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

Consumption of Alcohol and Oesophageal Cancer Risk

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

Oesophageal Cancer Statistics for the UK

2. Oesophageal cancer (squamous cell carcinoma (SCC) and adenocarcinoma (AC)) was the 13th most common cancer in the UK in 2011, accounting for 3% of all new cases. Currently it is the 8th most common cancer in males whilst it is the 14th most common in females (Cancer Research UK, accessed 2014). In 2011, there were 8,332 new cases of oesophageal cancer in the UK (5,582 (67%) in men and 2,750 (33%) in women), with crude incidence rates of 18 per 100,000 for males and 9.0/100,000 for females. The incidence of oesophageal cancer is strongly related to age, with 83% of cases diagnosed in men and women aged 60 years and over (data obtained from the UK between 2009 and 2011). Oesophageal cancer was the 6th most common cause of cancer death in the UK in 2012, accounting for 5% (7,701 persons) of all deaths from cancer. The crude mortality rate showed that there were 17 cancer deaths for every 100,000 men and 8 for every 100,000 females. In 2010, the lifetime risk of developing oesophageal cancer was 1 in 56 for men and 1 in 110 for women.

Oesophageal Cancer Risk Factors

3. Parkin et al. (2011) calculated that four lifestyle exposures – tobacco smoking, dietary factors, alcohol drinking and bodyweight, accounted for 34% of all cancers

occurring in 2010. Research has shown that tobacco use can increase the risk of both SCC and AC oesophageal cancer. Oesophageal SCC has also been strongly linked with alcohol consumption. By comparison, research has indicated that oesophageal AC is linked with excess body weight and long-term acid reflux (which can lead to a pre-cancerous condition called Barrett's oesophagus).

Mechanism of action of alcoholic beverages and oesophageal cancer

4. The exact mechanism by which ethanol causes oesophageal cancer has not been elucidated, but several possible pathways have been proposed. Carcinogenicity may occur via acetaldehyde, the major intermediary metabolite of ethanol. Alternatively, alcohol may act as a solvent that enhances the penetration of carcinogens from other environmental sources. Furthermore, regular intake of alcohol may reduce the intake and bioavailability of certain nutrients that have preventive properties. Another possibility is that alcohol may directly irritate the oesophageal epithelium, creating the potential for oesophageal SCC pathogenesis.

Previous COC discussion on Alcohol and oesophageal Cancer (2005)

5. The COC considered the possible quantitative relationship between alcohol and oesophageal cancer in 1995 as part of the review of alcohol and cancer. Several studies indicated that there was a quantitative relationship between alcohol intake and SCC of the oesophagus but a threshold level could not be defined. In 2005, COC conducted a review of new data (post 1995) on the quantitative relationship between alcohol and SCC of the oesophagus (COC, 2005). At the time, Members considered that the new data strengthened the overall picture, with an increased risk apparent at intakes above 30 g/day. However, it was not possible to identify a lower level of consumption below which there is no increase in risk. The COC conclusions from 2005 presented in the Annual report are provided in Annex A.

Updated review of Alcohol consumption and Oesophageal Cancer

6. In the evaluation of the carcinogenicity of alcohol (IARC monograph 96, 2010 (attached as Annex B) and IARC monograph 100e, 2012 (attached as Annex C)), IARC state that alcohol causes oesophageal cancer and classifies it as a group 1 carcinogen. Literature for the current review was obtained following a PubMed search and the search terms included alcohol, ethanol, drinking, consumption and oesophageal cancer. Studies published since January 2008 to December 2014 were included in the retrieval to ensure all studies published on this topic since the last IARC review to date were considered.

7. 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, such as smoking, body mass index (BMI), obesity and caffeine intake were also extracted from the papers.

Meta- and combined analyses of alcohol consumption and oesophageal cancer risk

Alcohol Consumption and Oesophageal Cancer Risk (Table 1)

8. Bagnardi et al (2013) carried out a meta-analysis of light alcohol drinking and cancer, including oesophageal cancer. They included 222 unique papers published before December 2010, 27 of which reported estimates for oesophageal SCC (9 cohort studies and 18 case-control studies). Since the included studies usually reported alcohol exposure in intervals, the authors considered as light every interval whose midpoint was <12.5 g/day (1 drink/d) of alcohol. Where studies reported two or more adjusted risk estimates for light drinking, they combined them into a single estimate. The reference category was non-drinkers or occasional drinkers. The reference category contained 504 cases while the light drinker category contained 846 cases. The site-specific pooled estimates for light drinkers vs. non-drinkers suggested a significant association between light drinking and oesophageal SCC overall (overall RR 1.30, 95% CI 1.09–1.56); it was also significant for men, 1.46 (95% CI 1.19-1.80), but not for women, 1.28 (95% CI 0.84-1.96). They stratified their results by study type and reported an RR of 1.34 (95% CI 0.96-1.87) for cohort studies and an RR of 1.28 (95% CI 1.04-1.59) for case-control studies. Their data stratified by geographical area gave RRs of 1.05 (95% CI 0.79-1.38), 1.21 (95% CI 0.96-1.54), 1.49 (95% CI 1.12-1.98) for European, North American and Asian populations, respectively.

9. Bagnardi et al. (2015) performed a further meta-analysis of data on alcohol drinking (light, moderate and heavy drinking) and cancer risk using data from 572 studies published between 1956 and 2012 including oesophageal SCC (54 studies in total; 13 cohort and 41 case-control studies). Criteria set for inclusion in the meta-analysis were: a) case-control studies, nested case-control studies or cohort studies published as original articles; b) studies that reported findings as odds ratios (ORs), relative risks (RRs) or hazard ratio (HRs) for at least two levels of alcohol consumption versus non-drinkers or occasional drinkers; c) studies that reported confidence intervals (CI) or standard errors of the risk estimates or sufficient data to calculate them. Criteria set for exclusion from the meta-analysis were studies reporting on specific alcohol beverage only, as the non-drinkers in those studies could be drinkers of another alcoholic beverage type. For the purposes of the analysis and to have unity in the expression of consumption, they used g per day as a standard measure of ethanol intake using the following: 0.8g/ml, 28g/ounce and 12.5 g/drink. For studies where the levels of consumption were reported in a range, the exposure was assigned as the midpoint of the range for the reported categories of alcohol intake. They considered as light, moderate and heavy drinking every interval whose midpoint was ≤12.5, ≤50 and > 50g per day of alcohol. The reference category included both non-drinkers and occasional drinkers. A pooled RR was estimated for oesophageal SCC for light drinkers versus non-drinkers, moderate drinkers versus non-drinkers and heavy drinkers versus non-drinkers using random-effects models. Statistical heterogeneity among studies was assessed using I^2. Subgroup analyses were also performed on cancer sites where 10 or more studies were available and considered study design, gender and geographical area. Bagnardi et al. (2015) observed a clear dose-response and reported RRs of 1.26 (95% CI 1.06-1.50) for light drinkers, 2.23 (95% CI 1.87–2.65) for moderate drinkers

and 4.95 (95% CI 3.86–6.34) for heavy drinkers, compared to the reference category. Case–control studies reported a stronger association with alcohol and oesophagus (SCC), liver and larynx, although the corresponding heterogeneity tests were not significant. For light drinkers, the risk of oesophageal SCC was statistically significant only in studies carried out in Asian populations (RR of 1.54, 95% CI 1.18-2.00) but not North American or European populations.

10. Rota et al (2010) performed a two-step meta-analysis, with the aim of presenting a method for analysing several components – within studies variability, between studies heterogeneity, and non-linear trend components – simultaneously. The first step fitted two-term fractional polynomial models within each study, taking into account correlation between reported estimates for different exposure levels. An estimate of β, the linear change in the natural log of the Relative Risk per unit of exposure, was obtained within each study, and then estimates were combined across studies. For the second step, the pooled dose–response relationship was estimated considering between-studies heterogeneity, using a bivariate random-effects model. Three thousand cases of oesophageal SCC were included, taken from 14 case–control studies and one cohort study. Studies used were mostly European, but included also one Japanese and one Chinese study. Pooled estimates of the RR (Relative Risk) were: 2.81 (95% CI 1.79-4.40) for alcohol consumption of 25g/day of ethanol; 5.11 (95 % CI 2.63-9.94) for an intake of 50g/day of ethanol; and 11.00 (95% CI 4.61-26.24) for an intake of 100g/day of ethanol. The authors did a pooling of results using g/day as a standard measure of alcohol intake from each study. Thus high levels of alcohol consumption were found to result in substantial risk of oesophageal SCC as compared to non-drinkers, and a statistically significant excess risk for moderate and intermediate doses of alcohol was also observed. The authors considered that they provided evidence of a strong, nonlinear, dose–risk relationship, without evidence of a threshold effect.

11. Tramacere et al (2012) performed a meta-analysis on alcohol drinking and oesophageal and gastric cardia adenocarcinoma risk. Twenty four studies were used, 8 of which were conducted in Europe, 1 in Russia, 9 in the United States, 1 in Australia, 1 in Uruguay and 4 in Asia. Of the 24 studies, 4 were cohort and 20 case-control. A total of 5500 oesophageal and/or gastric cardia adenocarcinoma cases were included. Relative Risk estimates for drinkers vs. non-drinkers were 0.96 (95% CI 0.85–1.09) overall; 0.87 (95% CI 0.74–1.01) for oesophageal adenocarcinoma, and 0.89 (95% CI 0.76–1.03) for gastric cardia adenocarcinoma. In stratified analyses, RRs for men were 1.02 (0.69–1.49), χ^2 heterogeneity 0.56 (P 0.454), and for women 0.86 (0.68–1.07). Unadjusted estimates for smoking habit were 1.05 (0.62–1.77), χ^2 heterogeneity 0.16 (P 0.687), and adjusted estimates were 0.94 (0.83–1.06). Unadjusted estimates for BMI were 1.05 (0.82–1.35), χ^2 heterogeneity 0.99 (P 0.319), and adjusted estimates were 0.91 (0.80–1.04). Unadjusted estimates for fruit and vegetable consumption were 1.01 (0.86–1.19), χ^2 heterogeneity 1.47 (P 0.225), while adjusted estimates were 0.88 (0.76–1.03), and for gastroeosophageal reflux unadjusted estimates were 1.02 (0.87–1.18), χ^2 heterogeneity 2.59 (P 0.107), with adjusted estimates of 0.82 (0.66–1.02). The authors concluded that this meta-analysis provides definite evidence of an absence of association between alcohol drinking and oesophageal and gastric cardia adenocarcinoma risk, even at higher doses of consumption.

12. Freedman et al (2011) carried out a pooled analysis from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON), which included information from 11 BEACON studies, mostly US based, but which comprised also 1 Swedish study, 1 Australian, 1 Canadian and 1 Irish. Two cohort studies and 9 case-control studies were analysed. Outcomes investigated were oesophageal AC, and adjacent tumours of the eosophagogastric junction (EGJA);4,140 cases (2,064 AC, 2,076 EGJA), and 13,676 controls were available. Seven of the studies also reported on oesophageal SCC, so pooled estimates were derived using 1,016 cases and 9,253 controls. Different measurement units were used for alcohol intake, so alcohol consumption levels for each study were converted into g ethanol/day. One drink was taken to contain 14g of ethanol. The reference category of non-drinkers was not the same across all studies: in seven studies the non-drinking category was life-long never drinkers, whereas in the other four non-drinkers were those who were not drinking at the reference timepoint. The authors estimated the covariance matrix, and besides non-drinkers considered three exposure levels to alcohol: light as drinkers of $\leq$1 drink per day, moderate as drinkers of 1 to <4 drinks per day, and heavy as drinkers of $\geq$4 drinks per day. Pooled ORs for the highest frequency category of ≥7 drinks per day were 0.97 (95% CI 0.68-1.36) for AC, and 0.77 (95% CI 0.54-1.10) for EGJA. Moderate intake, for example. 0.5 to <1 drinks per day, showed an inverse association with AC: OR 0.63 (95% CI 0.41-0.99) and EGJA OR 0.78 (95% CI 0.62-0.99). In contrast, a strong association was found for an increased risk of oesophageal SCC in those studies which reported on it, with a pooled OR, for ≥7 drinks per day, of 9.62 (95%CI 4.26-21.71).

13. Prabhu et al (2013) conducted a meta-analysis to investigate how racial and geographical background modifies the effect of alcohol; 34 studies overall, 9 cohort and 25 case-control, were analysed. Of these, only 18 studies reported on alcohol consumption, and 8 were from Europe, 8 from Asia. Levels of alcohol exposure had to be standardised across studies, and alcohol use was classified in g/week of alcohol.categories were 0, <200 g/week,and ≥200 g/week. Only results for the highest category of consumption, >200 g of alcohol/week (equivalent to 29g/day) vs. never, are reported in full in the paper. For all 18 studies, the summary OR was 4.65 (95% CI 3.6- 5.99).The Cochrane's Q statistic was used to test the heterogeneity of the pooled statistic, with a P-value of <0.10 considered as indicating heterogeneity. The inconsistency index (I^2) was also used to estimate the degree of heterogeneity, and low, moderate and high degrees of heterogeneity correlated with I^2 values of 25%, 50% and 75% respectively. For the 8 studies from Asia, results were 5.80 (3.64-9.24),with a high degree of heterogeneity. . For the 8 studies from Europe, results were 3.87 (2.57-5.82), again with significant heterogeneity. As there was only a small number of studies of African populations (n = 2), meta-analyses could not be performed for that stratum. There was a lot of heterogeneity in the results for the studies; the authors suggested it may have been due to differences in study design. No difference in the effects of alcohol on the risk of oesophageal SCC by continents of origin was found.

14. According to Li et al (2011), consumption of alcohol has increased markedly in China in recent years; the overall heavy drinking rate of adults in China has also increased rapidly, from 4.7% in 2002 to 37.04% in 2007, and 65.39% of drinkers have poor health. Li et al. (2011) carried out a systematic review on both cohort and case-control studies and a meta-analysis on case-control studies investigating the

association between alcohol consumption and cancer risk including oesophageal cancer in the Chinese population. 34 case-control studies and 2 cohort studies were identified that examined the association between alcohol consumption and oesophageal cancer. The sample size consisted of 10,189 cases and 60,318 controls for inclusion in the analysis. The types of alcohol consumed included beer, yellow rice wine, red wine and spirits. The authors noted the complexity of the definition of drinker and non-drinker. For the purposes of their meta-analysis, ORs and Relative Risks (RRs) were pooled. Participants who described drinking "the smallest amount" and those who never drank were classified as "non-drinkers" and the rest of subjects were classified as the "drinkers" category. Significant heterogeneity was found ($p \leq 0.10$, $I^2 > 50\%$) between the studies, and the meta-analysis was performed using a random effects model. It should be noted that the CI were estimated at 99%. Overall, the authors found an increased risk of oesophageal cancer with alcohol consumption (1.78, 99% CI 1.38–2.30). They also analysed the data for the cohort and case-control studies separately. They found that alcohol consumption was not significantly associated with oesophageal cancer in cohort studies (OR/RR 1.08, 99% CI 0.94–1.23, p 0.17). However, in case-control studies, comparing non-drinkers with drinkers, they reported that alcohol consumption was associated with oesophageal cancer (pooled RR 1.79, 99% CI 1.47–2.17). Stratifying the data by sex, they observed that alcohol consumption increased the risk of oesophageal cancer in men (OR/RR 1.82, 99% CI 1.49–2.22) but not in women OR/RR 0.91, 99% CI 0.47–1.77), compared to non-drinkers.

15. Oze et al (2011) conducted a systematic review of epidemiological studies on the association between alcohol drinking and oesophageal cancer among the Japanese population, and a random effects meta-analysis. The authors commented that most cases of oesophageal cancer in Japan are oesophageal SCC. Thirteen studies were analysed, 4 cohort and 9 case-control. The cohort studies included 399,182 subjects. In the case-control studies, there were 1,628 cases in all, and 14,728 controls. The definition and categorisation of alcohol consumption and frequency differed between studies, and was described for each individual study in the review; 2 cohort and 1 case-control study investigated type of alcoholic beverages, while 4 case-control studies evaluated ORs for oesophageal cancer by the acetaldehyde dehydrogenase Glu504Lys polymorphism. By assessment of the relevant studies, the polymorphism was judged to have a strong influence on the effects of drinking alcohol. The 4 cohort studies and 6 of the case–control studies had dose- or frequency-response relationships with oesophageal cancer. For the meta-analysis, results were calculated for ever drinkers, because the studies differed in their analysis of alcohol intake. The Relative Risk of oesophageal cancer was 3.30 (95% CI 2.30-4.74), with a Cochrane's Q of 53.90 and a P-value <0.001, suggesting considerable heterogeneity between the studies.

16. Liu et al (2014) carried out a systematic review and meta-analysis to evaluate the relationship between dietary patterns and oesophageal SCC. Four case-control studies were used in the meta-analysis relevant to alcohol consumption, 1 from Sweden (Bahmanyar et al 2006), 1 from the USA (Navarro Silvera et al 2011), and 2 from Uruguay (De Stefani et al 2008 and 2009). There were 789 cases and 4,502 controls from the four studies. The authors identified a dietary pattern which they called a drinker /alcohol pattern, which had a higher loading of wines, beers, and spirits than the two other dietary patterns analysed (a 'healthy' pattern, with a higher

loading of fruit and vegetables, and a 'western' pattern, with a higher loading of red meat and processed food). The quantities of alcohol consumed were not given in the review. A random effects model was used for the meta-analysis, giving a pooled OR of 2.34 (95% CI 1.22-3.45), suggesting that the drinker/alcohol pattern was significantly associated with an increased risk of oesophageal SCC. The I^2 statistic was 48.70%, suggesting some heterogeneity between the 4 studies analysed.

