arising in the orohypopharynx of men and women. However, there was no significant association between drinking status and cancer of the hypopharynx in Indian men, although RRs were not adjusted for tobacco smoking (Jayalekshmi et al., 2013).

Cohort studies examining alcohol consumption and oral cavity and pharyngeal cancer mortality and secondary events (Table 3)

38. Jerjes et al (2012) examined the effect of tobacco and alcohol consumption on oral cavity mortality and the effect of smoking and alcohol reduction/cessation at time of diagnosis on survival. Data relating to effects of alcohol only are summarised here. A total of 67 UK male patients aged between 25 and 96 (mean=62.2y) and diagnosed with oral squamous cell carcinoma of either the tongue, floor of mouth, lower alveolus, or buccal mucosa were referred to the Department of Oral and Maxillofacial Surgery, at University College Hospital, London between 1998 and 2003. All patients were fully staged prior to admission and tissue were pathologically analysed to grade tumours. Patients underwent surgical resection/identical treatment protocols were each followed up for a minimum of 5 years. Exposure information obtained at study entry (method not reported) stratified patients into the following categories: referents= non-drinkers (n=20 patients); ex drinkers (n=1); chronic drinkers defined as patients who had an ongoing drinking habit for > 20 years and consumed <10 units/week (n=2), 11-20 (n=9); >20 (n=35). Risk estimates were not determined. Authors summarised 3 and 5 year survival rates (fractions) and incidences of recurrence. No adjustments were made but the authors categorised 12 patients as non-smokers, 6 patients as ex-smokers and 48 patients as chronic smokers who smoked from <5 to ≥20 cig/day). Oral cancer recurred in a total of 26 patients (no further analyses were conducted in these patients with respect to

alcohol consumption). After 3 years follow-up, 22 patients were still alive and these were stratified as follows: 9/20 non-drinkers (45%); 1/1 ex-drinker (100%), and for chronic drinkers 2/2 (100%) who consumed <10 units/week; 3/9 (33%) who consumed 10-20 units/week and 7/35 (20%) patients who consumed >20 units/week. After 5 years 19 patients were still alive with numbers changing in higher drinking categories i.e. 4/9 (44%) who consumed 10-20 units/week and 3/35 (8.6%) patients who consumed >20 units/week. Causes of death were either tumour-related (loco-regional or distant metastasis) or non-tumour related (e.g. pneumonia, or condition leading to cardiorespiratory failure). A total of 15 chronic drinkers reduced their alcohol intake to < 10 units/week after being diagnosed and 9 patients stopped completely. NB. 12 chronic smokers reduced no of cigarettes smoked after diagnosis, 13 stopped completely. Reduction in drinking alcohol and/or drinking cessation lead to significant reduction of mortality at 3 ($p<0.001$) and 5 years ($p<0.001$).

39. Kim et al. (2010) examined the association between alcohol consumption and all-cause and cancer mortality in a large-scale prospective study among 1.34 million Koreans aged between 40-69 years (919,199m, 422,194f). Subjects were taken from the Korea National Health Insurance Corporation (KNHIC) periodic (mostly biennial) general health examination. Baseline health examinations were conducted by medical staff at local hospitals under standard procedures to ensure subjects were disease-free (subjects who died during the first year were excluded from the analysis). Information on alcohol consumption was obtained via a self-reported questionnaire. Subjects were asked to estimate frequency of consumption and amount of alcohol consumed per occasion in relation to a traditional Korean alcoholic drink “Soju”. Average daily alcohol consumption was divided into five categories for men (non-drinker, 1.0-14.9, 15.0-29.9, 30.0-89.9 and ≥ 90 g ethanol/day) and three categories for women (non-drinker, 1.0-14.9 and ≥15 g ethanol/day). Non-drinkers were the reference category for the analysis. Subjects were followed up for an inadequately short period of 5 years for mortality. Mortality follow-up was conducted by linking subjects records to national death certificate data from the Korea National Statistical Office. The authors used the 10th revision of the ICD codes to classify specific causes of death. There were 82 cases of death resulting from cancer of the lips, oral cavity and pharynx (as a group) including 46 cases of death resulting from cancer of the pharynx. Relative risks of death and 95% CI for alcohol consumption were obtained using Cox proportional hazard regression analysis and adjustments were made for age, residence, smoking, exercise, BMI, systolic and diastolic blood pressure, and fasting blood sugar. Only data for men were presented on oral cavity/pharyngeal cancers (data for women was not available/reported for these sites). Alcohol consumption was not significantly associated with risk of death by these cancers. Risk estimates for death from cancer of lips, oral cavity, pharynx in subjects who consumed 1-14.9 g/day were RR= 1.7 (95% CI=0.94-3.05); 5-29.9: RR= 0.82 (95% CI=0.38-1.80); 30-89.9: RR=1.65 (95% CI=0.82-3.35); ≥90: RR= 2.17 (95% CI=0.99-4.76). For death from cancer of the pharynx RR were: 1-14.9 g/day: 1.24 (95% CI=0.56-2.76); 15-29.9: RR= 0.75 (95% CI=0.27-2.06); 30-89.9: RR= 1.38 (95% CI=0.55-3.48); ≥90: RR= 2.15 (95% CI=0.82-5.64).

Summary of cohort studies on oral cavity and pharyngeal cancer mortality and secondary events

40. Two studies examined the risk of death from cancer of either the oral cavity (Jerjes et al., 2012), or cancer of the pharynx only and oral cavity and pharynx combined (that included the lips) (Kim et al., 2010). The UK study reported survival rates only and observed lower survival in higher drinking categories: 20% of these patients were alive after 3 years which reduced to 8.6% after 5 years (Jerjes et al., 2012). The Korean cohort study did not observe any significant associations, although the study was limited by self-reported exposure to one type of drink (Soju) and had a short follow-up of 5 years (Kim et al., 2010).

Case-Control studies

41. The case-control studies presented below examine oral cavity and pharyngeal cancer risk (9 studies). No studies were identified that examined oral cavity and pharyngeal cancer mortality. The studies are reported by geographical region (UK, European, US and others regions) and within each region in order of their Newcastle-Ottawa (NO) score, beginning with the highest scoring studies.

Case-control studies examining alcohol consumption and oral cavity and pharyngeal cancer risk (Table 4)

42. Marron et al. (2012) investigated the association of drinking different alcoholic beverage types and upper aero-digestive tract cancers (UADT) cancer including oral cavity and pharyngeal cancers in a large European case-control study. The data presented here was generated from the Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) study, which was initiated by IARC. It involved 14 centres in 10 European countries (Paris data was restricted to smokers). The majority of centres used hospital-based controls with the exception of the three UK centres where population-based controls were randomly selected from the same primary practices as cases. Subjects were recruited between 2002 and 2005 (Paris study: 1987 to 1992). Controls were frequency matched to cases by age, sex and referral (residential) areas. Non-response rates for hospital-based centres was 10% (cases) and 9% (controls) and for population-based centres was 48% (cases) and 71% (controls). Information on lifestyle and alcohol consumption was obtained by a trained interviewer using a questionnaire. This included data on volume of alcohol consumed, frequency and duration of various alcoholic beverages (beer, wine, hard liquor and aperitifs) in different periods of life, details of binge drinking (drinking large volumes in short periods of time, i.e. >10 drinks in 2h) and details on the specific type of alcohol consumed ("pure drinker" consuming one beverage type exclusively; "predominant drinker" consuming one beverage type to more than 66% of the time with unlikely confounding by other beverage types, and "mixed drinker" consuming more than one type of alcoholic beverage type to similar proportions; never wine drinkers included pure beer drinkers, pure liquor drinkers and beer and liquor drinkers (predominant and mixed), and so on). NB. The Paris centre used a slightly different approach to calculate exposure metrics due to different data being collected (calculation of lifetime cumulative consumption was not stratified by alcoholic beverage type). Odds ratios (OR) and 95 % confidence intervals (CI) were estimated using unconditional logistic regression and adjusted for the following potential confounding factors (age, sex, centre, education level, fruit and vegetable intake,

smoking (duration, frequency and time since quitting of tobacco, type of tobacco and smoking status) and alcohol drinking (adjusting liquor consumption on wine and beer, beer consumption on wine and liquor, and wine consumption on beer and liquor). The analysis included 489 oral cavity and 623 pharyngeal cancer cases and 2,125 controls. Cancers of the salivary gland, external lip and nasopharynx were excluded. Risk estimates stratified according to quantity of alcohol consumed were provided for overall UADT and not for cancer subtypes.

43. Stratifying the results for oral cavity cancer and adjusting for cumulative alcohol consumption, compared to never drinkers (n= 6m/34f cases, 110m/147f controls) the OR and 95 %CI of oral cavity cancer among 'pure drinkers' of wine, beer and liquor drinking, respectively, were 2.59 (0.94-7.17), 3.58(1.33-9.61), and 1.64 (0.34-7.86) in men and 0.65 (0.30-1.39), 0.85 (0.28-2.59), and 0.77 (0.22-2.70) in women. Among predominant drinkers, OR and 95% CI for wine, beer and liquor drinking, were respectively, 2.12 (0.82-5.46), 2.57(0.98-6.73) and 2.97 (1.03-8.58) in men, and 0.81 (0.38-1.72), 1.35 (0.46-3.93) and 1.58 (0.54-4.60) in women. Among mixed drinkers, OR and 95% CI for wine, beer and liquor drinking, were respectively 2.06 (0.82-5.2), 2.47(0.99-6.09) and 2.52 (1.01-6.28) in men and 1.36 (0.66-2.80), 1.08 (0.55-2.13) and 0.83 (0.40-1.70) in women. Among never drinkers of either wine, beer or liquor, respectively OR and 95% CI were 3.78 (1.49-9.61), 2.08(0.81-5.33) and 2.63 (1.07-6.48) in men and 1.09 (0.47-2.49), 0.79 (0.41-1.50) and 0.89 (0.48-1.63) in women.

44. Stratifying the results for pharyngeal cancer and adjusting for cumulative alcohol consumption, compared to never drinkers (n= 9m/12f cases, 110m/147f controls) the OR and 95 %CI of pharyngeal cancer among 'pure drinkers' of wine, beer and liquor drinking, respectively, were 1.71 (0.70-4.22), 2.45 (1.07-5.63) and 3.16 (1.05-9.44) in men, and 2.21 (0.88-5.54) , 2.03 (0.66-6.29) and 0.92 (0.21-4.01) in women. Among predominant drinkers, OR and 95% CI for wine, beer and liquor drinking, were respectively, 2.13 (0.93-4.87), 2.07 (0.92-4.65) and 1.88 (0.77-4.59) in men, and 2.30 (0.91-5.79), 2.69 (0.92-7.88) and 2.63 (0.86-8.05) in women. Among mixed drinkers, OR and 95% CI for wine, beer and liquor drinking, were respectively 2.07 (0.94-4.59), 1.97 (0.9-4.28) and 1.93 (0.88-4.22) in men, and 2.30 (0.95-5.59), 2.52 (1.06-5.97) and 2.18 (0.89-5.33) in women. Among never drinkers of either wine, beer or liquor, respective OR and 95% CI were 2.58 (1.17-5.7), 1.74 (0.79-3.82) and 1.88 (0.88-4.03) in men, and 2.18 (0.86-5.52), 2.18 (0.95-4.99) and 1.94 (0.87-4.33) in women. In summary, most ORs were approximately 2-fold higher for pharyngeal cancer than for oral cavity among women but were similar among men. Very few risk estimates reached statistical significance. However, significant findings were observed in men who never consumed wine, or who only drank beer and consumed liquor.

45. Polesel et al (2011) investigated the association of two risk factors (tobacco smoking and drinking alcohol) on the risk of nasopharyngeal carcinoma (NPC) in patients drawn from an established network of collaborating centres in Italy conducted between 1992 and 2008. Cases were patients with incident NPC admitted to major general hospitals in all study areas and controls comprised patients admitted for a wide spectrum of acute conditions (non-malignant neoplasms/non-tumour conditions) to the same hospitals where cases were interviewed. Three controls were frequency matched to each case according to sex, age and place of

residence. Details of alcohol consumption, such as lifetime drinking status, quantity, types of beverages drunk (i.e. wine, beer, herb liquors, grappa, and spirits) and age of starting to drink were obtained at study entry by trained interviewers using a structured questionnaire administered to subjects during their hospital stays. Former drinkers were defined as having abstained from any type of drinking for at least 12 months. There are no clear definitions for "current" drinkers and "abstainers" of which the latter comprised the reference category of "never" drinkers. Number of drinks consumed per week were based on one drink = 125ml wine, 330ml beer, 30ml hard liquor = 12g ethanol. With a non-response rate of 3%, the analysis included 150 histological confirmed cases of NPC (119m, 31f) and 450 controls (357m, 93f) with a median age of 52 years for each. Cases were further stratified into the following subtypes: undifferentiated NPC (WHO type 3) (n=118); keratinising squamous cell carcinomas/differentiated NPCs (WHO type 1) (n=22); and not otherwise specified NPCs (n=10). ORs and 95% CI for developing each NPC subtype were calculated using multiple logistic regression models, with adjustments for age, sex, place of residence, year of interview, education level, and smoking.

