CC/2015/05

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

Consumption of Alcohol and Head and Neck 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 reaffirmed 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.

2. This paper summarises evaluations of the role of alcohol consumption in head and neck cancers for data that have been reported by grouping specific upper aero-digestive tract cancer types (generally, squamous cell carcinomas (SCC) of the oral cavity, pharynx (excluding nasopharynx), larynx and/or oesophagus, and unspecified cancers in these groups). Where this information is available, the individual cancer sites included for each study (or their ICD-10 codes) are listed in a footnote. ‘Upper aero-digestive tract cancer’ (UADTC) and ‘head and neck cancer’ (HNC) are used as general terms to describe this group of cancers, depending on the terminology used in each individual study report.

Updated review of Alcohol consumption and Head and neck cancer risk

3. In the evaluation of the carcinogenicity of alcohol (IARC monograph 100e, 2012 (Annex A)), IARC state that there is evidence that consumption of alcoholic beverages is causally related to cancer of the upper aerodigestive tract, as it is for cancer of the oral cavity and pharynx, larynx and oesophagus separately. Literature for the current review was obtained following a PubMed search and the search terms included alcohol, ethanol, drinking, consumption and oral cavity cancer, pharyngeal cancer, mouth cancer, lip cancer, tongue cancer, laryngeal cancer, oesophagus and oesophageal cancer. Papers on oral cavity and pharyngeal, laryngeal and oesophageal cancers specifically are reviewed in papers CC-2015-02, CC-2015-03

and CC-2015-04 respectively. Other papers where cancers at these sites were analysed on a combined basis are included here. 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.

4. 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.

Meta- and combined analyses of alcohol consumption and head and neck cancer risk and mortality and secondary events

5. One pooled analysis of data from European and American case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) consortium, and two meta-analyses that were based on studies identified by literature search, are described.

Alcohol consumption and head and neck cancer risk (Table 1)

6. Hashibe *et al.* (2009) conducted a pooled analysis from 17 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 HNC. They also estimated the population attributable risk (PAR).

7. A total of 11,211 HNC cases[1] and 16,168 controls were included in the analysis. The majority of cases and controls were of European ethnic origin and there was a higher proportion of men among cases than controls. Most studies were hospital based and frequency matched controls to cases on age, sex and additional factors (study centre, hospital, race/ethnicity).

8. Exposure information was obtained by interview for all except one study where subjects completed self-administered questionnaires. Questionnaires were collected from all the individual studies to assess the comparability of the collected data and of the wording of interview questions among the studies. Data from individual studies were received at the International Agency for Research on Cancer (IARC). Cases and controls with missing data on age, sex, or race/ethnicity, and cases with missing information on the site of origin of their cancer were excluded (56 cases and 54 controls). In the alcohol section of the study questionnaires, subjects were asked if they were alcohol drinkers, if yes, frequency and duration of drinking and types of alcoholic beverages consumed (beer, wine, hard liquors and/or aperitif). Definitions were (variously, in different studies): 'ever' consumed alcohol, >4 drinks in a year; ≥1 drink/month for ≥6 months in a lifetime; ≥12 drinks of any kind of alcohol

[1] Oral cavity, oropharynx, hypopharynx, oral cavity or pharynx NOS, larynx, head and neck cancer unspecified

in a lifetime; ≥once/month; average ≥1 drink/week for ≥1 year; once/week for ≥1 year; ≥4 times/month of beer, wine or liquor. The volume specification for alcoholic beverages by type differed across studies. For example, a glass of wine was defined as 100-150 ml in the European studies, whereas the North American studies defined a wine glass as 3.6–5 ounces. In the pooled analysis, to estimate cumulative alcohol consumption (ml beverage over a lifetime), data from each study questionnaire on beverage volumes were used to harmonise intake to standardised drinks – one standardised drink containing 15.6 ml pure ethanol. For the overall frequency (drinks/day), the frequency of consumption of each alcoholic beverage type was weighted by the corresponding duration. For two of the American studies, data on duration by type of alcoholic beverage were not available and the average of the frequency of all alcoholic beverage types within those studies was used as the overall frequency.

9. Odds ratios (OR) and 95% CI were estimated using unconditional logistic regression models and were adjusted for age, sex, education, race/ethnicity and study centre. According to the random effects model, the OR (95% CI) for ever-alcohol use in non-smokers was 1.06 (0.88-1.28) [breakdown by drinking level in never-smokers, 1.03 (0.84-1.25) for 1-2 drinks/day; 1.91 (1.27-2.87) for ≥3 drinks/day], and that for ever-smoking in non-drinkers, 2.37 (1.66-3.39). A greater than multiplicative joint effect between ever tobacco and alcohol use was observed: OR = 5.73 (95% CI, 3.62-9.06); multiplicative joint interaction parameter, ψ = 2.15 (95% CI, 1.53-3.04). The PAR (95% CI) for tobacco or alcohol, alone and overlapped, was 72% (61-79), of which 4% (1.4-5.3) for alcohol alone, 33% (42.6-25.9) for tobacco alone, and 35% (17.2-48.0) for tobacco and alcohol combined. Stratification showed increased incidence with higher drinking and smoking levels, with the greatest proportion of head and neck cancers attributable to heavy drinking (≥3 drinks/day) among smokers: OR = 14.23 (95% CI, 8.30-24.40); PAR = 24.0 (95% CI, 22.7-24.8) for ≥3 drinks/day + >20 cigarettes/day.

Alcohol consumption and head and neck cancer mortality and secondary events (Table 2)

10. A meta-analysis by Druesne-Pecollo *et al.* (2014) evaluated studies reported in the PubMed and Embase databases for the association of alcohol exposure with incidence of a second primary cancer (all sites; UADTC[2]; UADTC + lung) in adults with UADT-site first primary cancer. Nineteen studies (5 Europe, 7 America, 7 Asia; 8 cohort, 11 case-control) were included. Patient data were extracted for details of the first (location/stage/treatment of index tumour) and second (diagnostic criteria, synchronous/metachronous, minimal time between diagnoses) primary tumours, alcohol consumption assessment (period of consumption targeted, time and method of assessment, type of alcoholic beverages), alcohol comparison and corresponding HR, RR and OR, and 95% CI, matching factors (case-control studies) and adjustments. The referent alcohol consumption varied between studies from never/non-drinker to 100 g ethanol/day, and highest category intakes were up to ≥170 g/day. Alcohol intake was evaluated retrospectively in most studies, with drinking habits prior to first tumour diagnosis reported.

[2] Oral cavity, pharynx, larynx and oesophagus

11. Random effects models were used to calculate summary RR and 95% CI for highest vs. lowest and dose-response analysis if at least two studies were available. Dose-response meta-analyses were performed by second cancer site. Highest vs. lowest meta-analyses were also conducted for sub-groups, according to study design, geographic location, adjustments, alcohol consumption assessment modalities (interview, self-assessment questionnaire, questionnaire with a non-specified method or medical record), alcohol consumption comparison (drinkers vs. non-drinkers or by categories), index tumour location, or the minimal time between the two diagnoses. Heterogeneity between the studies was assessed by the Q test and I^2 statistic, publication bias was assessed with funnel plots, Egger and Begg tests, with significance at $P \leq 0.05$.

12. Most studies examined indistinctly synchronous/metachronous second primary cancers or did not provide information on the delay between the two diagnoses. One study examined only synchronous and three studies only metachronous second primary cancers. Various criteria systems were used to define diagnosis of the second primary cancer (e.g., IARC, Berg, Warren and Gates, Hongs, Kuwano, endoscopy), however for many studies the diagnostic criteria were not stated.

13. For comparison of second primary cancer risk by highest vs. lowest alcohol intake: for all-sites second primary cancer, 6 studies (708 cases, 4,267 participants) were included, with a summary RR of 1.60 (95% CI, 1.22-2.10) [no heterogeneity, I^2 = 4.4%, P=0.388]; for UADT + lung second primary cancers, 7 studies (4 cohort, 3 case-control; 466 cases, 3,720 participants), with a summary RR of 1.91 (95% CI, 1.17-3.13) [heterogeneity, I^2 = 58%, P=0.025]; for UADT second primary cancer, 10 studies (3 cohort, 7 case-control; 493 cases, 6,385 participants), with a summary RR of 2.97 (95% CI, 1.96-4.50) [moderate heterogeneity, I^2 = 31%, P=0.158].

14. Sub-group analysis for UADT second primary cancers (by cohort/case-control study, Europe/Asia, method of assessment for alcohol intake, alcohol consumption levels, adjusted or not for age, gender, smoking, occupation, index tumour site) indicated similar overall results, with statistically significant RR values by all sub-group types except 'cohort studies' and 'alcohol intake assessment by questionnaire'. Dose-response meta-analysis for UADT-site second primary cancers (2 studies; 157 cases, 3,614 participants) indicated a summary RR of 1.09 (95% CI, 1.04-1.14) per 10 g/day increase in alcohol consumption, with no heterogeneity [I^2 = 0%, P=0.351].

15. Some limitations of the analysis were noted; alcohol consumption was estimated after cancer diagnosis in most studies, information on data collection about alcohol consumption assessment was mostly imprecise and only two studies provided information on beverage type, there was heterogeneity of reference categories across studies, and adjustments for potential confounding were not consistent across studies. However, results were consistent across studies for all-site and UADT-site second primary cancers, suggesting no residual confounding. Evaluation did not suggest publication bias, but it was noted that this was difficult to assess due to the small number of studies included.

16. Li *et al.* (2014) performed a meta-analysis to quantify the association between alcohol drinking and UADTC[3] mortality, based on epidemiological studies published to June 2013 and listed in PubMed and ISI Web of Science. Information was extracted on publication year, country, study name, cancer site, number of subjects, study period, study design, gender, age, variables adjusted or matched, categories of alcohol drinking, risk estimates and corresponding 95% CI. Studies were scored for quality regarding representation of objects, method of alcohol consumption data collection, and method of data analysis.

17. Multivariate-adjusted risk estimates were selected if they were reported in the original publication, otherwise the unadjusted risk estimates were calculated using the original data. Alcohol intake was converted into g ethanol per day either according to the definition in each individual publication or as follows: 28 g ethanol for 1 oz. alcohol, 12.5 g for 1 drink, 0.8 g for 1 ml. When a dose-range was given, the central value was taken as the exposure value, whilst for open-ended exposures the dose was defined as the lower bound added to ¾ the adjacent previous category. Study-specific risk estimates were obtained for light, moderate and heavy drinking, equating to, respectively, ethanol intake of ≤12.5 g/day (≤1 drink/day), 12.6-49.9 g/day (2-3 drinks/day) and ≥50 g/day (≥4 drinks/day). Non/occasional drinking was the reference category. Study heterogeneity was assessed by Cochran Q test and I^2 statistic (heterogeneous = P ≤0.10 and/or I^2 ≥50%).

18. Fixed- and random effects models were used depending on the level of heterogeneity between studies. Forest plots for association between alcohol drinking and UADTC mortality were generated for any, light, moderate, and heavy drinking vs. non/occasional drinking. Sub-group analyses were carried out by cancer site, sex, source of subjects, geographic area, major confounders (age, sex, cigarette smoking) adjusted or matched, length of follow-up and quality score. Dose-response analyses were carried assuming non-linearity, and publication bias was assessed by Egger and Begg tests. Type of alcoholic beverage, lifetime exposure to alcohol, and the drinking pattern were not studied as only a small proportion of the original studies provided this information.