17. Prabhu et al (2014) performed a meta-analysis to determine whether tobacco and alcohol act synergistically to increase the risk of oesophageal SCC. There were 5 studies in all that provided them with the required information, 3 from China, 1 from Japan, and 1 from Thailand. Two were cohort studies and 3 were case-control. Alcohol (and tobacco) use was classified into categories of ever vs. never-use. The summary OR was 1.21 (95% CI 0.81-1.81) for ever/never use of alcohol. The Cochrane's Q statistic was used to test the heterogeneity of the pooled statistic, with a P-value of <0.10 considered as indicating heterogeneity. Cochrane's Q P-value was 0.18 for this summary OR. The inconsistency index (I^2) was also used to estimate the degree of heterogeneity, and was calculated to be 34.41%. For ever-alcohol with ever-tobacco use, the summary OR was 3.28 (95% CI 2.11-5.08), Cochrane's Q P-value 0.05, and I^2 55.30%, indicating moderate heterogeneity. "Synergy Factors" were also calculated from the published adjusted ORs, and from the summary adjusted OR, for ever-use of alcohol with ever-use of tobacco. The authors stated that they found a positive synergistic effect of alcohol and tobacco use for oesophageal SCC, based on the 5 studies analysed, with an OR of 1.85 (1.45-2.38).

18. A meta-analysis by Druesne-Pecollo et al. (2014) evaluated studies reported in the Pubmed and Embase databases for the association of alcohol and second primary cancer incidence in adults with head and neck cancer as the first primary cancer site. Nineteen studies (5 Europe, 7 America, 7 Asia; 8 cohort, 11 case-control) were included in all; four of these were relevant for reporting results on oesophageal cancer as the second primary cancer. The four studies were observational studies, and included 199 cases out of 1888 participants. All four studies were based in Asia. Referent alcohol consumption varied between studies from never/non-drinker to 100 g ethanol/day, with highest category intakes up to ≥170 g/day. Alcohol intake was evaluated retrospectively in most studies, and drinking habits prior to first tumour diagnosis were reported. Random effects models were used to calculate summary RR and 95% CI for highest vs. lowest, with a P value for overall effect of alcohol consumption on secondary cancer development, and a Q value and I^2 value to indicate heterogeneity. For the 4 studies relating to oesophageal cancer, the RR was 3.760, 95% CI 2.42-5.85, with a P value of .0001 for overall effect, and a Q value of 0.576 and I^2 of 0.0%, indicating there was no heterogeneity between the studies. However, the small number of studies and cases limits the import of the results, and the applicability of the findings to Western populations.

19. Li et al (2014) performed a meta-analysis to quantify the association between alcohol drinking and upper aerodigestive tract (UADT) cancer mortality, and included an analysis for oesophageal cancer. There were 8 studies reporting on oesophageal cancer, 2 from the USA, and 6 from Asia; six were cohort studies, two case-control. A total of 2,656 cases were included. Epidemiological studies published to June

2013 and listed in PubMed and ISI Web of Science were considered. 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. Risk estimates were obtained for light, moderate, and heavy drinking, defined, respectively, as an 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. Fixed- and random effects models were used depending on the level of heterogeneity between studies. The risk estimates for all 4 categories of drinking suggested a significant association with risk of oesophageal cancer; for any drinking vs. non/occasional drinking, the RR/OR was 1.86, 95% CI 1.40–2.47, and for heavy vs. non/occasional drinking, the RR/OR was 3.37, 95% CI 2.30–4.93. P values indicated a lack of heterogeneity between the studies. However, 6 out of the 8 relevant studies related to Asian populations, and one of the US case-control studies described black males in Washington, so the results may not be readily applicable to European populations, or to both women and men.

Summary of meta-analysis and combined analysis studies

20. In summary, the meta-analyses and pooled analysis in this section that reported on oesophageal cancer or oesophageal SCC all indicated a positive, causal association between drinking alcohol and the disease. Studies range from the meta-analysis of Bagnardi et al (2015), which analysed studies from a range of geographical areas, to those which related to Asian populations only. The one study that reports on oesophageal AC did not find evidence for an association with alcohol consumption.

Cessation of Alcohol Consumption and Oesophageal Cancer Risk (Table 2)

21. Jarl and Gerdtham (2012) conducted a meta-analysis of nine studies to examine the effect of drinking cessation on the risk of developing oesophageal cancer. Four of the studies were European, 3 were from Eastern Asia, 1 was from South America, and 1 from Puerto Rico The data were analysed using a generalised least squares model (GLS) for trend estimation of summarised dose–response data from all the studies to estimate the effect of years since drinking cessation on risk of disease. The authors used the results of the meta-analyses to determine the length of time for the increased risk of oesophageal cancer due to alcohol consumption to decline until there was no elevated risk from prior alcohol consumption. Results from the meta-analysis indicated that drinking cessation reduced the risk of oesophageal cancer significantly. The study reported that it would take 16.5 years for the risk of a former drinker to be the same as that of a never drinker (using non-European studies). They found that the European studies were more likely to demonstrate an increase in risk following cessation. Therefore, when these studies were included in the analysis, the time required for the cancer risk to be the same as never drinkers was 29 years, with the first 12.5 years after cessation spent at a higher risk than current drinkers, but the authors cautioned that this may be more apparent than real because of the characteristics of these subjects. Furthermore, the definition of “former drinker” varied between studies, some required that those classified as former drinkers should have quit for at least 1 year before the interview, while others had no such requirement. These differences could potentially have biased the results of the study. Based on their best estimate of the dose-response relationship, the authors observed that the risk fell faster in the first few years following cessation.

Approximately half the elevated risk was gone after about a third of the total required time, reflecting an exponential decay in the dose–response relationship.

Cohort studies

22. The cohort studies have been divided into two categories: a) those examining oesophageal cancer Incidence and b) those examining oesophageal cancer mortality. Within each section, the studies are reported by geographical region (UK, European, US, then other regions) and within each region in order of their Newcastle-Ottawa (NO) score, beginning with the highest scoring studies.

Cohort studies examining alcohol consumption and oesophageal cancer incidence risk (Table 3)

23. Yates et al (2014) conducted a prospective cohort study in the UK, the European Prospective Investigation of Cancer-Norfolk (EPIC-Norfolk). There were 24,068 participants (54% of whom were women), aged 39–74 years, who were recruited between 1993 and 1997. Participants were initially without diagnosed BE (Barrett's Esophagus) or EAC (Esophageal Adenocarcinoma). They were registered in general practices in rural, suburban and inner city areas. The cohort was monitored to December 2008 to identify incident cases of BE and EAC. Exposure assessment was by self-report of alcohol consumption in a food frequency questionnaire, which listed different alcoholic beverages and asked for the frequency of intake at recruitment, and at age 20 years and 30 years. Sixty-six subjects were diagnosed with EAC in the duration of the study. Hazard Ratios (HR) and 95% CIs were reported for five categories of alcohol consumption, >0 to <7 units/week, 7 to <14 units/week, 14 to <21 units/week, 21 to <28 units/week and >28 units/week. The UK definition of a unit of alcohol is 8g ethanol. As intake was measured in units per week, 1 unit per week is equivalent to 1.1g ethanol/ day. No association was found for risk of EAC with any individual category of alcohol intake; for example, for the lowest category of >0 to <7 units/week, compared to "no alcohol" as reference, the HR was 1.34 (95% CI 0.63–2.88), indicating no association. This was based on a relatively small number of 40 cases, and 12,135 controls. However, when the trend across categories was examined, an inverse association was found: HR 0.83 (95% CI 0.67–1.03), *p* value 0.09. An alcohol intake of 7 units/week or more, compared to less, was inversely associated with risk (HR 0.51,95% CI 0.29–0.88,*p* 0.02), with inverse associations in both sexes (men HR 0.54,95% CI 0.30–0.96, and women HR 0.31, 95% CI 0.04–2.44). For alcohol intake at age 20 years and age 30 years, no significant associations were seen for categories or for the respective trends (HR trend 1.04,95% CI 0.86–1.26, HR trend 1.02,95% CI 0.84–1.24 respectively). However, recall bias is possible in this estimate, as subjects were asked to remember their alcohol intake from the past. For the sub-types of alcohol, comparing non-drinkers to drinkers, an inverse association of borderline statistical significance was detected for wine consumption (HR 0.49, 95%CI 0.23–1.04, *p* 0.06), but not beer (HR 1.91,95% CI 0.70–5.18) or spirits (HR 0.68, 95% CI 0.33–1.39). The finding of an inverse association may be due to the very small numbers of cases included in the different categories of alcohol consumption (2-10 cases in most categories, 40 in the >0 to <7 category), compared to large numbers of controls (930-12,135 in the different categories). Furthermore, the *p* values do not indicate significance for the HR values found for the various categories of exposure.

24. Steevens et al (2010) analysed the effects of alcohol consumption and the risk of subtypes of oesophageal and gastric cardia cancer in a prospective Dutch cohort study, the Netherlands Cohort Study (NLCS). The oesophageal SCC and AC types are relevant to this review. There were 120,852 participants aged 55 to 70 years, of whom 58,279 were men, and 62,573 women. Cases were derived from the entire cohort, while the number of person-years at risk was estimated from a sub-cohort of 5000, who were randomly sampled from the total cohort at baseline. Information on alcohol consumption of participants was obtained through a self-administered questionnaire. Incidence Rate Ratios were calculated using Cox proportional hazards models, and were adjusted for age, sex, cigarette smoking (current smoking status (yes/no), frequency and duration), body mass index, level of education, energy intake, and consumption of fruit, vegetables and fish. A daily alcohol consumption of >30 g, when compared with abstaining, was associated with a significantly increased risk of oesophageal SCC (multivariable adjusted RR 4.61, 95% CI 2.24-9.50, p trend <0.001). Women were at a somewhat higher risk than men, and the interaction with sex was statistically significant in continuous analyses (p 0.04), but not in categorical analyses (p 0.68). No association was observed between alcohol consumption and oesophageal AC (RR for >30 g/day 1.04, 95% CI 0.54-2.02). When the analyses were restricted to stable alcohol consumers (same consumption habits for 5 years before baseline), the association with oesophageal SCC became somewhat stronger, but results for oesophageal AC changed very little, and did not indicate an association. After adjustment for total alcohol intake, beer consumption was associated with an increased risk of SCC, although p trend was 0.23, but not AC. Wine consumption was inversely associated with risk of SCC (RR 0.30, 95% CI 0.07-1.23 for >2 glasses/day), but was not associated with AC. Consumption of liquor was not significantly associated with risks of either type of cancer.

25. Hardikar et al (2013) conducted a prospective cohort study in the United States of patients with Barrett's Esophagus (BE), and examined the progression to oesophageal AC. The study was the Seattle Barrett's Esophagus Study (SBES), and had 411 participants with BE enrolled for observation between February 1,1995 and September 30,2009, who had no history of oesophageal cancer, and who came to at least one follow-up visit. There were 397 participants included in the final analyses, 45 of whom developed oesophageal AC. Analyses were carried out for categories of total alcohol consumption of 0,>0-1,>1-3 and >3 drinks/day. A "standard" drink in the US contains 14g of ethanol. No association was found with any of the categories and development of oesophageal AC; for >3 drinks/day, the Hazard Ratio, adjusted for age, gender, waist-hip ratio and NSAID (non-steroidal anti-inflammatory drug) use, was 1.23 (95% CI 0.48–3.14), with a test for trend of *p* 0.941. The authors further examined the association by beverage type, and again found no evidence of increasing oesophageal AC risk with increasing intake of beer or hard liquor (test for trend *p* 0.877 for beer, and *p* 0.310 for hard liquor). Wine intake of up to one drink/day tended to suggest an inverse association with oesophageal AC development, but the association was not statistically significant (HR 0.70, 95% CI 0.37–1.30, 16 cases compared to 163 controls).

26. Kimm et al (2010) investigated the effects of smoking, alcohol consumption, and the ratio of serum aspartate aminotransferase (AST) to alanine aminotransferase (ALT) in a cohort of 782,632 Korean men enrolled in the Korean Cancer Prevention

Study. The AST/ALT ratio was used as a biomarker for alcohol consumption. Information on alcohol consumption of participants was obtained through a questionnaire conducted by medical staff in local hospitals. Hazard Ratios and 95% CIs were calculated using Cox proportional hazards modelling, and were adjusted for age, age^2, aspartate aminotransferase, body mass index and exercise. Linear and quadratic trends for age were examined because the authors state the incidence of oesophageal cancer varies steeply with age. They observed a statistically significant association between alcohol intake and oesophageal cancer, with an HR of 2.4 (95% CI 2.0-2.8) for drinkers. The HRs for oesophageal cancer associated with a daily intake of 1-24 g/day were 2.2 (95% CI 1.9-2.6), for 25-49 g/day 3.1 (95 % CI 2.5-3.8), for 50-99 g/day 3.8 (95% CI 3.0-4.8), and for ≥ 100 g/day 4.1 (95% CI 2.9- 5.8). The authors found that alcohol drinking, cigarette smoking, and AST/ALT ratios were independent risk factors for oesophageal cancer in men, with additive, not multiplicative (synergistic), interaction between them. One strength of this study was the large number of cases (1198 cases of drinkers), and the large cohort size of over 700,000 participants, but, as participants were government employees and their dependents, selection bias may be present, and the study was limited to men. The results may not be generalisable to Western populations.

27. Hsu et al (2014) investigated the association of three risk factors, betel chewing, smoking, and drinking alcohol, on lifetime head and neck cancer risk in 25,611 men, aged 30-80 years, drawn from three prospective, community-based studies in Taiwan. The mean follow-up period was 18.4 years, and a total of 269 incident head and neck cancers were identified from the National Cancer Registry and National Death Certification. Of those cases, 77 were instances of oesophageal cancer. 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, in 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 oesophageal cancer were calculated using Cox proportional hazard models, with adjustments for age, education, ethnicity, betel quid chewing, cigarette smoking and study cohort. In the multivariate adjusted Hazard Ratios (HR), all categories of alcohol consumption analysed showed a significant association with risk of oesophageal cancer, with a *p* value for significance of <0.01: for instance, for ever drinking, the HR was 3.80 (95% CI 2.31-6.28), and for cumulative drinking in g-years for the higher category of ≥1500 the HR was 4.70 (95% CI 2.41-9.16). The strength of the study was the large number of participants in the cohorts, but the oesophageal cancers were not divided into subtypes (SCC or AC), and it is not clear if all were histologically confirmed.

28. Lee et al (2011) recruited a cohort of 1,522 patients with upper aerodigestive tract (UADT) SCC in Taiwan to investigate the independent and synergistic effects of alcohol, tobacco-free betel-quid and cigarette smoking on the age of diagnosis of the cancer. This was a multi-hospital, multiple anatomic site cancer study originating from the National Health Research Institute of Taiwan. Patients were recruited from two major medical centres in the greater Kaohsiung area, and were from diverse socio-economic backgrounds. They were recruited from 2001-2007, and were

pathologically proven, newly diagnosed cases. There were 305 cases of oesophageal SCC. The authors used Kaplan-Meier failure functions to calculate cumulative risks (CR) for patients using 52, the median age of diagnosis for all UADT tumours, as the reference age, and adjusted HRs for the age of diagnosis associated with daily alcohol intake and age at which drinking started. The median age for onset of oesophageal cancer was 57, while for women considered separately it was 72, and for men 56. When considering daily quantity of alcohol intake, and the age at which drinking was started, only daily drinking ≥1 drink had a significant HR for affecting the age of cancer diagnosis: HR 1.6, 95% CI 1.1-2.4, with a median age of diagnosis of 54. One drink was defined as containing 15.75 g of ethanol. However, when considering cumulative risk of the joint effect of alcohol drinking and betel-quid chewing, a CR of 47.5% was obtained, which was significant with a P value <0.05. Cigarette smoking on its own was not seen, in this analysis, to have a significant impact on the age of oesophageal cancer diagnosis. The relevance of this study to populations in which betel-quid chewing is not common is limited, as it was betel-quid which had the major effect on the age of diagnosis of oesophageal SCC.

Summary of cohort studies on oesophageal cancer risk

29. In summary, four of the cohort studies found evidence for a causal association between alcohol consumption and oesophageal cancer or oesophageal SCC. The two studies reporting on AC did not find an association.

Cohort studies examining alcohol consumption and oesophageal cancer mortality and secondary events (Table 4)

30. Yaegashi et al (2014) conducted a cohort study in Japan on the joint effects of smoking and drinking on oesophageal cancer mortality in men. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) was established in the late 1980s, and included 46,395 men and 64,190 women aged 40 years and above and younger than 80. Follow-up of these participants was conducted until 2009. Cox proportional hazards models were used to analyse the data for 42,408 men in the final investigation; the authors stated they excluded women because of the small number of women who smoked and drank. There were 196 deaths from oesophageal cancer in the follow-up period, which was about 20 years overall and was completed in 2009, although in 4 areas follow-up stopped in 1999, in another 4 areas in 2003, and in 2 areas at the end of 2008. The reasons for these differences were not explained in the paper. Hazard Ratios (HRs) were obtained for death from oesophageal cancer according to smoking status at baseline, alcohol intake status at baseline, and from the joint effects of smoking and alcohol. In the analysis of alcohol intake, non-drinkers were used as the standard, and a unit of alcohol was taken to be about 22 g of ethanol. Compared to non-drinkers, current drinkers had a significantly increased risk of oesophageal cancer, HR2.28, 95% CI 1.40-3.72. In terms of amount of alcohol consumed per day, oesophageal cancer risk rose with increased alcohol intake, especially more than 2.0 units per day, and showed a dose-response relationship (p for trend 0.02). In subjects drinking 3.0 units per day, for instance, the risk was 4.62 times higher (HR 4.62, 95% CI 2.46-8.68). Looking at cumulative intake, the group of subjects with 40.0 unit-years or greater showed the highest risk (HR 3.34, 95% CI 1.96-5.70). By type of alcohol consumed, the highest risk was for whisky (HR 2.99, 95% CI 1.53-5.84), followed by shochu (HR 2.75, 95% CI 1.47-5.15), and sake (HR 2.45, 95% CI

1.44-4.18). No significant increase in risk was observed for consumption of beer or wine. Also, no dose-response relationship was observed for number of years of drinking. In looking at the joint effects of drinking with smoking, the HR was increased and significant for current drinkers who were also current smokers: 2.54, (95% CI 1.18-5.48). Risks were increased for higher levels of consumption of both cigarettes and alcohol: for example, for smokers of 21+ cigarettes/day who also drank 3.0+ units of alcohol/day, the HR was 6.05, 95% CI 1.87-19.6. However, the number of deaths used in the analyses were small – 10 in the latter case, and 119 for current smokers/drinkers, which may affect the generalisability of the results.