46. No clear relationship emerged between drinking status and NPC risk. Compared to never drinkers (n=16 cases, 54 controls), former and current alcohol drinking was not significantly associated with an increased risk of NPC (OR= 0.73 (0.21-2.50) and 1.14 (0.57-2.28) respectively. Current alcohol drinking of 28 drinks/week or more was not significantly associated with NPC (OR =0.95 (0.44-2.04) for <14 drinks/week, 1.05 (0.47-2.33) for 14-27 drinks/week and 1.91 (0.83-4.41) for ≥28 drinks/week; p=0.06). Duration of alcohol drinking and age at beginning were also unrelated to NPC risk: for duration (stratified into intervals <25, 25-39 and ≥40 years) OR were 1.36 (0.58-3.19), 1.05 (0.48-2.27), and 0.87 (0.35-2.20) respectively (p=0.74); for start age (stratified into intervals ≥21, 18-20, and <18 years) ORs were 1.05 (0.48-2.29), 1.24 (0.59-2.62), and 0.97 (0.43-2.20) respectively (p=0.97). No differences emerged according to histological subtype. For risk of undifferentiated NPC, compared to never drinkers (n=12 cases) ORs in former and current drinkers were 0.62 (0.13-2.83) and 1.35 (0.61-2.99) respectively; ORs in current drinkers consuming <14, 14-27, and ≥28 drinks/week was 1.11 (0.46-2.69), 1.32 (0.52-3.34) and 2.23 (0.84-5.89) respectively (p=0.06); ORs for duration of drinking for <25, 25-39 and ≥40 years was 1.52 (0.58-3.96), 1.24 (0.50-3.05), and 1.10 (0.37-3.25) respectively (p=0.88); ORs for start age of ≥21, 18-20, and <18 years was 1.35 (0.55-3.30), 1.53 (0.64-3.63), 0.95 (0.37-2.48), respectively (p=0.85). For risk of differentiated NPC, compared to never drinkers (n=2 cases) ORs in former and current drinkers were 0.94 (0.07-12.37) and 1.40 (0.29-6.71) respectively; ORs in current drinkers consuming <14, 14-27, and ≥28 drinks/week was 1.05 (0.18-5.96), 1.82 (0.30-11.05) and 3.18 (0.46-21.79) respectively (p=0.14); ORs for duration of drinking for <25, 25-39 and ≥40 years was 1.38 (0.17-11.05), 1.53 (0.28-8.54), and 1.43 (0.21-9.91) respectively (p=0.69); ORs for start age of ≥21, 18-20, and <18 years was 0.92 (0.15-5.65), 1.47 (0.27-7.88), 2.37 (0.42-13.44), respectively (p=0.16). It was suggested that these negative findings may be due to the lack of a direct contact of the nasopharynx with alcoholic beverages.

47. Takasc et al (2011) sought to clarify the alcohol dose-related risk of oral cancer in 1014 non-smoking age-matched Hungarian men and women. The analysis included 608 cases (466m, 142f) who were inpatients with histologically confirmed squamous cell oral carcinomas, and 406 (264m,142f) volunteer healthy controls who

agreed to participate in stomato-oncological screening during the study period. Ex-smokers for 10 years or more were considered eligible subjects. Details of alcohol consumption, such as quantity and frequency were obtained by questionnaire and case-reports of inpatients. Non-drinkers were defined as patients drinking only on special occasions. Regular drinkers were divided into moderate drinkers i.e. patients consuming alcohol containing < 25g alcohol per day (e.g. 1 bottle beer, 2dl wine, 0.5 dl spirit) for 5-7 days per week, and excessive drinkers i.e. patients regularly consuming above 25g/day. ORs and 95% CI were calculated by conditional logistic regression analysis. The authors considered that their data showed that a dose-related biphasic effect on OC risk whereby moderate drinking was associated with moderate OC risk in men (OR=1.4) but a decreased risk in women (OR= 0.7). Excessive drinking was associated with a high risk in both men (OR=2.2) and women (OR=3.6). No further information was provided.

48. Radoi et al (2013) investigated the association of two risk factors (tobacco smoking and drinking alcohol) on oral cavity cancer risk in subjects drawn from a large multicentre population-based case control study, Investigation of occupational and environmental CAuses of REspiratory cancers (ICARE), conducted from 2002 to 2007 in 10 French administrative areas covered by a general cancer registry per area. Cases were recruited in all healthcare establishments in selected areas of cancer registries and controls were drawn from the general population via random digit dialling, and frequency matched to cases by age, sex and residence (administrative area). Details of alcohol consumption, such as quantity and types of beverages drunk, were obtained at study entry by trained interviewers using a structured questionnaire performed within three months of cases being diagnosed. For sick participants, a shortened version was used or next of kin were interviewed. Ever drinkers were defined as having consumed at least one drink/month for at least one year. Former drinkers were defined as having stopped drinking for at least two years at the time of interview. Average daily consumption (glasses/day) was calculated by adding the average lifetime daily consumption of each beverage type and categorised into quartiles. NB. Quantity of alcohol contained in a standard glass= 15cl wine, 20cl beer, 5cl spirits, 10cl aperitif, 30cl cider. Never-drinkers were the reference category. ORs and 95% CI for developing squamous cell carcinoma of the oral cavity cancer were calculated using unconditional multiple logistic regression models, with adjustments for age, sex and area of residence, smoking. The analysis included a total of 772 cases (622m, 150f) and 3555 controls (2780m, 775f) and the non-participation rate was 18.2% and 19.4% respectively.

49. Compared with never drinkers (n=46 cases, 306 controls), ever drinking was associated with a reduced risk of oral cavity cancer in subjects who drank no more than 2 glasses/day (OR=0.4 (0.3-0.7) for <0.6 glasses/day and OR=0.6 (0.4-0.9) for 0.6-2.0 glasses/day). The risk was not significantly increased for individuals drinking less than 4.5 glasses/day (OR=1.2 (0.8-1.8) but was significantly increased above this (OR=3.2 (2.1-4.8). Analysis by type of alcoholic beverage was carried out only in subjects with a complete questionnaires (n=689 cases, 3481 controls); data was not collected in shortened version. Compared with never drinkers of wine (n= 66 cases, 543 controls); beer (n=195/1495); and spirits (n=200/1450) significantly increased risks of oral cavity cancer were apparent in subjects drinking higher number of glasses of wine:- ≤1 glasses/day: OR=0.8 (0.6-1.3); 2-3 glasses/day: OR=1.4 (0.9-2.1); 4-5 glasses/day: OR=2.4 (1.5-3.8); >5 glasses/day: OR=4.6 (2.9-7.4); and

beer:- ≤1 glasses/day: OR=1.1 (0.8-1.5); 2-3 glasses/day: OR=2.4 (1.6-3.6); 4-5 glasses/day: OR=3.2 (1.8-5.6); >5 glasses/day: OR=5.7 (3.2-10.1); and for spirits significant increases observed in subjects drinking between 4 and 5 glasses:- ≤1 glasses/day: OR=0.8 (0.6-1.1); 2-3 glasses/day: OR=0.9 (0.5-1.4); 4-5 glasses/day: OR=2.3 (1.2-4.9); >5 glasses/day: OR=1.8 (0.8-3.0). Compared with never drinkers of cider (n= 461 cases, 2362 controls) there was no increased risk of oral cavity cancer associated with cider drinking: ≤1 glasses/day: OR=0.6 (0.4-0.9); 2-3 glasses/day: OR=0.9 (0.5-1.7); 4-5 glasses/day: OR=0.6 (0.2-1.4); >5 glasses/day: OR=0.7 (0.2-2.1). Compared with never drinkers of aperitifs (n= 391 cases, 1898 controls) the results for aperitif drinking were not statistically significant: ≤1 glasses/day: OR=0.8 (0.6-1.0); 2-3 glasses/day: OR=2.5 (0.9-6.4); ≥4 glasses/day: OR=2.1(0.2-26.6).

50. The risk of oral cavity cancer in alcohol drinkers was also assessed by anatomical subsite (i.e. base of tongue, mobile tongue, floor of mouth, gums, soft palate and other parts of the oral cavity) via use of polytomous logistic regression (hard palate cases were excluded due to small numbers). There were significantly increased risks of cancer of the base of the tongue, mobile tongue, floor of the mouth, other part of the mouth and overall oral cavity in subjects who drank more than 2 glasses per day. Compared with never drinkers, ever drinkers who consumed either up to 2 glasses/day, or more than 2 glasses/day yielded the following ORs respectively: 0.5 (0.2-1.2) and 2.4 (1.1-5.4) for the base of tongue (n=145); 0.7 (0.4-1.4) and 2.3 (1.2-4.6) for the mobile tongue (n=179); 0.4 (0.1-1.1) and 0.7 (0.3-2.1) for the gums (n=44); 0.6 (0.3-1.4) and 3.4 (1.6-7.4) for the floor of mouth (n=214); 0.3 (0.1-0.8) and 1.7 (0.6-4.3) for the soft palate (n=83); 0.5 (0.2-1.6) and 3.1 (1.0-9.4) for the other mouth (n=89); and 0.6 (0.4-0.8) and 2.0 (1.5-3.0) for the oral cavity overall (n=772). Risk estimates were highest for floor of the mouth and lowest for the gums.

51. Smith et al (2010) conducted a US hospital-based case-control study to determine whether tobacco and alcohol represent a distinct risk factor profile for head and neck cancer (HNC) and whether this varies by tumour site. The existence of a second risk factor profile associated with the human papilloma virus (HPV) was also examined. Cases were patients with a mean age of 59.6 years diagnosed with primary HNC (oral cavity and oropharyngeal sites) between 2001 and 2004 at Iowa City Veterans Administration Hospital. Controls comprised of patients with a mean age of 59.6 years seeking routine medical care, screening or prescriptions with no prior history of HNC or requiring care/evaluation for an acute or chronic serious disease. Controls were recruited from Family and Internal Medicine clinics at the same hospital as cases and matched by gender and age. Details of alcohol consumption, such as drinking status and quantity were obtained at study entry via self-administered risk factor questionnaire (not clear whether an interview was performed). Never drinkers (referent category) were described as patients not having used alcohol on a regular basis during their lifetime for one year or more. Former drinkers were defined as not having used alcohol at least one year prior to cancer diagnosis (cases) or interview (controls). Current users of alcohol were defined as patients that used alcohol up to or less than one year prior to the time of cancer diagnosis/interview. Number of drinks consumed per week were based on one drink =12oz can/bottle beer, 4oz glass wine, 1.5 shot of hard liquor. This was used to stratify subjects into two groups: moderate consumers (drank ≤21 drinks /week) and

heavy consumers (>21 average drinks per week). The following reasons contributed to non-responses/exclusions in cases: illness (4%), refusal (<10%), and missed interview (6%); and in controls: failure to complete specimen collection (2%), refusal (4%). The analysis therefore included 201 cases (124m, 77f) that comprised of cancer of the oral cavity (n=139) and oropharynx (n=62), and 324 controls (212m, 112f) verified via hospital medical records and Iowa cancer registry. ORs and 95% CI for developing each cancer type were calculated using multiple logistic regression models, with adjustments for age, gender, HPV status (for analyses stratified according to drinking levels), tobacco-pack years

52. Compared to never drinkers (n= 51 cases, 134 controls) the adjusted risk estimates for tumours of the oral cavity were significantly elevated among heavy users of alcohol (OR= 3.8 (2.1-7.1) in patients who drank > 21 drinks/week cf. 0.9 (0.6-1.5) in consumers of ≤21 drinks/week. For oropharyngeal cancer, both moderate and heavy alcohol use carried a significantly elevated risk for oropharyngeal cancer. Compared to never drinkers (n= 9 cases, 134 controls), consuming ≤21 or > 21 drinks per week yielded ORs of 2.9 (1.3-6.5) and 6.2 (2.5-15.4) respectively. The association was also stronger compared to oral cavity. The authors also stratified the analysis according to HPV status as determined by enzyme-linked immunosorbent assay (ELISA) treatment and subsequent DNA sequencing of blood samples collected at interview and prior to cancer treatment to detect and determine HPV specific antibodies. The risk of cancer of the oral cavity was slightly increased among heavy alcohol users regardless of the HPV VLP status when compared to never alcohol users: OR= 3.7 (1.6-8.3) in seronegative consumers of >21drinks/week cf. 3.8 (95% CI= 1.4-10.1) in seropositive consumers of the same amount. The risk was higher in oropharyngeal cases (highest OR= 9.5 (2.3-38.6) in seronegative oropharyngeal heavy alcohol consumers) compared to oral cavity cases. The elevated risk of oropharyngeal cancer was similar in moderate alcohol users regardless of HPV status but was much greater among seronegative heavy drinkers cf. to seropositive heavy drinkers (OR= 5.0 (1.4-17.6) when compared to controls. The authors observed no interactive effect between HPV serology and alcohol and risk by tumour site.

53. Hakenewerth et al (2011) examined the association between SNPs/haplotypes for alcohol-related genes and alcohol exposure in subjects from a population-based case-control study of HNC in the US (Carolina Head and Neck Cancer Epidemiology Study, CHANCE). Cases were identified from the central cancer registry as subjects diagnosed with SCC of the oral cavity, pharynx and larynx in 46 counties of North Carolina between 2002 and 2006. Cancers of the salivary gland, and nasopharynx were not included. Controls were identified from vehicle registration lists from the same counties and frequency matched to cases for age, race and sex. Information on demographics, tobacco use, drinking of alcoholic beverages (beer, wine, and liquor), diet, oral health, medical history, and family history of cancer was obtained by trained interviewers. Lifetime alcohol consumption (in millilitres) was used as a measure of alcohol intake with 0 ml used as the reference category. A total of 1227 cases (938m, 289f) and 1325 controls (924m, 401f) were included in the analysis. Cases comprised of: 166 with oral cavity cancer, 310 oropharyngeal, 208 not otherwise specified (NOS) oral cavity, oropharyngeal, and hypopharyngeal cancer, and 51 hypopharyngeal cancer. Information for total of 46 cases and 43 controls were missing. ORs and 95% CI for developing each cancer

type were calculated using conditional logistic regression models, with adjustments for sex, race, age and smoking.

54. Odds of developing cancers at these subsites increased monotonically as lifetime alcohol consumption increased; these were generally not statistically significant at lowest and moderate drinking categories. However, in the highest drinking category, all subsites experienced significantly increased odds: tripled or greater odds for oropharyngeal and oral cavity cancer. For cancer of oral cavity, compared to subjects with 0ml lifetime consumption (n= 22 cases, 280 controls), OR in subjects drinking >0-133294, >133294-757550, and 757550+ ml alcohol in their lifetime were, 0.45 (0.23-0.89), 1.28 (0.68-2.41) and 5.34 (2.67-10.67) respectively. For oropharyngeal cancer, the corresponding ORs at the same increasing levels of consumption were 0.87 (0.53-1.44), 1.47 (0.89-2.45), and 3.47 (2.00-6.04) respectively compared to 0ml (n=27 cases). For NOS: Oral cavity, oropharyngeal, and hypopharyngeal cancer, OR were 0.93 (0.54-1.62), 1.48 (0.83-2.64), and 4.49 (2.40-8.39) cf. 0ml (n=23 cases). For hypopharyngeal, OR were 2.25 (0.26-19.84), 5.13 (0.61-43.04) and 28.74 (3.42-241.40) cf. 0 ml (n=51 cases). No interactions of SNPs/haplotypes with alcohol were detected for anatomic subsites (data reported for SCCHN as a whole).