19. Ten studies published between 1981 and 2012, reporting a total of 2,976 UADTC deaths, were included (8 prospective cohort / 1 nested case-control / 1 case-control; 2 North America / 8 Asia). The pooled RR (95% CI) for UADTC mortality for any, light, moderate, and heavy drinking vs. non/occasional drinking were, respectively: 2.01 (1.56-2.59), 1.26 (0.94-1.67), 1.79 (1.26-2.53) and 3.63 (2.63-5.00), and adjusted for major confounders (age, sex, cigarette smoking): 1.90 (1.47-2.46) [8 studies], 1.25 (0.90-1.73) [5 studies], 1.83(1.27-2.64) [8 studies], 3.73(2.66-5.25) [8 studies].

20. In sub-group analyses, no significant difference was found across strata of cancer site, gender, geographic area, major confounders adjusted or matched, or length of follow-up. The association between alcohol drinking and UADTC mortality was significantly higher for ≥median v. <median quality-score studies (RR=2.81; 95% CI, 1.50-2.61; $P_{heterogeneity}$ = 0.004) and for occupation- vs. population-specific studies (RR=1.84; 95% CI, 1.40-2.41; $P_{heterogeneity}$ = 0.001).

[3] Oral cavity, pharynx, larynx, oesophagus

21. Dose-response analysis indicated daily alcohol consumption increment associated with increased UADTC mortality continuously. A maximal RR of 4.73 (95% CI, 3.93-5.69) was reached at a daily intake of 86.5 g ethanol.

22. Sensitivity analysis indicated that exclusion of the most influential study did not alter the results. Tests for publication bias showed no significant asymmetry. However, there was significant heterogeneity between studies.

Summary of meta-analysis and combined analysis studies

23. A pooled analysis of HNC risk using data from 17 European and American case-controls studies indicated significantly increased risk associated with heavy drinking (≥3 drinks/day), and drinking + smoking, with the greatest proportion of HNC attributable to heavy drinking among smokers (Hashibe *et al.*, 2009).

24. A meta-analysis of cohort and case-control studies from Europe, American and Asia, by Druesne-Pecollo *et al.* (2014), indicated increased risk with amount of alcohol intake for the development of a second primary UADT-site cancer in patients with UADT index cancer. The authors noted that although the analysis had several limitations, the results were nonetheless consistent across studies for UADT-site second primary cancers.

25. A meta-analysis including 8 cohort, 1 nested case-control and 1 case-control study, from North America (2 studies) and Asia (8 studies) indicated a dose-dependent association of alcohol consumption with UADTC mortality. with a maximal RR of 4.73 (3.93-5.69) at a daily intake of 86.5 g ethanol. Significant heterogeneity between the studies included was noted (Li *et al.*, 2014).

Cessation (Table 3)

26. Marron *et al.* (2010) pooled data from a total of 13 case-control studies (9,167 cases[4], 12, 593 controls) from the International Head and Neck Cancer Epidemiology (INHANCE) consortium to estimate the number of years of quitting drinking required to observe a reduced risk of HNC, and determined whether the risk declines to the level of never drinkers. Information was obtained on frequency, duration and cumulative consumption of drinking, and by types of beverages (beer, wine, hard liquor), age at stopping drinking, and time since quitting. Former drinkers were classed as those who had stopped drinking >1 year ago. OR and 95% CI were calculated using unconditional logistic regression models for each case-control study, adjusted for sex, age, education, race/ethnicity, study centre, tobacco and alcohol (as continuous variables), BMI, involuntary tobacco smoking, and family history of HNC.

27. To calculate summary estimates of associations, the study-specific estimates were included in a two-stage random-effects logistic regression model using the maximum likelihood estimator, to allow for unexplained sources of heterogeneity among studies. Pooled ORs were also estimated with a fixed-effects logistic regression model that adjusted for age, sex, education level, race/ethnicity and study

[4] Oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified (NOS), larynx or head and neck cancer unspecified

centre. Significant heterogeneity was observed between studies, thus random effects estimates were reported. However, influence analysis indicated that the overall summary estimate was not dependent on any one study.

28. Compared with current drinkers, a significant decrease in HNC risk was seen in subjects who had quit for ≥20 years (OR=0.60; 95% CI, 0.40-0.89), but not for shorter time periods: OR (95% CI) = 0.99 (0.69-1.43) for >1-4 y; 0.90 (0.62-1.30) 5-9 y; 0.94 (0.75-1.18) 10-19 y. Stratification showed reversal of risk for all cancer sub-sites.

29. For subjects consuming one or more drinks per day, the overall risk of HNC decreased with time since quitting. OR (95% CI) for quitting drinking were 0.88 (0.64-1.23) for 1-4 years, 0.81 (0.54-1.22) 5-9 years, 0.82 (0.61-1.10) 10-19 years, 0.44 (0.25-0.77) ≥20 years, and 0.55 (0.36-0.84) for never drinking, compared with current drinking. Stratification by frequency of consumption indicated that the OR after quitting ≥20 years appeared to decrease with increasing frequency of alcohol drinking for HNC overall: OR (95% CI) = 1.00 (0.72-1.39) for <1 drink/day; 0.76 (0.52-1.12) for 1-2 drinks/day; 0.54 (0.31- 0.94) for ≥3 drinks/day, driven by a decreased risk for oral and laryngeal cancer.

30. Stratification by study type showed that risk reduction was more pronounced in hospital-based than population-based studies.

Cohort studies

31. The cohort studies have been divided into two categories: a) those examining HNC/UADTC incidence (3 studies) and b) those examining HNC/UADTC mortality (1 study). Within each section, the studies are reported by geographic region (UK, Europe, US, and other regions).

Cohort studies examining alcohol consumption and head and neck cancer risk (Table 4)

32. Maasland *et al.* (2014) investigated the effects of alcohol and tobacco consumption, both independently and jointly, on the risk of HNC in the large, prospective Netherlands Cohort Study (NLCS) including 120,852 participants from 204 Dutch municipal population registries, aged 55-69 years at baseline. After 17.3 years of follow-up, 395 microscopically confirmed incident HNC cases[5] were identified by record linkage to the Netherlands Cancer Registry and the nationwide network and pathology registry. Analyses were performed on these cases and a sub-cohort of 4,288 subjects randomly sampled from the entire cohort at baseline. Baseline information on alcohol consumption was obtained using a food frequency questionnaire (FFQ) including details 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 200 ml for beer (8 g ethanol), 105 ml for wine (10 g ethanol) and 45 ml for liquor/spirits (13 g ethanol). Information was also obtained on drinking habits 5 years prior to baseline. Abstainers were considered as those participants who indicated they never consumed alcohol or consumed alcohol less than once a month. RR and 95% CI

[5] Oral cavity, oro/hypo-pharynx, oral cavity or pharynx unspecified or overlapping, larynx

were estimated using the Cox proportional hazard model and adjusted for age (years), sex and smoking (status, frequency, duration). The different types of alcoholic beverages were also analysed and adjusted for ethanol intake to examine whether other components of the beverage may have an effect on the cancer risk. Abstainers were the reference category.

33. Alcohol consumption compared with abstinence was associated with a statistically significant increase in HNC with a strong dose-response relationship: RR (95% CI) = 1.11 (0.75-1.65) for >0 – <5 g ethanol/day; 1.15 (0.77-1.71) for 5 – <15 g ethanol/day; 1.52 (1.02-2.27) for 15 – <30 g ethanol/day and 2.74 (1.85-4.06) for ≥30 g ethanol/day. Breakdown by cancer sub-type showed significant association for oral cavity (strongest) and oro/hypo-pharyngeal, but not for laryngeal cancers. A significant interaction was noted between sex and continuous alcohol consumption for overall HNC (and oral cavity) risk, with RR for continuous 10 g/day increment higher for women (RR=1.40; 95% CI, 1.18-1.65) than men (RR=1.19; 95% CI, 1.12-1.27) [overall (RR=1.20, 95% CI, 1.12-1.27)]. After adjustment for total alcohol intake, beer, wine and liquor were not significantly associated with HNC risk. An inverse trend was observed for wine consumption, but this was not statistically significant.

34. Everatt *et al.* (2013) assessed the association of alcohol consumption with cancer incidence in 7,150 men from two population-based cohorts in Lithuania (KRIS, men aged 45-59; MIHDPS, men aged 40-59). During follow-up of 30 years, 95 UADTC[6] cases were identified from the Lithuanian Cancer Registry and the National and Regional Archives of Causes of Death. Participants were interviewed at baseline for details of alcohol consumption and potential confounders such as demographic factors and smoking. Alcohol intake frequency, type (beer, wine, vodka) and amount per occasion were recorded using a structured questionnaire. The amount of ethanol by type of beverage was calculated as follows: 175 ml wine was regarded as two units, 25 g spirits as one unit and 250 ml beer as one unit. A unit was defined as 10 g ethanol. Participants were categorised into 4 groups according to frequency of alcohol consumption (non-drinkers, a few times per year, 1-4 times per month, 2-7 times per week), 6 categories according to their amount of ethanol consumed per week (non-drinkers, 0.1-10.0, 10.1-40.0, 40.1-70.0, 70.1-140.0 and ≥140.1 g/week) and 6 groups according to alcohol consumption per one occasion (non-drinkers, 0.1-45.0, 45.1-60.0, 60.1-100.0, 100.1-120.0 and ≥120.1 g/occasion). Occasional drinkers (a few times per year) or participants with very light alcohol consumption (0.1-10.0 g ethanol/week or 0.1-45.0 g/occasion) were used as the reference. Cox proportional hazard regression was performed to compute HR and 95% CI for alcohol consumption frequency and amount per week or per one occasion, with adjustment for cigarette smoking (never, former, ≤10 cigarettes/day, 11-19 cigarettes/day, ≥20 cigarettes/day, missing), education level (primary, unfinished secondary, secondary and high school education, missing) and BMI (as a continuous variable). The analyses of quantity of alcohol consumed per occasion and frequency of alcohol intake were performed with mutual adjustment for these factors.

35. There was a significant, dose-dependent association between g/week ethanol and UADTC risk: HR (95% CI) = 1.24 (0.41-3.71) for non-drinkers; 1 (reference) for

[6] ICD10 (ICD9) codes: C00–06 (140–141), C09–14 (143–149), C15 (150), C32 (161)

0.1-10.0 g/week; 1.16 (0.54-2.47) for 10.1-40.0 g/week; 2.33 (0.92-5.88) for 40.1-70.0 g/week; 2.03 (0.92-5.88) for 70.1-140.0 g/week; 2.79 (1.23-6.34) for ≥140.0 g/week. For alcohol intake as a continuous variable, an RR of 1.18 (95% CI, 1.06-1.30) was observed for each additional 90 g. All-type cancer risk increased in a dose-dependent manner with frequency of alcohol use, but the findings were not statistically significant for UADTC. There was no significant association between quantity of alcohol consumed per occasion and UADTC risk. A PAR of 35.3% was calculated for UADTC in this cohort during the 30-year follow-up period.

36. Hsu *et al.* (2014) investigated the association of three risk factors (betel chewing, smoking, drinking alcohol) on lifetime UADTC risk in 25,611 men, aged 30-80 years, drawn from 3 prospective, community-based studies in Taiwan. During the mean follow-up period of 18.4 years, a total of 269 incident UADTC[7] were identified from the National Cancer Registry and National Death Certification. Details of alcohol consumption, such as duration, quantity and types of beverages drunk were obtained at study entry by research nurses using a structured questionnaire. Alcohol drinking habit was defined as having drunk alcohol regularly for at least 6 months. Total consumption of pure ethanol (g/day) was calculated by multiplying the average frequency of alcohol consumption and the volume percentage of pure ethanol by beverage type. Cumulative exposure (g/day-years) was calculated by multiplying g/day by years of alcohol drinking. Non-drinkers were the reference category. Adjusted HR and 95% CI for developing UADTC were calculated using Cox proportional hazard models, with adjustments for age, education, ethnicity, betel quid chewing, cigarette smoking and study cohort.

