

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

Cessation of Alcohol Consumption and Effect on Oesophageal and Head & Neck Cancer Risk.

1. As part of the strategy proposed to consider the role of alcohol consumption and cancer risk, Members agreed that a review of the literature on the effect of alcohol cessation on cancer risk would be helpful. From the literature, meta-analyses/pooled analyses on the effect of cessation of alcohol consumption on the risk of cancer have been identified for the following sites - head and neck (laryngeal, pharyngeal, oral cavity), oesophageal, liver and stomach. This review focuses on oesophageal cancer and head/neck cancers. For these cancer sites, a number of questions could be considered:

A) Is it possible to quantify the potential reduction in risk of developing oesophageal and head/neck cancer from alcohol cessation?

B) What time period is required to reduce the alcohol related elevated risk of oesophageal or head/neck cancer to baseline?

C) Is there a time period from the time of cessation where the reduction in risk is of such a magnitude that there would be a significant public health benefit?

Oesophageal cancer in the UK

2. Oesophageal cancer (squamous cell carcinoma (SCC) and adenocarcinoma (AC)) was the 9th most common cancer in the UK in 2010, accounting for 3% of all new cases. Currently it is the 8th most common cancer in males whilst it is the 13th most common in females (Cancer Research UK, accessed 2014). In 2010, there were 8,477 new cases of oesophageal cancer in the UK (5,637 (66%) in men and 2,840 (34%) in women, with crude incidence rates of 18.4 per 100,000 for males and 9.0/100,000 for females. The incidence of oesophageal cancer is strongly related to age, with an average of 70% of cases diagnosed in men and women aged 65 years and over (data obtained from the UK between 2008 and 2010). Oesophageal cancer was the 6th most common cause of cancer death in the UK in 2011, accounting for 5% (7,603 persons) of all deaths from cancer. The crude mortality rate showed that there were 16 cancer deaths for every 100,000 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.

3. Parkin et al. (2011) estimated that, in the UK, around 89% of oesophageal cancers are linked to lifestyle and environmental factors. 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).

Effect of alcohol cessation on oesophageal cancer risk

Pooled Analysis/Meta-analysis (Table 1)

4. In separate pooled analysis of four hospital-based case control studies, Castellsague et al. (1999 and 2000) examined the effect of drinking and smoking cessation on reducing oesophageal cancer risk. The studies used in the pooled analysis were Victoria et al. 1987; DeStefani et al. 1990; Castelletto et al. 1994 and Rolon et al., 1995. These four studies were conducted from 1986 to 1992 under the coordination of IARC. Castellsague et al. (1999) presented data for both males and females while Castellsague et al. (2000) performed analysis on male subjects only. The dataset contained a total of 655 male and 175 female cases diagnosed with incident squamous-cell carcinoma of the oesophagus and 1408 male and 371 female controls. Control subjects were individually matched to the cases with respect to the admitting hospital and age. Information on participant's lifetime histories of smoking and alcohol consumption were obtained by interview. Data were analysed using unconditional multiple logistic regression models with maximum-likelihood estimation of parameter values to obtain odds ratios (OR) and 95% confidence intervals (CI) and were adjusted for age group, hospital, years of schooling, average number of cigarettes smoked per day. Overall, both studies found that the risk of oesophageal cancer decreased the longer the period of abstention. For men, Castellsague et al. (1999) reported a statistically significant reduction in risk with increasing years since cessation of drinking ($p = 0.02$ for trend), however the magnitude of effect of cessation was much smaller in women and not statistically significant ($p = 0.56$). They also observed that the risk reduction associated with time since quitting alcohol drinking was greater the higher the amount of alcohol consumed (see table 1). The data from Castellsague et al. (1999) suggest that it takes greater than 10 years of abstention from alcohol before the risk of oesophageal cancer returns to within the upper risk levels for non-drinkers.