55. Ferreira-Antunes et al (2013) investigated the independent and joint effects of smoking and drinking on oral and oropharyngeal cancer (combined) in a homogenous sample of adults drawn from 4 hospital-based case-control studies in Brazil. The authors used two models: one that adopted a conventional method to assess individual effects of tobacco smoking and alcohol drinking (the OR for the ‘‘ever smoking, ever drinking’’ category was obtained by the inverse of the logarithm of the sum of the coefficients of smoking and drinking, as provided by logistic regression) and another that accounted for an interaction effects (the OR for the ‘‘ever smoking, ever drinking’’ category was obtained by the inverse of the logarithm of the sum of the coefficients of smoking, drinking and smoking-drinking interaction term). Only data relating to the independent effects of alcohol are summarised here. Cases were newly diagnosed patients with invasive SCC of the oral cavity and oropharynx confirmed histologically, who sought care in four hospitals of Sao Paulo and followed similar referral routes (GP) between 1998 and 2008. This included cancers of the tongue, floor of mouth, palate, other unspecified parts of mouth, tonsil. The following were not included: cancers of the lip, nasopharynx, and hypopharynx. Controls comprised outpatients of the same hospitals who sought care in same four hospitals of Sao Paulo and followed similar referral routes (GP, dentists) and were not affected by diseases potentially related with drinking and smoking exposures. Those with current/previous history of aerodigestive tract diseases were not included. Matching was made for gender and age. Details of alcohol consumption, such as drinking status and quantity (g ethanol/ day) were obtained at study entry by trained (non-blinded) examiners who interviewed participants immediately after clinical consultation in private. The methods deployed were endorsed by IARC and were validated, standardised and extensively used in studies within the INHANCE Consortium. Non-drinkers (referent category) were described as patients reporting never consuming at least one alcohol drink at a regular monthly basis. Ever drinkers were not defined. Median cumulative alcohol consumption (862 g-years) was used to split drinking into two levels: level 1 drinkers (moderate consumption of ≤ 862g-years); and level 2 drinkers (heavy consumption > 862g-years). The analysis

included 1144 cases (923m, 221f) of oral and oropharyngeal cancers and 1661 controls (1216m, 445f). Data on non-response rates was not reported. Unadjusted ORs and 95% CI were calculated using unconditional logistic regression. Adjusted risk estimates were calculated using one of two models: Model 1, described as simple and conventional that accounted exclusively for confounding and assumed smoking and drinking exert individual (non-interactive) effects; and the alternative Model 2, that accounted for both confounding and interaction and assumed smoking and drinking exert individual and interactive effects. Adjustments were made for age, gender and education.

56. For unadjusted risk estimates, there was a significant association between alcohol drinking and oral and oropharyngeal cancer. Compared to never drinkers (n= 199 cases, 769 controls), ever drinking and both levels of alcohol consumption were associated with an increased risk of oral and oropharyngeal cancer (OR= 4.21 (3.50-5.06), 1.68 (1.34-2.11) and 6.73 (5.35-7.91) respectively. For adjusted ORs (and restricting the data to never smokers), the independent effect of alcohol was highly and significantly associated with oral cancer in Model 1. Compared to never drinkers, ever drinking and both levels of alcohol consumption were again associated with an increased risk of oral and oropharyngeal cancer (OR= 3.60 (2.86-4.53), 1.68 (1.29-2.20) and 5.71 (4.41-7.39) respectively. However, in Model 2, ORs were generally lower than those estimated by Model 1; and the independent effect of alcohol was no longer associated with cancer. Compared to never drinkers, ever drinking and both levels of alcohol consumption were not significantly associated with an increased risk of oral and oropharyngeal cancer (OR= 0.78 (0.48-1.27), 0.63 (0.40-1.00) and 1.51 (0.88-2.57) respectively. The authors report that the joint effect of drinking and smoking was significantly associated with oral cancer (data not included here).

57. Szymanska et al (2011) conducted a multicentre hospital-based case control study to assess the role of two risk factors (tobacco and alcohol consumption, and their interactions) on the risk of squamous cell carcinoma (SCC) of four sites of the upper aerodigestive tract (UADT) in patients drawn from seven centres in Latin America (i.e. Brazil, Argentina and Cuba). Cases were patients from a participating hospital or referred for primary treatment that were newly diagnosed with the following UADT cancers: (1) oral cavity and oropharynx, including floor of mouth, other parts of oral cavity, oral cavity NOS, oropharynx, overlapping tumours with the origin in the oral cavity (overlapping oral cavity-oropharynx-hypopharynx NOS), (2) hypopharynx and larynx, (3) oesophagus. Cancers of the following sites were not included: salivary glands tumours with an unknown site, in-situ tumours and carcinomas other than squamous cell. Controls were identified by trained interviewers or study coordinators from hospital admission records or from relevant clinical wards (exact procedures varied by centre) and comprised in- or out-patients from the same hospitals as cases who were recently diagnosed with diseases not related to tobacco or alcohol (non-tumour/malignant). Controls were frequency matched to cases by sex, age and study centre. Details of alcohol consumption, such as drinking status, quantity, types of beverages drunk (i.e. wine, beer, spirits and aperitifs) were obtained at study entry by trained interviewers using a detailed lifestyle questionnaire administered face-to-face in hospital within days/weeks of diagnosis (cases). “Ever” drinkers were defined as having ever consumed alcoholic drinks at least once a month and former drinkers were patients who quit drinking for more than one year before interview (controls) or diagnosis (cases). Alcohol intake

was measured in ethanol grams/day on the basis that beer contains approx. 5% ethanol in volume, wine 12%, spirits 40%. Cumulative exposure was measured in gram-years and estimated by multiplying average grams of ethanol per day by the years of alcohol consumption. Non-response rate in cases and controls were 5% and 14% respectively. A total of 1030 cases of cancer of the oral cavity and oropharynx and were histologically confirmed by pathologists in each of the participating hospitals and included in the analysis. This included 1707 controls Cancers of the hypopharynx were combined with the larynx (n=997) and therefore not included in this summary. Never drinkers were the reference category. ORs and 95% CIs were calculated by unconditional multivariate logistic regression and adjusted for age, sex, centre, education, fruit and cruciferous vegetables consumption, cumulative tobacco consumption, alcohol gram years (assessing type of alcohol in ever drinkers), alcohol-g/day (assessing years since quitting). ORs were also estimated for an increase in 10 (or 1000) units on a continuous scale.

58. Alcohol drinkers had a significant association with the risk of developing oral cavity and oropharyngeal cancer. Compared to never drinkers (n= 73 cases, 442 controls), ever drinking was associated with an increased risk of cancer (OR= 4.62 (3.39-6.28)), there being a larger increase in risk for current than for former drinkers (OR=5.26 (3.76-7.37) for current drinkers and 3.62 (2.58-5.06) for former drinkers. Dose effect relationships were evident for alcohol quantity, drinking duration, and cumulative alcohol consumption. Compared to never drinkers (n= 73 cases, 442 controls), ORs for: daily consumption of 0.1-8.6, 8.61-24.8, 24.81-68.8 and >68.8 g/day were 2.92 (2.02-4.20), 3.39 (2.34-4.92), 6.60 (4.58-9.53) and 10.95 (7.6-15.78) respectively; ORs for duration of 15, 16-30, 31-40, and ≥41 years were 2.64 (1.70-4.09), 4.27 (3.03-6.01), 5.79 (4.10-8.17) and 5.65 (3.93-8.13) respectively; ORs for cumulative alcohol consumption of 0.1-233.66, 233.61-765, 765.1-2035.6, and >2035.6 gram-years were 2.74 (1.90-3.94), 3.64 (2.51-5.29), 6.16 (4.27-8.87) and 11.26 (7.83-16.20) respectively. A protective effect was also observed for quitting alcohol. Compared to current drinkers (n= 669 cases, 692 controls), ORs for years since quitting drinking in 2-4, 5-9, 10-19 and ≥ 20 were 0.81 (0.57-1.14), 0.63 (0.45-0.90), 0.50 (0.35-0.71), 0.42 (0.26-0.66). When analysing according to specific beverage type, a strong effect was observed for spirits and aperitifs category. Compared to never drinkers (n= 73 cases, 442 controls), ORs were 2.28 (1.49-3.49) for drinking beer only; 2.92 (1.61-5.29) for wine only; and 11.38 (7.36-17.59) for spirits and aperitifs only. To investigate whether this was due to differences in alcohol consumption between drinkers of different alcohol types, an analysis of drinkers only was conducted with beer drinkers as a reference category (n= 70 cases, 219 controls). The strong effect was still observed for pure drinkers of spirits and aperitifs (OR= 3.99 (2.60-6.14) cf. 1.69 (0.77-3.71) in wine only drinkers. No significant associations were apparent in never smokers adjusted for sex, age, centre, education and fruit and veg consumption. Compared to never drinkers (n= 33 cases, 247 controls), ORs were 1.12 (0.59-2.12) in ever drinkers, 0.89 (0.33-2.44) in former drinkers and 1.22 (0.45-3.34) in current drinkers.

59. Madani et al (2014) conducted a 19 month long population-based case control study to investigate the combined effect of alcohol drinking and tobacco/bidi smoking on oral cancer risk in 700 Indian men and women. A total of 350 cases (251m, 99f newly diagnosed patients) with an average age of 52.4 years, and 350 healthy controls (254m, 96f) average age of 51.8 years were included in the analysis. The

authors note that subjects were selected via random sampling between February 2005 and September 2006. Controls were selected from relatives, friends and caretakers of case subjects accompanying patients to hospital (which suggests they could have similar drinking exposures) and matched to cases by age, gender and residential status. Details on alcohol consumption were obtained for beverage type only (i.e. beer, hard liquor, country liquor and wine) via a trained interviewer who provided subjects with a self-reported structured questionnaire when appropriate. No further details are provided in relation to the referent category or drinking groups. Unadjusted ORs and 95% CIs were calculated via univariate analysis. Smoking and drinking rates were significantly different between cases and controls (smoking: 35.7% cases vs 17.4% controls) p<0.001. For overall alcohol consumption, a significant association was reported for risk of oral cancer (OR=3 (1.9-4.3); p=0.001; n=106/45. Significantly increased risks were reported for each type of alcohol beverage, with liquor consumption yielding the highest risk estimate (OR= 2.2 (1.2-5), p=0.026, n=29/12 for beer; 2.6 (1.2-5.5), p=0.002, n=29/10 for hard liquor; 2.5 (1.3-3.6), p=0.001, n=55/25 for country liquor and 1.7 (0.6-4.3), p=0.524, n=12/7 for wine).

Summary of case-control studies on oral cavity and pharyngeal cancer risk

60. There is a general lack of uniformity in the definitions used to describe oral cavity/ pharyngeal cancer among the evaluated studies. Six studies provided data on the associated risk of oral cavity cancer (as a whole) and alcohol drinking (Smith et al., 2010; Hakenewerth et al., 2011; Takasc et al., 2011; Marron et al., 2012; Radoi et al., 2013; Madani et al., 2014). Significantly elevated ORs were consistently reported for the highest levels of total alcohol consumption (that ranged from 2.0 to 5.3 for consumption of more than 2 glasses per day and a lifetime quantity of 757.6 litres respectively) with the lowest levels of consumption yielding negative associations (Smith et al., 2010; Hakenewerth et al., 2011; Radoi et al., 2013). A similar pattern was apparent in a Hungarian case-control study of moderate or excessive drinking patients stratified according to gender, although the authors did not report the levels of significance associated with each risk estimate (Takasc et al., 2011). Three studies analysed the risk of oral cavity cancer according to the type of beverage consumed (Marron et al., 2012; Radoi et al., 2013; Madani et al., 2014). The highest significant risks as reported in a European ARCAGE multicentre study were found in 'never wine' male drinkers (OR=3.8) compared to never drinkers, followed by men who only consumed beer (OR=3.6), never drank liquor (OR=2.6) or drank liquor and other beverages (OR=2.5) (Marron et al., 2012). Although this study did make several multiple comparisons, the positive association found for beer consumption was corroborated by the significant dose-response relationships observed in a multicentre population-based case control study of French men and women who drank between 2 to >5 glasses of beer/day (OR up to 5.7) and between 4 and 5 glasses of wine a day (OR up to 4.6) (Radoi et al., 2013). Radoi and colleagues was the only case control study that evaluated cancer risk according to different regions within the oral cavity. Subjects who drank more than 2 glasses of alcohol per day had between 2-3-fold significantly increased risks of cancer of the base of the tongue, mobile tongue and floor of the mouth relative to never drinkers. However, use of a modified questionnaire in sick participants may have compromised the strength of these findings.

61. Marron et al (2012) provided data on the associated risk of cancer of the whole pharynx and alcohol drinking and observed significant positive associations in pure drinkers of beer, wine and liquor, with OR of 2.5, 2.6 and 3.2 respectively. No significant associations were found in an Italian case control study of patients diagnosed with cancer of the nasopharynx (Polesel et al., 2011). In contrast, for cancer of the oropharynx, a significant dose-dependent increase was observed in patients who reported drinking up to more than 21 drinks/week (Smith et al., 2010), and there was a 3.5-fold increased risk of cancer of the oropharynx in US subjects who had a lifetime alcohol consumption of more than 757.6 litres (Hakenewerth et al., 2011). For cancer of the hypopharynx the risk increased a further 8 times (OR=28.7), however the study was subject to possible selection bias owing to lack of reporting of non-response rates and there being missing data for subjects. Finally, two Latin American studies evaluated the associated risk of cancer of the oral cavity and oropharynx (combined) and alcohol drinking (Szymanska et al., 2011; Ferreira-Antunes et al., 2013). Both studies reported significant positive associations with drinking status (OR ranged from 3.6 to 5.6) and observed dose-dependent increased ORs with cumulative exposure (ranged from 1.7 to 11.3). Szymanska et al (2011) also reported significant dose-related increases in the risk of cancer of the oral cavity and oropharynx with regard to the quantity of ethanol consumed and duration of drinking. Relative to never drinkers, consumption of more than 68.8 g/day for more than 41 years was associated with an 11 and 5.7-fold increased risk of cancer respectively. The risk was particularly elevated for subjects who consumed liquor only (OR=11.4) compared to wine only (OR=2.9) or beer only (OR=2.3).