37. There was a significant association between alcohol drinking and risk of UADTC at higher dose levels. Cumulative lifetime risks at 80 years were 4.77% and 1.85% for alcohol drinkers and non-drinkers, respectively. Adjusted for the factors described in the paragraph above, including substance use each other, as compared with 'never' drinkers 'ever' alcohol drinking was associated with an increased risk of UADTC (HR=1.9; 95% CI, 1.46-2.49), with a dose-response observed for quantity of alcohol per day (HR=1.73; 95% CI, 1.23-2.42, for <80 g/day and HR=2.49; 95% CI, 1.72-3.61, for ≥80 g/day; p for trend <0.001), duration of drinking (HR=2.07; 95% CI, 1.45-2.97, for ≤20 years and HR=1.91; 95% CI, 1.37-2.68, for >20 years; p for trend <0.001) and cumulative exposure (HR=1.79; 95% CI, 1.27-2.51, for <1500 g-years and HR=2.58; 95% CI, 1.78-3.74, for ≥1500 g-years; p for trend <0.001). Analysis by cancer sub-site showed a significant association of alcohol with risk of pharyngeal, oesophageal and laryngeal (but not oral) cancers, with the strongest associations for oesophagus and larynx.

38. Analysis of combined effects indicated the following results for HR (95% CI): Ever-alcohol/Never-betel/Never-cigarette, 1.42 (0.55-3.65); Ever-alcohol/ Never-betel/ Ever-cigarette, 4.90 (3.12-7.69); Ever-alcohol/ Ever-betel/ Never-cigarette, 15.69 (6.06-40.68); Ever-alcohol/ Ever-betel/ Ever-cigarette, 10.46 (6.31-17.34).

[7] Oral cavity, pharynx, oesophagus, larynx

Cohort studies examining alcohol consumption and head and neck cancer mortality and secondary events (Table 5)

39. Mayne *et al.* (2009) investigated the effect of pre- and post-diagnosis alcohol and tobacco use in determining all-cause mortality in a cohort of 264 (male and female) 'curatively treated' HNC patients[8] in a β-carotene supplementation trial in the US. Information on alcohol consumption was obtained at baseline, including details such as ever use of beer, wine and liquor, number of days/week used, number of drinks/day and total number of years drinking that beverage type. Changes in alcohol consumption and current drinking habits were recorded at yearly visits. RR and corresponding 95% CI were estimated using Cox proportional hazard regression and adjusted for age, sex, race, β-carotene randomisation group, educational level, body mass index, smoking before diagnosis (pack-years, current vs. former/never) and during follow-up, and drinking before diagnosis (in models for current drinking). To examine the effect of continued alcohol consumption on mortality risk, three categorical variables were created; 1) non-exposed (no drinking during follow-up), 2) transitionally exposed (exposed after diagnosis but not continuously), and 3) continuously exposed (reported exposure at each yearly follow-up interview).

40. Usual drinking prior to diagnosis was associated with a dose-dependent increased risk of dying during follow-up. RR (95% CI) for all-cause mortality during follow-up for drinking compared with non-drinking prior to diagnosis were 1.46 (0.35-6.14) for 1-7 drinks/week, 1.44 (0.39-5.35) for 8-21 drinks/week, 2.36 (0.60-9.31) for 22-35 drinks/week and 4.87 (1.46-16.27) for >35 drinks/week. Stratification by type of drink showed excess risk for beer: RR (95% CI) = 1.20 (0.53-2.73) for 1-7 drinks/week, 2.37 (1.03-5.44) for 8-21 drinks/week, 2.86 (1.34-6.12) for >21 drinks/week, and liquor: RR (95%CI) = 1.27 (0.59-2.75) for 1-7 drinks/week, 1.04 (0.47-2.33) for 8-21 drinks/week, 2.11 (1.04-4.28) for >21 drinks/week, but not wine: RR (95% CI) = 0.58 (0.25-1.35) for 1-7 drinks/week, 0.44 (0.14-1.35) for 8-21 drinks/week, 0.75 (0.32-1.76) for >21 drinks/week.

41. Continued (RR=2.72; 95% CI, 1.20-6.14) but not transitional (RR=0.73; 95% CI, 0.29-1.86) drinking after diagnosis was associated with increased risk of death during follow-up, compared with non-drinking.

Summary of cohort studies on head and neck cancer risk, mortality and secondary events

42. All three studies that evaluated alcohol intake and HNC/UADTC risk reported a significant, dose-dependent association. The Netherlands Cohort Study (Maasland *et al.*, 2014), which included both men and women, indicated significantly increased risk for ethanol intakes ≥15 g/day, with risk higher for women than men. The other two studies were based on cohorts that included only men. The study by Everatt *et al.* (2013) (Lithuania) showed a significantly increased risk of UADTC for ethanol intake ≥140 g/week whilst that of Hsu *et al.* (2014) (Taiwan) noted a significant risk in both ethanol-intake dose-brackets evaluated (<80 g/day, ≥80 g/day). Significant associations were generally not observed with either frequency of alcohol drinking or amount drunk per occasion.

[8] Patients with early stage cancers of the oral cavity, oropharynx, hypopharynx, pharynx or larynx having completed all treatment and classed as cancer-free

43. One study, reported by Mayne *et al.* (2009), evaluated all-cause mortality in a cohort of male and female HNC patients who had completed treatment and were considered to be cancer-free. Risk of dying during follow-up was significantly associated with high-level alcohol intake before HNC diagnosis and continued but not transitional alcohol drinking after diagnosis, but specific causes of mortality were not evaluated.

Case-Control studies

44. Five case-control studies examining HNC/UADTC risk are reported. Studies are reported by geographic region (UK, Europe, US, and others regions). No studies examining HNC/UADTC mortality were identified.

Case-control studies examining alcohol consumption and head and neck cancer risk (Table 6)

45. Marron *et al.* (2012) reported similar effects of wine, beer and liquor consumption on head and neck cancer, supporting the hypothesis that their carcinogenic effects are due to a common ingredient/ metabolite (ethanol/ acetaldehyde). This investigation evaluated the association of drinking different alcoholic beverage types with UADTC in a large European case-control study – Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE), which was initiated by IARC and involved 14 centres in 10 European countries. The majority of centres used hospital-based controls, with the exception of the three UK centres where population-based controls were recruited. Information on lifestyle, including information on alcohol consumption, was obtained by a trained interviewer using a questionnaire. Information was obtained on volume of drinking unit, frequency and duration of drinking 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, ascertained by asking more than 10 drinks in a couple of hours) 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%, and 'mixed drinker' consuming more than one type of alcoholic beverage type to similar proportions). OR and 95% CI were estimated using unconditional logistic regression and adjusted for age, centre, education level, fruit and vegetable intake, smoking (duration, frequency and time since quitting, type of tobacco and smoking status) and sex, and for drinking the other alcohol types evaluated when appropriate. The analysis included 2,001 UADTC cases[9] and 2,125 controls.

46. Compared with never drinkers, the risk of UADTC increased for wine, beer and liquor consumption, respectively, with increasing average frequency of drinks/day among 'pure drinkers', 'predominant drinkers', and 'mixed drinkers' (p-value for trend <0.001 for all except pure liquor drinkers, for which the number of subjects was small). Risks by frequency of drinks/day were similar for drinking wine, beer and liquor. Compared with never drinkers, and where appropriate adjusted for the consumption of other beverage types, OR (95% CI) for drinking 3+ drinks/day wine, beer and liquor, respectively, were 4.01 (2.22-7.25), 2.08 (1.20-3.63) and 1.74

[9] ICD 10 codes: C00–C10, C12–C13, C14.0, C14.8, C15.0, C15.3–C15.5, C15.8–C15.9, and C32; squamous cell carcinomas

(0.49-6.15) among 'pure drinkers', 2.51 (1.67-3.78), 2.32 (1.46-3.67) and 2.76 (1.40-5.42) among 'predominant drinkers' and 1.89 (1.07-3.32), 1.71 (0.97-3.03) and 1.42 (0.84-2.38) among 'mixed drinkers'.

47. Adjusting for cumulative alcohol consumption, compared with never drinkers, OR (95% CI) for ever drinking wine, beer and liquor, respectively, were 1.24 (0.86-1.78), 1.54 (1.05-2.27) and 0.94 (0.53-1.64) among 'pure drinkers', 1.05 (0.76-1.47), 1.25 (0.87-1.79) and 1.43 (0.95-2.16) among 'predominant drinkers', and 1.09 (0.79-1.50), 1.20 (0.88-1.63) and 1.12 (0.82-1.53) among 'mixed drinkers'.

48. Stratification by UADTC site indicated similar OR for all sites (oral cavity, pharynx, oesophagus, larynx), except for a higher risk of pharyngeal cancers in women.

49. Canova *et al.* (2010) reported an evaluation of the effects of alcohol and tobacco consumption on UADTC risk, and of potential gene-environment interactions for susceptibility, in a subset of patients from three centres in northern Italy, as part of the ARCAGE study. Details of current and previous alcohol and tobacco consumption were obtained by trained interviewer from 454 newly diagnosed UADTC cases[10] and 479 corresponding hospital-based controls. Subjects were classified as never drinkers or drinkers of <1, 1-2, 3-4 or ≥5 drink equivalents per day. The definition for one drink equivalent was 14 g ethanol, corresponding to approximately 150 ml wine, 330 ml beer and 36 ml spirits. Drinks per day were calculated by summing up each type of alcohol in drink-years and dividing the result by the total duration of alcohol drinking. The association of alcohol and/or tobacco intake with UADTC risk was calculated by unconditional logistic regression analysis, with adjustment for centre, sex, age at diagnosis (5-year groups) and educational level as categorical variables and cumulative tobacco and/or alcohol as continuous variables when appropriate. UADTC risk showed a dose-dependent association with frequency of alcohol consumption: RR (95% CI) = 1.18 (0.79-1.77) for 1-2 drinks/day, 2.78 (1.72-4.51) for 3-4 drinks/day, 6.29 (3.74-10.58) for 5+ drinks/day, as compared with <1 drink/day, but no association with duration. The risk for high level alcohol intake plus smoking was very high, suggestive of multiplicative effects: OR=34.81 (95% CI, 14.69-82.50) for >40 pack-years and 5+ drinks/day. The risk associated with alcohol alone was roughly equivalent between UADTC sub-sites, whilst that for alcohol + smoking combined was higher for cancers of the larynx/hypopharynx and oesophagus than for oral cancers.

50. Macfarlane *et al.* (2010) investigated the association of alcohol and tobacco exposure with UADTC in individuals aged <50 years as part of the ARCAGE study. Cases were squamous cell carcinomas (SCC) of the UADT[11], diagnosed in participating hospitals ≤6 months previously. The majority of centres used hospital-based controls with the exception of the three UK centres where population-based controls were recruited. Information on lifestyle, including information on alcohol consumption, was obtained by a trained interviewer using a questionnaire. Information was obtained on frequency and duration of drinking various alcoholic beverages (beer, wine, liquor) in different periods of life. OR and 95% CI were estimated using logistic regression, adjusted for age (years, continuous), sex,

[10] Oral cavity, pharynx, larynx, oesophagus
[11] Oral cavity, pharynx (other than nasopharynx), larynx, oesophagus

smoking, education and centre. The analysis included 356 UADTC cases and 419 controls.