5. Castellseque et al. (2000) reported that male ex-drinkers required a minimum of 19 years from quitting drinking for a statistically significant reduction in oesophageal cancer risk (OR = 0.4, 95% CI 0.2- 0.8, current drinkers as referent group) to the risk level of never drinkers (OR = 0.3, 95% CI 0.1 - 0.7). They observed that after 10 years of drinking cessation, the risk estimate fell within the risk interval of never drinkers (OR = 0.6, 95% CI 0.3 – 1.1). The risk reduction was statistically significant regardless of intensity or duration of drinking. They found that the downward trend associated with drinking cessation was marginally significant for drinkers of less than 62 millilitres of ethanol/day ($p = 0.05$) and highly significant for heavy drinkers ($p = 0.009$). The inverse trend with time since quitting was also statistically significant for subjects who had been exposed to the habit for 40 years or less ($p = 0.005$) as well as those exposed for longer periods (40 years +) ($p = 0.04$). The type of alcoholic beverage did not exert an influence on the effect of cessation on oesophageal cancer risk, with a statistically significant inverse trend observed for both drinkers of spirits ($p = 0.005$) and drinkers of spirits with beer/wine ($p = 0.009$). The study also examined the effect of smoking cessation on oesophageal cancer risk. When they analysed the effect of smoking and alcohol cessation on oesophageal cancer risk,

the highest risk reduction occurred when both smoking and drinking were simultaneously discontinued. For example, quitting simultaneously both smoking and drinking for 5 – 9 years was accompanied with a 70 % risk reduction (OR = 0.3, 95% CI 0.1 - 0.4).

6. In a pooled analysis, Rehm et al. (2007) examined the effect of alcohol drinking cessation on oesophageal cancer risk. Five studies were included and these were Bosetti *et al.* 2000, Cheng *et al.* 1995, Castellsague *et al.* 1999, Zambon *et al.* 2000 and Martinez, 1969. Pooled estimates were calculated from logarithmised OR, weighted by reciprocals of squared standard errors (SEs). 1873 cases with oesophageal cancer and 4985 controls were analysed in the dataset. Although, they observed an increased risk of oesophageal cancer among those who recently stopped drinking (OR = 2.50, CI 95% 2.23 – 2.80), there was a clear decrease in oesophageal cancer risk with longer periods of abstinence. They observed that after 15 years of drinking cessation, the risk estimate was the same as that of a never drinker (OR = 0.37, 95% CI 0.33 – 0.41 after 15 years cessation; OR = 0.37, 95% CI 0.35-0.39 for never drinker). In total 63% of risk reduction was observed after 15 years of quitting drinking compared to current drinkers.

7. 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. The studies included in the meta-analysis were Bosetti et al. 2000, Lee et al. 2005, Cheng et al. 1995, Castellsague et al. 2000, Ozasa 2007, Launoy et al. 1997, Zambon et al. 2000, Vioque et al. 2008 and Martinez, 1969. The data were analysed using a generalized least squares model (GLS) for trend estimation of summarized 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 to baseline following drinking cessation. 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 into 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 caution that this may be more apparent than real because of the characteristics of these subjects. Based on their best estimate of the dose-response relationship, they 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.

Case-Control Studies (Table 2)

8. Zambon et al. (2000) examined the role of cessation of alcohol consumption and tobacco smoking in a case-control study of oesophageal cancer between January 1992 and December 1997 in three areas in Northern Italy. The study included 275 male cases and 593 controls. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated using unconditional multiple logistic

regression models and adjusted for age, area of residence and years of education. They reported that drinking cessation was associated with some risk excess compared with current drinkers in the first 10 years following cessation (OR 2.4, 95% CI 1.2–4.9) and with a non-significant risk reduction after cessation for ≥ 10 years (OR 0.54, 95% CI 0.22–1.35).

9. Castelletto et al. (1994) investigated the role of alcohol and other risk factors in oesophageal cancer in a hospital based case-control (131 cases and 262 controls) study in Argentina. A trained interviewer using a standard questionnaire obtained information on lifestyle habits including alcohol consumption. Odds ratios and the corresponding 95% confidence intervals were estimated using unconditional multiple logistic regression models and adjusted for age, sex, hospital, education and average number of cigarettes/day. When they examined the effect of years since cessation of alcohol drinking on oesophageal risk, they did not observe a significant risk reduction (Current drinker OR = 2.9 (95% CI 1.4 – 6.0), 2-7 years since quitting 2.0 (0.7 – 5.5), ≥ 8 years since quitting OR = 2.5 (95% CI 0.9 – 7.2).