Risk Factors (Table 5)

62. A short research communication was identified that highlighted the challenges associated with predicting the progression of precancerous lesions (Goodson et al 2009). The potential ability of invasive SCC to arise without any premalignant dysplastic lesion led Goodson and colleagues to compare a subjective (self-reported) measure of alcohol intake with an objective measure i.e. mean corpuscular volume (MCV) in patients with oral precancerous lesions to determine whether it provided an effective assessment of the degree of dysplasia at presentation and the risk of further disease after treatment. Furthermore, macrocytosis (increased volume of red blood cells) has been used to predict oesophageal carcinoma in alcoholics.

63. Goodson et al (2009) performed a clinical study in 54 consecutive new patients presenting to the maxillofacial dysplasia clinic in Newcastle General Hospital with single histologically confirmed, dysplastic oral precancerous lesions. All 34 men and 20 women aged between 35 and 91 years (mean age of 64 years) were smokers (10-20 cigs /d) with no previous history of oral cancer/lesions. All patients received identical treatments by same clinician which involved a clinical examination of the lesion, and formal laser excision of any dysplastic lesion by one surgeon (which was assessed for degree dysplasia using standardised criteria. Alcohol consumption data was recorded as weekly alcohol units with high intake defined as consuming more than 28 units per week. Venous blood was taken preoperatively for MCV measurement within 2h values. Macrocytosis was defined as MCV > 100 femtolitres. Patients were excluded if there was evidence of other causes of macrocytosis e.g. Vit B12 or folate deficiency. Patients were then followed up for two years after which the clinical outcome was categorised as being either disease-free

or with further disease (i.e. recurrent oral precancerous lesions at the same site, further development of lesions at new site, or development of SCC at any site). Raised MCV at presentation was not significantly related to incidence of further disease (p=0.8): 12 out of 38 patients who presented with MCV≤ 100 developed further disease (rate =32%) cf. 6 out of 16 patients who presented with MCV > 100 developed further disease (rate=34%). Reported high levels of consumption predicted the development of further disease. Patients who regularly drink high levels of alcohol (> 28units/week; n=20) had an increased risk of developing further disease after treatment: 9 cases i.e. 45% with further disease cf. 26% rate of further disease in patients who drank ≤ 28 units/week (n=34). The authors concluded that there was no significant difference between both measures of alcohol intake.

Genetic Polymorphisms (Table 6)

64. Matsuo et al 2012 conducted a hospital-based Japanese case-control study to investigate the interaction between folate and alcohol and to evaluate the potential effect modification by aldehyde dehydrogenase 2 (ALDH2) genotype in oral and pharyngeal cancer (OPC) risk. Data relating to alcohol exposure and risk of OPC and its modification by ALDH2 genotype is summarised here. Cases were patients histologically diagnosed with OPC between Jan 2001 to Dec 2005 at Aichi Cancer Centre hospital. OPC included cancers of the oral cavity, oropharynx and hypopharynx according to ICD codes. Malignant neoplasms of the lip, salivary glands and nasopharynx were not included. Randomly-selected controls were composed of outpatients of the Aichi Cancer Centre hospital between Jan 2001 to Dec 2005 who were medically and radiologically confirmed not to have cancer or history of cancer. Controls were age and sex matched to cases at a ratio of 3:1. Details of alcohol consumption such as, quantity and types of beverages drunk (i.e. Japanese sake, beer, shochu, whiskey, and wine converted into a Japanese sake equivalent) were obtained at study entry via self-administered questionnaire. Alcohol intake was based on the assumption that 1 drink = 180ml sake (contains 23g ethanol) = Large bottle beer (633 ml), two shots whiskey (57ml), 2.5 glasses wine (200ml) and 1 unit=12.5g ethanol. Drinking groups were defined as either being intermediate (< 4 units/day) or high (≤ 4 units/day). Never drinkers were the referent category. A total of 409 (296m, 113f) cases were included in the analysis which comprised of 257 oral cavity; 72 oropharyngeal; 80 hypopharyngeal cases of cancer, with 1227 controls (888m, 339f). DNA samples were available for approximately 60% of study participants (251 cases and 759 controls), which underwent TaqMan assaying for genotyping for ALDH2 Glu504Lys. This allele encodes a catalytically inactive subunit such that individuals experience marked elevation in blood acetaldehyde after alcohol ingestion and also have higher susceptibility to upper aerodigestive tract (UADT) cancer compared to the ALDH2 Glu/Glu genotype due to decreased acetaldehyde elimination. The ALDH2 genotypes detected among participants were: Glu/Glu (encodes a catalytically active subunit): 103 cases, 372 controls; and Lys+ (148 cases, 387 controls). Average daily intake of folate was estimated from responses to FFQs after calculating the sums of their intakes in the single food items as estimated from a food composition table according to the indicated portion size, multiplied by the food frequency. ORs and 95% CIs were calculated by multiple logistic regression models and adjusted for age, occupation, BMI, smoking, non-alcoholic energy intake, and smoking.

65. Alcohol displayed a significantly positive association with OPC risk. Compared to never drinkers (n=113 cases, 454 controls) consumption of ≤ 4 units/day was associated with a significantly increased risk of OPC (OR= 2.67 (1.83-3.88) p for trend <0.001. With regards to the interactive effect of ALDH2 genotype and alcohol (stratified according to folate intake) the effect of alcohol was only significantly elevated in heavy drinking ALDH2 Lys allele carriers (not in ALDH2 Glu/Glu), and the risk of OPC was further increased in those with low-intermediate folate intake (<243.5ug/day) compared to those with high folate intake (≥ 378.4ug/day). Compared to never drinkers with high folate intake (n=11 cases, 75 controls), ORs for OPC in high drinkers were 11.9 (3.95-36.1) in those with low folate intake, and 4.36 (1.04-18.2) in those with high folate intake. P value = 0.001 for a 3-way interaction term for genotype, folate and alcohol consumption.

Overall Summary

66. There is a general lack of uniformity in the definitions used to describe oral cavity/ pharyngeal cancer among the evaluated studies. Sixteen studies provided data on the risk of cancer of the oral cavity (as a whole) and alcohol consumption. A statistically significant positive association between alcohol consumption and cancer of the oral cavity (as a whole) was reported by the majority of studies regardless of study type (5 meta-analyses, 2 cohort and 6 case control studies), and the risk in these studies was consistently elevated at the highest levels of alcohol consumption. There is less consistent evidence of a positive association at lower alcohol drinking levels although one cohort (Shanmugham et al 2010) and two case-control studies (US/French) (Hakenewerth et al., 2011; Radoi et al., 2013) provide evidence of significantly negative associations at lower levels of intake. There are no clear indications from the reported evidence that consumption of a specific type of alcoholic beverage is associated with an increased risk of cancer of the oral cavity. With regard to the subtypes within the oral cavity, the findings from a French case-control study (Radoi et al 2013) and an international meta-analysis (Turati et al 2010) suggest that the tongue (and possibly the floor of the mouth) may present significant target sites within the mouth.

67. Five studies provided data on the risk of cancer of the pharynx (as a whole) and alcohol consumption. All studies, regardless of study type (3 meta-/pooled analyses, 1 cohort and 1 case-control study) showed a statistically significant positive association between alcohol consumption and risk of cancer of the pharynx. Similar to the oral cavity, there was no consistent evidence of an association at lower levels of alcohol drinking, and no consistent evidence that consumption of a specific type of alcoholic beverage is associated with a particularly elevated risk of cancer of the pharynx. However, you may note the findings of a European case-control study that observed that “pure liquor drinkers” (i.e. drinkers of liquors solely) yielded the highest risk estimates relative to never drinkers, followed by pure wine and pure beer drinkers (Marron et al 2012). With regard to the subtypes within the pharynx, four studies (2 meta-/pooled analyses and 2 case control studies) all reported significant positive associations for the risk of cancer of the oropharynx in drinkers (Turati et al 2010; Lubin et al 2011 and Smith et al., 2010; Hakenewerth et al., 2011 respectively). This risk was found to be notably elevated in North American/European women compared to their male counterparts, although there was no significant association with cumulative exposure (drink-years) for either sex

(Lubin et al., 2011). The same studies reported similar and stronger associations for cancer of the hypopharynx. Cancer arising in the 'orohypopharynx' was investigated in a Dutch cohort study that observed a significant positive association with heavy alcohol consumption (Maasland et al 2014). There was no strong evidence to suggest that alcohol consumption was associated with the risk of cancer of the nasopharynx.

68. Three international meta-analyses provided data on the risk of cancer of the oral cavity and pharynx (combined) and alcohol consumption (Tramacere et al 2010; Bagnardi et al. 2013; 2015). All studies showed a statistically significant positive association between alcohol consumption and cancer of the oral cavity and pharynx (combined) at both light and heavy levels of consumption. Finally, two Latin American case-control studies reported significant positive associations for ever drinking and increasing cumulative exposure of alcohol and the risk of cancer of the oral cavity and oropharynx (combined) (Szymanska et al., 2011; Ferreira-Antunes et al., 2013). The risk was particularly elevated for drinkers who consumed liquor only (Szymanska et al., 2011).

Questions for the Committee

1) What are the views of the Committee on the recently available epidemiological studies (case-control, cohort, pooled and meta-analysis) on alcohol exposure and oral cavity and pharyngeal cancer risk?

2) Do the studies reviewed here add further weight to the existing view that alcohol consumption is causally associated with oral cavity and pharyngeal cancer risk?

PHE Toxicology Unit/COC Secretariat
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Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009							
Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
Hashibe et al. (2009) Pooled analysis Europe & N. America: 17 studies	Used data from INHANCE consortium.	Oral cavity cancer: 2875 cases, 15751 controls; Pharyngeal cancer: 3899 cases, 1571 controls	Face-to-Face interviews (mostly)	Referents =never drinkers Drinkers = 1-2 drinks/day; ≥ 3 drinks/day Drinkers = 1-2 drinks/day; ≥ 3 drinks/day NB. Restricted to never smokers	Common odds ratio Never=1.0 Oral cavity 0.88 (0.65-1.20) 1.05 (0.62-1.77) Pharyngeal cancer 1.26 (0.92-1.73) 2.94 (1.73-5.02)	Age, sex, education level, race/ethnicity and study centre	Missing values for tobacco and alcohol frequency categories led to reduced number of cases and controls Study limitations: regional differences in social acceptance of tobacco and alcohol habits may have influenced response obtained during interviews; recall bias (subjects knew their disease status when interviewed); lack of adjustment for unmeasured potential confounders such as HPV infection and nutritional factors

Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009							
Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
Lubin et al (2010) Pooled analysis Europe and N. America: 15 studies Est. 2004 (ongoing)	Used data from INHANCE consortium	2563 (oral cavity), 3089 (pharynx) / 14794	Not given	**[Drink-years]:-** 0 (ref); 1-49; 50-99: 100-149: 150-199: ≥200: Drink-years]:- 0 (ref); 1-49; 50-99: 100-149: 150-199: ≥200: **[Drinks/day]:-** 0.01-0.9 (ref); 1.0-2.9; 3.0-4.9; 5.0-10.0 [Drinks/day]:- 0.01-0.9 (ref); 1.0-2.9; 3.0-4.9; 5.0-10.0	**Oral cavity:** Pooled OR=1 1.04 (0.9-1.3); 1.66 (1.2-2.3); 2.24 (1.5-3.3); 2.81 (1.8-4.4); 3.22 (2.0-5.2); p for linear trend<0.01 **Pharynx:** 1.30 (1.1-1.5); 1.50 (1.1-2.0); 1.41 (1.0-2.0); 1.57 (1.1-2.3); 1.96 (1.3-3.0); p for linear trend<0.01 **Oral cavity:** 1.0; 1.26 (1.0-1.6); 1.29 (0.9-1.8); 1.87 (1.2-3.9); p for linear trend<0.01 **Pharynx:** 1.52(1.3-1.9); 2.30 (1.7-3.1); 3.67(2.6-5.3); p for linear trend<0.01	Sex, education, BMI, pack years of smoking, cigarettes/day, use of other tobacco products (and either drinks/day or drink-years)	Hypothesis tests using polytomous regression did not reject homogeneity of odd ratios for both sites (P=0.73). Risks greater at lower BMI NB. Authors do not specify no. of grams ethanol per drink

Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009

Reference, location, name of study	Cohort description (No. in analysis)	No. of cases/ controls, n	Exposure assessment	Exposure categories	Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]	Adjustment factors	Comments
Lubin et al (2011) Pooled analysis Europe and N. America: 15 studies Est. 2004 (ongoing)	Used data from INHANCE consortium	2441 (oral cavity), 2297 (oropharynx), 508 (hypopharynx)/ 13829	Not given	**Drink-years:-** 0 (ref); 1-49; 50-99: 100-149: 150-199: ≥200: 0 (ref); 1-49; 50-99: 100-149: 150-199: ≥200: 0 (ref); 1-49; 50-99: 100-149: 150-199: ≥200:	**Oral cavity:** **Females** OR: 1.00 (ref) 0.94 (0.7-1.2) 1.61 (0.9-2.9) 1.44 (0.6-3.3) 1.96 (0.5-6.6) 1.82 (0.6-6.5) **Males** 1.00 (ref) 1.01 (0.9-1.5) 1.95 (1.2-2.7) 1.58 (1.7-4.1) 1.94 (1.9-5.5) 1.93 (2.2-6.6) P-homogeneity=0.66 **Oropharynx:** **Females** 1.00 (ref) 1.38 (1.0-1.8) 2.20 (1.2-4.0) 1.73 (0.8-3.7) 2.65 (1.0-7.1) 1.98 (0.6-7.0)	Study, age, sex, education, BMI, pack-years, cigarettes per day (CPD), years since smoking cessation, use of other tobacco products, and (DPD or drink-years)	Joint ORs by categories of drinks-years of alcohol consumption and DPD also estimated Possible study limitations: misclassification of smoking, drinking, BMI or confounding from other risk factors e.g. HPV, diet, occupation may have influence results; possible underreporting of consumption in women and overestimation of alcohol-related ORs (since drinking in some populations may be less socially acceptable in women NB. Authors do not specify no. of grams ethanol per drink

Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009							
Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
				0 (ref); 1-49; 50-99: 100-149: 150-199: ≥200: 0 (ref); 1-49; 50-99: 100-149: 150-199: ≥200: 0 (ref); 1-49; 50-99: 100-149: 150-199: ≥200:	**Males** 1.00 1.31 (1.1-1.6) 1.25 (0.9-1.7) 1.30 (0.9-1.9) 1.64 (1.0-2.6) 1.98 (1.2-3.2) P-homogeneity=0.60 **Hypophraynx: Females** 1.00 0.59 (0.3-1.3) 3.49 (0.8-15) 1.40 (0.2-8.4) 1.07 (0.1-11) 1.25 (0.1-18) **Males** 1.00 0.84 (0.4-1.7) 1.63 (0.6-4.2) 1.46 (0.5-4.2) 1.22 (0.4-3.8) 2.65 (0.8-8.4) P-homogeneity=0.50		

Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009							
Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
				Drinks per day:- 0.01-0.9 (ref); 1.0-2.9; 3.0-4.9; 5.0-10.0 0.01-0.9 (ref); 1.0-2.9; 3.0-4.9; 5.0-10.0 0.01-0.9 (ref); 1.0-2.9; 3.0-4.9; 5.0-10.0 0.01-0.9 (ref); 1.0-2.9; 3.0-4.9; 5.0-10.0	**Oral cavity:** **Females** 1.00 1.23 (0.8-1.9) 1.81 (0.8-4.0) 2.37 (0.8-7.5) **Males** 1.00 1.25 (0.9-1.6) 1.20 (0.8-1.8) 1.75 (1.1-2.8) P-homogeneity=0.78 **Oropharynx:** **Females** 1.00 1.60 (1.1-2.4) 3.21 (1.6-6.4) 7.63 (2.8-21) **Males** 1.00 1.46 (1.2-1.8) 1.91 (1.3-2.7) 2.82 (1.8-4.3) P-homogeneity=0.29		

Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009							
Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
				0.01-0.9 (ref); 1.0-2.9; 3.0-4.9; 5.0-10.0 0.01-0.9 (ref); 1.0-2.9; 3.0-4.9; 5.0-10.0	**Hypophraynx:** **Females** 1.00 1.35 (0.4-4.3) 5.95 (1.1-30) 19.6 (1.8-217) **Males** 1.00 1.62 (0.8-3.3) 3.33 (1.4-8.2) 7.03 (2.6-19) P-homogeneity=0.68 P for trend<0.01 for all categories		

Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009

Reference, location, name of study	Cohort description (No. in analysis)	No. of cases/ controls, n	Exposure assessment	Exposure categories	Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]	Adjustment factors	Comments
Tramacere et al 2010 Meta-analysis America: 18 studies (US=12 studies); Europe: 17 studies; Asia: 10 studies Published up to September 2009	43 case control (CC), 2 cohort C) examining cancer of oral cavity and pharynx (combined)	CC: 17278 cases and 80041 controls; C: 192 cases and 2854647 non-cases)	Authors restricted analysis to studies that reported at least 3 levels of alcohol consumption	Referent: Non or occasional drinkers Drinkers: Low alcohol intake = ≤ 1 drink/day Heavy alcohol drinking = ≥ 4 drinks/day 1 drink = 12.5g ethanol	Pooled relative risk **Light alcohol drinking (n=19 CC, 1C)** All: 1.21(1.10-1.33); p=0.71 CC: 1.23(1.11-1.34) C: 0.78 (0.46-1.36) **Heavy drinking (n=29 CC, 2C)** All: 5.24 (4.36-6.30); p=<0.01 CC: 5.33 (4.40-6.47); p <0.01 C: 4.25 (3.03-5.96); p=0.55 **Dose response, g/day** 10: 1.29 (1.25-1.32) 25: 1.85 (1.74-1.96) 50: 3.24 (2.89-3.64) 75: 5.24 (4.58-6.40) 100: 8.61 (6.91-10.73) 125: 13.02 (9.87-17.18)	Tobacco, social class, selected dietary factors, oral hygiene and other recognised risk factors for OPC	Used only one search engine so may not be as comprehensive a literature search Authors also computed either unadjusted RRs provided from papers or SE for risk estimates of studies that did not report CIs P values (for heterogeneity) Possible study limitations: under-reporting of alcohol consumption may explain the observed association for light drinking (resulting in overestimation of the RR for the low doses); other limitations and biases associated with use of retrospective exposure assessments; possible residual confounding by tobacco or other risk factors of oral and pharyngeal cancers

Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009							
Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
Turati et al (2010) Meta-analysis Related to Tramacere et al 2010 Published up to September 2009	30 case control (CC), 1 cohort C) Oral cavity cancer (O): 22 studies; tongue cancer (T): 6 studies Pharyngeal cancer (P): 22 studies; oropharyngeal cancer (OP): 4 studies; hypopharyngeal cancer (HP): 4 studies	O: 7419 cases: T: 558 cases; P: 4664 cases; OP: 1060 cases; HP: 910 cases.	Authors restricted analysis to studies that reported at least 3 levels of alcohol consumption	Referent: Non or occasional drinkers Drinkers: Low alcohol intake = ≤ 1 drink/day Heavy alcohol drinking = ≥ 4 drinks/day 1 drink = 12.5g ethanol	Pooled relative risk **Oral Cavity:** **Light drinking (n=8 CC, 1C)** All: 1.17 (1.01-1.35); p=0.62 CC: 1.20 (1.03-1.40) C: 0.78 (0.46-1.33) **Heavy drinking (n=16 CC, 1C)** All: 4.64 (3.78-5.70); p=0.001 CC: 4.70 (3.76-5.88); C: 4.41(3.07-6.33); **Pharynx:** **Light drinking (n=5 CC)** All: 1.23 (0.87-1.73); p=0.152 **Heavy drinking (n=17 CC)** All: 6.62 (4.72-9.29); p<0.001 **Tongue:** **Heavy drinking (n=5 CC)** All: 4.11 (2.46-6.87); p=0.154	Tobacco, social class, selected dietary factors, oral hygiene and other recognised risk factors for OPC	Used only one search engine so may not be as comprehensive a literature search Authors also computed either unadjusted RRs provided from papers or SE for risk estimates of studies that did not report CIs P values (for heterogeneity) Possible study limitations: underreporting of alcohol consumption; other limitations and biases associated with use of retrospective exposure assessments in CC studies; lack of data from cohort studies; possible residual confounding by tobacco or other risk factors of oral and pharyngeal cancers; used mathematically different best-fitting models for

Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009							
Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
				Dose-response, g/day	**Oropharynx:** **Heavy drinking (n=4 CC)** All: 7.76 (4.77-12.62); p<0.008 **Hypopharynx:** **Heavy drinking (n=4 CC)** All: 9.03(4.46-18.27); p<0.001 **Oral Cavity:** 10: 1.28 (1.23-1.32) 25: 1.80 (1.66-1.95) 50: 3.00 (2.75-3.49) 75: 4.64 (3.72-5.75) 100: 6.65 (5.07-8.72) **Pharynx** 10: 1.32 (1.23-1.42) 25: 1.99 (1.69-2.34) 50: 3.76 (2.80-5.04) 75: 6.76 (4.55-10.05) 100: 11.58 (7.16-18.72)		dose-risk analyses; DR analysis assumed there was no threshold

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Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
					Tongue 10: 1.05 (1.03-1.06) 25: 1.22 (1.17-1.28) 50: 1.79 (1.57-2.04) 75: 2.75 (2.21-3.42) 100: 4.15 (3.09-5.57) **Oropharynx** 10: 1.20 (0.74-1.95) 25: 1.57 (0.91-2.71) 50: 2.46 (1.56-3.87) 75: 3.83 (2.59-5.65) 100: 5.96 (3.51-10.13) **Hypopharynx** 10: 1.08 (1.06-1.09) 25: 1.39 (1.30-1.48) 50: 2.52 (2.09-3.06) 75: 4.86 (3.42-6.91) 100: 8.83 (5.08-15.35)		

Table 1. Pooled and meta-analysis studies examining Alcohol Consumption and Oral Cavity/Pharyngeal Cancer Risk, published since 2009							
Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
Bagnardi et al (2013) Meta-analysis Asia: 16 studies; Europe: 13 studies; N America: 23 studies Studies published before December 2010	3 cohort and 20 case control studies examined cancer of oral cavity and pharynx combined	Not given	Not given	Non-drinkers = reference category 12.5g/d alcohol (1 drink/day) exposed group	Pooled relative risk 1.17(1.06-1.29)	Only comment was that only a small no. of studies (all cancer sites) reported the effect of light drinking in different smoking strata.	Did not assess different drinking patterns as an effect modifier; Possible underreporting and inclusion of former drinkers in the non-drinkers category No evidence of publication bias (funnel plot/Beggs rank correlation method) Slight variance in RR when stratified according to geographical region: 1.44, 1.15, 1.34 for European, North American and Asian populations, respectively

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Reference, location, name of study	**Cohort description (No. in analysis)**	**No. of cases/ controls, n**	**Exposure assessment**	**Exposure categories**	**Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
Bagnardi et al. (2015) Meta-analysis Europe: 18 studies; N America: 15 studies Asia: 12 studies; Others/mixed: 7 Studies published between 1956 and 2012	5 cohort; 47 case controls studies examined cancer of oral cavity and pharynx combined	13895 cases in exposed; 4942 cases in reference category	Not given	Non drinkers= reference category Light, moderate and heavy drinking was defined as every interval whose midpoint was: - ≤12.5g, ≤50g > 50g per day of alcohol respectively. 1 drink = 12.5g ethanol ≤12.5g ≤50g > 50g per day	Pooled relative risk 1.13 (1.00-1.26); I^2= 26 1.83 (1.62-2.07); I^2= 72 5.13 (4.31-6.10); I^2= 77 **Subanalyses Cohort** 0.86 (0.60-1.23); n=4; I^2= 68 1.25 (1.02-1.53); n=5; I^2= 16 3.13 (1.59-6.19); n=3; I^2= 69	Not discussed	Random effect meta-regression model based on a nonlinear dose response relationship framework (where doses of alcohol were treated as a continuous variable) showed risk of cancer of oral cavity and pharynx steeply increased with increasing dose of alcohol (graphically presented) Heterogeneity across studies was high in some analyses so some of the estimates should be interpreted with caution; no assessment of the influence of different drinking patterns/types of beverages consumed in modifying the effect of alcohol on oral cavity and pharynx cancer risk; underreporting of alcohol consumption in drinkers may partly or largely explain the association with light alcohol drinking;

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				≤12.5g ≤50g > 50g per day ≤12.5g ≤50g > 50g per day ≤12.5g ≤50g > 50g per day	**Case control** 1.22 (1.10-1.35); n=22; I^2= 0 1.91 (1.69-2.16); n=47; I^2= 70 5.34 (4.46-6.39); n=35; I^2= 77 P test for heterogeneity = 0.007 **Men** 1.20 (1.06-1.35); n=12; I^2= 0 2.01 (1.69-2.40); n=26; I^2= 73 5.33 (4.28-6.63); n=21; I^2= 71 **Women** 1.0 (0.78-1.27); n=8; I^2= 51 1.67 (1.25-2.22); n=9; I^2= 52 5.70 (3.75-8.66); n=3; I^2= 0 P test for heterogeneity = 0.165		possible inclusion of former drinkers in the non-drinkers category (misclassification bias) due to subjects with preclinical cancer symptoms stopping drinking more frequently than healthy individuals diluting the risk of cancer among drinkers;

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					Europe		
				≤12.5g	0.95 (0.80-1.12); n=5; I^2= 0		
				≤50g	1.51 (1.22-1.89); n=16; I^2= 67		
				> 50g per day	5.41 (3.79-7.72); n=14; I^2= 81		
					N. America		
				≤12.5g	1.09 (0.92-1.29); n=11; I^2= 38		
				≤50g	2.02 (1.74-2.34); n=15; I^2= 46		
				> 50g per day	5.58 (4.35-7.15); n=12; I^2= 71		
					Asia		
				≤12.5g	1.33 (1.06-1.68); n=7; I^2= 21		
				≤50g	2.18 (1.64-2.91); n=12; I^2= 78		
				> 50g per day	3.02(1.93-4.73); n=4; I^2= 62		

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Reference, location, name of study	Cohort description (No. in analysis)	No. of cases/ controls, n	Exposure assessment	Exposure categories	Odds ratio (OR) (Common or pooled) or Pooled Relative Risk (RR) and confidence intervals (95% CI)[a]	Adjustment factors	Comments
Chen et al 2009 Systematic review/ Meta-analysis US: 7 studies; Asian: 4 studies 1976-2001	14 studies from World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR)-funded project entitled "Food, Nutrition, Physical Activity and Prevention of Cancer: a Global Perspective". Nasopharyngeal carcinoma (NPC) only	2866/ 4257	Most studies provided few details on how alcohol consumption was measured. Only 7 studies reported that use of structured or validated questionnaire	Referent= lowest reported alcohol intake category (drinks/wk); Drinkers= highest alcohol intake category 1 drink =13.7g ethanol	Pooled OR 1.33 (1.09-1.62) **Sub-analyses: higher vs. lower intake categories** **Smoking adjusted smoking?** Y: 1.26 (95% CI=0.99-1.62), n=6 N: 1.47(95% CI=1.02-2.12); n=5 **Country** Chinese: 1.21 (0.98-1.62) US: 1.50 (1.08-2.10) **Alcohol intake duration** (n=2) 0 to > 30y: 1.84 (0.97-3.47) 0 to > 15y: 1.1 (0.7-1.6) **Type-specific alcohol intake** Beer: 1.32 (0.69-2.52)n=3 Spirits: 1.09 (0.43-2.77)n=3 Wine (unadj) n=2: 0.58 (0.23-1.46); 0.7 (0.49-0.992) Chinese rice wine: 0.56 (0.35-0.90 (n=1)	Varied (more or less of following): smoking, salted fish, gender, age, education, ethnicity, residence, occupational exposure, family history of NPC or ear nose disease, other food	11 studies provided total alcohol intake Beer/spirits were positively associated with NPC risk in Asian studies but not 2 US studies Publication bias not detected J-shaped pooled dose response curve for 6 studies providing ≥3 categories of exposure (graphically presented): 15 drinks/wk (OR=0.82); 28-30 drinks/wk (OR=1.12) p=0.005 Limited methodological quality of many of the studies; certain biases could not have been accounted for in the original studies (EBV is a major risk factor and was not addressed in any study; salted fish intake was controlled for in only two studies)