51. Risk was correlated with alcohol consumption. There was an excess risk relative to never drinkers for current drinkers (OR=1.8; 95% CI, 0.97-3.3) and a strong excess risk for past (OR=3.4; 95% CI, 1.6-7.4) drinkers, the risk increasing with the number of alcohol drink-years. Compared with current drinkers, those who had stopped within the past 9 years had a significant excess risk (OR=2.4; 95% CI, 1.1-5.2), while there was no significant difference in risk for those who had given up >10 years previously (OR=1.17; 95% CI, 0.57-2.41). There was a strong relationship between UADTC risk and consumption of alcohol before noon (as a marker of addiction) (OR=4.5; 95% CI, 1.9-10.9, compared with never drinkers).

52. Samoli *et al.* (2010) reported UADTC risk associated with alcohol intake in the Greek arm of the ARCAGE study, as part of an evaluation of the influence of Mediterranean-type diet on UADTC risk. The analysis included 239 UADTC cases[12] from 4 hospitals in Athens and 194 hospital-based controls. Information on lifestyle, including information on alcohol consumption, was obtained by trained interviewer using a questionnaire. Detailed information on alcohol intake was obtained according to the standard ARCAGE protocol. Subjects were classed as either non/light, moderate or heavy drinkers (respectively, <10, 10-49·99 and 50+ g/day for males, <5, 5-24·99 and 25+ g/day for females). Analyses were performed by multiple logistic regression, with adjustment for age (continuous), sex, BMI, height (continuous), education and smoking status (never, former, current; pack-years). As compared with non/light drinkers, OR (95% CI) for UADTC risk were 1.24 (0.76-2.03) for moderate and 2.08 (0.96-4.51) for heavy drinkers.

53. Boing *et al.* (2011) reported that socio-economic differences in HNC incidence in Brazil are partially attributable to the distribution of tobacco smoking and alcohol consumption across socioeconomic strata. The analysis included a total of 1,017 incident HNC cases[13] from 2 multicentre studies – 1] the Latin-American section of the 'International study of environment, viruses and cancer of the oral cavity and the larynx' (7 collaborating centres from three Latin-American countries – coordinated by IARC), 2] the Clinical Genome of Cancer Project (18 collaborating centres in the state of São Paulo) – and 951 hospital-based controls (in- or outpatients from the same hospitals). Information on education, occupation, smoking (pack years) and alcohol intake were obtained by trained interviewer. Patients who reported having never consumed at least one drink at a regular monthly basis were considered non-drinkers. Alcohol drinking was measured by g ethanol, considering that 1 l ethanol weighs 798 g and that beer contains 5% ethanol in volume, wine 12%, liqueurs 30% and distilled spirits 41%. Cumulative exposure to alcohol was expressed in g-years (g ethanol per day multiplied by number of drinking years). Categorisation used quartiles of the distribution in the overall sample. OR and 95% CI were assessed by unconditional logistic regression. Multivariate analysis used a hierarchical framework considering socioeconomic position (education, occupation) as distal covariates and behavioural factors (tobacco, alcohol consumption) as proximal exposures. All covariates were adjusted for sex and age. Behavioural covariates (alcohol and smoking) were adjusted for each other and for socioeconomic covariates.

[12] Oral cavity or pharynx (excluding nasopharynx), larynx, oesophagus
[13] Oral cavity, pharynx, larynx

54. Alcohol consumption was directly related to HNC risk, which increased with cumulative exposure. Compared with non-drinkers, OR (95% CI) for drinkers were as follows. *Adjusted for education:* 3.01 (2.10-4.31) for <723 g-years; 5.40 (3.72-7.84) for 723-2,241 g-years; 7.88 (5.33-11.64) for 2,242-5,562 g-years; 8.47 (5.69-12.59) for ≥5,562 g-years. *Adjusted for occupation:* 3.02 (2.11-4.32) for <723 g-years; 5.39 (3.72-7.82) for 723-2,241 g-years; 7.88 (5.34-11.64) for 2,242-5,562 g-years; 8.38 (5.64-12.45) for ≥5,562 g-years.

Summary of case-control studies on head and neck cancer risk

55. Four analyses were reported from the large European case-control study, Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE), which was initiated by IARC and involved 14 centres in 10 European countries. In an analysis by type of alcoholic drink. Marron *et al.* (2012) reported dose-dependent increased risks of UADTC that were of similar magnitude for wine, beer and liquor. Macfarlane *et al.* (2010) found that UADTC risk was strongly correlated with alcohol consumption in ARCAGE participants <50 years old, with increased risk for both current and past drinkers compared with never drinkers, and for the number of alcohol drink-years. Canova *et al.* (2010) reported that UADTC risk showed a dose-dependent association with frequency, but not duration, of alcohol consumption in a subset of patients from northern Italy. A very high risk was noted for high level alcohol intake plus smoking, suggestive of multiplicative effects. Samoli *et al.* (2010) reported (non-significant) increased UADTC risk associated with alcohol intake in the Greek arm of the ARCAGE study, as part of an evaluation of the influence of Mediterranean-type diet

56. Boing *et al.* (2011) reported that alcohol consumption was directly related to HNC risk, which increased with cumulative exposure, in an analysis of the role of alcohol and tobacco smoking in explaining socio-economic differences in HNC risk in a study including subjects from two multicentre studies in Brazil.

Genetic Polymorphisms

57. Three studies described analysis of potential interactions between genotype and alcohol exposure.

58. Canova *et al.* (2010) reported an evaluation of the effects of alcohol and tobacco consumption on UADTC risk, and of potential gene-environment interactions for susceptibility, in a subset of patients from three centres in northern Italy as part of the ARCAGE study. Subjects were classified as never drinkers or drinkers of <1, 1-2, 3-4, and ≥5 drink equivalents per day (further details in paragraph 49). The association of alcohol and/or tobacco intake with UADTC risk was calculated by unconditional logistic regression analysis, with adjustment for centre, sex, age at diagnosis (5-year groups) and educational level as categorical variables and cumulative tobacco and/or alcohol as continuous variables when appropriate. UADTC risk showed a dose-dependent association with frequency of alcohol consumption, as reported in paragraph 49. A subset of 386 cases and 394 controls were evaluated for the influence on alcohol- or smoking-associated UADTC risk of homo-/ heterozygosity for variants of a range of genes involved in carcinogen metabolism. The CYP1A11VS1+606T >G (rs2606345) (phase I metabolism) and ADH1CIVS6-892 A >G (rs1662058) (alcohol dehydrogenase) variants were

associated with increased risk. Analysis for ADH1C indicated that, taking individuals who were homozygous or heterozygous for the common allele and light drinkers (≤2 drinks/day) as the referent group, those who were homo/heterozygous for the common allele who drank 3+ drinks/day had an OR of 3.71 (95% CI, 2.51-5.48), whilst those who were homozygous for the rare variant allele and drank 3+ drinks/day had an OR of 9.27 (95% CI, 4.01-21.46).

59. 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[14] were identified from the central cancer registry, controls were identified from vehicle registration lists and frequency matched to cases for age, race and sex. Information on demographics, tobacco use, drinking of alcoholic beverages, diet, oral health, medical history and family history of cancer was obtained by trained interviewers. Genotypes were analysed on DNA prepared from blood or buccal cell samples. The analysis included 75 polymorphic SNPs in 12 genes: ADH1B, ADH1C, ADH4, ADH7, ALDH2, and CYP2E1 in the alcohol metabolism pathway in the upper aero-digestive tract; and CAT, SOD1, SOD2, GPX1, GPX2 and GPX4 in the oxidative stress pathway. Data were evaluated separately for African-Americans and European-Americans. Questions about alcohol use, designed to estimate lifetime history of consumption, included age of starting/stopping, years of drinking, type (beer/wine/hard liquor) and number of drinks per day/week/month/year, and drink size. Information was also collected on smoking habits (duration of smoking, ever use of non-cigarette tobacco, ever exposed to environmental tobacco smoke). Additional potential confounders considered were health insurance at reference date, oral health parameters, family history of HNC, poverty and education levels. OR for the independent effects of SNPs and alcohol, and their interactive effects, were computed using conditional logistic regression. OR for the main effects of haplotypes were computed using unconditional logistic regression. A dominant genetic model (at least one minor allele vs. referent of no minor alleles) was used, as the number of homozygous-minor-allele subjects was too small in the case of many of the SNPs. Departures from additive interaction were evaluated by computing interaction contrast ratios (ICR) and Bonferroni-corrected CI. ICR were calculated using cancer OR of subjects in three categories: (1) the highest drinking category and no minor allele (OR_{01}); (2) never-drinkers with at least one minor allele (OR_{10}); and (3) subjects in the highest drinking category and at least one minor allele ($OR10_{11}$), compared with never-drinkers homozygous for the major allele (i.e. the referent: $OR_{00} = 1.0$). The ICR was calculated as: $ICR=OR_{11} - OR_{01} - OR_{10} + 1$. ICR significantly different from zero indicated departure from additive interaction.

60. The odds of developing HNC increased with lifetime alcohol consumption. Subjects in the lowest consumption category had reduced HNC odds compared with non-drinkers (OR=0.8; 95% CI, 0.6–1.0), mostly due to laryngeal and oral cavity tumours: OR (95% CI) = 0.7 (0.4–1.1) and 0.4 (0.2–0.9), respectively. Successively higher levels of alcohol consumption were associated with increasing odds. The middle tertile of lifetime consumption was associated with 30% higher HNC odds than never-drinkers, and the highest tertile of consumption with tripled odds.

[14] SCC of oral cavity, pharynx, larynx

61. None of the SNP associations with HNC had a significant Bonferroni-corrected p-value, although 5 SNPs in ADH1B, ALDH2, and SOD2 showed evidence of reduced or increased cancer OR overall and in oral cavity, laryngeal, and hypo-pharyngeal sub-sites. In ADH1B, the rs1229984 A allele was associated with 30% decreased HNC odds, and the rs17028834 C allele with 50% increased odds of laryngeal tumours. In ALDH2, the rs2238151 C allele was associated with 10% increased odds of HNC, driven largely by 20% increased odds of laryngeal tumours. In SOD2, the rs4342445 A allele was associated with 30% greater odds for oral cavity tumours, and the rs5746134 T allele with doubled odds for hypo-pharyngeal cancer. Four haplotypes in ALDH2, CYP2E1, GPX2 and SOD1 were associated with HNC, either in European-Americans and/or African-Americans. One GPX2 haplotype was significantly associated with 30% decreased odds of HNC in European-Americans. An ALDH2 haplotype was associated with 50% reduced odds in African-Americans and a CYP2E1 haplotype was associated with 30% reduced odds in European-Americans. The SOD1 AGGC haplotype was associated with increased odds in European-Americans and reduced odds in African-Americans. SNP effect estimates were mostly similar in European- and African-Americans. Evaluation by race indicated similar effects in African- and European-Americans, with a small number of exceptions.

62. Four SNPs showed evidence of synergistic additive interaction with alcohol consumption. Heavy drinkers carrying the C allele of rs2238151 in ALDH2 showed statistically significant evidence of synergistic additive interaction. In addition, the T allele at rs1159918 in ADH1B, the A allele at rs1154460 in ADH7, and the T allele at rs2249695 in CYP2E1 showed some evidence for synergistic additive interaction between alcohol consumption and SNP. The magnitude of effects for these four SNPs did not differ between African- and European-Americans.