10. Rolon et al. (1995) examined the role of risk factors (socioeconomic indicators, tobacco smoking and alcohol consumption) for oesophageal cancer in a hospital-based case-control study in Paraguay. From a total of 131 cases of oesophageal cancer and 381 controls included in the study, they observed risk reduction following alcohol cessation with a risk ratio of 3 when long-term to short term quitting were compared. Despite the risk reduction observed, they did note that alcohol abstention for > 15 years was still associated with a 4-fold excess risk of oesophageal cancer, although the confidence interval was very wide (Non-drinker OR = 1.0, current drinker OR = 7.7 95% CI 3.6 - 16.5; 15 + years since quitting drinking OR = 4.3 95% CI 0.9–20.4).

11. Victora et al. (1987) investigated the role of risk factors for oesophageal cancer including Mate (tea prepared as an infusion of the herb *flex paraguavensis* and that is usually drunk very hot) and alcohol consumption in a case-control study in South America (Southern Brazil, Uruguay and parts of Argentina). A total of 171 confirmed cases of squamous cell carcinoma and 372 matched controls were included in the study. In this study, consumption of a common alcoholic drink in Brazil, a distilled sugar cane spirit known as Cachaça, represented approximately 80% of total alcohol consumption among the controls. In their analysis, they observed little effect on oesophageal cancer risk in ex-drinkers of Cachaça who stopped drinking 1-9 years ago (OR = 1.08, 90% CI = 0.54 – 2.18, current drinkers as referent group). Hence, the risk was similar to that of a current drinker. A decreased risk of oesophageal cancer was observed in those who had stopped drinking Cachaça 10 or more years ago (OR = 0.78; 90% CI = 0.36 – 1.69) but the authors noted that the confidence intervals were wide. In a similar study in Uruguay, De Stefani et al. (1990) conducted a case-control study to examine the effect of risk factors (alcohol, tobacco and Mate consumption) on oesophageal cancer risk. A total of 261 cases of squamous cell carcinoma and 522 hospital matched controls were included in the study. When they examined the effect of years since cessation of alcohol drinking on oesophageal risk, they observed a significant reduction in cancer risk in male ex-drinkers with a significant trend with years since quitting (Current regular drink OR = 1.0; 1-9 years since quitting OR = 0.78, 95% CI, 0.48-1.26; >10 years OR = 0.46, 95% CI 0.23-0.92; non-drinkers and occasional drinkers OR = 0.48, 95% CI 0.29-0.81).

12. Using data from a multicentre case-control study conducted in Italy and Switzerland, Bosetti et al. 2000 evaluated the pattern of risk after stopping drinking (and smoking) on oesophageal cancer. A total of 404 (356 men and 48 women) histologically confirmed cases of oesophageal squamous cell carcinoma and 1070 controls (878 men and 192 women) were included in the study. ORs and the corresponding 95% CIs were estimated using unconditional multiple logistic regression models. When they examined oesophageal cancer risk since cessation, they did not observe a consistent reduction in risk. They reported that drinking cessation was associated with some reduced risk compared with current drinkers in the first 1- 5 years following cessation (OR 0.85, 95% CI 0.41 – 1.75), followed by some excess risk compared to current drinkers following cessation of 6 -14 years (OR = 1.74, 95% CI 0.83 – 3.57), followed by a risk reduction after cessation for ≥ 15 years (OR 0.53, 95% CI, 0.15 – 1.85). It was only after 15 years of cessation that the risk of oesophageal cancer approached that of never drinkers (OR =0.31, 95% CI 0.14 – 0.69). When they examined the combined effect of smoking and alcohol, the risk of oesophageal cancer decreased with time since smoking cessation across strata of time since drinking cessation. In contrast, a reduced risk of oesophageal cancer in relation to time since drinking cessation was observed only 10 or more years after drinking cessation, adjusted for time since smoking cessation (OR = 0.37, 95% CI 0.14–0.99) and the OR was more strongly and significantly reduced 10 or more years since cessation of both habits (OR = 0.11, 95% CI 0.01–0.90).