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Li et al. (2011) Meta-analysis Chinese population	7 case control studies investigating either nasopharyngeal cancer, NPC (n=4) or oral cancer, OC (n=3)	NPC: 1698/ 1874 OC: 347/ 539	Not given	Reference category ("non-drinkers") = participants described as drinking the smallest amount and those who said that they never drink. "Drinkers" = all other subjects.	Pooled OR **Nasopharynx** 1.21 (1.00-1.46); p= 0.009; (n=1698 cases:571 drinking/1127 non-drinking), 1874 controls: 536/1338) **Oral** 1.71(1.2-2.44); p= 0.0001; (n=342 cases:172 drinking/170 non-drinking), 631 controls: 243/388)	Not discussed	Types of drinks consumed included beer, yellow rice wine, red wine and spirits. Studies on NPC had significant heterogeneity (p,0.10 and I^2>50%) so meta-analyses conducted using random effect model. Study limitations include: small sample size and number of studies; possible bias from the exclusion of non-published data and papers published in languages other than English or Chinese; lack of uniformity among drinking definitions; possible recall bias

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Petti et al 2013 India: 7 studies Taiwan: 7 studies 1989-2012	14 case control studies Cancer of oral cavity assessed only	5192/48041	History, anamnesis, questionnaire at the time of diagnosis	Referent= never user Drinking categories= ever usage	Pooled OR 2.2 (1.6-3.0). **[Ethnicity]** India: 2.69 (1.73-4.18) Taiwan: 1.8 (1.17-2.77)	Publication bias	Summary restricted to never smokers and never betel quid chewers Drinking category yielded high level of publication bias Possible study limitations: different sets of confounders accounted for in studies leading to incomparable OR estimates

Table 2. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer risk, published since 2009								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of subjects/ cases**	**HR/OR/RR and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Maasland et al. (2014) Netherlands Start date: Sept 1986	Large prospective Netherlands cohort study (NLCS) of 120,852 participants, aged 55-69 years Follow-up: 17.3y	Self-completed food frequency questionnaire	Referent category= abstainers (never drank/< once a month) Drinkers: Consumption (g ethanol per day) >0 to <5 5 to < 15 15 < 30 ≥ 30 Continuous exposure (10 glass/day increments)	395 incident head and neck cancer (HNC) cases and 4288 subcohort members, which included 110 (65m, 45f) cases of oral cavity cancer (OC), 83 (61m, 22f) cases of oro-hypopharyngeal cancer (OHPC) (96% completeness for follow-up)	Relative Risk **Oral Cavity** Abstainers: 1.0; n=12 cases; 1.25 (0.59-2.65); n=17; 1.91 (0.91-4.03); n=19; 3.88 (1.86-8.12); n=30; 6.39 (3.13-13.03); n=32; p for trend = <0.001 Continuous: 1.28 (1.18-1.39); n=110; **Oro-hypopharynx** Abstainers: 1.0; n=11 cases; 1.06 (0.47-2.40); n=14; 0.90 (0.38-2.13); n=12; 0.99 (0.41-2.38); n=13; 3.52 (1.69-7.36); n=33; p for trend = <0.001 Continuous: 1.27 (1.16-1.38); n=83;	Age, sex, cigarette smoking	Completeness of cancer follow-up estimated to be ≥96% Study limitations include: Single measurement of exposure data; lack of data on subjects HPV status; no assessment of cancers located in the nasopharynx due to low numbers	8

Table 2. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer risk, published since 2009								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of subjects/ cases**	**HR/OR/RR and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
			Subanalysis Referent category= either no beer, wine or liquor (no further details provided) Drinkers: Consumption (glass/day) >0 to <1 1 to <2 ≥ 2 Continuous exposure (1 glass/day increments)		**Subanalysis** **Oral Cavity: Beer** 1.0; n=59 1.10 (0.65-1.86); n=34; 1.17 (0.49-2.77); n=8; 0.99 (0.34-2.82); n=9; p for trend = 0.95 Continuous: 0.97 (0.80-1.16); n=110; **Oro-hypopharynx: Beer** 1.0; n=36 0.98 (0.54-1.76); n=24; 1.04 (0.41-2.66); n=6; 2.48 (1.03-5.98); n=17; p for trend = 0.03 Continuous: 1.19 (1.01-1.40); n=83; **Oral Cavity: Wine** 1.0; n=44 1.07 (0.67-1.71); n=40; 1.31 (0.67-2.55); n=14; 0.93 (0.34-2.57); n=11; p for trend = 0.93 Continuous: 0.89 (0.69-1.16); n=109;			

Table 2. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer risk, published since 2009								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of subjects/ cases**	**HR/OR/RR and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
					Oro-hypopharynx: Wine 1.0; n=38 1.01 (0.59-1.75); n=33; 0.52 (0.19-1.39); n=5; 0.52 (0.15-1.81); n=7; p for trend = 0.16 Continuous: 0.86 (0.64-1.17); n=83; **Oral Cavity: Liquor** 1.0; n=40 1.10 (0.67-1.80); n=31; 1.65 (0.87-3.15); n=18; 2.26 (1.02-4.99); n=20; p for trend = 0.03 Continuous: 1.18 (0.89-1.56); n=109; **Oro-hypopharynx: Liquor** 1.0; n=34 0.86 (0.48-1.53); n=23; 0.79 (0.39-1.62); n=12; 0.83 (0.33-2.13); n=14; p for trend = 0.64 Continuous: 0.89 (0.68-1.15); n=83			

Table 2. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer risk, published since 2009								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of subjects/ cases**	**HR/OR/RR and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Shanmughami et al (2010) US 1980 to 2006	Ongoing prospective cohort study of 87,621 registered female nurses from the Nurses' Health Study; mean age of 47 years Follow-up: up to 26y	Self-reported FFQ	Referent category= Non drinkers Drinkers: Cumulative average intake (g ethanol per day) 0.1-14.9 15-29.9 ≥30	147 confirmed cases of oral cancer	Relative Risk **[age only adjusted]:** 1.0; n=43 0.57 (0.39-0.84); n=64; p≤0.01 1.29 (0.76-2.18); n=21 2.70 (1.57-4.65); n=19; p≤0.001 **[multivariate adjusted]:** 1.0; n=43 0.59 (0.39-0.87); n=64; p≤0.01 1.15(0.67-1.97); n=21 1.92 (1.08-3.40); n=19; p≤0.001	Age only or age, follow-up time, pack-years of smoking, smoking status, folate intake	Study limitations: Conducted in women only; self-administered diet questionnaire (measurement error); some concern over the representativeness of the women for the US population of women	8

Table 2. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer risk, published since 2009								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of subjects/ cases**	**HR/OR/RR and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Jayalekshmi et al. (2013) India 1990 to 2009	65,553 men from the Karunagappally area in India. Subjects selected from a 1991 Consensus, and were all healthy local non-factory workers aged between 30-84 years old Follow-up: Jan 1997 to Dec 2009	Standardised interview questionnaire	Drinking status: Never (Referent); n=33296 Former= 7857; Current= 24399	52 cases of hypo-pharyngeal cancers diagnosed	Relative risk 1; n=23 cases; 1.2 (0.6-2.6); n=9 1.3 (0.7-2.4); n=20	Age, income and education	0.7% Lost to follow-up Subjects are stratified according to never or current cigarette/bidi smoking or tobacco chewing, however there are no groups containing never smokers and chewers to examine independent effects of alcohol. Study did not attempt to address potential lifestyle changes among subjects during follow up	8

Table 2. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer risk, published since 2009								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of subjects/ cases**	**HR/OR/RR and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Hsu et al (2014) Taiwan 1982 to 2009	25,000 men sourced from three community-based long term prospective cohort studies in Taiwan, recruited between 1982 and 1992 with a mean age that ranged from 48.1 to 52 years Follow-up period: mean 18.4 years (472,096 person-years)	Structured questionnaires at interview	Referent = never drinkers (n=20074) Drinkers (following variables):- Drinking status Ever drinkers (n=5218); **Quantity of alcohol** (g/day) <80 ≥80; <80 ≥80;	Oral cavity cancer: 97 cases Pharyngeal cancers: 70 cases	HR and cumulative risk (CR) **p<0.01, *p<0.05 NB. n= total no of participants **Drinking status** **Oral Cavity** 0.86 (0.52-1.42); **Pharynx** 1.72 (1.03-2.90)*; **Quantity of alcohol** **Oral Cavity** 0.56 (0.27-1.19); n= 2804 1.54 (0.81-2.92); n= 1434 P for trend=0.597 CR: ≥80g/day: 2.22 (1.33-3.72) **Pharynx** 1.17 (0.56-2.45); n= 2804 3.27 (1.73-6.19)**; n= 1434 P for trend=0.001 CR: ≥80g/day: 3.44 (2.05-5.77)	Age, ethnicity, education, smoking, betel quid chewing, and study cohort	CR for between 30-80y Authors limited the analyses to only men due to low prevalence of these habits in women (1.8% of participants)	8

Table 2. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer risk, published since 2009								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of subjects/ cases**	**HR/OR/RR and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
			Duration (years) ≤20 >20 ≤20 >20 Cumulative exposure to alcohol drinking (g-years) <1500 ≥1500 <1500 ≥1500		**Duration of alcohol** **Oral Cavity** 0.86 (0.43-1.71); n= 2126 0.98 (0.52-1.85); n= 2654 P for trend= 0.836 **Pharynx** 2.16 (1.15-4.07)*; n= 2126 1.53 (0.74-3.15); n= 2654 P for trend=0.065 **Cumulative exposure** **Oral Cavity** 0.66 (0.32-1.34); n= 2602 1.33 (0.67-2.65); n= 1410 P for trend= 0.842 CR: ≥1500 g-years: 1.78 (1.0-3.18) **Pharynx** 1.58 (0.81-3.07); n= 2602 2.86 (1.43-5.75)**; n= 1410 P for trend= 0.003 CR: ≥1500 g-years: 2.96 (1.57-5.59)			

Table 2. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer risk, published since 2009								
Reference, location, period	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of subjects/ cases**	**HR/OR/RR and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Lin et al (2011) Taiwan Mar 2005 to Dec 2008	10657 male patients aged between 18-96 years visiting a tertiary referral hospital centre in central Taiwan average age = 55.2 years (±18.6y); Follow-up: (biopsy) conducted in patients with abnormal lesions (n=344, 170 lost to follow-up)	Unclear (interview?)	Patients with no personal habits (n=7775) Drinkers: habitual drinkers (n=1569)	230 cases (pathologically proven oral cavity cancer); 10257 controls	1.33 (0.48-3.74); p=0.584	None reported	Possible cancer screening study Study limitations: No quantitative data on alcohol consumption; no collection of data wrt type of alcoholic beverage; study conducted at a single institution and only included patients visiting the clinic for otolaryngological problems; recruited only male patients Authors limited the analyses to only men due to low prevalence of these habits in women (1.8% of participants)	2

Table 3. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Mortality and Secondary Effects, published since 2009

Reference, location, period	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of subjects/ cases	Survival rates (fractions) or Relative Risk and 95% CI	Adjustment factors	Comments	Star Rating for Quality
Jerjes et al (2012) UK	67 male patients aged between 25 and 96 (mean=62.2y); diagnosed with oral squamous cell carcinoma and referred to University College Hospital, London between 1998 and 2003 Follow-up: 5 years	Unclear	Referent= non drinker (n=20) Drinkers: Ex (n=1); Chronic ongoing habit > 20y (n=46) (units/week) <10 (n=2), 11-20 (n=9); >20 (n=35) Ex (n=1); Chronic ongoing habit > 20y (n=46) (units/week) <10 (n=2), 11-20 (n=9); >20 (n=35)	Recurrence in 26	Survival rates (fractions) 3-y FU (46.8%, n=22) Non-drinker=9/20; Ex drinker=1/1; Chronic: 2/2 3/9 7/35 5-y FU (40.4%, n=19) Non-drinker=9/20; Ex drinker=1/1; Chronic: 2/2; 4/9; 3/35	Authors reported smoking characteristics: non-smokers (n=12); ex-smokers (n=6); chronic smokers (n=48) and ranged from <5 to ≥20cig/day)	Risk estimates not determined and no adjustments made Causes of death either tumour related or non-tumour related Reduction in drinking alcohol and/or drinking cessation lead to significant reduction of mortality at 3 ($p<0.001$) and 5 years ($p<0.001$).	3

Table 3. Cohort studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Mortality and Secondary Effects, published since 2009

Reference, location, period	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of subjects/ cases	Survival rates (fractions) or Relative Risk and 95% CI	Adjustment factors	Comments	Star Rating for Quality
Kim et al. (2010) Korea Jan 2001 to Dec 2005	Prospective study among 1.34 million Koreans aged between 40-69 years (919,199m, 422,194f). Korea National Health Insurance Corporation (KNHIC) periodic (mostly biennial) general health examination Mortality follow-up: 5 years	Self-reported questionnaire	Reference category= non-drinker Participants categorised into 5 categories (men): non drinker, 1-14.9, 15-29.9, 30-89.9, ≥90 g/day	Lips, oral cavity and pharynx: 82 cases Pharynx cancer: 46 cases NB. Data for men only	Relative Risk **Lips, oral cavity and pharynx** non drinker: 1 1.7 (0.94-3.05) 0.82 (0.38-1.80) 1.65 (0.82-3.35) 2.17 (0.99-4.76) P for trend =0.089 **Pharynx cancer** non drinker: 1 1.24 (0.56-2.76) 0.75 (0.27-2.06) 1.38 (0.55-3.48) 2.15 (0.82-5.64) P for trend =0.11	Age, residence, smoking, exercise, BMI, systolic and diastolic blood pressure, and fasting blood sugar	Subjects asked to estimate alcohol exposure based on Soju consumption. Study limitations: short follow-up for mortality; alcohol consumption limited to one type of beverage; self-reported data, lack of data on duration of drinking	6