63. Tsai *et al.* (2014) investigated the inter-relation of alcohol consumption, oral hygiene and alcohol- and aldehyde dehydrogenase–metabolising phenotypes. This study, carried out in Taiwan, included 436 newly diagnosed HNC cases[15] aged 20-80 years and 514 hospital-based controls matched for age and sex. Information on alcohol drinking and oral hygiene habits was obtained by trained interviewer. Information on alcohol drinking included starting and quitting age (if quit for more than 6 months), type of beverage (beer, wine, hard liquor), frequency (never, monthly, weekly, daily) and quantity (number of cups, where 1 cup = 150 ml). Subjects were genotyped for alcohol dehydrogenase, *ADH1B rs1229984*: fast (*2/*2), slow (*1/*2 or *1/*1), and aldehyde dehydrogenase, *ALDH2 rs671*: fast (*2/*2), slow (*1/*2), non-functional (*2/*2). Genotype combinations were also categorised into 4 sub-groups; Group 1: fast *ADH1B* /fast *ALDH2*, Group 2: fast *ADH1B*/slow or non-functional *ALDH2*, Group 3: slow *ADH1B*/fast *ALDH2*, Group 4: slow *ADH1B*/slow or non-functional *ALDH2*. Unconditional logistic regression, adjusted for sex, age, education, cigarette smoking (pack-year categories) and betel quid chewing (pack-year categories) was used to calculate OR and 95% CI for associations between HNC risk and 1] alcohol drinking, 2] oral hygiene, 3] *ADH1B*/*ALDH2* genotype sub-groups, 4] *ADH1B*/*ALDH2* genotype sub-groups by alcohol status sub-group, 5] *ADH1B*/*ALDH2* genotype sub-groups by oral hygiene status sub-group in regular drinkers.

[15] SCC of oral cavity, pharynx (oropharynx and hypopharynx), larynx

1] Compared with never or occasional alcohol drinkers, current regular alcohol drinkers had an elevated risk of HNC (OR=1.95; 95% CI, 1.38-2.75). This was seen mainly for daily drinkers (OR=1.97; 95% CI, 1.37-2.84). The association between HNC and the duration of alcohol drinking showed an increasing trend, with those drinking more than 15 years having a higher HNC risk. There was a 7% increase in the risk of HNC (OR=1.07; 95% CI, 1.02-1.13) for every 5 years of alcohol drinking.

2] Poor oral hygiene was associated with an increased risk of HNC. Each one point increment increase of oral hygiene score (poorer oral hygiene) was associated with a 46% increase in the risk of HNC (OR=1.46; 95% CI, 1.20-1.77).

3] Increased risk was seen for slow *ADH1B* (OR=2.08; 95% CI, 1.14-3.80) and slow *ALDH2* (OR=1.89; 95% CI, 1.36-2.62) genotypes.

4] Regarding HNC risk associated with alcohol drinking vs. non/occasional drinking: Group 1 (fast *ADH1B*/fast *ALDH2*) showed no increase. The risk in this group was reduced for former regular drinkers, weekly drinkers, and <50 g/day. Group 2 (fast *ADH1B*/ slow/non-functional *ALDH2*) showed increased risk. Groups 3 and 4 (slow *ADH1B* genotypes) had increased risk. The magnitude of effect was larger with increased alcohol consumption. Among regular alcohol drinkers, the association between HNC risk and poor oral hygiene score was stronger in slow than fast *ADH1B* groups.

5] Further sub-analysis indicated that regardless of the measures of alcohol consumption (drinking status, frequency, g/day or duration), the positive association between alcohol drinking and HNC risk remained the strongest among those with the slow *ADH1B* genotypes in combination with the poorest oral hygiene.

Overall Summary

64. A dose-dependent increase in risk of HNC/UADTC with alcohol intake was noted in the majority of the analyses reported. A pooled analysis of case-control studies from the INHANCE consortium indicated significantly increased risk associated with heavy drinking (≥3 drinks/day). A strong and multiplicative combined effect of alcohol and tobacco smoking was noted.

65. Analyses from two large studies (The Netherlands Cohort Study and the ARCAGE Study) indicated that the increased risk for alcohol intake overall was not significantly different by breakdown for different types of alcoholic drinks.

66. An association of risk with alcohol drinking level was noted in ARCAGE study subjects homozygous for a rare ADH1C allele. Polymorphisms in ALDH2, ADH1B, ADH7 and CYP2E1 showed some evidence for synergistic additive interaction with alcohol consumption in subjects in the US Carolina Head and Neck Cancer Epidemiology Study (CHANCE). Increased HNC risk associated with alcohol drinking was noted in Taiwanese subjects with ‘slow’ ALDH2 genotypes, the magnitude of effect being larger with increased alcohol consumption.

67. A meta-analysis that included 2 studies from North America and 8 studies from Asia indicated a dose-dependent association of alcohol drinking with HNC mortality.

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 head and neck cancer risk?

2) Do the studies reviewed here add further weight to the existing view that alcohol consumption is causally associated with head/neck cancer risk?

Secretariat
April 2015

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Table 1.Pooled and meta-analysis studies examining alcohol consumption and head and neck cancer risk, published since 2009

Reference, location, name of study	Description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases / controls, n	Pooled odds ratio and confidence intervals (95% CI)[a]	Adjustment factors	Comments
Hashibe et al 2009 European and American studies, International Head and Neck Cancer Epidemiology (INHANCE) consortium	Pooled analysis from 17 case-control studies 11,211 head and neck cancer cases, 16,168 controls	Varied	Alcohol only ***Sex*** Women Men ***Age (years)*** <45 45-60 >60 ***Geographic region*** Europe North America Latin America Tobacco only ***Sex*** Women Men ***Age (years)*** <45 45-60 >60 ***Geographic region*** Europe North America Latin America Tobacco and alcohol ***Sex*** Women Men ***Age (years)*** <45 45-60 >60	831 / 1587 389 / 608 442 / 979 65 / 213 330 / 687 436 / 687 208 / 543 403 / 741 220 / 304 247 / 1348 426 / 2305 130 / 547 286 / 1650 257 / 1456 216 / 2101 380 / 1162 77 / 390 1247 / 1181 7899 / 7393 745 / 1036 4241 / 3818 4160 / 3720	1.06 (0.88-1.28) 0.93 (0.73-1.19) 1.07 (0.80-1.44) 0.71 (0.46-1.09) 1.22 (0.88-1.69) 0.98 (0.75-1.30) 1.21 (0.75-1.96) 0.98 (0.74-1.30) 1.07 (0.49-2.36) 2.83 (1.97-4.06) 2.06 (1.34-3.18) 1.01 (0.56-1.82) 2.7 (1.71-4.25) 2.68 (1.94-3.70) 3.72 (2.24-6.18) 1.48 (0.95-2.30) 3.35 (1.69-6.65) 6.66 (3.89-11.41) 5.19 (3.11-8.65) 2.17 (1.22-3.86) 6.65 (3.63-12.16) 6.02 (3.94-9.22)	Age, sex, education, race/ethnicity and study centre	

Table 1.Pooled and meta-analysis studies examining alcohol consumption and head and neck cancer risk, published since 2009							
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
			Tobacco and alcohol (cont) ***Geographic region*** Europe North America Latin America Alcohol and smoking frequency ***Never smoker*** never drinker 1–2 drinks/day ≥3 drinks/day ***1–20 cigs/day*** never drinker 1–2 drinks/day ≥3 drinks/day ***>20 cigs/day*** never drinker 1–2 drinks/day ≥3 drinks/day	 3641 / 4225 3205 / 3026 2300 / 1323	 11.72 (5.58-24.59) 2.84 (2.05-3.94) 9.78 (5.36,17.85) 1.00 1.03 (0.84–1.25) 1.91 (1.27–2.87) 2.20 (1.57–3.09) 3.09 (2.13–4.50) 9.92 (6.36–15.46) 4.15 (2.44–7.07) 4.81 (3.21–7.20) 14.23 (8.30–24.40)		

Table 2.Pooled and meta-analysis studies examining alcohol consumption and head and neck cancer mortality and secondary events, published since 2009

Reference, location, name of study	Description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases / controls, n	Pooled odds ratio and confidence intervals (95% CI)[a]	Adjustment factors	Comments
Druesne-Pecollo 2014 Meta-analysis of observational studies (8 cohort studies, 11 case-control studies) identified by PubMed and Embase searches to July 2012	Patients with a head and neck cancer as the first primary cancer site 493 cases and 6385 participants for analysis of UADT second primary cancers 466 cases and 3720 participants for analysis of UADT + lung second primary cancers 708 cases and 4267 participants for analysis of all sites second primary cancer	Varied	**<u>Alcohol intake</u>**			Yes/no – age, gender, smoking, occupation, index tumour site	
			UADT second 1° cancer				
			Highest vs. lowest	493 / 5892	2.97 (1.96-4.50)		
			Sub-group analysis				
			Case-control		3.41 (2.05-5.69)		
			Cohort		2.07 (0.96-4.46)		
			Europe		3.06 (1.51–6.17)		
			Asia		3.47 (1.90–6.31)		
			By interview		2.76 (1.44–5.31)		
			By questionnaire		5.45 (0.69–42.98)		
			By medical record		2.64 (1.79–3.89)		
			Drinker vs. non-drinker		2.70 (1.28-5.70)		
			By drinking category		3.21 (1.83-5.63)		
			For UADT (i.e. not specifying individual UADT cancer site)		4.43 (1.46-13.48)		
			Adjustment for:				
			Age				
			-yes		2.85 (1.69–4.80)		
			-no		2.85 (1.69–4.80)		
			Gender				
			-yes		3.22 (1.72–6.03)		
			-no		2.79 (1.47–5.31)		
			Smoking				
			-yes		2.79 (1.47–5.31)		
			-no		3.09 (1.00–9.50)		
			Occupation				
			-yes		3.06 (1.51–6.17)		
			-no		3.05 (1.69–5.49)		
			Index tumour site				
			-yes		2.85 (1.20–6.78)		
			-no		2.80 (1.97–3.97)		
			Per 10 g/day alcohol	157 / 3457	1.09 (1.04-1.14)		

Table 2.Pooled and meta-analysis studies examining alcohol consumption and head and neck cancer mortality and secondary events, published since 2009							
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
			UADT + lung second 1° cancers Highest vs. lowest ***All sites second 1° cancer*** Highest vs. lowest	 466 / 3254 708 / 3559	 1.91 (1.17-3.13) 1.60 (1.22-2.10)		
Li 2014 Epidemiological studies listed in Pubmed, ISI Web of Science, published to 30 June 2013 North America (2 studies), Asia (8 studies)	8 cohort, 1 nested case-control, and 1 case-control study 2976 UADT cancer deaths	Alcohol drinking	<u>Alcohol intake level</u> ***Drinking*** All studies Men Women Population-based Occupation-based Asia North America Adjusted[1] Not/partially adjusted Follow-up <12 y Follow-up ≥12 y Quality score <6.55 Quality score ≥6.55 ***Light drinking*** All studies Men Women Population-based Occupation-based Asia North America Adjusted[1] Not/partially adjusted		 2.01(1.56–2.59) 2.09(1.60–2.73) 1.38(0.64–2.97) 1.84(1.40–2.41) 2.81(1.43–5.52) 1.93(1.46–2.54) 2.51(1.22–5.16) 1.90(1.47–2.46) 3.41(0.86–13.46) 1.93(1.41–2.64) 2.16(1.42–3.27) 1.98(1.50–2.61) 2.20(1.35–3.58) 1.26(0.94–1.67) 1.26(0.94–1.67) - 1.16(0.94–1.43) 1.90(1.58–2.28) 1.41(1.09–1.83) 0.78(0.23–2.59) 1.26(0.94–1.67) -	adjusted for major confounders: age, sex, cigarette smoking	Reference category, never or occasional drinking Light drinking, ≤12.5 g ethanol/day (≤1 drink/day), Moderate drinking, 12.6-49.9 g/day (2-3 drinks/day), Heavy drinking, ≥50 g/day (≥4 drinks/day).