13. Lee et al. (2005) conducted a case-control study to investigate the independent and combined effects of alcohol intake, tobacco smoking and betel quid chewing on the development of oesophageal cancer in Taiwan. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were computed using unconditional logistic regression analyses and adjusted for age, gender, study hospital, education, consumption of vegetables and fruits, pack-years of cigarette smoking and of betel quid chewing. A total of 513 confirmed cases of squamous cell carcinoma and 818 matched controls were included in the study. They reported that drinking cessation was associated with some risk excess compared with current drinkers in the first 1-5 years following cessation (OR 1.3, 95% CI 0.7 – 2.4) and with a non-significant risk reduction after cessation of between 6 - 10 years (OR 0.54, 95% CI 0.22–1.35) and a 70% reduction in risk after 10 years of abstinence (OR = 0.3, 95% CI 0.1-0.6). A similar pattern of results was obtained by Launoy et al (1997) when they investigated the effect of a number of alcohol exposure measures (intake, duration and cessation) on oesophageal cancer risk in a French case-control study. A total of 208 cases and 399 controls were included in the study. With current drinkers used as the referent group, the study found an initial increase in oesophageal cancer risk following cessation followed by decrease in risk after a longer periods of abstinence (Current drinker OR = 1; 1-5 years since quitting, OR = 2.23, 95% CI 1.01-4.89; 6-10 years since quitting, OR = 1.86, 95% CI 0.58-5.87 and 11 years or more since quitting OR = 1.15, 95% CI 0.63-3.24).

14. Szymanska et al. (2011) investigated the role of alcohol (and tobacco) in the development of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and larynx (head and neck) and of the oesophagus from a multicentre hospital-based case-control study across three different countries in Latin America (Brazil, Argentina and Cuba). A total of 171 cases and 1,707 controls were included

in the analysis. ORs were estimated by unconditional multivariate logistic regression and adjusted for sex, age, centre, education, tobacco pack-years, and fruit and cruciferous vegetable consumption. With current drinkers used as the referent group, the study found an initial increase in oesophageal cancer risk following cessation followed by a decrease in risk after longer periods of abstinence (current drinker OR = 1.0; 2–4 years since quitting OR = 2.15, 95 %CI 1.10–4.2; 5–9 years since quitting OR = 0.89, 95 %CI 0.43–1.85; 10–19 years since quitting OR = 0.75, 95 %CI 0.36–1.55 and ≥ 20 since quitting OR = 0.46, 95 %CI 0.19–1.16). These results are similar in pattern to those observed by Launoy et al. (1997) and Lee et al. (2005).

15. Cheng et al. (1995) examined the effect of alcohol cessation on oesophageal cancer risk in a hospital-based case-control study in Hong Kong. A total of 400 cases were included in the study (345 men and 55 women) and 1598 controls. ORs were computed using unconditional logistic regression analyses and adjusted for age, education, place of birth, smoking and diet. In their analysis, they reported that an increased risk was observed in those who had recently quit drinking (0–1 years since quitting OR = 2.5, 95% CI 1.4 – 4.4). After this time, there was a decrease in oesophageal cancer risk with longer periods of abstinence (1–4 years since quitting OR = 1.5, 95% CI 0.9 – 2.6; 5–9 years since quitting OR = 0.5, 95% CI 0.3 – 0.9; 10–14 years OR = 0.8, 95% CI 0.4–1.5; 15 years since quitting OR = 0.2, 95% CI 0.1 – 0.6; never drinkers 0.6, 95% CI 0.4 – 1.0). In current drinkers and those who stopped drinking within the past 10 years they observed a dose-response relationship between amount of alcohol consumed and risk, with the rate of decrease greater in moderate drinkers (200–599 g ethanol/week) and heavy drinker (≥ 600 g ethanol/week) than in light drinkers (<199 g ethanol/week).