31. Kim et al (2010) evaluated the association between alcohol consumption and all-cause and cancer mortality in a large-scale prospective study of 1,341,393 Korean men and women aged 40–69 years who participated in health examination in 2000. After 5 years follow-up for mortality, from 2001 to 2005, 19,375 deaths were identified, and Cox regression was used for longitudinal analyses. Participants were classified into five categories for men (non-drinker, 1.0–14.9,15.0–29.9, 30.0–89.9, ≥90.0 g/day), and three categories for women (non-drinker, 1.0–14.9, ≥15.0 g/day).Light-to-moderate alcohol consumption was defined as less than 30.0 g/day for men and less than 15.0 g/day for women. The all-cancer mortality increased by daily alcohol consumption in heavy drinking for men (RR 1.21, 95% CI 1.11-1.33), but the non-parametric regression curve for all-cancer mortality was not linear. The risk of oesophageal cancer had the strongest association with alcohol consumption of all the cancer sites investigated (RR 3.33, 95% CI 2.17-5.12 for ≥90.0 g/day alcohol consumption). For women, daily alcohol consumption showed a linear relationship with all-cancer mortality (RR 1.39, 95% CI 1.08–1.79 for ≥15g/day), but no association was found with oesophageal cancer, and the detailed values are not reported. The limitation of this study is the relatively short follow-up period of 5 years, and the fact that details for oesophageal cancer are not reported for women, such as the number of cases that occurred.

32. In their analysis from the Korean Cancer Prevention Study described previously, Kimm et al (2010) also examined mortality from oesophageal cancer. This was a 14-year prospective cohort study of 782,632 men, of 30-93 years of age. During the 14 years of follow-up, a total of 996 oesophageal cancer deaths were observed in this population. Age-adjusted death rates were calculated for alcohol consumption, and Hazard Ratios were obtained for categories of 1-24, 25-49, 50-99 and ≥ 100 g/day. All four categories were significantly associated with risk of oesophageal cancer; for one of the categories of heavy drinking, 50-99 g/day, for instance, the HR was 3.7, 95% CI 2.8-5.0. However, there were some limitations to the study, such as possible misclassification of cause of death from death certificates, and the results being limited to men only. Furthermore, participants were government employees and their dependents, raising the possibility of selection bias, and some data was collected through insurance plans, as participants received health insurance from the Korean National Health Insurance Corporation, with the possibility of inaccuracies.

33. Yang et al (2012) report on their findings from a prospective cohort study in China that included 220,000 men aged 40–79 years, recruited from 45 areas in the country in 1990–91. There were 15 years of follow-up, during which 440,000 deaths occurred. Cox regression was used to relate alcohol drinking to overall and cause-specific mortality, adjusting for age, area, smoking and education. Overall, 33% of

the participants reported drinking alcohol regularly at baseline, consuming mainly distilled spirits, with an estimated mean amount consumed of 372 g ethanol/week (equivalent to about 53 g ethanol/day). The number of deaths from oesophageal cancer, excluding the first 3 years of follow-up, was 242 among all-drinkers, compared to 606 deaths among non-drinkers. The HR for all-drinkers compared to non-drinkers suggested a significant risk associated with alcohol consumption: HR 1.25, 95% CI 1.07-1.47. However, in the 5 categories of amount of alcohol consumed per week, not all results suggested significance. The categories were <140, 140–279, 280–419, 420–699 and 5700 g ethanol/week (equivalent to approximately <20, 20-40, 41-52, 53-99 and ≥100g ethanol/day). Significant associations were suggested for 20-40 g/day, HR 1.28 (95% CI 1.00-1.65), with 62 deaths in this category, and for ≥100g/day, HR 1.63 (95% CI 1.12-2.39) with 30 deaths in this category. The *P*-value for trend was not significant, 0.2. However, the results are based on relatively small numbers of deaths from oesophageal cancer in each category.

Summary of cohort studies on oesophageal cancer mortality and secondary events

34. The four studies in this section relate to Asian populations. All find a significant risk of oesophageal cancer, not divided into subtypes, associated with alcohol consumption, although some have limitations such as short follow-up period, or reporting only on men, which may limit the impact of the findings.

Case-Control studies

35. The case-control studies have also been divided into two categories: a) those examining oesophageal cancer incidence and b) those examining oesophageal cancer mortality. Within each section, the studies are reported by geographical region (UK, European, US and others regions) and within each region in order of their Newcastle-Ottawa (NO) score, beginning with the highest scoring studies.

Case-control studies examining alcohol consumption and oesophageal cancer risk (Table 5)

36. Marron et al (2012) conducted a case-control analysis which included 2,001 head and neck cancer cases and 2,125 controls, drawn from 14 centres in 10 European countries. The aim of the study was to evaluate the association of drinking different alcoholic beverage types with upper aerodigestive tract cancers (UADT). Cases and controls were taken from the Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) study, which was initiated by IARC. The analysis by cancer subsite is most relevant to this summary, and for oesophageal cancer there were 144 cases. Cases were histologically or cytologically confirmed within the previous 6 months, and all were SCC. 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 about more than 10 drinks consumed in a couple of hours), and details on the specific type of alcohol consumed (a 'pure drinker' was defined as someone who consumed one beverage type exclusively; a 'predominant drinker' consumed one beverage type to more than 66%, and a 'mixed drinker' consumed more than one type of alcoholic beverage type to similar proportions). Adjustments were also made

for smoking status by frequency of consumption of cigarettes, and years since quitting. For risk of UADT cancer overall, strong dose-response relationships were observed for each alcoholic beverage type (see Discussion Paper on UADT cancers); however, for oesophageal cancer in the subsite analysis, confidence intervals do not suggest significant association of risk in any of the categories, even for ORs above 1. For example, for men who were "pure" drinkers of wine, the OR was 2.11, but the 95% CI was 0.36-12.3. For "pure" drinkers of liquor there were insufficient cases for the analysis, but for "predominant" drinkers of liquor OR was 3.55, with 95% CI 0.64-19.55). Results were also similar for women: for "pure" drinkers of liquor, OR was 2.82, with 95% CI 0.41-19.21, and most ORs were under 1, with none of the CIs suggesting significance.

37. Navarro Silvera et al (2011) conducted a multi-centre, population-based, case-control study of oesophageal AC and SCC in the United States, based in 3 geographic areas with population-based tumour registries: the state of Connecticut, a 15-county area of New Jersey, and a 3-county area of western Washington State. Patients were aged 30-79, and newly diagnosed in 1993-95. There were 282 cases with AC, 206 with SCC, and 687 controls randomly selected from the general population of the study areas, frequency-matched to the expected distribution of target cases by 5-year age group and sex. A principal component analysis (PCA) was undertaken. Twenty-eight diet and lifestyle variables were selected for evaluation due to their associations with either oesophageal or gastric cancers, and were included in the initial principal component analysis. PCA was used for variable reduction in the face of redundant, correlated exposures, so that a more meaningful logistic regression could be performed. The following variables were included in the PCA – 19 food groups, usual adult body mass index (BMI), average number of cigarettes smoked per day, consumption of beer, wine and liquor (drinks per day, each separately), intake of fibre (g/day), vitamin C (mg/day) and nitrite (mg/day), and reported frequency of GERD (gastro-oesophageal reflux disease) symptoms (ordered as a categorical variable with 6 levels). The PCA included weighted sums of the exposure variables, and had a "factor loading" up to 1, where values above 0.2 were considered to be making a reasonable contribution to the principal component, while values above 0.4 were highlighted. In this analysis, consumption of beer had a factor loading of 0.67, consumption of wine a factor loading of 0.58, and consumption of liquor a factor loading of 0.78. Six patterns of food intake, smoking and drinking, and BMI or GERD symptoms, were then described. For the principal component which loaded most heavily on alcohol and cigarette use, the category was termed a Smoking/Alcohol pattern Subjects were divided into quartiles, with quartile 1 being the lowest. Adjusted linear regression was then performed, giving a non-significant OR and 95% CI for the smoking/alcohol component of the diet of 0.89 (0.54-1.46) for the highest quartile and the risk of oesophageal AC, but significant values for oesophageal SCC (OR 10.82 (5.16-22.68) for quartile 4), and a *P* for trend of <0.001.

38. Pandeya et al (2013) conducted a population-based case-control study in Australia. There were 305 eligible oesophageal SCC cases, recruited through major treatment centres or state cancer registries, and diagnosed between July 1, 2002 (July 1, 2001 in Queensland) and June 30, 2005. The 1580 controls were randomly selected from the national electoral roll and frequency matched by age (in 5-year age bands) and state of residence to cases. The response rate was 70% for cases and

49% for controls. Participants were asked about their typical weekly intake for 6 classes of alcoholic beverages (reduced-alcohol beer, regular beer, white wine, red wine, port/ sherry, and spirits/ liqueurs), recorded in categories of none, less than 1, 1, 2–4, 5–6, 7–13, 14–20, 21–27, and 28 or more drinks per week. A "standard" drink in Australia contains 10g of ethanol. Total weekly alcohol consumption was calculated by summing average weekly consumption of all beverages by the standard drink volume and alcohol content by weight (in grams of alcohol), and then total lifetime consumption was calculated. The authors decided to dichotomise participants into low to moderate drinkers (≤17 drinks/week) and heavy drinkers (>17 drinks per week), for both men and women. Non-drinkers were combined with low to moderate drinkers. The OR for heavy drinkers and risk of oesophageal SCC was 3.3 (95% CI 2.4-4.7), with a value of 3.2 (95% CI 2.2-4.7) for men and 2.8(95% CI 1.2-6.1) for women. A population attributable fraction (PAF) of oesophageal SCC due to heavy alcohol consumption was also calculated, and was found to be 31.7% (95% CI 24.5-39.9) overall, with a value of 48.4% (95% CI 36.2-60.8) for men and 7.9% (95% CI 3.5-16.9) for women. When heavy alcohol consumption was combined with smoking, more than 75% of the oesophageal SCC burden in men could be attributed to these risk factors (77.7%, 95% CI 65.5-86.5). The highest burden was among >30 pack- years smokers who also consumed alcohol heavily, and this differed significantly between men (PAF 36%, 95% CI 29–44) and women (PAF 5%, 95% CI 2–10), with a *p* value of < 0.001.

39. Szymanska et al (2011) performed a multicentre hospital-based case–control study, initiated in 1998, based in 2 centres in Brazil which reported on oesophageal SCC. There were 171 cases and 496 controls in all. Cases were identified from hospital admission records or from relevant clinical wards, while controls were recruited from in- or out- patients at the same hospitals as the cases, and were frequency-matched on sex, age and centre, from a defined list of diseases not related to alcohol. Four broad exposure categories were identified: never-drinkers, ever-drinkers (drinkers who had ever consumed alcoholic drinks at least once a month), former drinkers (individuals who quit drinking more than a year before the interview (for controls) or the diagnosis date (for cases)), and current drinkers. For ever-drinkers, an increased risk of developing oesophageal SCC was found of 4.41 (95% CI 2.41–8.07). A number of different analyses were performed, including alcohol intake in g/day, dividing the subjects into quartiles, and an OR was also calculated for an increase in 10 units on a continuous scale. Drinking duration in years, and cumulative alcohol consumption in gram-years, were also examined, and all three investigations showed dose-effect relationships. For alcohol intake in g/day, the OR for the quartile with the highest intake was 9.28 (95% CI 4.4–19.59); for the highest duration of drinking of 41 years or more, the OR was 5.74 (95% CI 2.76–11.94), and for the quartile with the highest cumulative alcohol consumption, the OR was 9.26 (95% CI 4.46–19.23). An analysis was done on type of alcohol consumed, comparing beer as the reference category with wine only, and aperitif or spirits only. A very strong effect was observed for aperitif or spirits, with an OR of 12.99 (95% CI 3.67–46.02). A protective effect of quitting alcohol drinking was also observed: OR 2.15 (95% CI 1.10–4.21) for 2 to 4 years since quitting drinking, and OR 0.46 (95% CI 0.19–1.16) for more than 20 years since quitting drinking. An adjustment was also made for tobacco pack-years of smoking.

40. Chen et al (2010) performed a matched-pair case-control study to investigate risk of oesophageal SCC in Hebei Province, China. The individual and combined risks of alcohol consumption and tobacco smoking were considered. The subjects included 835 pairs, each of which consisted of a patient with oesophageal cancer, the case, and a healthy individual (control) matched by age (±2 years) and gender. Cases were drawn from patients who had a diagnosis of primary invasive cancer of the oesophagus between January 2002 and December 2006 at the Fourth Hospital of Hebei Medical University in Shijiazhuang. All diagnoses were histologically confirmed. Eligible subjects had been residents of the city of Shijiazhuang, Hebei Province, China, for at least 20 years and were younger than 60 years of age. A univariate analysis was first performed, to give ORs for duration of alcohol use in years, and for alcohol intake in g/day of ethanol. For the highest category of alcohol use of more than 20 years, an OR of 3.10 (95% CI 2.13-4.52) was obtained, although a dose-response relationship for increasing number of years of alcohol use was not seen. For the highest category of alcohol intake of more than 60 g a day, an OR of 1.97 (95% CI 1.45-2.69) was found. However, when conditional logistic regression was performed and duration of use was combined with g/day of ethanol, significant associations with risk of oesophageal SCC were seen in every category, for instance, for <15 yrs and <30 g of use, an OR of 6.99 (95% CI 3.14-15.56) was obtained. For the highest category of use, ≥20 yrs and ≥60 g/day, the OR was 183.12 (95% CI 49.10-682.91). Numbers of cases and controls for the various categories were small, for instance, 55 cases and 13 controls for the highest category of use.

41. Wu et al (2011) conducted a population-based case–control study in Jiangsu province, China, from 2003 to 2007. The cases were 1,520 newly diagnosed primary oesophageal cancer patients, recruited using data from local population-based cancer registries, and 3,879 controls, derived from the same county as the cases, and randomly selected from the county demographic database. Controls were frequency matched with cases by gender and age (±5 years). Unconditional multivariate logistic regression analysis was performed. Analyses were performed for the total number of cases and controls, and also stratified by gender separately. Analyses were done for categories of never drinking (never drinkers were defined as those who drank less than once per month), ever drinking and former and current drinkers (defined as those who were drinking at the time of interview, or who had stopped within one year before interview). An adjustment was made for pack-years of smoking as a continuous variable. A significant association of risk of oesophageal cancer was found with ever drinking alcohol, OR 1.50 (95% CI 1.29-1.74), and positive associations were also found for frequency of drinking, duration of drinking in years and ethanol intake per week, with dose-response relationships observed (*P* for trend <0.001). A significant association was still found for those who had stopped drinking 10 years previously, as compared to never drinkers: OR 1.80 (95% CI 1.14-2.85). Stratifying by gender, alcohol drinking increased the risk among men with an OR of 1.76 (95% CI: 1.48–2.09) for ever drinkers, and a similar pattern of significant association was found for the same categories of frequency and duration of drinking and ethanol intake per week, and an association even after stopping drinking for 10 years, with similar dose-response relationships. However, no significant associations were found for women in any of the categories (for ever drinking, OR was 0.82, 95% CI 0.59-1.16).

42. Kumagai et al (2013) performed a hospital-based case-control study at the Fourth Hospital of Hebei Medical University in China to investigate oesophageal SCC in Chinese male patients <60 years of age. There were 535 pairs, where the patient was age-matched to a healthy control. Controls were selected from the same geographic area, and had medical check-ups to verify the absence of any medical conditions. Conditional logistic regression analysis, both univariate and multivariate, was performed to investigate the effects of duration of drinking in years, and amount of ethanol (in grams) consumed per day. Fisher's exact test was also performed to compare the proportion of oesophageal SCC cases between males aged 30‑49, and males aged 50‑59 years, for four categories of the combined alcohol variable. The OR associated with an intake of ≤53.3 g ethanol/day for ≤20 years was 1.20 (95% CI 0.83-1.74); with an intake of ≤53.3 g ethanol/day for >20 years, 2.28 (1.32‑3.94); with an intake of >53.3 g ethanol/day for ≤20 years, 1.91 (1.25-2.92); and with an intake of >53.3 g ethanol/day for >20 years, 7.25 (3.12‑16.83). Three of the categories of the combined alcohol variable, apart from an intake of ≤53.3 g ethanol/day for ≤20 years, were significantly associated with risk. Alcohol intake for >20 years was a risk factor, as was a heavy alcohol intake of >53.3 g ethanol/day. Heavy alcohol intake was significantly associated with oesophageal SCC risk, even if the duration of alcohol intake was ≤20 years. Among subjects who consumed alcohol for ≤20 years, the proportion of oesophageal SCC cases was higher among older men compared with younger men with an intake of ≤53.3 g ethanol/day (P 0.035). In contrast, the proportion was higher among younger men compared with older men with an intake of >53.3 g ethanol/day, although the difference was not statistically significant (P 0.250). This finding may suggest that heavy alcohol intake could lead to the development of oesophageal SCC at a younger age.

43. Tai et al (2010) investigated the effect of alcohol drinking and oesophageal SCC risk in Taiwanese women. They performed a multi-centre, hospital-based, case-control study, with 51 cases taken from three large medical centres, the National Taiwan University Hospital (NTUH) in northern Taiwan, and the Kaohsiung Medical University Hospital (KMUH) and Kaohsiung Veterans General Hospital located in southern Taiwan. There were 204 controls recruited, all women, and each case was matched with 4 healthy women based on age (within 3 years) and hospital of origin, from the Department of Preventive Medicine in each hospital. Subjects who had drunk beer, wine or distilled spirits more than once a week for at least 6 months were defined as alcoholic beverage drinkers. Results were adjusted for smoking and areca chewing status. There were only 11 cases and 9 controls who were drinkers, compared to 40 cases and 195 controls who were non-drinkers. An OR of 3.55 (95% CI 1.03-12.27), with a *P* value of 0.0378, was calculated for risk of oesophageal SCC in drinkers compared to non-drinkers. The study authors further distinguished heavy from less-heavy drinkers; for 3 cases and 8 controls with an alcohol consumption of ≤158 g/week, no significant risk was found in the OR: 2.06 (95% CI 0.44-9.63), but for consumption of > 158 g/week the OR was 20.58 (95% CI 1.72-245.62). The number of cases with this level of consumption was 8, and there was 1 control. The limitations of these findings are the very small numbers of subjects who consumed alcohol.