Table 2.Pooled and meta-analysis studies examining alcohol consumption and head and neck cancer mortality and secondary events, published since 2009							
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
			Follow-up <12 y Follow-up ≥12 y Quality score <6.55 Quality score ≥6.55 ***Moderate drinking*** All studies Men Women Population-based Occupation-based Asia North America Adjusted[1] Not/partially adjusted Follow-up <12 y Follow-up ≥12 y Quality score <6.55 Quality score ≥6.55 ***Heavy drinking*** All studies Male Female Population-based Occupation-based Asia North America Adjusted[1] Not/partially adjusted		1.25(0.90–1.73) 1.21(0.80–1.84) 1.55(1.17–2.05) 1.01(0.64–1.59) 1.79(1.26–2.53) 1.77(1.22–2.55) 2.06(0.74–5.73) 1.68(1.11–2.55) 2.51(1.82–3.46) 1.48(1.06–2.06) 4.27(2.62–6.96) 1.83(1.27–2.64) 1.27(0.47–3.40) 1.29(0.97–1.73) 2.61(1.48–4.61) 1.50(1.00–2.26) 2.34(1.15–4.76) 3.63(2.63–5.00) 3.63(2.63–5.00) - 3.69(2.54–5.35) 3.67(1.62–8.33) 2.97(2.15–4.09) 6.11(4.34–8.60) 3.73(2.66–5.25) 3.41(0.86–13.46)		

Table 2.Pooled and meta-analysis studies examining alcohol consumption and head and neck cancer mortality and secondary events, published since 2009							
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
			Follow-up <12 y Follow-up ≥12 y Quality score <6.55 Quality score ≥6.55		3.03(2.20–4.18) 4.47(2.50–7.98) 3.44(2.70–4.39) 4.06(2.12–7.79)		

Table 3.Pooled and meta-analysis studies examining cessation of alcohol consumption and head and neck cancer risk, published since 2009

Reference, location, name of study	Description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases / controls, n	Pooled odds ratio and confidence intervals (95% CI)[a]	Adjustment factors	Comments
Marron et al. (2010) European and American studies, International Head and Neck Cancer Epidemiology (INHANCE) consortium	Pooled analysis including 13 studies on drinking cessation (9,167 cases and 12,593 controls) and 17 studies (12,040 cases and 16,884 controls) on smoking cessation	Interview	<u>Drinking status</u> Current drinker Former drinker Never drinker <u>Cessation of drinking</u> Current drinker >1–4 y 5–9 y 10–19 y ≥20 y Never drinker <u>Cessation of smoking and/or drinking</u> ***Current smoker*** Current drinker >1–4 y 5–19 y ≥20 y Never drinker ***>1–4 y former smoker*** Current drinker >1–4 y 5–19 y ≥20 y Never drinker ***5–19 y former smoker*** Current drinker >1–4 y 5–19 y ≥20 y Never drinker ***≥20 y former smoker*** Current drinker >1–4 y 5–19 y ≥20 y Never drinker	 4668 / 5915 2521 / 2646 1602 / 3693 4668 / 5915 564 / 505 575 / 576 790 / 802 591 / 762 1602 / 3693 2619 / 1556 295 / 132 648 / 294 245 / 144 737 / 538 168 / 167 94 / 55 62 / 58 23 / 23 54 / 56 409 / 810 53 / 67 240 / 260 72 / 98 77 / 198 249 / 696 25 / 52 82 / 164 73 / 166 91 / 237	 1.00 (reference) 0.85 (0.63–1.14) 0.73 (0.51–1.06) 1.00 (reference) 0.99 (0.69–1.43) 0.90 (0.62–1.30) 0.94 (0.75–1.18) 0.60 (0.40–0.89) 0.74 (0.51–1.06) 1.00 (reference) 0.94 (0.53–1.65) 0.90 (0.61–1.33) 0.53 (0.32–0.88) 0.74 (0.36–1.52) 0.75 (0.49–1.14) 0.74 (0.47–1.17) 0.42 (0.26–0.7) 0.55 (0.24–1.26) 0.57 (0.26–1.28) 0.40 (0.33–0.48) 0.44 (0.27–0.72) 0.43 (0.27–0.68) 0.32 (0.21–0.49) 0.28 (0.13–0.61) 0.27 (0.17–0.42) 0.29 (0.09–0.92) 0.31 (0.17–0.55) 0.25 (0.13–0.48) 0.26 (0.11–0.59)	Adjusted for age, sex, race/ethnicity, study centre, education level, tobacco pack-years and drinking frequency	7

Table 3.Pooled and meta-analysis studies examining cessation of alcohol consumption and head and neck cancer risk, published since 2009							
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
			Never smoker				
			Current drinker	288 / 1554	0.21 (0.11–0.41)		
			>1–4 y	21 / 96	0.24 (0.09–0.68)		
			5–19 y	48 / 216	0.17 (0.07–0.46)		
			≥20 y	37 / 114	0.27 (0.11–0.68)		
			Never drinker	503 / 1720	0.26 (0.12–0.56)		

Table 4. Cohort studies examining the effect of alcohol consumption on head and neck cancer risk, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative Risk and 95% confidence intervals (95% CI)[b]	Adjustment factors	Comments	Star rating
Maasland et al. (2014) Netherlands cohort study (NLCS) of 120,852 participants, aged 55-69 years from 204 Dutch population registries	Prospective cohort 395 cases of HNC and a sub-cohort of 4,288 members	Food Frequency Question naire (FFQ) at baseline	<u>Alcohol consumption (g ethanol/day)</u>: Abstainers >0 - <5 g/day 5 - <15 g/day 15 - <30 g/day ≥30 g/day Continuous 10 g ethanol/day increments -Overall -Men -Women <u>Alcohol consumption (g ethanol/day) stable users</u>: Abstainers >0 - <5 g/day 5 - <15 g/day 15 - <30 g/day ≥30 g/day Continuous 10 g ethanol/day increments <u>Alcoholic beverages (glasses/day)</u>: ***Beer*** None >0-<1 1-<2 ≥2 Continuous 1 glass/day increments ***Wine*** None >0-<1 1-<2 ≥2 Continuous 1 glass/day increments	 49 67 72 92 115 395 314 81 38 36 38 45 69 226 183 129 37 46 395 197 132 39 24 392	 1 (reference) 1.11 (0.75-1.65) 1.15 (0.77-1.71) 1.52 (1.02-2.27) 2.74 (1.85-4.06) 1.20 (1.12-1.27) 1.19 (1.12-1.27) 1.40 (1.18–1.65) 1 (reference) 0.98 (0.60-1.61) 0.96 (0.58-1.59) 1.27 (0.76-2.11) 2.90 (1.78-4.73) 1.26 (1.16-1.36) 1 (reference) 0.94 (0.71-1.24) 1.12 (0.72-1.74) 1.39 (0.83-2.34) 1.07 (0.97-1.19) 1 (reference) 0.88 (0.67-1.14) 0.95 (0.63-1.14) 0.56 (0.29-1.07) 0.88 (0.74-1.05)	Age (years), sex, cigarette smoking (status (never/former/current), frequency (continuous; centred), and duration (continuous; centred)	Measured outcome, microscopically confirmed incident head and neck cancer Abstainers were the reference category Stable users = subjects who had not changed their continuous alcohol consumption habits in the 5 years before baseline: for “beer” and “other alcoholic beverages”, participants could indicate whether 5 years before baseline they drunk (1) more than, (2) equal amounts of or (3) less than at baseline; the fourth answer option was (4) “I never use this”	8

Table 4. Cohort studies examining the effect of alcohol consumption on head and neck cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Relative Risk and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star rating**
			Liquor None >0-<1 1-<2 ≥2 Continuous 1 glass/day increments <u>Cigarette smoking and alcohol consumption (g ethanol/day)</u> ***Never smokers*** 0 g/day >0 - <5 g/day 5 - <15 g/day 15 - <30 g/day ≥30 g/day ***>0 – <20 cigs/day*** 0 g/day >0 - <5 g/day 5 - <15 g/day 15 - <30 g/day ≥30 g/day ***≥ 20 cigs/day*** 0 g/day >0 - <5 g/day 5 - <15 g/day 15 - <30 g/day ≥30 g/day	 137 133 67 56 393 10 13 7 11 3 21 25 37 40 32 18 29 28 41 80	 1 (reference) 1.09 (0.84-1.43) 1.09 (0.76-1.57) 1.18 (0.71-1.95) 1.01 (0.86-1.18) 1 (reference) 1.20 (0.52-2.75) 1.23 (0.46-3.29) 5.53 (2.27-13.49) 2.97 (0.78-11.40) 1.89 (0.83-4.34) 1.56 (0.71-3.41) 2.04 (0.95-4.40) 2.63 (1.22-5.67) 3.82 (1.71-8.51) 2.78 (1.18-6.54) 3.88 (1.77-8.49) 2.85 (1.28-6.34) 3.32 (1.52-7.25) 8.28 (3.98-17.22)			
Everatt et al. (2013) Men from 2 population-based cohorts in Kaunas, Lithuania: Kaunas Rotterdam Intervention Study (KRIS) and	7,150 men aged 45-59 (KRIS) or 40-59 (MIHDPS), randomly sampled from men living in the city of Kaunas	Interview at baseline using structured questionnaire	<u>Alcohol consumption</u> ***g/week[1]*** Non-drinkers 0.1-10.0 10.1-40.0 40.1-70.0 70.1-140.0 ≥140.1 continuous[a]	 5 9 29 10 23 19	 1.24 (0.41-3.71) 1 (reference) 1.16 (0.54-2.47) 2.33 (0.92-5.88) 2.03 (0.92-5.88) 2.79 (1.23-6.34) 1.18 (1.06-1.30)	[1]Stratified by study, adjusted for smoking (never, former, B10 cig/day, 11–19 cig/day, C20 cig/day); education (primary, unfinished secondary, secondary, high school); BMI	Measured outcome, upper aerodigestive tract cancer registration or cause of death [a] per 90 g/week [b] per 41.9 g/occasion	8

Table 4. Cohort studies examining the effect of alcohol consumption on head and neck cancer risk, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative Risk and 95% confidence intervals (95% CI)[b]	Adjustment factors	Comments	Star rating
Multifactorial Ischemic Heart Disease Prevention Study (MIHDPS)			***g/occasion***[2] 0.1-45.0 45.0-60.0 60.1-100.0 100.1-120.0 ≥120.1 continuous[b] <u>Frequency of alcohol consumption</u>[3] Non-drinkers A few x per year 1-4 x per month 2-7 x per week	 8 11 47 10 14 5 9 68 13	 1 (reference) 2.19 (0.76-6.33) 1.69 (0.77-3.70) 1.59 (0.61-4.19) 1.88 (0.75-4.71) 1.13 (0.87-1.46) 1.64 (0.48-5.54) 1 (reference) 1.23 (0.59-2.55) 2.31 (0.94-5.69)	[2]Stratified by study, adjusted for smoking (never, former, B10 cig/day, 11–19 cig/day, C20 cig/day); education (primary, unfinished secondary, secondary, high school); BMI, alcohol consumption frequency [3]Stratified by study, adjusted for smoking (never, former, B10 cig/day, 11–19 cig/day, C20 cig/day); education (primary, unfinished secondary, secondary, high school); BMI, alcohol intake per one occasion (g/occasion)	A population attributable risk of 35.3% was calculated for head and neck cancers in this cohort during the 30-year follow-up period	
Hsu et al. (2014) 3 community cohorts in Taiwan: Six-community Hypertension Intervention Project cohort; Multiple Risk Factors for Multiple diseases cohort; Community-based Cancer Screening Project cohort	Prospective cohort of 25,611 men	Interview with structured questionnaire	<u>Alcohol drinking</u> Never Ever ***Quantity (g/day)*** Never <80 ≥80 ***Duration (years)*** Never ≤20 >20 ***Cumulative exposure (g-years)*** Never <1500 ≥1500		 1.0 (reference) 1.90 (1.46-2.49) 1.00 (reference) 1.73 (1.23-2.42) 2.49 (1.72-3.61) 1.00 (reference) 2.07 (1.45-2.97) 1.91 (1.37-2.68) 1.00 (reference) 1.79 (1.27-2.51) 2.58 (1.78-3.74)	age, educational level, ethnicity, study cohort, substance use each other (betel quid chewing, cigarette smoking, alcohol)	Measured outcome, head and neck cancer registration or cause of death Total number of cases = 269 during 18 years follow-up	**7**