16. Ozasa (2007) examined the effect of alcohol consumption on mortality from cancer and circulatory diseases in the Japanese Collaborative Cohort. Hazard ratios (HR) were calculated using Cox proportional hazard models. They observed a risk reduction in oesophageal cancer mortality following cessation (< 5 years, HR = 1.66 0.51–5.36; 5–15 years since quitting HR = 1.22, 95% CI 0.34–4.43; 15 + years since quitting, HR = 0.46 95% CI 0.06–3.64).

17. Vioque et al. 2008 conducted a case-control study to determine the independent effects of different alcoholic beverage types on the risk of all oesophageal cancers and the histological type of squamous cell carcinoma of the oesophagus. They also examined the effect of different tobacco types. A total of 202 cases (160 squamous cell carcinoma) and 455 matched controls were included in the study. Odds ratios (OR), as an estimate of relative risk, and corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression. The data were adjusted for sex, age, hospital, educational level, alcohol intake and tobacco smoking, fruit and vegetable intake and energy intake. When they examined the effect of alcohol cessation in the last five years and total oesophageal cancer risk, they observed a strong excess risk compared with current drinkers (current drinker OR = 1; <5 year since quitting OR = 3.60, 95% CI (1.34 – 9.69)) but the risk decreased thereafter although the risk still remained higher than in current drinkers (≥ 5 year since quitting OR = 1.71, 95% CI (0.86 – 3.41)). A similar pattern was observed when they examined only cases of squamous cell carcinoma (current drinker OR = 1; < 5 year since quitting OR = 5.89, 2.01 – 17.25; ≥ 5 year since quitting OR = 1.70, 95% CI 0.79 – 3.66).

18. Martinez (1969) conducted a case-control community based study of 400 patients with oesophageal, mouth and pharyngeal cancer and 1200 controls to assess the effect of dietary and environmental factors on these cancers in Puerto Rico. The original study did not offer odds ratios. Jarl and Gerdtham (2012) calculated the associated odds ratios following quitting alcohol consumption for more than 10 years ago based on the information given in the study. The study reported an initial increased risk following cessation in women but not men and estimated that 15 years was approximate time until total risk reduction could be achieved following cessation. The calculated ORs from Jarl and Gerdtham (2012) found that 10 years or more since quitting gave an OR = 0.38, 95 % CI (0.17–0.82) compared to current drinkers (OR = 1.0).

19. Takezaki et al. (2000) conducted a hospital-based case-control study in Nagoya, Japan to investigate the sub-site-specific risk factors for oesophageal cancer. A total of 284 male oesophageal cancer cases were included in the study of which 53 were upper oesophageal cancer, 159 were middle oesophageal cancer and 72 cases were lower oesophageal cancer. 11,936 male controls were used as the referent group. ORs were estimated by logistic regression and adjusted for age, year and season of visit, smoking and consumption of raw vegetables. The risk of total oesophageal cancer and for all the subsites (lower, middle and upper oesophageal cancer) remained high when compared to never drinkers. For total oesophageal cancer, they observed an OR for current drinkers of 4.4 (95% CI 2.9 – 6.7), 1–9 years since quitting drinking OR = 5.10 95% CI 2.6 – 10.0 and ≥10 years since quitting drinking OR = 3.5 95% CI 1.4 – 9.1 compared to never drinkers with an OR = 1.0.

Head and Neck Cancers in the UK

20. Oral cancer represents a group of cancers including cancer of the lip, tongue, mouth, oropharynx, piriform sinus, hypopharynx and other ill-defined sites of the lip, oral cavity and pharynx. Cancer Research UK addresses laryngeal cancer separately. In 2010, approximately 2,300 people (1,900 men and 400 women) and approximately 6,500 people (4,300 men and 2,200 women) were diagnosed with laryngeal cancer and oral cancer respectively in the UK. Nearly 75% of all laryngeal cases occurred in people aged 60 years or over and laryngeal cancer was almost five times more common in men than in women. Laryngeal cancer incidence rates in men rose until the early 1990s and have steadily fallen since then. Laryngeal cancer incidence rates in women have been stable over the last 40 years. 40% of oral cancer cases were diagnosed in individuals over the ages of 65. In the past 10 years, incidence rates of oral cancer have risen by a third. In 2011, around 800 people in the UK died from laryngeal cancer with 8 in 10 laryngeal cancer deaths occurring in men. Approximately 2,100 people died of oral cancer in the UK with two-thirds of oral cancer deaths occurring in men. Oral cancer mortality rates have remained stable in the UK since the early 1970s.