44. Gao et al (2011) performed a case-control study in Shanxi Province, China, including 600 cases of oesophageal SCC in subjects over 20 years old from the region. The authors stated that they chose Shanxi Province in north central China

because it was an area with some of the highest oesophageal cancer rates in the world. There were 1514 controls, matched on age (± 5 years), gender, and neighbourhood of residence; controls were selected by asking cases to suggest a suitable neighbour. The analysis of alcohol consumption was restricted to men in the study, because the authors said very few women reported ever drinking any alcohol (8.6%). No significant associations of alcohol consumption with risk of oesophageal SCC were found in the study. For ever vs. never consumption of alcohol, based on information from 270 cases and 731 controls, the OR was 1.23 (95% CI 0.95-1.60); for ever vs. never consumption of beer, with 186 cases and 474 controls, the OR was 1.23(95% CI 0.96-1.56); for ever vs. never consumption of wine, with 99 cases and 253 controls, OR was 1.11 (95% CI 0.84-1.46), and for ever vs. never consumption of liquor, 258 cases and 700 controls, the OR was 1.20 (95% CI 0.93-1.55).

45. Lin et al (2011) conducted a multi-centre study in three medical centres in Taiwan, the National Taiwan University Hospital (NTUH) in Taipei, Kaohsiung Medical University Hospital (KMUH) and Kaohsiung Veterans General Hospital (KVGH) in Kaohsiung, between 2000 and 2009. Details of recruitment to the study are given in a previous paper, Lee et al (2005). Study subjects were Taiwanese men newly diagnosed with oesophageal SCC. The controls were derived from the same geographic areas as cases. They were chosen from healthy community residents who attended the hospitals for routine physical check-ups at the Departments of Preventive Medicine from the same hospitals. Out of 668 cases of oesophageal SCC, 543 (81.3%) reported habitual alcohol drinking. Exposure assessment was by a standardised questionnaire, completed in an in-person interview at the medical centre. Exposure categories were never/ever drinkers, and a daily average of <3 drinks/day or >3 drinks/day. Information is not provided on the ethanol content of a "standard" drink in Taiwan. The study authors investigated the effects of alcohol drinking on the age of diagnosis with oesophageal SCC. Adjustment were made for cigarette smoking and areca nut chewing. Ever drinkers diagnosed with oesophageal SCC were on average 3.58 years younger than non-drinkers (p 0.002). Subjects who consumed, on average, >3 drinks per day were diagnosed with oesophageal SCC approximately 2.5 years younger than those who consumed <3 drinks per day (p 0.02). The age at which subjects starting drinking (<20 yrs vs. >20 yrs) was not found to be significant in relation to age of diagnosis with oesophageal SCC.

46. Liu et al (2010) conducted a case-control study in China, with 166 newly diagnosed oesophageal cancer (EC) patients on Nanao Island recruited between 2003 and 2004; Nanao Island was one of the highest risk areas for EC in China. A total of 1450 first-degree family members (parents, siblings and offspring) of probands were recruited to the study and their history elicited in detail. There were also 455 healthy adult residents on Nanao Island selected as high risk population controls, and 134 healthy adult residents recruited from Shanwei, a low risk region for EC, as low risk population controls. It is not stated how they were matched. The aim of this paper was to ascertain the aetiology of EC by using logistic regression analysis among high and low morbidity regions, and also to analyse the characteristics of familial aggregation of EC on Nanao Island. Alcohol consumption was examined as a risk factor in the logistic regression analysis, and the Logistic coefficient (*B*) was found to be 0.1, with the Exp (*B*) as 1.105 (95% CI 1.013-1.205),

and an OR of 1.7 was calculated for consumption of alcohol. The main findings of the study related to family cancer history, which was found to be a significant risk factor for EC in the area studied. A positive family history of EC was strongly associated with increased risks of EC, which, the authors stated, indicated a genetic susceptibility influencing the local high risk population on Nanao, and the disease was more frequent among those who had a family history of EC.

47. Nasrollahzadeh et al (2008) conducted a case-control study in Golestan Province in northeastern Iran to examine risk factors for oesophageal SCC. From December 2003 to June 2007, the authors administered a validated structured questionnaire to 300 oesophageal SCC cases and 571 controls, matched on neighbourhood of residence, age (±2 years), and sex. The major risk factors examined for association with oesophageal SCC were tobacco and opium use, as only a small number of the population used alcohol. Only 2% of the cases and 2% of the controls had consumed alcohol for 6 months or more, and the results for alcohol are based on 7 cases and 14 controls. Subjects were asked about type of alcohol used (beer, imported spirit, country spirit, and others), starting and stopping ages, and the amount and frequency of use. An OR of 0.93 (95% CI 0.37–2.34) was obtained by conditional logistic regression, and the authors reported that no significant association between intensity, duration, cumulative use, or age of first use of alcohol with oesophageal SCC risk was found, without reporting the specific data in the paper.

48. Sun et al (2010) conducted a multi-centre case-control study in China, including five areas with high incidence of oesophageal cancer and good quality cancer registration data: Cixian, Shexian from Hebei Province, Linxian from Henan Province, Feicheng from Shandong Province and Zhuanghe from Liaoning Province. There were 250 cases randomly recruited from the cancer registration database, and diagnosed as having cancer arising in the lower oesophageal segment since January 1, 2009. Controls were matched 3:1 with cases on gender, age ±2 years, and same village, and 750 were recruited in all. Controls had no history of malignancy and no family history of upper gastrointestinal cancer. Exposure assessment was by questionnaire in a face-to-face interview; the question on consumption of alcohol was a yes/no answer, with no quantities or further details elicited. On the basis of that answer, an OR was calculated in univariate analysis of 1.941(95% CI 1.290-2.921) for the risk associated with alcohol drinking. Eighty cases and 178 controls responded “Yes” to alcohol drinking, 170 cases and 572 controls responded “No”. In multivariate analysis, including other risk factors such as passive smoking, history of digestive diseases, BMI, and consumption of vegetables, pickled or hot food, the OR was 2.074(95% CI 1.190-3.616).

Summary of case-control studies on oesophageal cancer risk

49. Out of the 13 case-control studies that report on oesophageal cancer, 8 relate exclusively to Asian populations, and one to an Iranian population. These results may not be directly comparable to the situation in Britain. Most find significant associations between alcohol consumption and oesophageal cancer. Marron et al (2012), which is a European study, does not find significant associations between drinking alcohol and oesophageal SCC. The Brazilian (Szymanska et al 2011) and

US (Navarro Silvera et al 2011) studies find significant associations with SCC, and the Australian study (Pandeya et al 2013) finds an association with heavy drinking.

Alcohol consumption and genetic risk factors for oesophageal cancer (Table 6)

50. Tanaka et al (2010) conducted a case-control and genome-wide association study in Japan to investigate the environmental and genetic risk factors for oesophageal SCC. There were 1071 cases, patients newly diagnosed with oesophageal SCC, aged between 35 and 85, and identified from six hospitals between 2000-2008; 2762 healthy controls without previous cancer history were recruited from Kyushu University Hospital (and related hospitals) during the same time period. All controls were enrolled after receiving an upper gastrointestinal endoscopy test to ensure they had no disease. From the genome-wide association study, two SNPs (single nucleotide polymorphisms) were identified as being highly associated with oesophageal SCC: risk alleles of rs1229984 (from chromosome 4 of the ADH1B gene) and rs671 (from chromosome 12 of the ALDH2 gene) were highly associated with OSCC (OR 4.08, 95% CI 3.27- 5.09, $p=4.43x\ 10^{-40}$ for rs1229984, and OR 3.54, 95% CI 3.04- 4.14,$p=5.53x10^{-62}$ for rs671). Next, the study authors estimated the genetic risk of specific genotypes of rs671 and rs1229984. For rs671, the genotype GG was taken to be genetic risk no.=0, while the genotype AG/AA was a genetic risk no.=1. For rs1229984, the genotype of genetic risk no.=0 was AA/AG, while genotype GG was a genetic risk no.=1. If both risk genotypes were present, then the genetic risk no.=2. Environmental risk was estimated separately, with an environmental risk no.=0 for a non-drinker and non-smoker, an environmental risk no.=1 for an ever-drinker and non-smoker or a non-drinker and ever-smoker, and an environmental risk no.=2 for an ever-drinker and ever-smoker. For an ever-drinker and non-smoker, there was a significant association with risk of oesophageal SCC with an OR of 3.5 (95% CI 2.1- 5.8), based on 67 cases and 170 controls. The genetic and environmental risks were then combined. For an ever-drinker and non-smoker with no genetic risk factors, the OR of oesophageal SCC was 1.5 (95% CI 0.7- 3.3), suggesting that without the genetic factors, alcohol consumption was not significantly associated with risk of the disease. However, when either of the genetic risk genotypes was present, the OR rose to 12.1(95% CI 5.5 -26.6), with a p value <0.001for the interaction of genetic risk with alcohol consumption. The combination of smoking with drinking and the presence of either genetic risk factor further increased the OR to 62.1(95% CI 30.3-127.4), based on 612 cases and 309 controls, strongly suggesting that, if the genetic risk factors are present, drinking significantly increases the risk of disease.

51. A case-control study was performed by Ding et al (2010) in China to investigate the relationship between alcohol dehydrogenase-2 (ADH2) and aldehyde dehydrogenase-2 (ALDH2) genetic polymorphisms, alcohol consumption and susceptibility to oesophageal cancer. There were 221 cases, who were histopathologically diagnosed as having oesophageal cancer, between January 2005 to December 2006. There were 191 population-based controls, recruited from healthy residents in the villages or towns in which the patients lived. Alcohol drinkers with the ALDH2 A allele showed a significantly increased risk of oesophageal cancer compared with drinkers with the ALDH2 G/G genotype (OR 3.08, 95% CI 1.65–5.78) or non-drinkers with any genotype (OR 3.05, 95% CI 1.49–6.25). Furthermore,

drinkers with the ALDH2 A allele and a cumulative amount of alcohol consumption ≥2.5 kg*years were at a significantly higher risk of developing oesophageal cancer (OR 11.93, 95% CI 3.17–44.90) compared with individuals with ALDH2 G/G genotypes and a cumulative amount of alcohol consumption <2.5 kg *years. Regarding the relationship between the ADH2 genotype, drinking habit and oesophageal cancer risk, the study results did not indicate any significant associations. When looking at interactive effects of the genotypes, drinkers carrying both ALDH2 A and ADH2 G alleles and with a cumulative amount of alcohol consumption ≥2.5 kg*years, compared to individuals carrying ALDH2 G/G and ADH2 A/A alleles and with a cumulative amount of alcohol consumption of <2.5 kg* years, showed a significantly elevated risk of oesophageal cancer (OR 53.15, 95% CI 4.24–666.84). However, this result was based on information from only 13 cases and 1 control. Overall, the authors concluded that to help lower their risk for oesophageal cancer, persons carrying the ALDH2 A allele should be encouraged to reduce their consumption of alcohol.

52. Talukdar et al (2013) conducted a case-control study on a population of North East India, in the Assam and Mizoram states, which they reported as having a high incidence of oesophageal cancer, with an age-adjusted rate of around 17/100,000 to 27 per/100,000 population. The aim of the study was to investigate the interaction of various habits-related factors, including alcohol consumption, and polymorphism of *GSTM1*/*GSTT1* genes, and the effect of promoter hypermethylation in four tumour suppressor genes. The *GSTM1* and *GSTT1* genes are involved in metabolising carcinogens, in particular several of the carcinogenic compounds present in tobacco. In the population studied, cigarette smoking and betel quid chewing were common. The authors also included alcohol as one of the risk factors. There were 112 histopathologically confirmed oesophageal SCC patients from different cancer hospitals of NE India, recruited during January 2011 to October 2012. Oral swabs from 130 age and gender matched healthy controls were also collected; no other details are provided on controls. Cases and controls with family history of oesophageal or other cancers were excluded. Genotyping of the *GSTM1* and *GSTT1* genes was performed by PCR, and promoter methylation status of 4 tumour suppressor genes (TSG), *p*16, *DAPK*, *GSTP1* and *BRCA1,* was determined by Methylation Specific PCR. A methylation index (MI) was calculated, as the ratio of the number of methylated promoters to the total number of promoters under study. Logistic regression analysis of the risk factors for oesophageal SCC was performed. The major risk factors for oesophageal SCC were tobacco chewing and smoking, and the effect of alcohol was not seen to be a significant association: OR 1.23, 95% CI 0.67-2.46. Considering the genes themselves, the risk of oesophageal SCC was significantly higher for *GSTT1* null variants only, among the cases. When the effect of alcohol as a risk factor for oesophageal SCC was considered together with TSG promoter methylation, cases who were alcohol drinkers with promoter methylation were seen not to have significant risk of oesophageal SCC, whereas alcohol-drinking cases with a zero methylation index had increased ORs for all 4 tumour suppressor genes, suggesting that alcohol consumption is not associated with promoter hypermethylation. When all cases with zero methylation were considered together, alcohol drinkers had an OR of 2.47, 95% CI 1.00-6.04, of developing oesophageal SCC compared to controls. An MDR (Multifactor Dimensionality Reduction) analysis was performed to detect gene-gene and gene-environment interactions. The best predictive models of interaction between environmental and genetic parameters up

to four orders of interaction are described in the paper. The best model for a 2nd order interaction was tobacco chewing and alcohol consumption (OR 5.01,95% CI 2.54–9.88), and for occurrence of oesophageal SCC without promoter hypermethylation, the best model suggested an interaction of betel quid chewing, alcohol consumption and null *GSTT1*, with an OR of 9.88, 95% CI 3.67-26.54. Thus, alcohol was seen to be a risk factor when combined with other risk factors. However, the number of cases and controls was small, drinkers were not categorised by quantity or type of alcohol consumed, and the study relates to a very specific population with prevalence of tobacco and betel quid chewing, so that results may not be generalisable to other populations.

53. Shi et al (2012) conducted a case-control study in China to study a common genetic CYP variant which has been described recently, CYP2C19*3 (G636A), and its possible role in oesophageal SCC. The authors commented that Asian people have a higher incidence of CYP2C19*3, usually about 13–16%, whereas in Caucasians the incidence is only 1–3%. They wanted to investigate whether the high incidence of oesophageal SCC in China correlates with increased frequency of the CYP2C19*3 variant in the Chinese population. Patients (n= 350) were diagnosed with histologically confirmed oesophageal SCC at Kunming General Hospital in the Chengdu Military Region. Controls (n= 350) were age, sex, and geographically-matched individuals to the patients, but with no obvious sign of disease. Controls with prior history of cancer were excluded. Patients and controls were recruited between 2009 and 2011. Both patients and controls were of Chinese Han ethnic origin. In their results, the authors found that participants who carried the CYP2C19*3 A allele (AA or AG genotype) had a higher risk of oesophageal SCC compared with GG genotype carriers. Among participants with the CYP2C19*3 GG genotype, drinking was associated with a 5-fold higher risk (OR 5.05, 95% CI 3.371–10.712). For drinking and carrying the CYP2C19*3 A allele (AA or AG genotype), there was an 8-fold risk for oesophageal SCC (OR = 8.747, 95% CI: 6.321–18.122), when compared with non-drinking CYP2C19*3 GG genotypes. However, the number of cases and controls was small, and there was no quantification of the amount of alcohol that drinkers consumed.

54. Wang et al (2011) conducted a case-control study in China to evaluate the contribution of ADH1B and ALDH2 polymorphisms to the risk of oesophageal SCC in Chinese females. Alcohol dehydrogenase-IB (ADH1B) and aldehyde dehydrogenase-2 (ALDH2) are key enzymes for elimination of ethanol and acetaldehyde, and it is thought that genetic variation in the ability to metabolise alcohol might be associated with oesophageal cancer risk. The authors describe that the homodimer of ADH1B encoded by ADH1B*1/*1 has only 1/100 and 1/200 of the ethanol oxidising capacity of the isozymes encoded by ADH1B*1/*2 and ADH1B*2/*2, respectively. The ALDH2*2 allele is also prevalent in east Asians and encodes a catalytically inactive subunit, and ALDH2*2 allele carriers experience unpleasant flushing responses after drinking small amounts of ethanol. There were 81 Chinese female cases, recruited from the hospital of the Armed Police College of Medicine from June 2009 to December 2010. All were newly diagnosed with primary oesophageal cancer. There were 162 controls, randomly selected from people who requested general health examinations in the same hospital during the same period and who were confirmed to have no malignancy, digestive diseases or chronic diseases and also no prior history of malignancy. The controls were matched with

cases by age within five years. Alcohol drinking was categorised into former, never and current drinking. Individuals who had quit drinking for more than one year were considered as former drinkers, and individuals who drank more than 200ml beer, 125ml wine and 50 ml white spirit per month and for at least 6 months were regarded as current drinkers. Current drinkers were divided into three groups: 1-20 g/d alcohol, 21-40g/d alcohol and >40 g/d alcohol. When compared with the ADH1B*2/*2 genotype, subjects with ADH1B*1/*2 had an OR of 1.47, 95% CI 0.84-2.58 for risk of oesophageal SCC, while those with ADH1B*1/*1 had an increased risk with an OR of 2.36, 95% CI1.14-5.79). For ALDH2, the ALDH2*1/*2 genotype was significantly associated with increased SCC risk compared with ALDH2*1/*1, OR 3.24, 95% CI 1.45-5.36. When the risk of SCC was stratified by quantity of alcohol drinking (never/light/moderate/heavy), no significant associations were found across the genotypes.

Summary of studies describing genetic risk factors for oesophageal cancer and alcohol consumption

55. All five studies in this section relate to Asian populations, and there are differences in the incidence of some genes between Asian people and Caucasians. These studies may therefore be of limited relevance. Furthermore, the Indian study describes a specific population with particular dietary habits, and the results of the study may not be generalisable to other populations.