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
Marron et al. (2012) 14 centres in 10 European countries participating in the Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) study Recruitment: 2002 to 2005	n=1112. Men and women with cytologically confirmed UADT cancer diagnosed within the past 6 months. Oral cavity (n=489) Pharyngeal (n=623)	n=2,125. Mostly hospital based controls; (population-based controls used in 3 UK studies)	Questionnaire	Referent category: Never drinkers Drinkers stratified according to: Pure: 1 type consumed exclusively; Wine Beer Liquor Predominant: 1 type dominated (>66%); Wine Beer Liquor Mixed: >1 type consumed in similar proportions (<66%) Wine Beer Liquor	**Oral cavity** **Men** **Pure** 2.59 (0.94-7.17) n=23/101 3.58(1.33-9.61) n=39/124 1.64 (0.34-7.86) n=3/25 **Predominant** 2.12 (0.82-5.46) n=73/318 2.57(0.98-6.73) n=68/322 2.97 (1.03-8.58) n= 21/79 **Mixed** 2.06 (0.82-5.2) n=107/595 2.47(0.99-6.09) n= 160/659 2.52 (1.01-6.28) n= 185/764	Age, sex, centre, education level, fruit and vegetable intake, smoking, and alcohol drinking (adjusting liquor consumption on wine and beer, beer consumption on wine and liquor, and wine consumption on beer and liquor)	Paris study had some study design differences. Possible recall bias, under and overreporting of alcohol amounts consumed influenced by social norms,	7

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Never: wrt a particular type only (were pure, predominant and mixed drinkers of other types) Wine Beer Liquor Pure: 1 type consumed exclusively; Wine Beer Liquor Predominant: 1 type dominated (>66%); Wine Beer Liquor	**Never** 3.78 (1.49-9.61) n=107/317 2.08 (0.81-5.33) n=51/260 2.63 (1.07-6.48) n= 107/484 **Women** **Pure** 0.65 (0.30-1.39) n=17/73 0.85 (0.28-2.59) n=7/25 0.77 (0.22-2.70) n=5/23 **Predominant** 0.81 (0.38-1.72) n=28/101 1.35 (0.46-3.93) n=9/29 1.58 (0.54-4.60) n= 10/31			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Mixed: >1 type consumed in similar proportions (<66%) Wine Beer Liquor Never : wrt a particular type only (were pure, predominant and mixed drinkers of other types) Wine Beer Liquor Pure: 1 type consumed exclusively; Wine Beer Liquor	**Mixed** 1.36 (0.66-2.80) n=37/131 1.08 (0.55-2.13) n=46/147 0.83 (0.40-1.70) n=37/153 **Never** 1.09 (0.47-2.49) n=18/60 0.79 (0.41-1.50) n= 38/159 0.89 (0.48-1.63) n=48/160 **Pharynx** **Men** **Pure** 1.71 (0.70-4.22) n=25/101 2.45 (1.07-5.63) n=59/124 3.16 (1.05-9.44) n=11/25			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Predominant: 1 type dominated (>66%); Wine Beer Liquor Mixed: >1 type consumed in similar proportions (<66%) Wine Beer Liquor Never : wrt a particular type only (were pure, predominant and mixed drinkers of other types) Wine Beer Liquor	P**redominant** 2.13 (0.93-4.87) n=98/318 2.07 (0.92-4.65) n= 143/322 1.88 (0.77-4.59) n= 35/79 **Mixed** 2.07 (0.94-4.59) n=199/595 1.97 (0.9-4.28) n= 237/659 1.93 (0.88-4.22) n= 307/764 **Never** 2.58 (1.17-5.7) n=191/317 1.74 (0.79-3.82) n=82/260 1.88 (0.88-4.03) n= 152/484			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Pure: 1 type consumed exclusively; Wine Beer Liquor Predominant: 1 type dominated (>66%); Wine Beer Liquor Mixed: >1 type consumed in similar proportions (<66%) Wine Beer Liquor	**Women** **Pure** 2.21 (0.88-5.54) n=17/73 2.03 (0.66-6.29) n=10/25 0.92 (0.21-4.01) n=4/23 **Predominant** 2.30 (0.91-5.79) n= 26/101 2.69 (0.92-7.88) n= 14/19 2.63 (0.86-8.05) n=12/31 **Mixed** 2.30 (0.95-5.59) n= 43/131 2.52 (1.06-5.97) n=49/147 2.18 (0.89-5.33) n= 44/153			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Never : wrt a particular type only (were pure, predominant and mixed drinkers of other types) Wine Beer Liquor	**Never** 2.18 (0.86-5.52) n= 24/60 2.18 (0.95-4.99) n= 39/159 1.94 (0.87-4.33) n= 47/160			
Polesel et al (2011). Italy. Subjects drawn from established network of collaborating centres between 1992 and 2008	n=150 (119m/31f) Patients with incident nasopharyngeal carcinoma (NPC) admitted to major general hospitals in all study areas. Median age 52y Cases stratified according to NPC subtype: undifferentiated NPC (n=118); differentiated NPCs (n=22); not otherwise specified NPCs	n= 450 (357m/93f), As for cases except admitted for a wide spectrum of acute conditions (non-malignant neoplasms/non-tumour conditions); Median age 52y	Structured questionnaire administered during hospital stays	Referent category= Never drinkers **Drinking status**: Former Current NB. Following exposure variables measured among current drinkers: **Intensity (drinks/wk)** <14: 14-27: ≥28:	**[All NPCs]** **Drinking status** Never: 1; n=16/54 (cases/controls) 0.73 (0.21-2.50); n=5/25 1.14 (0.57-2.28); n=129/371 **Intensity (drinks/week)** 0.95 (0.44-2.04); n=40/124 1.05 (0.47-2.33); n=34/119 1.91 (0.83-4.41); n=55/128 Chi-squared for trend=3.66; p=0.06	Age, sex, place of residence, year of interview, education level, smoking	Analysis conducted in Caucasians only. 57 undifferentiated NPC cases and 2/4 differentiated NPC cases were EBV+ (status was available for only 61 NPC cases) Some missing values in duration and age analyses; small sample size, long study time period, EBV	6

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
	(n=10)			**Duration (years)** <25: 25-39: ≥40: **Start age (years)** ≥21: 18-20: <18: **Drinking status**: Former Current	**Duration (years)** 1.36 (0.58-3.19); n=40/91 1.05 (0.48-2.27); n=48/155 0.87 (0.35-2.20); n=40/124 Chi-squared for trend=0.11; p=0.74 **Start age (years)** 1.05 (0.48-2.29); n=41/105 1.24 (0.59-2.62); n=57/152 0.97 (0.43-2.20); n=30/113 Chi-squared for trend=0.00; p=0.97 **[Undifferentiated NPCs]** **Drinking status** Never: 1; n=12 (cases) 0.62 (0.13-2.83); n=3 1.35 (0.61-2.99); n=103		status only obtained for a minority of subjects; possible information and selection biases	

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Among Current drinkers: **Intensity (drinks/week)** <14: 14-27: ≥28: **Duration (years)** <25: 25-39: ≥40: **Start age (years)** ≥21: 18-20: <18:	 **Intensity (drinks/week)** 1.11 (0.46-2.69); n=34 1.32 (0.52-3.34); n=27 2.23 (0.84-5.89); n=42 Chi-squared for trend=3.58; p=0.06 **Duration (years)** 1.52 (0.58-3.96); n=35 1.24 (0.50-3.05); n=38 1.10 (0.37-3.25); n=29 Chi-squared for trend=0.02; p=0.88 **Start age (years)** 1.35 (0.55-3.30); n=35 1.53 (0.64-3.63); n=46 0.95 (0.37-2.48); n=21 Chi-squared for trend=0.04; p=0.85			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Drinking status: Former Current **Among Current drinkers:** **Intensity (drinks/week)** <14: 14-27: ≥28: **Duration (years)** <25: 25-39: ≥40:	**[Differentiated NPCs]** **Drinking status** Never: 1; n=2 (cases) 0.94 (0.07-12.37); n=1 1.40 (0.29-6.71); n=19 **Intensity (drinks/week)** 1.05 (0.18-5.96); n=5 1.82 (0.30-11.05); n=6 3.18 (0.46-21.79); n=8 Chi-squared for trend=2.17; p=0.14 **Duration (years)** 1.38 (0.17-11.05); n=3 1.53 (0.28-8.54); n=7 1.43 (0.21-9.91); n=9 Chi-squared for trend=0.15; p=0.69			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Start age (years) ≥21: 18-20: <18:	**Start age (years)** 0.92 (0.15-5.65); n=4 1.47 (0.27-7.88); n=8 2.37 (0.42-13.44); n=7 Chi-squared for trend=1.93; p=0.16			
Takasc et al (2011). Hungary Non-smoking subjects. Oral and Maxillofacial Surgery Dept, Semmelweis University Study period unspecified.	n=608 (466m/142f). Inpatients with histologically confirmed squamous cell oral carcinomas	406 (264m/142f) Tumour-free volunteers who agreed to participate in stomato-oncological screening during the study period.	Questionnaire and case-reports of inpatients	Referent category: Non-drinkers (drinking on special occasions) Regular drinkers (for 5-7 days/week): Moderate (< 25g/day) Excessive (> 25g/day)	Men Moderate: OR=1.4 Excessive: OR=2.2 Women Moderate: OR=0.7 Excessive: OR=3.6	None specified	Ex-smokers for 10 years or more were considered eligible. Study lacked data	5

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
Radoi et al (2013) France Subjects drawn from large multicentre population-based case control study, Investigation of occupational and environmental CAuses of Respiratory cancers (ICARE), conducted in 10 French administrative areas Between 2002 and 2007	n=772 (622m/150f). Primary SCC oral cavity aged ≤ 75y (at interview) and resided in one of the 10 administrative areas Cases divided according to subsites: base of tongue (n=145); mobile tongue (n=179); gums (n=44); floor of mouth (n=214); soft palate (n=83); other mouth (n=89);	n=3555 (2780m/775f). From healthcare establishments within same areas	Standardised questionnaire during face to face interviews. NB. For sick participants, a shortened questionnaire was used or next of kin were interviewed	Reference category: Never drinkers / Never drinkers of specific beverage type (see below) **Drinking groups**: Former: [Ever (glasses/day):] <0.6: 0.6-2.0: 2.1-4.5 >4.5 [By beverage type:] Wine / Beer / Cider / Liquor / Aperitifs Ever (glasses/day) ≤1: 2-3: 4-5 >5:	**[Oral cavity]** Never drinkers: OR=1; n=46/306 Ever drinkers 0.4 (0.3-0.7); n=65/921 0.6 (0.4-0.9); n=81/932 1.2 (0.8-1.8); n=161/787 3.2 (2.1-4.8); n=396/583 **Wine** Never: OR=1; n=66/543 0.8 (0.6-1.3); n=131/1600 1.4 (0.9-2.1); n=159/811 2.4 (1.5-3.8); n=118/294 4.6 (2.9-7.4); n=179/187	Age, sex and area of residence, smoking	Lack of account of diet, HPV infection or physical activity as potential confounders , recall bias, possible misclassification of tumour sites	5

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Ever (glasses/day) ≤1: 2-3: 4-5 >5: Ever (glasses/day) ≤1: 2-3: 4-5 >5: Ever (glasses/day) ≤1: 2-3:	**Beer** Never: OR=1; n=195/1495 1.1 (0.8-1.5); n=202/1565 2.4 (1.6-3.6); n=105/227 3.2 (1.8-5.6); n=50/60 5.7 (3.2-10.1); n=80/44 **Cider** Never: OR=1; n=461/2362 0.6 (0.4-0.9); n=80/733 0.9 (0.5-1.7); n=20/130 0.6 (0.2-1.4); n=16/85 0.7 (0.2-2.1); n=6/24 **Spirits** Never: OR=1; n=200/1450 0.8 (0.6-1.1); n=282/1755 0.9 (0.5-1.4); n=64/125			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				4-5 >5: Ever (glasses/day) ≤1: 2-3: ≥4: NB. For aperitifs, highest category: ≥4 glasses/day **Subtype analysis** Ever (glasses/day) ≤2 >2 Ever (glasses/day) ≤2 >2 Ever (glasses/day) ≤2 >2	2.3 (1.2-4.9); n=34/26 1.8 (0.8-3.0); n=46/24 Aperitif Never: OR=1; n=391/1898 0.8 (0.6-1.0); n=159/1288 2.5 (0.9-6.4); n=15/17 2.1(0.2-26.6); n=3/6 **Subtypes:** **Base of tongue** Never: OR=1; n=8 cases 0.5 (0.2-1.2); n=27 2.4 (1.1-5.4); n=107 **Mobile tongue** Never: OR=1; n=13 0.7 (0.4-1.4); n=46 2.3 (1.2-4.6); n=115 **Gums** Never: OR=1; n=6 0.4 (0.1-1.1); n=14 0.7 (0.3-2.1); n=23			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Ever (glasses/day) ≤2 >2	**Floor of mouth** Never: OR=1; n=9 0.6 (0.3-1.4); n=33 3.4 (1.6-7.4); n=166			
				Ever (glasses/day) ≤2 >2	**Soft palate** Never: OR=1; n=6 0.3 (0.1-0.8); n=12 1.7 (0.6-4.3); n=63			
				Ever (glasses/day) ≤2 >2	**Other mouth** Never: OR=1; n=4 0.5 (0.2-1.6); n=13 3.1 (1.0-9.4); n=69			
				Ever (glasses/day) ≤2 >2	**Oral cavity overall** Never: OR=1; n=46 0.6 (0.4-0.8); n=146 2.0 (1.5-3.0); n=557			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
Smith et al (2010) Iowa City Veterans Administration Hospital US Diagnosis between 2001 and 2004	n=201 (124m/77f) Patients diagnosed with primary head and neck cancer (HNC) with mean age of 59.6y (SD 13.5) Oral cavity (n=139) and oropharynx (n=62),	n=324 (212m/112f). Patients seeking routine medical care, screening or prescriptions with no prior history of HNC or requiring care/evaluation for an acute or chronic serious disease; mean age 59.6y (SD 14.7)	Self-administered questionnaire	Reference category: Never drinkers (not having used alcohol on a regular basis during their lifetime for one year or more) **Drinking groups:** Current (used alcohol ≤1y prior to diagnosis) drinks/week: ≤21; > 21 Used alcohol ≤1y prior to diagnosis drinks/week: ≤21; > 21 Used alcohol ≤1y prior to diagnosis drinks/week: ≤21; > 21	**[Oral cavity]:** Never: OR= 1; n= 51 /134 0.9 (0.6-1.5); n= 43 /147 3.8 (2.1-7.1); n= 45 /41 **[Oropharynx]:** Never: OR= 1; n= 9 /134 2.9 (1.3-6.5); n= 30 /147 6.2 (2.5-15.4); n= 23 /41 **[HPV Negative] Oral cavity** Never: OR= 1; n= 31 /77 1.0 (0.5-1.9); n= 28 /93 3.7 (1.6-8.3); n= 23 /24 P for trend=0.06	Age, gender, HPV status (for analyses stratified according to drinking levels), tobacco-pack years	HPV status also determined	6