21. Parkin et al. (2011) estimated that around 79% of laryngeal cancers in the UK in 2010 were caused by smoking, and 25% were linked to alcohol. The combined effect of smoking and alcohol consumption has been estimated to account for 89% of laryngeal cancers, smoking has a stronger effect than alcohol on risk of laryngeal

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

Effect of alcohol cessation on head and neck cancer risk

Pooled analysis/meta-analysis (Table 3)

22. In a pooled analysis, Rehm et al. (2007) examined the effect of alcohol drinking cessation on head and neck cancer risk. Eight studies were included in the pooled analysis and these were Altieri et al. 2002; Balaram et al., 2002; DeStefani et al., 2004; Castellsague et al., 2004; Franceschi et al., 2000; Garrote et al., 2001 and Hayes et al., 1999 and Martinez, 1969. Pooled estimates were calculated from logarithmised OR, weighted by reciprocals of squared standard errors (SEs). A total of 3075 cases with head and neck cancer and 6061 controls were analysed in the dataset. They observed an elevated risk for head and neck cancers for a time period of 5–10 years following drinking cessation (OR = 1.26, 95% CI: 1.18–1.35). For ex-drinkers, they found that 10 to 16 years was the required minimum cessation time for a statistically significant risk reduction (OR = 0.67, 95% CI: 0.63–0.73), and this risk reduction prevailed for longer periods of quitting (16 + years, OR = 0.72, 95% CI: 0.65–0.78). For never drinkers, the level of risk was lower (OR = 0.46, 95% CI: 0.43–0.48).

23. Using eight case–control studies from the International Head and Neck Cancer Epidemiology (INHANCE) consortium, Marron et al. (2010) estimated the number of years of quitting required to observe a reduced risk of head and neck cancers and determined whether the risk declines to the level of never drinkers. They calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression models for each case–control study. Overall, after ≥ 20 years of cessation, they found a 40% decreased risk of head and neck cancer (OR 0.60; 95% CI 0.40–0.89) compared with current drinkers and this was observed for all sub-sites of head and neck cancers. They observed that for subjects consuming one or more drinks per day, the overall risk of head and neck cancers decreased with time since quitting (OR for quitting drinking were 0.88 (95% CI 0.64–1.23) for 1–4 years, 0.81 (95% CI 0.54–1.22) for quitting drinking 5–9 years, 0.82 (95% CI 0.61–1.10) for quitting drinking 10–19 years, 0.44 (95% CI 0.25–0.77) for quitting drinking ≥ 20 years and 0.55 (95% CI 0.36–0.84) for never drinking compared with current drinking). When Marron et al. (2010) stratified the data based on frequency of consumption, they observed an increased risk among low frequency drinkers who quit drinking 1–4 years ago for pharyngeal and laryngeal cancer. The ORs after quitting drinking ≥ 20 years appeared to decrease with increasing frequency of alcohol drinking for head and neck cancer overall (< 1 drink/day: OR = 1.00, 95% CI 0.72–1.39; 1–2 drinks/day: OR = 0.76, 95% CI 0.52–1.12; ≥ 3 drinks/day: OR = 0.54, 95% CI 0.31–0.94). A similar pattern of results was obtained for oral cavity cancer (< 1 drink/day: OR 0.98, 95% CI 0.54–1.77; 1–2 drinks/day: OR 0.59, 95% CI 0.22–1.57; ≥ 3 drinks/day: OR = 0.43, 95% CI 0.028 – 0.67) and laryngeal cancer (< 1 drink/day: OR = 0.99, 95% CI 0.56 – 1.74; 1–2 drinks/day: OR = 0.78, 95% CI 0.39 – 1.55; ≥ 3 drinks/day: OR = 0.28, 95% CI 0.09 – 0.86). It was noted that the risk of pharyngeal

cancer after quitting drinking ≥ 20 years decreased only slightly with increasing frequency of drinking (<1 drink/day: OR = 1.16, 95% CI 0.65 – 2.05; 1–2 drinks/day: OR = 0.80, 95% CI 0.47 – 1.37; ≥ 3 drinks/day: OR = 0.77, 95% CI 0.45 – 1.30).