Overall Summary

56. Since 2009 there has been a range of published papers on alcohol and oesophageal cancer. The results of a number of meta-analyses, cohort and case-control studies add weight to the finding of an association between oesophageal cancer and consumption of alcohol. With regard to two of the major subtypes of oesophageal cancer, SCC incidence is affected by alcohol intake, whereas the incidence of AC does not appear to be associated with alcohol consumption. Where studies have stratified results for men and women, the results for men generally report an increased risk of oesophageal or specifically SCC cancer, while results for women are less consistent. The relevance of the results from Asian populations to the UK population needs consideration.

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 oesophageal cancer risk?

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

Secretariat
April 2015

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Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort/case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Bagnardi et al 2013	222 papers comprising ~92,000 light drinkers and 60,000 non-drinkers with cancer; 27 (9/18)	Varied	**Drinking status** Non-drinker Light Drinker (≤ 1drink/day)	 504 846	**Results for oesophageal squamous cell carcinoma** **Overall RR** 1.30 (1.09-1.56), *p* value 0.0041 **Study type** Cohort 1.34 (0.96-1.87) Case-control 1.28 (1.04-1.59) **Sex** Men 1.46 (1.19-1.80) Women 1.28 (0.84, 1.96) **Geographical area** Europe 1.05 (0.79-1.38) North America 1.21 (0.96-1.54) Asia 1.49 (1.12-1.98)	Not stated	Light drinking was defined as ≤ 1 drink/day (≤12.5 g ethanol/day)

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk													
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	Alcohol intake	All		Study Type			Sex			Population groups		
			RR (95%CI)	I^2 (%)	N	RR (95%CI)	I^2 (%)	N	RR (95%CI)	I^2 (%)	N	RR (95%CI)	I^2 (%)
Bagnardi et al (2015)	Total of 572 studies published between 1956 and 2012, including total of 486 538 cancer cases; 54 (13/41)	Oesophageal Squamous Cell Carcinoma											
			All			Cohort			Men			European	
		Light	1.26 (1.06-1.50)	68	10	1.20 (0.84-1.71)	84	16	1.39 (1.11-1.74)	61	7	1.05 (0.79-1.38)	22
		Moderate	2.23 (1.87-2.65)	85	13	1.92 (1.44-2.58)	83	28	2.25 (1.78-2.85)	85	10	1.91 (1.32-2.77)	71
		Heavy	4.95 (3.86-6.34)	91	9	3.56 (2.25-5.64)	91	24	4.69 (3.49-6.31)	88	8	4.76 (2.69-8.41)	85
						Case-control			Women			North-American	
		Light			24	1.29 (1.07-1.55)	49	8	1.14 (0.87-1.49)	43	12	1.07 (0.84-1.37)	32
		Moderate			40	2.34 (1.87-2.92)	86	8	2.18 (1.42-3.35)	72	13	2.95 (2.38-3.67)	37
		Heavy			32	5.43 (4.04-7.32)	91	3	8.32 (2.95-23.45)	72	10	7.63 (5.34-10.91)	59
												Asian	
		Light									11	1.54 (1.18-2.00)	71
		Moderate									23	2.20 (1.65-2.94)	91
		Heavy									18	4.24(2.93-6.14)	93

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk													
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	Alcohol intake	All		Study Type			Sex			Population groups		
			RR (95%CI)	I^2 (%)	N	RR (95%CI)	I^2 (%)	N	RR (95%CI)	I^2 (%)	N	RR (95%CI)	I^2 (%)
Bagnardi et al (2015) (cont)		Oesophageal adenocarcinoma & gastric cardia											
			All			Cohort			Men			European	
		Light	0.86 (0.76-0.98)	32	4	0.88 (0.74-1.03)	6	3	0.94 (0.42-2.08)	78	7	0.79 (0.68-0.93)	0
		Moderate	0.97 (0.78-1.22)	72	4	0.82 (0.62-1.07)	50	5	0.92 (0.46-1.86)	76	5	0.90 (0.60-1.36)	61
		Heavy	1.15 (0.95-1.39)	36	1	1.11 (0.48-2.56)	0	6	1.17 (0.72-1.88)	57	4	1.52 (0.80-2.88)	65
						Case-Control			Women			North-American	
		Light			17	0.88 (0.74-1.04)	38	2	0.85 (0.63-1.14)	0	10	0.95 (0.78-1.16)	41
		Moderate			17	1.06 (0.78-1.43)	75	2	0.62 (0.42-0.93)	0	10	0.99 (0.78-1.25)	56
		Heavy			17	1.16 (0.95-1.41)	40	1	3.80 (0.89-16.32)	0	9	1.23 (0.93-1.63)	38
												Asian	
		Light									2	1.18 (0.24-5.79)	82
		Moderate									4	0.97 (0.24-3.83)	91
		Heavy									3	0.89 (0.49-1.64)	36

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Rota et al, 2010 Overall 14 case–control studies and one cohort study, including 3000 cases of esophageal SCC, were included; papers of European studies, and 1 Japanese, 1 Chinese	Meta-regression model; 3000 cases; 1/14	Methods not reported	**<u>Alcohol intake (g/day)</u>** 25 50 100	3,000 cases	Random-effects model-based pooled estimates of the RR (Relative Risk) were: 2.81 (95% CI 1.79-4.40); 5.11 (95 % CI 2.63-9.94); 11.00 (95% CI 4.61-26.24) High levels of alcohol consumption resulted in substantial risk of oesophageal SCC as compared to non-drinkers; statistically significant excess risk for moderate and intermediate doses of alcohol also observed, with no evidence of a threshold effect; ethanol intake related to oesophageal SCC risk in a nonlinear fashion	ORs in the meta-analysis were adjusted for age, residence, and cigarette smoking	Meta-analysis conducted using a two-step process, firstly fitting two-term fractional polynomial models within each study, taking into account correlation between reported estimates for different exposure levels. For the second step, the pooled dose–response relationship was estimated considering between-studies heterogeneity, using a bivariate random-effects model

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Tramacere et al, 2012 24 studies used; 8 were conducted in Europe, 1 in Russia, 9 in the United States, 1 in Australia, 1 in Uruguay and 4 in Asia	Total of 5500 oesophageal and/or gastric cardia adenocarcinoma cases included; 24 studies, 4/20	Methods not reported	**<u>Alcohol intake (drinks/day)</u>** Drinkers vs. non-drinkers <1 drink (light) 1 to <4 (moderate) >4 (heavy) **In strata:** Men Women Smoking habit, (unadjusted; (adjusted estimates) BMI (unadjusted; adjusted estimates) Fruit and vegetable consumption (unadjusted; adjusted estimates)	5500 cases **Studies, n** 9 5 6 19 12 12 18 6	**Relative Risk (RR) estimates**: 0.96 (95% CI 0.85–1.09) overall; 0.87 (95% CI 0.74–1.01) for oesophageal adenocarcinoma; 0.89 (95% CI 0.76–1.03) for gastric cardia adenocarcinoma **Pooled RRs**: 0.86 0.90 1.16 **RR(95% CI) χ^2 heterogeneity** 1.02(0.69–1.49) 0.56 (P = 0.454) 0.86 (0.68–1.07) 1.05 (0.62–1.77) 0.16 (P= 0.687) 0.94 (0.83–1.06) 1.05 (0.82–1.35) 0.99 (P =0.319) 0.91 (0.80–1.04) 1.01 (0.86–1.19) 1.47 (P =0.225) 0.88 (0.76–1.03)	Multivariate adjusted risk estimates used whenever possible, adjusting for major risk factors of: gastroesophageal reflux, overweight and obesity, smoking and low fruit and vegetable consumption	One drink was defined as12.5 g of ethanol

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
			Gastroeosophageal reflux (unadjusted; adjusted estimates)	20 4	1.02 (0.87–1.18) 2.59 (P =0.107) 0.82 (0.66–1.02)		
Freedman et al, 2011 Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON), including information from 11 BEACON studies, mainly US based, but including also 1 Swedish study, 1 Australian, 1 Canadian and 1 Irish	Outcomes analysed were esophageal adenocarcinoma (EA) or adjacent tumors of the esophagogastric junction (EGJA): 4,140 cases (2,064 EA, 2,076 EGJA), 13,676 controls; 11 studies (2 cohort/9 case-control) 7 studies also collected cases of esophageal squamous cell carcinoma (ESCC), 1,016 cases and 9,253 controls	Varied – some interviewer administered questionnaires, some computer based, some administered by mail	Drinks/day categories of >0-<0.5, 0.5-<1.0, 1-<3, 3-<5, 5-<7, ≥7 Separate analyses done for beer, liquor and wine	For EA and EGJA, 4,140 (2,064 EA, 2,076 EGJA)/ 13,676; for ESCC, 1,016/ 9,	ORs for highest frequency category (≥7 drinks per day)= 0.97 (95% CI = 0.68-1.36) for EA ,0.77 (95% CI = 0.54-1.10) for EGJA. Moderate intake (e.g. 0.5 to <1 drinks per day) linked to decreased risk of EA, OR = 0.63 (95% CI = 0.41-0.99) and EGJA OR = 0.78 (95% CI = 0.62-0.99). Strong association with increased risk of ESCC, OR (for ≥7 drinks per day)= 9.62, (95%CI=4.26-21.71)	Age (years: <50, 50 to <60, 60 to <70, ≥70); total cigarette smoking exposure (pack years: 0, 0< to <15, 15 to <30, 30 to <45, ≥45); BMI (<25, 25 to <30, ≥30); gastroesophageal reflux status (yes versus no); study centre (for multi-centre studies).	Alcohol intake standardised across the studies to14 g ethanol/day

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk

Reference, location, year of study	Description (No. in analysis; cohort / case-control)	Exposure assessment	Exposure categories	No. of cases / controls, n	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments
Prabhu et al, 2013 34 studies analysed in all; 13 studies provided data on individuals of European descent (including 1 from Australia), 14 studies on people of Asian descent, 5 on people of South American and 2 on people of African descent.	Aim of meta-analysis was to investigate how racial and geographical background modifies the effect of alcohol; 34 studies, 9/25; 18 of the studies reported on alcohol consumption	Details not given	Alcohol use classified into average weekly use (0, <200 g/week, ≥200 g/week of alcohol); **alcohol intake (g/week)** >200 g alcohol/ week vs. never (equivalent to 29g/day of ethanol)	Numbers of individuals not given **Race or continent / no.of studies** All/18 Asia/8 Europe/8 small number of studies of African populations (n = 2), meta-analyses could not be performed for that stratum	**Summary Adjusted OR (95% CI)** **Q** **P-value** **I^2 (%)** 4.65 (3.6- 5.99) 57.99 <0.001 71 5.80 (3.64-9.24) 51.83 <0.001 77 3.87 (2.57 5.82) 15.75 <0.003 56 Lot of heterogeneity in the studies; no difference in the effects of alcohol on the risk of oesophageal SCC by continents of origin was found	Most studies controlled for age, sex, and tobacco use	Heterogeneity of pooled estimate tested with the Cochrane's Q statistic, with a P-value <0.10 considered as indicating heterogeneity;. inconsistency index (I^2) used to estimate degree of heterogeneity; low, moderate and high degrees of heterogeneity correlated with I^2 values of 25%, 50% and 75% respectively.

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Li et al, 2011 China	Systematic review of cohort and case-control studies; meta-analysis of case-control studies on association between alcohol consumption and oesophageal cancer in Chinese population; 2/34	Not detailed	Participants who described drinking the smallest amount, and those who never drank, classified as “non-drinkers”; remaining subjects classified as “drinkers”	10,189/60,318 **Oeso-phageal cancer**, drinkers / non-drinkers: Case-control Cohort Overall drinkers / non-drinkers: Case-control Cohort Overall	**Pooled OR/RR (99%CI) / Test for overall effect (p)** 1.79 (1.47-2.17) <0.00001 1.08 (0.94-1.23) 0.17 1.78 (1.38-2.30) <0.00001 **Variance between studies Q(p) / I^2 (%)** <0.00001 87 <0.00001 96 <0.00001 90 There was significant heterogeneity between the studies	Not detailed	CI estimated at 99%

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
				Subgroup analysis drinkers/non-drinkers: Men Women Subgroup analysis drinkers/non-drinkers: Men Women	**Pooled OR/RR (99%CI)** **Test for overall effect (p)** 1.82(1.49–2.22) <0.00001 0.91(0.47–1.77) 0.72 **Variance between studies** **Q(p)** **I^2 (%)** <0.00001 >50% 0.88 <50% There was heterogeneity between the studies for results for men, but not for women		

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Oze et al, 2011 Japan	Systematic review of epidemiological studies on the association between alcohol drinking and oesophageal cancer among the Japanese population, and random effects meta-analysis; 13 studies, 4/9	Questionnaire	Definition and categorisation of alcohol consumption and frequency differed between studies; 2 cohort and 1 case-control study investigated type of alcoholic beverages; 4 case-control studies evaluated OR for oesophageal cancer by ALDH2 Glu504Lys genotype **Alcohol intake for meta-analysis** Ever drinkers	399,182 subjects in cohort studies; in case-control, 1,628 cases, 14,728 controls	Results of systematic review: 1) all cohort studies and 6 case–control studies had dose- or frequency-response relationships with oesophageal cancer; 2) four case–control studies showed that acetaldehyde dehydrogenase Glu504Lys polymorphism had strong effect modification on alcohol drinking. **Summary estimate** **RR Cochrane's Q P-value** 3.30 (2.30-4.74) 53.90 <0.001 There was considerable heterogeneity between the studies	Most studies adjusted for age, and some for additional factors such as sex or smoking	Most cases of oesophageal cancer in Japan are oesophageal SCC

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Liu et al, 2014 9 studies analysed in all, 4 studies used for the meta-analysis of drinker/alcohol dietary pattern, 1 from Sweden, 1 from USA, 2 from Uruguay,	Systematic review and meta-analysis to evaluate relationship between dietary patterns and oesophageal squamous cell carcinoma (ESCC); 4 case-control studies	Not detailed	Dietary pattern called drinker /alcohol pattern, had a higher loading of wines, beers, and spirits than the 2 other dietary patterns analysed ('healthy' pattern, higher loading of fruit and vegetables; 'western' pattern, higher loading of red meat and processed food)	789 cases, 4,502 controls	**Pooled OR** 2.34 (1.22-3.45) **I^2 statistic (%)** 48.70	age, sex, BMI and education	Quantities of alcohol consumed not given

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Prabhu et al, 2014 5 studies analysed in all; 3 from China, 1 from Japan, and 1 from Thailand	Aim of study was to determine whether tobacco and alcohol act synergistically to increase the risk of oesophageal SCC; 5 studies, 2/3;	Details not given	Ever use vs. never-use of alcohol; **Alcohol use** (ever/never use) **Ever-alcohol with ever-tobacco use** **Ever-alcohol with ever-tobacco use**	Numbers of individuals not given	**Summary Adjusted OR (95% CI)** **Cochrane's Q P-value** **I^2 (%)** 1.21 (0.81-1.81) 0.18 4.41 3.28 (2.11-5.08) 0.05 55.30 There was moderate heterogeneity for the estimates of their combined effect; **Summary "Synergy Factor"** 1.85 (1.45-2.38) 0.49 0.0	Age and sex in all 5 studies; also BMI in 2 studies, dietary intake in 3 studies, education in 2 studies, and recruitment centre in 2 studies	intensity of alcohol use could not be calculated because only 1 study provided crude values for cases/ controls; "Synergy Factors" were also calculated from the published adjusted ORs, and from the summary adjusted OR;

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Druesne-Pecollo et al, 2014 Nineteen studies in all (5 Europe, 7 America, 7 Asia); for cases of oesophageal cancer, 4 studies, Asia	4 observational studies for oesophageal cancer, 199 cases out of 1888 participants		**Drinking status** Referent consumption from non-drinker to 100 g ethanol/day; highest category intakes up to ≥170 g/day Analysis for **Alcohol drinking (highest vs. lowest)**	199	**RR (95% CI)** **Overall Effect(P)** **Q(P)** **I^2(%)** 3.760 (2.42–5.85) .0001 0.576 0.0	Not stated	Analysis is for for the association of alcohol and oesophageal cancer as a second primary cancer, in adults with head and neck cancer as the first primary cancer site

Table 1. Meta-analysis and combined analysis studies examining alcohol consumption and oesophageal cancer risk							
Reference, location, year of study	**Description (No. in analysis; cohort / case-control)**	**Exposure assessment**	**Exposure categories**	**No. of cases / controls, n**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**
Li et al 2014 China	8 studies reporting on oesophageal cancer, 2 from USA, 6 from Asia; 6/2		**Drinking status** Drinking vs. non/occasional Light vs. non/occasional Moderate vs. non/occasional Heavy vs. non/occasional	2,656 **No. of studies** 8 5 7 8	**RR/OR** **P value** 1.86(1.40–2.47) 0.081 1.43(1.09–1.87) 0.028 1.92(1.25–2.96) 0.662 3.37(2.30–4.93) 0.044	All at least adjusted for age	The P value is for heterogeneity test between strata; light, moderate, and heavy drinking defined as 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) respectively; non/occasional drinking was the reference category

Table 2. Meta-analysis and combined analysis studies examining cessation of alcohol consumption and oesophageal cancer risk

Reference, location, year of study	Description (No. in analysis; cohort/case-control)	Exposure assessment	Exposure categories	No. of cases/controls, n	Odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments
Jarl and Gerdtham, 2012 Of the 9 studies in the analysis, 4 were European, 3 from Eastern Asia, 1 from South America, and 1 from Puerto	9 studies, 1/8 The age span of the cases, where reported, generally encompassed middle age and up, with an average age of about 60 years	Not described	Definition of "former drinker" varied between studies: some required those classified as former drinkers to have quit at least 1 year before interview, whereas other studies had no such requirement	sample sizes varied between 131-513 cases and 262-1,598 controls	**Years after drinking cessation until complete reduction of alcohol-related elevated risk of oesophageal cancer**: **World** **Europe** Estimated risk for never-drinkers, odds ratio 0.36 0.36 Estimated dose–response odds ratio of additional year since drinking cessation 0.94 (0.92–0.96) 0.94+2.17* (2.53–3.88) Years until no elevated risk from prior alcohol consumption 16.53 (12.68-23.75) 29.05 (18.55-48.70) *2.17 added to estimate to accommodate higher values found for studies conducted in Europe	Smoking controlled for in some studies	The differences in definition of "former drinker" could have potentially biased the results of the study