Table 4. Cohort studies examining the effect of alcohol consumption on head and neck cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Relative Risk and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star rating**
			<u>Combined exposures</u> Ever-alcohol/Never-betel/Never-cigarette Ever-alcohol/Never-betel/Ever-cigarette Ever-alcohol/Ever-betel/Never-cigarette, Ever-alcohol/Ever-betel/Ever-cigarette		 1.42 (0.55-3.65) 4.90 (3.12-7.69) 15.69 (6.06-40.68) 10.46 (6.31-17.34)			

Table 5. Cohort studies examining the effect of alcohol consumption on head and neck cancer mortality and secondary events, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Relative risk and 95% confidence intervals (95% CI)[b]	Adjustment factors	Comments	Star Rating for Quality
Mayne et al. (2009) Cohort of patients in the US with early stage head and neck cancers, aged 20-79 years, enrolled in a b-carotene supplementation trial	264 patients with early stage squamous cell carcinoma of the oral cavity, pharynx or larynx	Interview-based structured questionnaire, at baseline and yearly up to 60 months	<u>Alcohol prior to diagnosis (drinks/week)</u> ***Total*** 0 1-7 8-21 22-35 >35 ***Beer*** 0 1-7 8-21 >21 ***Wine*** 0 1-7 8-21 >21 ***Liquor*** 0 1-7 8-21 >21 <u>Alcohol exposure after diagnosis</u> None Transitional Continuous		 1 (reference) 1.46 (0.35-6.14) 1.44 (0.39-5.35) 2.36 (0.60-9.31) 4.87 (1.46-16.27) 1 (reference) 1.20 (0.53-2.73 2.37 (1.03-5.44) 2.86 (1.34-6.12) 1 (reference) 0.58 (0.25-1.35) 0.44 (0.14-1.35) 0.75 (0.32-1.76) 1 (reference) 1.27 (0.59-2.75) 1.04 (0.47-2.33) 2.11 (1.04-4.28) 1 (reference) 0.73 (0.29-1.86) 2.72 (1.20-6.14)	age, sex, race, b-carotene randomization group, educational level, body mass index, smoking before diagnosis (pack-years, current vs. former/never) and during follow-up, and drinking before diagnosis (models for current drinking)	Measured outcome, all-cause mortality Alcohol intake after diagnosis: non-exposed = abstained throughout follow-up, transitionally exposed = exposed after diagnosis but not continuously, continuously exposed = reported exposure at each yearly follow-up interview.	**8**

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure category	Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]	Adjustment factors	Comments	Star Quality
Marron et al 2012 Europe Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) study 14 centres in 10 European countries	2,001 cases Male and female cases identified with histologically or cytologically confirmed UADT cancer diagnosed within the past 6 months	2,125 controls UK population-based controls randomly selected from the same primary practice list as the corresponding case Hospital controls were randomly selected from subjects admitted as in- or out-patients in the same hospital as the case	Interviewer based questionnaire	**Drinking frequency** Wine ***Drink only this type*** <1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day ***Drink predominantly this type*** <1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day ***Drink this and other types*** <1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day Beer ***Drink only this type***[a] <1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day ***Drink predominantly this type*** <1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day ***Drink this and other types*** <1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day	 1.49 (0.95-2.33) 0.86 (0.49-1.50) 1.94 (0.88-4.28) 7.03 (3.12-15.84) 1.04 (0.69-1.57) 0.98 (0.66-1.47) 2.13 (1.34-3.39) 2.99 (1.76-5.07) 1.11 (0.80-1.54) 1.25 (0.82-1.92) 1.67 (0.90-3.13) 2.61 (0.99-6.88) 1.89 (1.18-3.01) 1.99 (1.12-3.55) 1.43 (0.73-2.81) 3.82 (1.69-8.60) 1.25 (0.82-1.91) 1.27 (0.82-1.97) 1.81 (1.05-3.10) 3.44 (1.89-6.24) 1.12 (0.82-1.54) 1.77 (1.16-2.69) 1.74 (0.89-3.42) 2.00 (0.90-4.43)	age, sex (when appropriate), centre, education level, fruit and vegetable intake, smoking (frequency and years since quitting), drinking frequency of other types (when appropriate), cumulative alcohol consumption (when stated)	Reference group for all evaluations = 'never alcohol' Drink predominantly this type = drink 66 % or more of this beverage type cumulative over lifetime Drink this and other types = drink less than 66 % of this beverage type cumulative over lifetime	7

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
				Liquor ***Drink only this type*** <1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day ***Drink predominantly this type*** <1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day ***Drink this and other types*** <1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day **Drinking Status (adjusted for cumulative alcohol consumption)** ***Wine*** Drink only this type Drink predominantly this type Drink this and other types Drink never this type ***Beer*** Drink only this type Drink predominantly this type Drink this and other types Drink never this type ***Liquor*** Drink only this type Drink predominantly this type Drink this and other types Drink never this type	 0.76 (0.39-1.51) 2.22 (0.65-7.56) 1.38 (0.30-6.32) 3.01 (0.30-30.17) 1.30 (0.76 -2.23) 1.57 (0.87-2.83) 4.27 (1.40-13.01) 2.28 (1.03-5.03) 1.05 (0.77-1.45) 1.57 (1.05-2.33) 1.44 (0.78-2.65) 1.59 (0.78-3.24) 1.24 (0.86-1.78) 1.05 (0.76-1.47) 1.09 (0.79-1.50) 1.63 (1.17-2.28) 1.54 (1.05-2.27) 1.25 (0.87-1.79) 1.20 (0.88-1.63) 1.13 (0.83-1.54) 0.94 (0.53-1.64) 1.43 (0.95-2.16) 1.12 (0.82-1.53) 1.20 (0.89-1.62)			

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
				Men ***Wine*** Drink only this type Drink predominantly this type Drink this and other types Drink never this type ***Beer*** Drink only this type Drink predominantly this type Drink this and other types Drink never this type ***Liquor*** Drink only this type Drink predominantly this type Drink this and other types Drink never this type Women ***Wine*** Drink only this type Drink predominantly this type Drink this and other types Drink never this type ***Beer*** Drink only this type Drink predominantly this type Drink this and other types Drink never this type ***Liquor*** Drink only this type Drink predominantly this type Drink this and other types Drink never this type	 1.84 (1.08-3.14) 1.43 (0.88-2.33) 1.40 (0.88-2.24) 2.20 (1.37-3.55) 2.01 (1.19-3.38) 1.53 (0.93-2.51) 1.51 (0.96-2.38) 1.57 (0.99-2.50) 1.55 (0.70-3.42) 1.88 (1.07-3.29) 1.51 (0.95-2.40) 1.64 (1.04-2.56) 0.81 (0.47-1.4) 0.98 (0.57-1.68) 1.10 (0.65-1.85) 1.10 (0.65-1.85) 0.82 (0.38-1.80) 1.29 (0.62-2.68) 1.20 (0.73-1.99) 0.90 (0.56-1.44) 0.74 (0.31-1.79) 1.56 (0.75-3.24) 0.98 (0.58-1.65) 0.90 (0.57-1.41)			

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure category	Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]	Adjustment factors	Comments	Star Quality
Macfarlane et al. (2010) Europe ARCAGE study 14 centres in 10 European countries	356 cases Patients aged <50 years with histologically or cytologically confirmed UADT-SCC diagnosed within the past 6 months	419 controls Most centres used hospital-based controls, randomly selected from subjects admitted as in- or out-patients in the same hospital as the case UK centres used similarly matched population-based controls	Interviewer-based questionnaire	<u>Alcohol consumption</u> Never Past Current (1 control missing) <u>Alcohol drink-years</u> Never <20 20–39 40–59 60–79 80+ (9 cases, 13 controls missing) <u>Time since stopped drinking</u> Current >1–9 years 10+ years Never drunk alcohol 19 (5.17) 59 (7 cases, 2 controls missing) <u>How often drink alcohol before noon</u> Never Never before noon Less 1 per month 1–4 per month 1–3 per week Most days or every day (25 cases, 16 controls missing; 90 cases, 76 controls - data not collected [Paris])	<u>OR (95% CI)</u> 1.00 (reference) 3.42 (1.59, 7.37) 1.80 (0.97, 3.34) 1.00 (reference) 1.23 (0.63, 2.38) 1.77 (0.85, 3.70) 2.01 (0.93, 4.34) 3.41 (1.49, 7.77) 3.92 (1.96, 7.83) 1.00 (reference) 2.38 (1.08, 5.23) 1.17 (0.57, 2.41) 0.55 (0.30, 1.03) 1.00 (reference) 1.71 (0.80, 3.67) 3.26 (1.15, 9.27) 1.54 (0.46, 5.12) 19 (1.32, 13.31) 4.52 (1.87, 10.92)	adjusted for age (years, continuous), gender, smoking, education and centre	The largest number of cases were recruited in France (n = 90), Italy(n = 53), Germany (47), and the United Kingdom (n = 46).	6

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure category	Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]	Adjustment factors	Comments	Star Quality
Canova et al. (2010) 3 centres in northern Italy (Aviano, Padua, Turin) Subset of ARCAGE study	449 (386 for genetic analyses) UADT cases histologically or cytologically confirmed UADT cancer diagnosed within the past 6 months	479 (394 for genetic analyses) controls frequency-matched controls selected from same hospital as cases	Interviewer-based questionnaire	Alcohol drinking Never Former Current ***Frequency*** < 1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day ***Duration*** Never 1-19 years 20-29 years 30-39 years 40+ years ADH1C genotype[1] ***1*1* + 1*2**** ≤2 drinks/day 3+ drinks/day ***2*2**** ≤2 drinks/day 3+ drinks/day Smoking (packs per day) and alcohol intake (drinks/day) interaction ***Never smokers*** < 1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day Total ***<20 pack year*** < 1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day Total	OR (95% CI) 1.00 (reference) 3.19 (1.67-6.09) 1.79 (1.07-3.01) 1.00 (reference) 1.18 (0.79-1.77) 2.78 (1.72-4.51) 6.29 (3.74-10.58) 1.00 (reference) 3.19 (1.35-7.54) 2.19 (1.11-4.31) 2.26 (1.25-4.07) 1.56 (0.89-2.72) 1 (reference) 3.71 (2.51-5.48) 1.74 (0.96-3.15) 9.27 (4.01-21.46) 1 0.98 (0.49-1.94) 1.65 (0.59-4.60) 1.65 (0.60-4.56) 1 1.13 (0.58-2.20) 1.42 (0.73-2.77) 3.09 (1.45-6.61) 7.81 (2.52-24.16) 1.52 (0.99-2.32)	adjusted for sex, age in quinquennia, area of residence, educational level, pack year and alcohol intake as continuous variables	[1]ADH1C IVS6-892 A>G rs1662058 1* common allele 2* rare variant allele	7