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Used alcohol ≤1y prior to diagnosis drinks/week: ≤21; > 21 Used alcohol ≤1y prior to diagnosis drinks/week: ≤21; > 21 Used alcohol ≤1y prior to diagnosis drinks/week: ≤21; > 21	**Oropharynx** Never: OR= 1; n= 3 /77 3.3 (0.8-12.6); n= 12 /93 9.5 (2.3-38.6); n= 12 /24 P for trend=<0.001 **[HPV Positive]** **Oral cavity** Never: OR= 1; n= 20 /57 0.8 (0.4-1.8); n= 15 /54 3.8 (1.4-10.1); n= 22 /17 P for trend=0.004 **Oropharynx** Never: OR= 1; n= 6 /57 3.0 (1.1-8.3); n= 18 /54 5.0 (1.4-17.6) n= 11 /17 P for trend=<0.001			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
Hakenewerth et al (2011) Subjects drawn from The Carolina Head & Neck Cancer Epidemiology (CHANCE) Study, US Diagnosis between Jan 2002 and Feb 2006	n=1227 (938m/289f) Cases diagnosed with SCC of the oral cavity, pharynx and larynx diagnosed in 46 counties in North Carolina. Cases divided into subtypes: oral cavity cancer (n=166), oropharyngeal (n=310), NOS oral cavity, oropharyngeal, and hypopharyngeal cancer (n=208), and hypopharyngeal cancer (51)	n=1325 (924m/401f) Population based	Interview to collect self-reported non proxy data	Reference category: 0ml Drinking group: (lifetime alcohol consumption (ml)): >0-133294, >133294-757550, 757550+ Reference category: 0ml Drinking group: (lifetime alcohol consumption (ml)): >0-133294, >133294-757550, 757550+	**[Oral cavity]** Missing: n= 6/43 OR=1; n= 22/280 0.45 (0.23-0.89); n= 19/466 1.28 (0.68-2.41); n= 41/360 5.34 (2.67-10.67); n= 84/173 **[Oropharyngeal]** Missing: n= 22/43 OR=1; n= 27/280 0.87 (0.53-1.44); n= 69/466 1.47 (0.89-2.45); n= 94/360 3.47 (2.00-6.04); n= 120/173	Sex, race, age, smoking	Association between SNPs/haplotypes for alcohol-related genes and alcohol exposure also evaluated (data reported for SCCHN as a whole). Conducted in both African and European Americans	5

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Reference category: 0ml Drinking group: (lifetime alcohol consumption (ml)): >0-133294, >133294-757550, 757550+ Reference category: 0ml Drinking group: (lifetime alcohol consumption (ml)): >0-133294, >133294-757550, 757550+	**[NOS: Oral cavity, oropharyngeal, or hypopharyngeal cancer]:** Missing: n= 15/43 OR=1; n= 23/280 0.93 (0.54-1.62); n= 48/466 1.48 (0.83-2.64); n= 51/360 4.49 (2.40-8.39); n= 86/173 **[Hypopharyngeal]** Missing: n= 3/43 OR=1; n= 1/280 2.25 (0.26-19.84); n= 5/466 5.13 (0.61-43.04); n= 9/360 28.74 (3.42-241.40); n= 36/173			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
Ferreira-Antunes et al (2013) 4 hospital-based case control studies in one of four hospitals of Sao Paulo, Brazil Enrolment: Nov 1998 to Dec 2008	n=1144 (923m/221f). Newly diagnosed patients with invasive SCC of the oral cavity and oropharynx	n=1661 (1216m/445f). Outpatients of the same hospitals not affected by diseases potentially related with drinking and smoking exposure	Participants interviewed using methods endorsed by IARC and validated in studies within the INHANCE Consortium.	Referent category: Non-drinkers (never consuming at least one alcohol drink at a regular monthly basis) Drinking groups: Ever drinkers Level 1 (cumulative exposure): moderate consumption of ≤ 862g-years Level 2: heavy consumption > 862g-years	**[Unadjusted]:** 1; n= 199/769 4.21 (3.50-5.06); n= 945/ 906 1.68 (1.34-2.11); n= 194/446 6.73 (5.35-7.91); n= 751/446 **[Adjusted] – data in never smokers** Model 1: 3.60 (2.86-4.53); 1.68 (1.29-2.20); 5.71 (4.41-7.39); Model 2: 0.78 (0.48-1.27); 0.63 (0.40-1.00); 1.51 (0.88-2.57);	Age, gender, schooling level Non-participation: <10 subjects per cases or control Two models used to assess effect modification by alcohol, and tobacco; Model 1: assesses individual effects of tobacco smoking and alcohol drinking; Model 2: accounts for potential interaction effects		7

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
Szymanska et al (2011) Latin America Multicentre hospital based case control study from 7 centres in Brazil, Argentina, Cuba Start date: 1998	Patients newly diagnosed with UADT cancers that included: (1) oral cavity and oropharynx combined (2) hypopharynx and larynx (analysed together) Oral cavity + oropharynx (n=1030), Hypopharynx (n=997)	n=1707. In or outpatients from same hospitals as cases recently diagnosed with diseases not related to tobacco or alcohol (non-tumour/ malignant)	Lifestyle questionnaire administered face to face	Referent category: Never drinkers **[Drinking status]** Ever: once/month (min) Former: quit >1year before interview / diagnosis Current **[Dose response] Quantity (g/day):** 0.1-8.6 8.61-24.8 24.81-68.8 >68.8	**[Drinking status]** 1; n= 73/442 4.62 (3.39-6.28); n= 957/1089 3.62 (2.58-5.06); n= 285/396 5.26 (3.76-7.37); n= 672/693 **[Alcohol quantity]** 1; n= 73/442 2.92 (2.02-4.20); n= 112/274 3.39 (2.34-4.92); n= 136/270 6.60 (4.58-9.53); n= 257/266 10.95 (7.6-15.78); n= 447/268 OR-10 continuous: 1.07 (1.05-1.08)	Age, sex, centre, education, fruit and cruciferous vegetables consumption, cumulative tobacco consumption, alcohol gram years (assessing type of alcohol in ever drinkers), alcohol-g/day (assessing years since quitting)	Hypopharynx analysed together with larynx (so not included) Centres were identified based on age-standardised incidence rates reported in the Globocan database Significant protective effect also observed for years since quitting alcohol (OR range 0.8-0.4, for 2 to > 20y respectively)	6

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
				Duration (years): 15, 16-30, 31-40, ≥41 **Cumulative exposure (gram-years):** 0.1-233.66, 233.61-765, 765.1-2035.6, >2035.6	**[Duration]** 1; n= 73/442 2.64 (1.70-4.09); n= 58/130 4.27 (3.03-6.01); n= 312/399 5.79 (4.10-8.17); n= 309/293 5.65 (3.93-8.13); n= 273/256 OR-10 continuous: 1.41 (1.32-1.50) **[Cumulative alcohol consumption]** 1; n= 73/442 2.74 (1.90-3.94); n= 109/277 3.64 (2.51-5.29); n= 137/276 6.16 (4.27-8.87); n= 238/262 11.26 (7.83-16.20); n= 468/263			

Table 4. Case-Control studies examining the effect of alcohol consumption on Oral Cavity/Pharyngeal Cancer Risk, published since 2009								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure categories**	**Odd Ratio (OR) and confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality Rating**
					OR-1000 continuous: 1.21 (1.17-1.26)			
				[Type of alcohol]	**[Type of alcohol]**			
				Beer only:	1; n= 73/442 2.28 (1.49-3.49); n= 70/219			
				Wine only:	2.92 (1.61-5.29); n= 42/65			
				Aperitif /spirits only:	11.38 (7.36-17.59); n= 190/121			
Madani et al (2014) India Conducted within 19 months, from Feb 2005 to Sept 2006	350 (251m/99f) Newly diagnosed patients of oral cancer; average age 52.4y	350 (254m/96f) Healthy friends and caretakers of cases accompanying patients to hospital and did not reportedly have cancer; average age 51.8y	Self-reported structured questionnaire	Referent category: not specified	Unadjusted OR	None	Control group not ideal; likely to have similar drinking habits	4
					[Alcohol overall]: 3 (1.9-4.3); p=0.001; n=106/45			
				Drinking groups (beverage type consumption) beer,	2.2 (1.2-5); p=0.026; n=29, 12			
				hard liquor,	2.6 (1.2-5.5); p=0.002; n=29/10			
				country liquor	2.5 (1.3-3.6); p=0.001; n=55/25			
				wine	1.7 (0.6-4.3); p=0.524; n=12/7			

Table 5. Clinical study investigating other oral cavity cancer risk factors and alcoholic beverages							
Reference, study location, period	**Cohort description**	**Exposure assessment**	**Exposure categories**	**Cases**	**Relative risk (95% CI)**	**Adjustment factors**	**Comments**
Goodson et al (2009) UK Clinical study Maxillofacial dysplasia Clinic in Newcastle General Hospital	n=54 (34m/20f) Patients with single histologically confirmed, dysplastic oral precancerous lesions aged between 35 and 91 years (mean age of 64 years); all smokers with no previous history of oral cancer/lesions. All patients received clinical examination of the lesion, and formal laser excision of any dysplastic lesion by one surgeon. Follow-up: 2 years	Drinking data recorded (no further details Blood taken preoperatively for MCV measurement within 2h values.	Weekly alcohol units consumed. High intake = >28 units/w Macrocytosis defined as MCV > 100 femtolitres	Clinical outcome categorised as: disease-free or with further disease (i.e. recurrent oral precancerous lesions at the same site, further development of lesions at new site, or development of SCC at any site)	**[Reported intake]** **Further disease** ≤ 28 units (n=34): 9 cases (26%) 28 units (n=20): 9 cases (45%) P values not reported **[MCV]** **Further disease** MCV≤ 100 (n=38): 12 cases (32%) MCV> 100 (n=16): 6 cases (34%) P=0.8	None	Patients excluded for other causes of macrocytosis e.g. Vit B12 or folate deficiency

Table 6. Case-Control study of consumption of alcohol consumption and Oral Cavity/Pharyngeal Cancer risk by genetic polymorphisms and susceptibility

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	ORs (95% CI)	Adjustment factors	Comments
Matsuo et al (2011) Japan Hospital-based case control study Subjects recruited within the framework of the Hospital-based Epidemiologic Research Program at Aichi Cancer Centre (HERPACC) Diagnosis between Jan 2001 to Dec 2005	n=409 (296m/113f) Patients histologically diagnosed with oral and pharyngeal cancer (OPC) Oral cavity (n=257); oropharyngeal (n=72); hypopharyngeal (n=80)	n=1227 (888m/339f). Outpatients were medically and radiologically confirmed not to have cancer or history of cancer.	Self-administered questionnaire Note: DNA samples were available for approximately 60% of study participants (251 cases and 759 controls). Authors used TaqMan assay for genotyping for (ALDH2 Glu504Lys).	Referent category: never drinkers **Drinking groups (units/day):** Intermediate drinker=< 4; High drinker= ≥ 4; 1 unit = 12.5g ethanol **[Polymorphisms]** ALDH2 genotypes among participants: Glu/Glu: 103 cases, 372 controls Lys+: 148 cases, 387 controls **[Folate (ug/day)]** Participants with: lowest quartile of folate (<243.5) highest quartile of folate (≥ 378.4)	OR=1; n=113 cases, 454 controls 1.21 (0.88-1.65); n=151/560 2.67 (1.83-3.88); n=128/192 P for trend = <0.001 **[ALDH2 (Glu/Glu)]** **Never drinkers:** High folate:1; n=7/35 Low folate:1.95(0.66-5.70); n=12/34 **Intermediate drinkers:** High folate:0.77(0.25-2.32); n=9/36 Low folate:1.18(0.45-3.11); n=32/148 **High drinkers:** High folate:1.63(0.41-6.43); n=5/17 Low folate:2.17(0.78-6.02) n=28/59	Age, occupation, BMI, smoking, non-alcoholic energy intake, and smoking	Drinking status was unknown for 17 cases and 23 controls Average daily folate intakes estimated using data from FFQ Limitations include: Potential inaccurate confounders, small sample size

					[ALDH2 Lys+] **Never drinkers:** High folate:1; n=11/75 Low folate:1.08(0.42-2.78); n=29/138 **Intermediate drinkers:** High folate:1.48(0.49-4.48); n=13/47 Low folate:2.42(0.90-6.49); n=41/94 **High drinkers:** High folate:4.36(1.04-18.2); n=7/7 Low folate: 11.9 (3.95-36.1); n=39/16 P for interaction = <0.001 (a 3-way interaction term for genotype, folate and alcohol consumption)		

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Consumption of Alcohol and Oral Cavity and Pharyngeal Cancer Risk

Extract from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 96: Alchol Consumption and Ethyl Carbamate
Pages 237-329

Full document is available here:
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Consumption of Alcohol and Oral Cavity and Pharyngeal Cancer Risk

Extract from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100E: Personal Habits and Indoor Combustions

Pages 377-379, 446, 472 and Tables 2.3, 2.4, 2.5, and 2.6

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