Table 3. Cohort studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Yates et al 2014 UK study, the European Prospective Investigation of Cancer-Norfolk (EPIC-Norfolk) study .	24,068 participants (54 % women) aged 39–74 years, recruited between 1993 and 1997, who were initially without diagnosed BE (Barrett's Esophagus) or EAC (Esophageal Adenocarcinoma); participants were registered in general practices in rural, suburban and inner city areas; cohort monitored to December 2008 to identify incident cases of BE and EAC	Self-report of alcohol consumption recorded in a food frequency questionnaire, which listed different alcoholic beverages and the frequency of intake at recruitment, aged 20 years and aged 30 years.	**Alcohol (units per week)** No alcohol >0 to <7 7 to <14 14 to <21 21 to <28 >28 **7 or more, compared to less** **Men** **Women** **Intake at 20 yrs** **Intake at 30 yrs** **Wine consumption** **Beer consumption** **Spirits consumption**	*No.of cases (total n=66) / No. of controls (total n=23,755)* 8/3,104 40/12,135 10/4,563 3/2,015 2/930 3/1,008	**Hazard Ratio(HR) *p* value** 1.00 1.34 (0.63–2.88) 0.45 0.73 (0.28–1.86) 0.50 0.47 (0.12–1.79) 0.27 0.59 (0.12–2.80) 0.51 0.83 (0.22–3.18) 0.79 **Trend across categories** 0.83(0.67–1.03) 0.09 **Hazard Ratio** 0.51 (0.29–0.88) 0.02 0.54 (0.30–0.96) 0.31 (0.04–2.44) **Trend** 1.04 (0.86–1.26) 1.02 (0.84–1.24) **Hazard Ratio** 0.49 (0.23–1.04) 0.06 1.91 (0.70–5.18) 0.68 (0.33–1.39)	age at recruitment and gender	One unit of alcohol contains 8g ethanol; thus 1 unit per week is equivalent to 1.1g ethanol/ day	8

Table 3. Cohort studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Steevens et al 2010 Dutch study, the Netherlands Cohort Study (NLCS)	Prospective cohort of 120 852 participants aged 55-70 years who completed baseline questionnaire on diet and other cancer risk factors in 1986; follow-up of16.3 years, from 17 September 1986 - 31 December 2002; follow-up for incidence performed by record linkage to Netherlands Cancer Registry (NCR) and nationwide network of histopathology and cytopathology (PALGA); follow-up nearly 100% complete, only 1 male cohort member lost to follow-up	Self-administered food frequency questionnaire	**Oesophageal SCC:** **Alcohol (g/day)** Abstainer >0 to <5 5 to <15 15 to <30 ≥30 **Oesophageal AC:** Abstainer >0 to <5 5 to <15 15 to <30 ≥30 **Oesophageal SCC:** **Beer (glasses/day)** No beer >0-1 >1-2 >2 **Wine (glasses/day)** No wine >0-1 >1-2 >2	*(cases/person time at risk in years)* 16/13,336 15/16,740 23/12,714 24/8,979 29/5,037 25/13,336 38/16,740 30/12,714 31/8,979 21/5,037 60/38,324 28/14,606 8/2,543 11/1,333	incidence Rate Ratio (RR) 1 (reference) 0.85 (0.42-1.73) 1.65 (0.85-3.17) 2.11 (1.08- 4.14) 4.61 (2.24- 9.50) p trend <0.001 1 (reference) 1.17 (0.69-1.98) 0.91 (0.51-1.60) 1.01 (0.56-1.82) 1.04 (0.54-2.02) p trend 0.93 1 (reference) 0.98 (0.57 to 1.67) 1.36 (0.59 to 3.16) 1.62 (0.64 to 4.09) p trend 0.23 1(reference) 0.93 (0.60 to 1.44) 0.51 (0.22 to 1.17) 0.30 (0.07 to 1.23) p trend 0.05	Adjusted for age, sex, cigarette smoking (current smoking status (yes/no), frequency and duration), body mass index, level of education, energy intake, consumption of fruits, vegetables, fish	Further analysis done for "stable users", subjects who had not changed consumption habits in the 5 years before baseline; association with oesophageal SCC became slightly stronger, no change for oesophageal AC; a glass of beer was taken to be 200ml, and a glass of wine 105ml	8

Table 3. Cohort studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Hardikar et al 2013 US cohort, Seattle Barrett's Esophagus Study (SBES)	Prospective cohort of patients with Barrett's Esophagus (BE); 411 participants with BE enrolled for observation between February 1, 1995 and September 30, 2009, who had no history of oesophageal cancer, and who had at least one follow-up visit	At baseline evaluation, structured personal interview with trained staff; self-reported alcohol consumption; fasting blood samples and endoscopy to check oesophagus	**Total Alcohol (drinks/day)** 0 >0-1 >1-3 >3 **Beer (drinks/day)** 0 >0-1 >1-3 >3 **Wine (drinks/day)** 0 >0-1 >1-3 >3 **Liquor (drinks/day)** 0 >0-1 >1-3 >3	*Cases of EA (Esophageal Adeno-carcinoma) / Total 45/397* 8/75 (ref) 9/135 16/102 12/85 12/143 (ref) 21/171 8/47 4/33 27/214 (ref) 16/163 2/16 0/2 11/138 (ref) 21/185 9/45 4/24	**Hazard Ratio (HR),** adjusted for age, gender, WHR and NSAID use Ref 0.65 (0.25–1.68) 1.43 (0.60–3.45) 1.23 (0.48–3.14) Test for trend *p 0.941* Ref 1.61 (0.76–3.43) 1.79 (0.69–4.61) 1.53 (0.46–5.05) Test for trend *p 0.877* Ref 0.70 (0.37–1.30) 1.19 (0.28–5.02) - Test for trend *p 0.100* Ref 1.29 (0.62–2.71) 2.86 (1.17–7.01) 1.40 (0.42–4.62) Test for trend *p 0.310*	Age, gender, NSAID use (decreased risk of progression from BE to oesophageal adenocarcinoma with NSAID use); waist-hip ratio (WHR)	Separate analysis done with the 4 adjustment factors and cigarette smoking; a "standard" drink in the US contains 14g of ethanol	8

Table 3. Cohort studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Kimm et al 2010 Korean cohort, the Korean Cancer Prevention Study	14-year prospective cohort study of 782,632 men, 30-93 years of age, who received health insurance from the National Health Insurance Corporation and had a medical evaluation from 1992 to 1995; participants were government employees and their dependents	Questionnaires conducted by medical staff at local hospitals	**<u>Drinking status</u>** Non-drinker Drinker **Alcohol intake (g/day)** 1-24 25-49 50-99 ≥ 100	*No.cases / incidence rate per 100,000 person years* 185/6.2 1198/17.9 858/16.2 184/24.9 112/25.0 44/19.1	Hazard Ratio (HR) 1.0 (ref) 2.4 (2.0 - 2.8) 2.2 (1.9 - 2.6) 3.1 (2.5 - 3.8) 3.8 (3.0 - 4.8) 4.1 (2.9 - 5.8)	age, age^2, alcohol intake, aspartate aminotransferase, body mass index, and exercise	Authors calculated linear and quadratic trends for age, because incidence of oesophageal cancer varies steeply with age	8

Table 3. Cohort studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Hsu et al 2014 Taiwan	25,611 men, aged 30-80 years, drawn from three prospective, community-based studies in Taiwan	Research nurses using a structured questionnaire	**Alcohol drinking** Never Ever **Quantity of alcohol drinking (g/day)** Never <80 ≥80 P for trend **Duration of alcohol drinking (years)** Never ≤20 >20 P for trend **Cumulative exposure to alcohol drinking (g-years)** Never <1500 ≥1500 P for trend	77/25,292 20,074 5,218 20,074 2,804 1,434 20.074 2,126 2,654 20,074 2,602 1,410	**Hazard Ratio (HR)** 1.00 Ref 3.80 (2.31-6.28) 1.00 Ref 4.15 (2.33-7.39) 3.71 (1.81-7.61) <0.001 1.00 Ref 4.57 (2.39-8.75) 3.53 (1.95-6.39) <0.001 1.00 Ref 3.91 (2.15-7.13) 4.70 (2.41-9.16) <0.001	age, education, ethnicity, betel quid chewing, cigarette smoking and study cohort	*p* value for significance of the HRs was <0.01	7

Table 3. Cohort studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Lee et al 2011 Taiwan; two major medical centres, Kaohsiung Medical University Hospital (KMUH) and Kaohsiung Chang-Gen Memorial Hospital (KCGMH) in the greater Kaohsiung area	305 cases of SCC, recruited from 2001-2007; patients newly diagnosed, recruited within 4 weeks of diagnosis, and histo-pathologically confirmed	Standardised questionnaire administered by in-person interview in hospitals	**Alcohol drinker** No Yes Starting at ≥20 years Starting at <20 years *P* for trend Daily <1 drink Daily ≥1 drink *P* for trend **Joint effects, alcohol and betel-quid chewing** Drinker/chewer No/No No/Yes Yes/No Yes/Yes *P* for log-rank[1] *P* for interaction[2] Yes/Starting at ≥20 years Yes/Starting at <20 years Yes/Daily 1-19 quids Yes/Daily ≥20 quids	**No. Median Age** 53 68 194 56 58 56 <0.001 75 60 177 54 <0.001 43 10 94 158	**Hazard Ratio(HR)** 1.00 Ref 1.4(0.9-2-2) 1.3(0.8-2.1) 0.347 1.2(0.8-1.9) 1.6(1.1-2.4) 0.008 **CR% HR *P*** 23.3 1.0 30.0 2.8 <0.05 30.0 1.5 47.5 3.4 <0.05 <0.001 0.603 40.2 3.1 <0.05 68.3 4.9 <0.05 43.9 3.1 <0.05 49.5 3.7 <0.05	HRs adjusted for sex, ethnicity, education, intake of vegetables and fruit and, where appropriate, cigarette smoking.	One drink was defined as containing 15.75 g of ethanol; Notes: [1] *P* value obtained from log-rank tests for homogeneity of Kaplan–Meier failure curves across groups studied [2] *P* value obtained from likelihood ratio tests based on a multiplicative Cox model for interaction	5

Table 4. Cohort studies examining the effect of alcohol consumption on oesophageal cancer mortality, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Kimm et al 2010 Korean cohort, the Korean Cancer Prevention Study	14-year prospective cohort study of 782,632 men, 30-93 years of age, who received health insurance from the National Health Insurance Corporation and had a medical evaluation from 1992 to 1995; outcomes for mortality ascertained from death certificates	Questionnaires conducted by medical staff at local hospitals	**<u>Drinking status</u>** Non-drinker Drinker **Alcohol intake (g/day)** 1-24 25-49 50-99 ≥ 100	*No.cases/ incidence rate per 100,000 person years* 163/5.4 833/13.3 622/12.3 110/17.5 76/13.7 25/15.9	**Hazard Ratio (HR)** 1.0 2.1 (1.7-2.5) 1.9 (1.6-2.3) 2.7 (2.1-3.5) 3.7 (2.8-5.0) 3.4 (2.2-5.3)	Age-adjusted death rates	Same cohort also used to analyse oesophageal cancer incidence, described in Table 3	8

Table 4. Cohort studies examining the effect of alcohol consumption on oesophageal cancer mortality, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Kim et al 2010 Korea, dataset from the Korea National Health Insurance Corporation (KNHIC), which provides health insurance to most Korean citizens	Prospective cohort, final sample size of 1,341,393, approx.10% of Korean population aged 40–69 years, based on census data from 2000; included were Korean men and women aged 40–69 years who received health insurance from the KNHIC and who had a health examination in 2000 (Health Examinee Cohort in 2000, HEC 2000). 5-year follow-up from January 2001-December 2005	Health examinations conducted by medical staff in local hospitals; self-report of estimated average frequency of alcohol consumption	**<u>For men</u>:** **Alcohol consumption, g/day** Non-drinker 1.0–14.9 15.0–29.9 30.0–89.9 ≥90.0 Non-drinker 1.0–14.9 15.0–29.9 30.0–89.9 ≥90.0 **<u>For women</u>:** **Alcohol consumption, g/day** Non-drinker 1.0–14.9 ≥15.0	6,921 213 1,486	**Relative Risk(RR) *p* value** **All-cancer** 1.00 0.91(0.85-0.97) 0.93(0.87-1.00) 1.06(0.98-1.15) 1.21(1.11-1.33) 0.017* **Oesophageal cancer** 1.00 1.23 (0.82–1.85) 1.43 (0.92–2.22) 2.09 (1.37–3.20) 3.33 (2.17–5.12) <.0001 **All-cancer** 1.00 0.99 (0.85–1.15) 1.39 (1.08–1.79) 0.015	All analyses were multivariate models and included age, residential (urban, rural), smoking status (current, former, never), ≥3 times/week regular exercise (yes/no), BMI (kg/m^2, continuous), systolic and diastolic blood pressure (mmHg, continuous), and fasting blood sugar (mg/dl, continuous)	the $p_{curvature}$ for non-linearity was obtained by restricted cubic spline	6

Table 4. Cohort studies examining the effect of alcohol consumption on oesophageal cancer mortality, published since 2009

Reference, location, year of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases	Odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Yaegashi et al 2014 Japan, Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study	46,395 men and 64,190 women aged 40-79 in the JACC Study, 42,408 men included in this analysis; participants recruited from late 1980s, follow-up till 2009 overall, though stopped earlier in some areas; 196 deaths in overall follow-up period of approximately 20 years	Self-administered questionnaire	**Alcohol intake** Non-drinkers Ex-drinkers Drinkers **Alcohol units consumed per day** Non-drinkers <1.0 units/day 1.0-1.9 2.0-2.9 3.0+ **Cumulative alcohol intake (unit-years)** Non-drinkers 1-29.9 30.0-39.9 40.0+ **Type of alcohol** Non-drinkers Sake Shochu Beer Whisky Wine	**No.of deaths** 18 12 166 18 6 36 64 34 18 20 12 96 18 103 32 47 25 7	**HR** ***p* for trend** 1.00 reference 2.10(0.99-4.42) 2.28(1.40-3.72) 1.00 reference 1.16(0.41-3.24) 1.48(0.82-2.69) 3.34(1.90-5.87) 4.62(2.46-8.68) 0.02 1.00 reference 1.25(0.63-2.50) 1.83(0.85-3.93) 3.34(1.96-5.70) 0.07 1.00 reference 2.45(1.44-4.18) 2.75(1.47-5.15) 1.72(0.96-3.08) 2.99(1.53-5.84) 2.61(0.86-7.94)	Age, centres, intake of fruit and vegetables; joint effects of smoking	One unit contains about 22 g of ethanol	6

Table 4. Cohort studies examining the effect of alcohol consumption on oesophageal cancer mortality, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
			Joint smoking + drinking *Smokers and*: Non-drinkers Ex-drinkers Drinkers **Cigarettes units/day alcohol** ***Non-smokers*** Non-drinker or <1.0 1.0-2.9 3.0+ ***1-20 cigarettes per day*** Non-drinker or <1.0 1.0-2.9 3.0+ **21+ cigarettes per day** Non-drinker or <1.0 1.0-2.9 3.0+	 7 7 119 7 5 1 7 63 15 2 13 10	 0.74(0.25-2.16) 2.55(0.85-7.66) 2.54(1.18-5.48) 1.00 reference 0.63(0.19-2.13) 0.64(0.07-5.96) 0.88(0.30-2.57) 3.57(1.53-8.30) 4.29(1.57-11.7) 0.80(0.15-4.15) 3.64(1.26-10.5) 6.05(1.87-19.6)			

Table 4. Cohort studies examining the effect of alcohol consumption on oesophageal cancer mortality, published since 2009								
Reference, location, year of study	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Yang et al 2012 China; participants from 45 areas, 23 urban and 22 rural, randomly selected from China's national Disease Surveillance Points	220,000 men aged 40–79 years,recruited in 1990–91; 15 years of follow-up, during which 440,000 deaths occurred; deaths from oesophageal cancer included 242 among all-drinkers, and 606 among non-drinkers; response rate about 80%; about 1% per annum lost to follow-up	Standardised questionnaire in in-person interview	 All-drinkers Non-drinkers **<u>Amount drunk (g/week)</u>** <140 140-279 280-419 420-699 ≥700	**No.of deaths** 242 606 62 62 52 36 30	**Hazard Ratio(HR)** ***P* value for trend** 1.25(1.07-1.47) 1.00(0.91-1.10) 1.19(0.93-1.53) 1.28(1.00-1.65) 1.11(0.84-1.46) 1.38(0.99-1.94) 1.63(1.12-2.39) 0.2	All variables, other than percentage from urban locality and mean age, were adjusted for individual area and age (5-year group) by direct standardisation to the whole study population (aged 40-79 years); joint analysis of smoking status and alcohol		7

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Marron et al 2012 Europe, 10 countries: Croatia, Czech Republic, France, Germany, Greece, Ireland, Italy, Norway, Spain, UK	Multi-centre study, 14 centres in 10 European countries, part of Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) study, initiated by IARC; 2,001 head and neck cancer cases and 2,125 controls overall; 144 cases of oesophageal cancer, histologically or cytologically confirmed and diagnosed within the previous 6 months; Controls frequency matched to cases by sex, age in 5-year	Questionnaire administered by trained interviewers	**Men – drinking status adjusted for cumulative alcohol consumption** Never alcohol Drink only this type Wine Beer Liquor Drink predominantly this type Wine Beer Liquor Drink this and other types Wine Beer Liquor Drink never this type Wine Beer Liquor	 2/110 6/101 11/124 -/25 15/318 33/322 9/79 35/595 34/659 55/764 37/317 15/260 31/484	**OR** ***p* value** 2.11(0.36-12.3) 1.68(0.29-9.63) - 0.856 0.79(0.16-3.95) 1.32(0.26-6.73) 3.55(0.64-19.55) 0.441 1.61(0.33-7.81) 1.27(0.28-5.86) 1.15(0.24-5.37) 0.953 2.56(0.5-13.05) 1.76(0.35-8.77) 1.65(0.35-7.68) 0.918	Centre, age, education level, smoking status by frequency and years since quitting, fruit and vegetable intake, cumulative alcohol consumption	For hospital-based centres, response rate was 90% among cases and 91% among controls; for population-based centres, response rate was 52% among cases and 29% among controls; the *p* values given are for heterogeneity among the ORs of the three beverage types; "Drink predominantly this type" =drink 66% or more of this beverage type	5