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
				20-39 pack year < 1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day Total ***>40 pack year*** < 1 drink/day 1-2 drinks/day 3-4 drinks/day 5+ drinks/day Total	 3.13 (1.49-6.58) 4.54 (2.33-8.83) 7.08 (3.43-14.62) 29.24 (12.60-67.89) 4.58 (2.98-7.02) 3.36 (1.39-8.15) 4.34 (2.08-9.06) 26.75 (9.21-77.72) 34.81 (14.69-82.50) 6.19 (3.83-10.00)			
Samoli et al. (2010) Greece (Athens) Subset of ARCAGE study	239 cases patients with cancer of the oral cavity/pharynx (excluding nasopharynx), larynx and oesophagus	194 controls hospital-based controls	Interviewer-based questionnaire	Alcohol drinking Non- or light drinker Moderate drinker Heavy drinker	OR (95% CI) Reference 1.24 (0.76-2.03) 2.08 (0.96-4.51)	age, sex, smoking (never, former, current; pack years), BMI, height, education	For males, <10, 10-49·99 and 50+ g/day for non/light, moderate and heavy drinker, respectively. For females, <5, 5-24·99 and 25+ g/day for non/light, moderate and heavy drinker, respectively.	7
Hakenewerth et al. (2011) US, population-based case-control study Caroline Head and Neck Cancer Epidemiology Study (CHANCE)	1227 cases	1325 controls	Interviewer-based questionnaire	Lifetime alcohol consumption (ml) 0 0 – 133,294 133,294 – 757,550 757,500+ Gene (haplotype definition) *ALDH2* (rs4767939, rs2238151, rs7312055, rs2158029, rs16941667, rs16941669) ***Haplotype (race)*** ACAGCT (AA) ATGGCT (AA)	 1.0 (reference) 0.75 (0.56–1.02) 1.29 (0.95–1.76) 3.22 (2.29–4.52) 1.0 (reference) 0.5 (0.3–0.8)	adjusted for age, sex, race, and duration of cigarette smoking	AA, African-American EA, European-American	5

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
				CYP2E1 (rs915908, rs7092584, rs743535, rs2249695) ***Haplotype*** GCCC (EA) GCCT (EA) *GPX2* (rs11623705, rs2412065, rs2737844) ***Haplotype*** GGC (EA) GCT (EA) *SOD1* (rs4998557, rs10432782, rs2070424, rs1041740) ***Haplotype*** GTAC (EA) AGGC (EA) GTAC (AA) AGGC (AA) <u>Gene – alcohol (ml-lifetime) interaction</u> *ALDH2*, rs2238151, T/C ***Homozygous major allele*** never-drinkers >0 to <134,699 134,699 to <757,550 757,550+ ***One or two copies of minor allele*** never-drinkers >0 to <134,699 134,699 to <757,550 757,550+ ICR (CI Bonferroni-corrected) *ADH1B*, rs1159918, G/T ***Homozygous major allele*** never-drinkers >0 to <134,699 134,699 to <757,550 757,550+	 1.0 (reference) 0.7 (0.6–0.9) 1.0 (reference) 0.7 (0.5–0.9) 1.0 (reference) 1.4 (1.1–1.9) 1.0 (reference) 0.6 (0.4–0.9) 1.0 (reference) 0.5 (0.3–0.9) 0.8 (0.5–1.3) 1.7 (1.0–2.8) 0.7 (0.4–1.1) 0.6 (0.4–1.0) 1.2 (0.8–1.9) 3.3 (2.0–5.3) 1.9 (0.1–3.8) 1.0 (reference) 0.7 (0.4–1.1) 1.1 (0.7–1.8) 2.4 (1.4–4.1)			

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
				One or two copies of minor allele never-drinkers >0 to <134,699 134,699 to <757,550 757,550+ ICR (CI Bonferroni-corrected) *ADH7*, rs1154460, G/A ***Homozygous major allele*** never-drinkers >0 to <134,699 134,699 to <757,550 757,550+ ***One or two copies of minor allele*** never-drinkers >0 to <134,699 134,699 to <757,550 757,550+ ICR (CI Bonferroni-corrected) *CYP2E1*, rs2249695, C/T ***Homozygous major allele*** never-drinkers >0 to <134,699 134,699 to <757,550 757,550+ ***One or two copies of minor allele*** never-drinkers >0 to <134,699 134,699 to <757,550 757,550+ ICR (CI Bonferroni-corrected)	 0.9 (0.6–1.5) 0.7 (0.5–1.1) 1.3 (0.8–2.0) 3.3 (2.1–5.4) 1.0 (−0.9, 3.0) 1.0 (reference) 0.5 (0.3–0.9) 0.8 (0.5–1.4) 1.9 (1.1–3.5) 0.6 (0.4–1.1) 0.6 (0.3–0.9) 1.0 (0.6–1.6) 2.5 (1.5–4.2) 0.9 (−0.6, 2.4) 1.0 (reference) 0.6 (0.4–0.9) 1.1 (0.7–1.6) 2.1 (1.4–3.3) 0.6 (0.4–0.9) 0.5 (0.3–0.8) 1.0 (0.6–1.4) 2.9 (1.8–4.6) 1.2 (−0.6, 3.0)			

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure category	Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]	Adjustment factors	Comments	Star Quality
Tsai et al. (2014) Taiwan	436 newly diagnoses HNC cases aged 20-80 years,	514 age- and sex-matched hospital-based controls	Interviewer-based questionnaire	Alcohol ***Status*** Never+occasional Former regular Current regular ***Frequency*** Never monthly weekly daily ***Duration (years)*** 0 0.1-15.0 15.1-30.0 >30.0 ***g/day*** 0 0.1-50.0 >50.0 Genotype ***ADH1B rs1229984*** TT (*2/*2)(Fast) CT (*1/*2) CC (*1/*1)(Slow) ***ALDH2 rs671*** GG (*1/*1)(Normal) AG (*1/*2) AA (*2/*2) (Non-functional) Alcohol and genotype Group 1: fast ADH1B (*2/*2); fast ALDH2 (*1/*1) ***Status*** Never+occasional Former regular Current regular	 1.0 (reference) 0.96 (0.59–1.57) 1.95 (1.38–2.75) 1.0 (reference) 1.20 (0.60–2.38) 1.11 (0.68–1.81) 1.97 (1.37–2.84) 1.0 (reference) 1.42 (0.76–2.64) 1.68 (1.11–2.55) 1.66 (1.12–2.48) 1.0 (reference) 1.18 (0.81–1.72) 2.34 (1.49–3.68) 1.0 (reference) 0.92 (0.67–1.26) 2.08 (1.14–3.80) 1.0 (reference) 1.89 (1.36–2.62) 1.20 (0.62–2.32) 1.0 (reference) 0.17 (0.05–0.59) 0.74 (0.33–1.64)	adjusted for sex, age, education, cigarette smoking (pack-year categories), and betel quid chewing (pack-year categories)		7

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
				Frequency Never monthly weekly daily ***g/day*** 0 0.1-50.0 >50.0 ***years of drinking*** every 5 y Group 2: fast ADH1B (*2/*2); slow ALDH2 (*1/*2 1*2/*2) ***Status*** Never+occasional Former regular Current regular ***Frequency*** Never monthly weekly daily ***g/day*** 0 0.1-50.0 >50.0 ***years of drinking*** every 5 y Group 3: slow ADH1B (*1/*1 1*1/*2); Group 3: slow ADH1B (*1/*1 1*1/*2); ***Status*** Never+occasional Former regular Current regular	 1.0 (reference) 0.76 (0.20–2.99) 0.22 (0.07–0.67) 0.76 (0.31–1.86) 1.0 (reference) 0.42 (0.17–1.04) 0.85 (0.31–2.34) 0.92 (0.82–1.04) 1.0 (reference) 2.07 (0.78–5.45) 6.64 (2.82–15.68) 1.0 (reference) 1.14 (0.27–4.70) 2.74 (0.87–8.68) 1 5.50 (2.42–12.46) 1.0 (reference) 2.61 (1.19–5.75) 7.28 (2.00–26.49) 1.20 (1.07—1.34) 1.0 (reference) 2.24 (0.57–8.87) 2.31 (0.77–6.95)			

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
				Frequency Never monthly weekly daily ***g/day*** 0 0.1-50.0 >50.0 ***years of drinking*** every 5 y Group 4: slow ADH1B (*1/*1 1*1/*2); slow ALDH2 ***Status*** Never+occasional Former regular Current regular ***Frequency*** Never monthly weekly daily ***g/day*** 0 0.1-50.0 >50.0 ***years of drinking*** every 5 y Group 3 + group 4: slow ADH1B (*1/*1 1*1/*2) ***Status*** Never+occasional Former regular Current regular	 1.0 (reference) 1.65 (0.24–11.58) 3.61 (0.85–15.30) 2.16 (0.57–8.24) 1.0 (reference) 1.75 (0.46–6.60) 2.32 (0.55–9.86) 1.20 (1.00–1.45) 1.0 (reference) 1.62 (0.60–4.38) 4.01 (2.06–7.81) 1.0 (reference) 2.05 (0.53–7.94) 1.45 (0.51–4.12) 4.81 (2.37–9.77) 1.0 (reference) 1.99 (0.92–4.34) 7.09 (2.88–17.42) 1.27 (1.14–1.42) 1.0 (reference) 1.29 (0.64–2.63) 2.17 (1.32–3.58)			

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
				Frequency Never monthly weekly daily ***g/day*** 0 0.1-50.0 >50.0 ***years of drinking*** every 5 y	 1.0 (reference) 1.28 (0.46–3.57) 1.63 (0.79–3.38) 2.10 (1.24–3.59) 1.0 (reference) 1.32 (0.74–2.33) 2.72 (1.43–5.17) 1.12 (1.04–1.21)			
Boing et al. (2011) Brazil Head and Neck Genome Project (GENCAPO)	1017 cases Incident, histologically confirmed cases of oral, pharyngeal and laryngeal cancer from 3 hospitals in Sao Paolo Drawn from 2 multicentre studies: 1] the Latin-American section of the "International study of environment, viruses and cancer of the oral cavity and the larynx (7 collaborating centres from three Latin-American countries –	951 controls in- and out-patients from the same hospitals as patients	Interviewer-based questionnaire	<u>Alcohol drinking (g-years)</u> ***Adjusted for education*** Non-drinker < 723.4 723.4 – 2241.18 2241.9 – 5562.1 ≥ 5562.2 ***Adjusted for occupation*** Non-drinker < 723.4 723.4 – 2241.18 2241.9 – 5562.1 ≥ 5562.2	 1.00 3.01 (2.10-4.31) 5.40 (3.72-7.84) 7.88 (5.33-11.64) 8.47 (5.69-12.59) 1.00 3.02 (2.11-4.32) 5.39 (3.72-7.82) 7.88 (5.34-11.64) 8.38 (5.64-12.45)	sex, age, smoking (pack-years), education or occupation	g-years = g ethanol consumed per day multiplied by the number of years of drinking.	6

Table 6. Case-Control studies examining the effect of alcohol consumption on head and neck cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Pooled odds ratio (OR) and 95% confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
	coordinated by IARC; 2] the Clinical Genome of Cancer Project (18 collaborating centres in the state of São Paulo)							

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

Consumption of Alcohol and Head and Neck Cancer Risk

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

Pages 382-383, 412-413, 428, 442-443, 444-445, 446, 472 and Tables 2.6, 2.11, and 2.12

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Secretariat
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