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
	intervals, and referral or residential area; 3 UK centres used population-based controls (N=390),from same primary practice list as corresponding case, other centres used hospital controls (N=1837)		**Women – drinking status adjusted for cumulative alcohol consumption** Never alcohol Drink only this type Wine Beer Liquor Drink predominantly this type Wine Beer Liquor Drink this and other types Wine Beer Liquor Drink never this type Wine Beer Liquor	10/147 5/73 2/25 5/23 13/101 3/29 2/31 7/131 14/147 14/153 9/60 15/159 13/160	 0.65(0.17-2.46) 0.06(0.01-1.16) 2.82(0.41-19.21) 0.095 0.61(0.16-2.30) 2.05(0.30-14.00) 0.81(0.09-7.58) 0.588 0.46(0.11-1.95) 0.64(0.16-2.52) 0.48(0.12-1.93) 0.937 1.12(0.26-4.85) 0.74(0.23-2.32) 0.59(0.19-1.81) 0.789		cumulative over lifetime; “Drink this and other types”= drink less than 66% of this beverage type cumulative over lifetime	

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Navarro Silvera et al, 2011 USA Study conducted in 3 geographic areas of USA with population-based tumour registries: entire state of Connecticut, a 15-county area of New Jersey,and 3-county area of western Washington State	multi-centre, population-based, case-control study of oesophageal AC and SCC; patients aged 30-79, newly diagnosed in 1993-95, 282 cases with EA; 206 with ESCC; 687 controls randomly selected from general population of study areas, frequency matched to expected distribution of target cases by 5-year age group and sex; complete interviews for 80.6% subjects and 70.2% eligible controls	Structured food frequency questionnaire in an in-person interview, or close relative as proxy respondent if necessary	**Intake of:** Beer Wine Liquor **Results for oesophageal AC** **Quartiles** 1 2 3 4 **Results for oesophageal SCC** **Quartiles** 1 2 3 4	282 cases with EA; 206 with ESCC; 687 controls	**Factor loading:** 0.67 0.58 0.78 (values above 0.40 make considerable contribution to principal component) **Adjusted linear regression, smoking/alcohol components** **OR (95% CI)** 1.00 1.15 (0.73-1.81) 1.19 (0.74-1.90) 0.89 (0.54-1.46) *P* for Trend 0.74 1.00 3.72 (1.78-7.77) 5.91 (2.93-12.37) 10.82 (5.16-22.68) *P* for Trend <0.001	gender, age, site, race, income, education, proxy status, energy intake, and mutual adjustment for other principal component/s	Dietary/lifestyle patterns were created using principal component analysis (PCA), then impact of the resultant scores on cancer risk estimated through logistic regression; variables that had loadings of 0.20 or greater were considered to be making a reasonable contribution to the principal component	6

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Pandeya et al 2013 Australia-wide study	Population-based case-control study; 305 eligible oesophageal SCC cases, recruited through major treatment centres or state cancer registries; diagnosed between July 1, 2002(July 1, 2001 in Queensland) and June 30, 2005; 70% response rate; 1580 controls randomly selected from national electoral roll and frequency matched by age (in 5-year age bands) and state of residence to cases;	Self-administered questionnaire	**Lifetime alcohol consumption** None to moderate drinkers (≤17 drinks/week) **Overall** Heavy drinkers (>17 drinks/ week) **Men** Heavy drinkers **Women** Heavy drinkers **Combination of drinking and smoking** **All** **Men** **Women** Heavy drinkers and also heavy smokers (30 or more pack-years)	300/1558	**Population Attributable fraction, %(PAF) (95% CI)** 1.00 Ref 3.3(2.4-4.7) 31.7(24.5-39.9) 3.2(2.2-4.7) 48.4(36.2-60.8) 2.8(1.2-6.1) 7.9(3.5-16.9) 58.2(49.1-66.7) 77.7(65.5-86.5) 38.2(25.9-52.1) p < 0.001 comparing PAF between men and women 22.4(17.8-27.9)	Age, sex, education, frequency of reflux symptoms, frequency of NSAID or aspirin use and body mass index	Typical weekly intake for 6 classes of alcoholic beverages (reduced-alcohol beer, regular beer, white wine, red wine, port/ sherry, and spirits / liqueurs) recorded in categories of none, less than 1, 1, 2–4, 5–6, 7–13, 14–20, 21–27, and 28 or more drinks per week. Total weekly alcohol consumption calculated by summing average weekly con-sumption of all beverages by the standard	5

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
	49% response rate						drink volume and alcohol content by weight (in grams of alcohol), and then for total lifetime; A “standard” drink in Australia contains 10g of ethanol; Participants dichotomised to low to moderate drinkers (≤17 drinks/week) and heavy drinkers (>17 drinks/week) for both men and women. Non-drinkers combined with low to moderate drinkers	

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009

Reference, location, year of study	Characteristics of cases/controls	Exposure assessment	Exposure categories	No. of cases/ controls	Odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Szymanska et al 2011 Latin America; 2 centres in Brazil for oesophageal SCC	international multicentre hospital-based case–control study initiated in 1998; 2 centres reporting on oesophageal SCC; 171 cases, 496 controls in all; cases identified from hospital admission records or from relevant clinical wards; controls recruited from in- or out- patients at the same hospitals as the cases, frequency-matched on sex, age and centre, from a defined	Lifestyle questionnaire administered face-to-face in the hospital by a trained interviewer	**Never-drinkers** **Ever-drinkers** **Former drinkers** **Current drinkers** **Alcohol quantity (g/day)** Never-drinkers Quartile 1 (0.1-8.6) Q2 (8.61–24.8) Q3 (24.81–68.8) Q4 (>68.8) ***OR-10 continuous*** **Duration (years)** Never-drinkers 1-15 16-30 31-40 ≥41 ***OR-10 continuous*** **Cumulative alcohol consumption (g-years)** Never-drinkers Q1 (0.1–233.6) Q4 ([2,035.6) ***OR-1000 continuous***	23/174 148/322 70/138 78/184 23/174 28/105 22/83 37/61 58/71 23/174 8/39 57/136 36/74 44/71 23/174 23/111 60/65	1.00 (ref) 4.41 (2.41–8.07) 4.24 (2.26–7.94) 4.10 (2.19–7.69) 1.00 (ref) 2.92 (1.42–6.03) 2.79 (1.31–5.97) 7.03 (3.34–14.83) 9.28 (4.4–19.59) *1.06 (1.03–1.09)* 1.00 (ref) 2.14 (0.81–5.69) 4.29 (2.18–8.46) 4.61 (2.24–9.49) 5.74 (2.76–11.94) *1.41 (1.23–1.61)* 1.00 (ref) 2.26 (1.1–4.65) 9.26 (4.46–19.23) *1.18 (1.08–1.29)*	sex, age, centre, education, tobacco pack-years, and fruit and cruciferous consumption (vegetables of the cabbage family)	Ever-drinkers: drinkers having ever consumed alcoholic drinks at least once a month; Former drinkers: individuals who quit drinking more than a year before the interview (for controls) or the diagnosis date (for cases); Intervals calculated in years; Alcohol amounts presented as ethanol-grams per day, with the assumption that beer	7

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
	list of diseases not related to alcohol		**<u>Type of alcohol</u>** Beer only Wine only Aperitif or spirits only **<u>Years since quitting drinking</u>** Current drinkers 2-4 ≥20 ***OR-10 continuous***	 4/64 2/10 56/51 184 30 30	 1.00 (ref) 1.45 (0.18–11.77) 12.99 (3.67–46.02) 1.00 (ref) 2.15 (1.10–4.21) 0.46 (0.19–1.16) *0.72 (0.54–0.96)*		contains approximately 5% of ethanol in volume, wine 12% and spirits 40%; Cumulative consumption (gram-years) estimated by multiplying average grams of ethanol/day by the years of alcohol consumption; *<u>OR-10 (1000) continuous</u>*: OR for an increase in 10 (1,000) units on a continuous scale	

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Chen et al 2010 China, Hebei Province	Matched-pair case-control study to Investigate risk of oesophageal SCC in Hebei Province, China; Cases drawn from patients who had diagnosis of primary invasive cancer of the esophagus between January 2002 and December 2006 at the Fourth Hospital of Hebei Medical University in Shijiazhuang; all diagnoses histologically confirmed; 835 cases of oesophageal SCC, matched with healthy	Questionnaire administered in interview	**Duration of alcohol use (years)** 0 <15 15 to <20 ≥20 **Alcohol intake (g/day)** 0 <30 30 to <60 ≥60 **Dose intensity(yrs/g per day)** 0 <15yrs; <30 g 15-<20yrs; <30 g ≥20 yrs; <30 g <15 yrs; 30 - <60 g 15-<20yrs; 30-<60g ≥20 yrs; 30 - <60 g	835/835 530/613 33/20 27/16 18/4 19/27 43/56 37/24	**Univariate analysis** **OR(95% CI) P value** 1.00 1.22(0.84-1.77) 0.310 1.26(0.96-1.66) 0.090 3.10(2.13-4.52) 0.001 1.00 2.26(1.51-3.35) <0.001 1.07(0.80-1.44) 0.650 1.97(1.45-2.69) <0.001 - 6.99(3.14-15.56) <0.001 8.86(3.53-22.26) 0.002 21.56(5.28-88.06) <0.001 5.23(2.19-12.46) <0.001 9.34(4.13-21.11) <0.001 13.59(5.34-34.63) <0.001	Cases paired to controls by age (±2 years) and gender	non-drinker defined as someone who consumed less than one drink per month; drinks consumed were baijiu (40-60% ethanol by volume), beer (5% ethanol by volume),wine (12% ethanol by volume) and hard liquor (40% ethanol by volume); drinks were converted into g of ethanol/day	7

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
	individuals by age (±2 years) and gender, living in the same area, Hebei Province		<15 yrs; ≥60 g 15-<20 yrs; ≥60 g ≥20 yrs; ≥60 g	10/12 63/50 55/13	45.26(10.53-194.56) <0.001 49.94(16.65-149.83) <0.001 183.12(49.10-682.91) <0.001			
Wu et al 2011 China, Jiangsu province, counties of Dafeng and Ganyu	Population-based case–control study, conducted from 2003 to 2007; 1,520 cases, newly diagnosed primary oesophageal cancer patients were recruited using data from local population-based cancer registries; 3,879 controls recruited, derived from same county as cases,	Standardised questionnaire in face-to-face interview	**Alcohol drinking** Never drinking Ever drinking *Former* *Current* **Frequency of drinking** Never drinking Occasionally Often Every day *P* for trend **Duration of drinking (years)** Never drinking <20 20- 30- 40- *P* for trend	 490/1,631 1,030/2,248 454/293 576/1,955 490/1,631 281/727 278/574 471/974 490/1,631 102/314 181/476 271/565 414/812	 1.00 (referent) 1.50 (1.29-1.74) 5.16 (4.23-6.29) 0.94 (0.80-1.10) 1.00 (referent) 1.32 (1.09-1.59) 1.70 (1.40-2.06) 1.54 (1.29-1.84) <0.001 1.00 (referent) 1.04 (0.81-1.34) 1.16 (0.94-1.44) 1.36 (1.12-1.63) 1.30 (1.10-1.54) <0.001	age (continuous), gender, study area, previous income (continuous), BMI (continuous), pack-years of smoking (continuous), and family history of cancer	never drinkers defined as those who drank less than once per month; current drinkers defined as those who had the habit at the time of interview or stopped the habit within 1 year before interview; consumption calculated in g ethanol/week; significant	7

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
	randomly selected from the county demographic database. Controls were frequency matched with cases by gender and age (±5 years); 68% and 75% response rate of cases from Dafeng and Ganyu, respectively; response rate of controls was 87% in Dafeng and 85% in Ganyu		**Ethanol intake (ml/Week)** 0 1- 250- 500- 750- *P* for trend **Age at start drinking (years)** 30- 25- 20- <20 *P* for trend **Time since stopping drinking (years)** Never drinking 10- 5- <5 *P* for trend	 624/1,929 125/331 198/519 204/478 354/562 391/895 244/447 280/652 104/231 490/1,631 32/502 27/35 237/13	 1.00 (referent) 1.21 (0.96–1.53) 1.19 (0.97-1.45) 1.30 (1.06-1.59) 1.90 (1.58-2.28) <0.001 1.00 (referent) 1.45 (1.20-1.75) 1.25 (1.05-1.49) 1.24 (0.96-1.61) <0.001 1.00 (referent) 1.80 (1.14-2.85) 2.22 (1.32-3.75) 5.28 (4.19-6.65) <0.001		associations found for men for categories of alcohol drinking, (OR=1.76 (1.48–2.09) for ever drinking), frequency and duration of drinking, ethanol intake, and time since stopping drinking, all with *P* for trend <0.001; age at start of drinking was not a significant association with risk; no significant associations were seen for women	

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Kumagai et al, 2013 China, Fourth Hospital of Hebei Medical University	Chinese male patients <60 years of age with esophageal SCC from the Fourth Hospital of Hebei Medical University in China and healthy individuals were enrolled between January, 2002 and December, 2006; hospital-based study; each ESCC patient age-matched to a control subject and a total of 535 pairs were enrolled in this study	Structured questionnaire administered by interviewer	**Alcohol intake (g/ day) / Duration (years)** 0 ≤53.3/ ≤20 ≤53.3/ >20 >53.3/ ≤20 >53.3/ >20 **Combined alcohol variable** **Alcohol intake (g/ day) / Duration (years)** (Reference = no drinking) ≤53.3/ ≤20 ≤53.3/ >20 >53.3/ ≤20 >53.3/ >20 **Alcohol intake (g ethanol/ day)/Duration (years)** ≤20 years/ ≤53.3 g ethanol/day ≤20 years/ >53.3 g ethanol/day	535/535 269/364 89/92 53/24 73/47 51/8	**Univariate conditional logistic regression** **OR(95% CI) P value** 1.00 1.26(0.89-1.79) 0.196 2.71(1.62-4.54) <0.001 1.98(1.32-2.95) <0.001 8.50(3.81-18.94) <0.001 **Multivariate conditional logistic regression** **OR(95% CI) P value (adjusted)** 1.20(0.83-1.74) 0.329 2.28(1.32-3.94) 0.003 1.91(1.25-2.92) 0.003 7.25(3.12-16.83) <0.001 **Fisher's exact test** More cases among older than younger men, P=0.035; More cases among younger than older men, P=0.250	Duration of alcohol intake (years) and amount of alcohol intake in the multi-variate analysis	non-drinker defined as someone who consumed <1 alcoholic drink/month; younger age category,30-49 years; older age category, 50-59 years	6

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Tai et al 2010 Taiwan; three large medical centres: National Taiwan University Hospital (NTUH) in northern Taiwan, Kaohsiung Medical University Hospital (KMUH) and Kaohsiung Veterans General Hospital located in southern Taiwan	multi-centre, hospital-based, case-control study; 51 cases, Taiwanese women women who were newly diagnosed and pathology-proven to have oesophageal SCC, between August 2000 and December 2008; 204 controls; each oesophageal SCC patient matched with 4 healthy women based on age (within 3 years) and hospital of origin, from the Department of Preventive Medicine in each hospital	Standardised questionnaire administered by interviewer	**Alcohol consumption** Non-drinkers Drinkers ≤ 158 g/wk > 158 g/wk	 40/195 11/9 3/8 8/1	**Adjusted OR** ***P* value** 1.00 Ref 3.55(1.03-12.27) 0.0378 2.06 (0.44-9.63) 20.58 (1.72-245.62)	adjustments for age (≤ 65 years vs > 65 years old), educational level (≤ 9 y vs > 9 yr), tea consumption (yes vs no), and status of smoking and areca chewing	subjects who had drunk beer, wine or distilled spirits more than once a week for at least 6 months were defined as alcoholic beverage drinkers; averaged alcohol intake, g/week, for each type of beverage, estimated by multiplying the midpoint value for each intake frequency by standard drink volume per week and median % alcohol content (categorised: < 10%, 10%-19%, 20%-49%, ≥ 50%)	6

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Gao et al 2011 China, Shanxi Province	600 oesophageal SCC cases,over 20 years old, residents of Taiyuan, Linfen, Jinzhong, Changzhi, and Xinzhou; recently diagnosed with oesophageal SCC without previous treatment, or had surgical treatment for tumour at Shanxi Cancer Hospital; diagnoses histologically confirmed by pathologists at Shanxi Cancer Hospital and National Cancer Institute in USA; 1514 controls,matched on age (± 5	interviewer-administered questionnaire	**Alcohol consumption** Ever vs never **Beer consumption** Ever vs never **Wine consumption** Ever vs never **Liquor consumption** Ever vs never	270/731 186/474 99/253 258/700	1.23 (0.95-1.60) 1.23(0.96-1.56) 1.11 (0.84-1.46) 1.20 (0.93-1.55)	Cases and controls matched on age (± 5 years), gender, and neighbourhood of residence;	As very few women reported ever drinking any alcohol (8.6%), analysis of alcohol consumption was restricted to males; analyses for beer and wine also done for pre- and post-1984, as rapid economic development occurred in 1984, and for summer vs. winter consumption of beer; liquor also analysed for pre- and post-1984, and for <weekly, weekly and	5

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
	years), gender, and neighbourhood of residence; controls identified by asking cases to suggest a suitable neighhour						daily categories; similar values obtained to the "ever vs. never" categories, and no significant associations with risk of oesophageal SCC	

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Lin et al 2011 Taiwan, 3 medical centres, the National Taiwan University Hospital (NTUH) in Taipei, Kaohsiung Medical University Hospital (KMUH) and Kaohsiung Veterans General Hospital (KVGH) in Kaohsiung	Multi-centre cancer patient conducted between 2000 and 2009, 668 cases of men with newly diagnosed oesophageal SCC; controls were from same geographic areas as cases, chosen from healthy community residents who attended the hospitals for routine physical check-ups at the Departments of Preventive Medicine from the same hospitals	Standardised questionnaire in an in-person interview	Never/ever drinking; Daily average of <3 drinks/day or >3 drinks/day	668 cases of oesophageal SCC; 543 (81.3%) reported habitual alcohol drinking; no comparisons with controls, because study looking at age of onset of oesophageal SCC in cases	Ever drinkers diagnosed with oesophageal SCC were 3.58 years younger than non-drinkers (p= 0.002); subjects who consumed, on average,>3 drinks per day were diagnosed with oesophageal SCC approximately 2.5 years younger than those who consumed <3 drinks per day (p= 0.02); age at starting drinking (<20 yrs vs. >20 yrs) was not found to be significant in relation to age of diagnosis with oesophageal SCC	educational level, study hospital, clinical stage of oesophageal SCC, cigarette smoking, and areca nut chewing	There is no information on the ethanol content of a “standard” drink in Taiwan	5

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Liu et al 2010 China	166 newly diagnosed EC patients on Nanao Island between 2003 and 2004; Nanao Island was the highest risk area for EC in China; 1,450 first-degree family members (parents,siblings and offspring) of probands also recruited to the study; 455 healthy adult residents on Nanao Island selected as high risk population controls; 134 healthy adult residents recruited from	Questionnaire administered in face-to-face interview	Categories of alcohol consumption: 0(little), 1(≤365 x 50 ml), 2(≤730 x 50 ml), 3(≤1460 x 50 ml), 4(≤2920 x 50 ml), 5(≤5840 x 50 ml), 6(≤11680 x 50 ml), 7(≤23360 x 50 ml), 8(≤46720 x 50 ml), 9(≤93440 x 50 ml), 10(≤186880 x 50 ml)	166 cases from Nanao Island; 455 controls from Nanao, and 134 controls from Shanwei	**Logistic coefficient (*B*)** 0.1 **Exp (*B*)** 1.105 (1.013-1.205) As a risk factor for cases and controls on Nanao and Shanwei, OR=1.7 for consumption of alcohol	Family history of oesophageal cancer; age, sex, and lifestyle and dietary habits	Aim of study was to ascertain the aetiology of EC by using logistic regression analysis among high and low morbidity regions, and also to analyse the characteristics of familial aggregation of EC on Nanao Island, so information on alcohol as a risk factor was limited	5

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Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
	Shanwei, a low risk region for EC, as low risk population controls; most of the cases (about 97%) were oesophageal SCC							
Nasrollahzadeh et al 2008 Golestan Province in northeastern Iran	300 oesophageal SCC cases and 571 controls, matched on neighbourhood of residence, age (±2 years), and sex; cases recruited at Atrak Clinic in Gonbad City, specialised clinic covering oesophageal SCC	validated structured questionnaire, administered by interviewers	Alcohol use for 6 months or more; Subjects were asked about type of alcohol used (beer, imported spirit, country spirit, and others), starting and stopping ages, and the amount and frequency of use;	21 subjects, 7/14	0.93 (0.37–2.34); no significant association between intensity, duration, cumulative use, or age of first use of alcohol with oesophageal SCC risk (data not shown in paper)	age (±2 years), sex, education, ethnicity, place of residence	Alcohol consumption was seen in only 2% of the cases and 2% of the controls, so limited information	5

Table 5. Case Control studies examining the effect of alcohol consumption on oesophageal cancer risk, published since 2009								
Reference, location, year of study	**Characteristics of cases/controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Sun et al 2010 China; five areas with high incidence of oesophageal cancer and good quality cancer registration data were selected: Cixian, Shexian from Hebei Province, Linxian from Henan Province, Feicheng from Shandong Province and Zhuanghe from Liaoning Province	250 cases randomly recruited from the cancer registration database diagnosed as having cancer arising in the lower oesophageal segment since January 1, 2009; 750 controls, matched 1:3 with cases on gender, age ±2 years, and same village. Also, controls had no history of malignancy and no family history of upper gastrointestinal cancer.	Questionnaire in face-to-face interview	**Univariate analysis:** **<u>Alcohol drinking</u>** No Yes **Multivariate analysis:** **<u>Drinking</u>**	250/750 170/572 80/178	1.941(1.290-2.921) 2.074(1.190-3.616)	age (±2 years), sex, place of residence	No quantities of alcohol consumption reported	5

Table 6. Studies examining the effect of alcohol consumption and genetic risk factors on oesophageal cancer risk								
Reference, location, year of study	**Character-istics of cases / controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Quality Rating**
Tanaka et al 2010 Japan, cases identified from 6 hospitals (Juntendo University Hospital, National Cancer Centre Hospital, Kurume University Hospital, Saitama Cancer Centre, Kagoshima University Hospital and Kyushu University Hospital)	Case-control and genome-wide association study; 1071 cases, patients newly diagnosed wiith oesophageal SCC, aged 35-85, and identified from the 6 hospitals between 2000-2008; 2762 healthy controls without previous cancer history recruited from Kyushu University Hospital (and related hospitals) during the same time period. All controls enrolled after receiving an	Standardised questionnaire		1071/ 2762	**SNP Genotype association (Chromosome; gene) test OR(95% CI) *p* value** rs1229984 (Chr.4;ADH1B) 4.08(3.27-5.09) $4.43x10^{-40}$ rs671 (Chr.12; ALDH2) 3.54(3.04-4.14) $5.53x10^{-62}$	logistic regression models to evaluate genetic and environmental factors together were adjusted for sex, age (5-year categories) and study area (Honshu and Kyushu islands)		6
				742/820	**Risk of oesophageal SCC associated with alcohol and smoking**			
			Non-drinker non-smoker (env. risk No=0)	36/252	1.0 Reference			
			Ever-drinker non-smoker (env. risk No=1)	67/170	3.5 (2.1- 5.8)			
			Non-drinker ever-smoker (env. risk No=1)	27/89	2.3 (1.2-4.3)			
			Ever-drinker ever-smoker (env. risk No=2)	612/309	16.0 (9.7- 26.3)			
			p value for interaction of drinking and smoking		0.048			

Table 6. Studies examining the effect of alcohol consumption and genetic risk factors on oesophageal cancer risk

Reference, location, year of study	Character-istics of cases / controls	Exposure assessment	Exposure categories	No. of cases/ controls	Odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Quality Rating
	upper gastrointestinal endoscopy test to ensure they had no disease				rs671 GG and rs1229984 AA/GG (genetic risk No=0) / rs671 AG/AA or rs1229984 GG (genetic risk No=1or2) / p value for interaction of genetic risk and drinking / smoking			
			Non-drinker non-smoker (env. risk No=0)		1.0 Ref / 1.1 (0.5- 2.4)			
			Ever-drinker non-smoker (env. risk No=1)		1.5 (0.7- 3.3) / 12.1 (5.5 -26.6) / <0.001			
			Non-drinker ever-smoker (env. risk No=1)		4.5 (1.3-15.9) / 2.4 (1.1- 5.3) / 0.44			
			Ever-drinker ever-smoker (env. risk No=2)		5.0 (2.5-10.1) / 62.1 (30.3-127.4) / <0.001			
			p value for interaction of drinking and smoking		0.55 / 0.048			

Table 6. Studies examining the effect of alcohol consumption and genetic risk factors on oesophageal cancer risk								
Reference, location, year of study	**Character-istics of cases / controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjust-ment factors**	**Comments**	**Star Quality Rating**
Ding et al, 2010 China, Taixing city in Jiangsu Province	221 cases, patients who were histopatho-logically diagnosed as having oesophageal cancer from January 2005 to December 2006; 191 population-based controls, recruited from healthy residents in the villages or towns in which the patients lived	Questionnaire administered by interviewer	**Drinking status** Drinking Never OR (95% CI) **Cumulative amounts of alcohol consumption** ≥2.5 kg*years <2.5 kg*years OR (95% CI) **INTERACTIVE EFFECT** **Cumulative alcohol consumption (kg*years)** <2.5 <2.5 <2.5 <2.5 ≥2.5 ≥2.5 ≥2.5 ≥2.5	**ALDH2** **G/A+A/A** 61/25 70/52 1.79 (0.97-3.32) 23/3 108/74 5.99 (1.69-21.16) **ALDH2 genotype** G/G G/G G/A or A/A G/A or A/A G/G G/G G/A or A/A G/A or A/A	**G/G** 64/72 26/42 0.92 (0.48-1.78) 32/27 58/87 1.16 (0.58-2.35) **ADH2 genotype** A/A G/A or G/G A/A G/A or G/G A/A G/A or G/G A/A G/A or G/G	27/52 31/35 52/38 56/36 17/16 15/11 10/2 13/1	**ALDH2** 3.08 (1.65–5.78) 1.78 (0.94–3.37) 3.05 (1.49–6.25) 21.84 (2.91–163.76) 1.96 (1.23–3.14) 11.93 (3.17–44.90) 1.00 1.77 (0.87–3.62) 2.46 (1.27–4.78) 2.52 (1.30–4.90) 1.60 (0.61–4.19) 1.21 (0.42–3.49) 7.54 (1.38–41.09) 53.15 (4.24–666.84)	income, age, occupa-tion, education and smoking in the logistic regression analyses		5

Table 6. Studies examining the effect of alcohol consumption and genetic risk factors on oesophageal cancer risk

Reference, location, year of study	Character-istics of cases / controls	Exposure assessment	Exposure cate-gories	No. of cases/ controls	Odds ratio and confidence intervals (95% CI)	Adjust-ment factors	Comments	Star Quality Rating
Talukdar et al 2013 a population of North East India, in the Assam and Mizoram states, which is reported as having high incidence of oesophageal cancer	112 histo-pathologically confirmed oesophageal SCC patients from different cancer hospitals of NE India, recruited January 2011-October 2012; oral swabs collected from 130 age and gender matched healthy controls	Structured questionnaire administered by interviewer	**Drinking status** Drinkers Non-drinkers Drinkers Non-drinkers Drinkers Non-drinkers Drinkers Non-drinkers Drinkers Non-drinkers Drinkers Non-drinkers	 26/25 86/105	**Adjusted OR** **P value** 1.23(0.67-2.46) 0.43 1 Reference Cases with promoter methylation vs. controls ***p16*** ***DAPK*** ***GSTP1*** ***BRCA1*** 0.84 0.88 0.75 0.88 (0.3-2.11) (0.41-1.89) (0.33-1.67) (0.27-2.82) 1 Reference Cases without promoter methylation vs. controls ***p16*** ***DAPK*** ***GSTP1*** ***BRCA1*** 1.80 2.02 2.24 1.37 (0.91-3.52) (0.93-4.39) (1.06-4.72) (0.72-2.64) 1 Reference **Cases with 0 Methylation Index vs. controls** **OR** **P value** 2.47(1.00-6.04) 0.04 1 Reference **Cases with 0.25-0.5 Methylation Index vs. controls** 1.35(0.60-3.04) 0.45 1 Reference **Cases with 0.75-1.0 Methylation Index vs. controls** 0.61(0.21-1.73) 1 Reference 0.36	Age, gender, betel quid chewing, tobacco chewing, smoking	best model 2nd order interaction by MDR (Multi-factor Dimen-sionality Reduction) was tobacco chewing and alcohol consumption (OR 5.01, 95% CI 2.54-9.88); for occurrence of oesophageal SCC without promoter hypermethyl-ation, best model sug-gested inter-action of betel quid chewing, alcohol consumption and null *GSTT1*, with OR 9.88, 95% CI 3.67-26.54	5

Table 6. Studies examining the effect of alcohol consumption and genetic risk factors on oesophageal cancer risk

Reference, location, year of study	Character-istics of cases / controls	Exposure assessment	Exposure categories	No. of cases/ controls	Odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Quality Rating
Shi et al 2012 China	350 cases who were patients diagnosed with histologically confirmed oesophageal SCC at Kunming General Hospital in the Chengdu Military Region	Questionnaire administered by interviewer	**Drinking status** No No Yes Yes **Interaction CYP2C19*3 A allele + drinking**	**CYP2C19*3 genotype** GG 115/219 AA+AG 16/6 GG 200/119 AA+AG 19/	**OR** ***P* value** 1 Reference 3.42(2.421-8.332) 5.05(3.371-10.712) 10.25(8.121-24.243) 8.747(6.321-18.122) 0.009	Controls matched on age, sex and geographical area	Subjects who drank alcohol in the preceding 6 months were considered to be "drinkers"	5
Wang et al 2011 China	81 Chinese female cases, recruited from hospital of the Armed Police College of Medicine from June 2009 - December 2010; all cases newly diagnosed with primary oesophageal cancer; 162 controls, randomly selected from	Questionnaire administered in face-to-face interview	**Drinking status** Former Never Light Moderate Heavy Former Never Light Moderate Heavy	**ADH1B*2 genotype** 67/145 2/1 33/77 21/59 9/7 2/1 **ADH1B*1/*1 genotype** 15/17 2/0 4/10 3/4 3/2 2/1	- Reference 1.03(0.49-2.03) 1.69(1.24-6.58) 2.72(0.55-79.6) - 0.97(0.21-3.62) 1.76(0.31-11.7) 2.71(0.41-44.2) 3.70(0.34-281.7)	Age, smoking, fruit and vegetable intake		5

Table 6. Studies examining the effect of alcohol consumption and genetic risk factors on oesophageal cancer risk								
Reference, location, year of study	**Character-istics of cases / controls**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls**	**Odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Quality Rating**
	people who had general health examinations in same hospital during same period and confirmed to have no malignancy,digestive diseases or chronic diseases and also no prior history of malignancy. Controls matched with cases by age within five years			**ALDH2*1/*1 genotype** 42/60				
			Former	1/1	-			
			Never	23/57	Reference			
			Light	7/21	0.92(0.32-2.75)			
			Moderate	4/4	2.27(0.44-19.4)			
			Heavy	1/2	1.03(0.07-27.5)			
				ALDH2*1/*2 genotype 85/36				
			Former	3/1	-			
			Never	18/29	1.59(0.87-3.71)			
			Light	16/26	2.17(1.29-4.52)			
			Moderate	2/3	1.93(0.29-16.6)			
			Heavy	3/1	7.05(0.48-331.4)			

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

Consumption of Alcohol and Oesophageal Cancer Risk

Extract from COT/COM/COC Annual Report 2005; COC Section: Review of the quantitative relationship between alcohol consumption and squamous cell carcinoma. p. 139

Full document is available here:
http://cot.food.gov.uk/cotreports/cotcomcocrep2005

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chronic hepatocellular injury with "cholangiofibrosis" and there was no risk of the lesion occurring in the absence of severe hepatic toxicity. A number of representative sections were shown to COC members. It was noted that the lesions termed "cholangiocarcinoma" were quite unlike the usual pattern seen in human cholangiocarcinoma. COC members supported the view that the lesions were not neoplastic but were a florid inflammatory response to severe acute and chronic hepatocellular damage.

3.26 The COC concluded that it was uncertain that the lesions termed "cholangiocarcinomas" were truly neoplastic but accepted the conventionality, used by the study pathologist in the report of the carcinogenicity study, of classifying them as neoplastic. Members considered that a satisfactory non-genotoxic Mode of Action explanation had been submitted. The COC agreed that a threshold approach to risk assessment could be used and agreed that there was a satisfactory margin of safety between the NOAEL for putative cholangiocarcinoma and the Acceptable Daily Intake proposed by the Pesticide Safety Directorate. A full statement of the committees' assessment of proquinazid is attached at the end of this report.

Review of the quantitative relationship between alcohol consumption and squamous cell carcinoma

3.27 The COC reviewed the relationship between alcohol and oesophageal cancer in 1995 as part of the review of alcohol and cancer. Several studies indicated that there was a quantitative relationship between alcohol intake and squamous cell carcinoma (SCC) of the oesophagus but a threshold level could not be defined. Therefore, the COC had estimated levels of alcohol intake for which there was convincing evidence of an increased risk of SCC. In 2004, a paper on oesophageal cancer had suggested that further consideration of alcohol-induced SCC was necessary. Following consultation, it was decided that a review should be conducted to review the post 1995 data on the quantitative relationship between alcohol and SCC. The COC also reviewed data on the risk in smokers who drink heavily and the possible existence of any susceptible groups.

3.28 Twenty-four new epidemiological studies were retrieved for review by the COC. It was noted that the data suffer from the same limitations as were noted in 1995 including a lack of data in women, poor study design, and imprecise estimates of alcohol intake. The studies rarely considered confounding by other risk factors, such as dietary intake, lack of vitamins and, possibly, Barrett's oesophagus. Also, members did not consider that the studies were easily comparable and suggested that it may only be necessary to consider the meta-analysis data, as these give the best estimates. Nevertheless, it was considered that they strengthened the overall picture. An increased risk was apparent at intakes above 30 g alcohol per day. However, the COC could not identify a level of consumption below which there is no increase in risk, due to both lack of data and the intrinsic weakness of the data (in particular, the fact that the 'non-drinkers' group may include light drinkers).

3.29 The COC considered that the data provided evidence of potentially susceptible groups. It noted the multiplicative effects of alcohol and smoking on the incidence of SCC and that smoking increased the risk of SCC at even moderate doses of alcohol. However, gender and ethnic differences were considered possibly to reflect temporal differences in drinking habits rather than a real difference in susceptibility.

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

Consumption of Alcohol and Oesophageal Cancer Risk

Extract from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 96: Alchol Consumption and Ethyl Carbamate
Pages 351-399

Full document is available here:
http://monographs.iarc.fr/ENG/Monographs/vol96/mono96.pdf

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Consumption of Alcohol and Oesophageal Cancer Risk

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

Pages 380-382, 412-413, 428, 442,444-445, 446, 472 and Tables 2.6, 2.9, and 2.10

Full document is available here:
http://monographs.iarc.fr/ENG/Monographs/vol100E/mono100E.pdf
Tables are available here:
http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.6.pdf
http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.9.pdf
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