24. Ahmad-Kiadaliri et al. (2013) performed a meta-analysis to determine the effect of alcohol cessation on the risk of developing laryngeal and pharyngeal cancers. They also performed a systematic review of thirteen studies (Altieri et al., 2002; Balaram et al., 2002; Castellsague et al., 2004; De Stefani et al., 2004; Franceschi et al., 2000; Garrote et al., 2001; Hayes et al., 1999; Marron et al., 2010; Martinez, 1969; Rehm et al., 2007; Szymanska et al., 2011; Takezaki et al., 1996 and Takezaki et al., 2000). Nine of these were included in the meta-analysis. The generalized least squares (GLS) technique developed by Greenland et al. (1992) was used to model the dose-response relationship between years since drinking cessation and the risk of disease. For laryngeal cancer, overall they found an increased risk over the initial years after quitting drinking but this was followed by a decreasing risk in subsequent years. They found that the risk of developing laryngeal cancer fell by 2% on average per year of cessation and stated that subjects who quit drinking alcohol ten years earlier had 82% of the risk of a current drinker. They reported that the risk of developing laryngeal cancer was 47% (OR 0.53, 95% CI 0.37–0.75) lower for never drinkers than for current drinkers and the time periods required for the risk of laryngeal cancer following cessation to equal that of never drinkers was 36 years (95% CI 11 years –106 years). For pharyngeal cancer, they found that alcohol cessation reduces the risk by 2% per year on average, corresponding to an 18% fall in the risk of pharyngeal cancer after 10 years compared with current drinkers, when controlled for smoking. They reported that the risk of developing pharyngeal cancer was 53% (OR 0.47; 95% CI 0.31 – 0.70) lower for never drinkers than for current drinkers and the time periods required for the risk of laryngeal cancer following cessation to equal that of a never drinkers was 39 years (95% CI 13 years –103 years).

Case-Control studies (Table 4)

25. A case-control study of 527 cases of squamous cell carcinoma and 1297 controls was conducted between 1992 and 2000 in two centres in Northern Italy and Switzerland and investigated the effect of alcohol (and tobacco) on laryngeal cancer risk (Altieri et al., 2002 and Talamini et al. 2002). The two papers discuss the effect of alcohol cessation on laryngeal cancer risk. Altieri et al. (2002) stratified the data into shorter time-periods but both studies compare the data using different referent groups. Altieri et al. (2002) used current drinkers as their referent group and Talamini et al. (2002) used never-drinkers as their referent group. ORs and corresponding 95% CIs were estimated using multiple logistic regression models adjusted for age, sex, area of residence, education and smoking. Talamini et al. (2002) reported no evidence of decreasing risk by years of drinking cessation with an increased risk found both for < 10 years since quitting drinking (OR = 2.3, 95% CI 0.9 – 5.7) and for 10 or more years since quitting drinking (OR = 2.4, 95%CI 1.0 - 6.1) compared with never drinkers (OR = 1.0). They reported an OR = 1.8, 95% CI 1.0 – 3.3 for current drinkers. In their analysis, Altieri et al. (2002) found an inconsistent pattern of risk up to 20 years since quitting similar to that observed by Talamini et al. (2000) (Current drinkers OR = 1.0 (referent); never-drinkers OR = 0.56, 95% CI 0.31 – 0.99); 1 - 5 years since quitting drinking OR = 1.24, 95% CI 0.69 – 2.24 and 6 -19 years since

quitting drinking OR = 1.29, 95% CI 0.68 – 2.47). However, they observed some risk reduction after 20 years after cessation compared to current drinkers (OR = 0.53, 95% CI 0.15 – 1.94).

26. Garrote et al. (2001) examined the risk factors for oral cavity and oro-pharynx cancer using data from a case-control study in Cuba. The study included 200 hospital controls and 200 cases (143 men and 57 women) with 153 of the cases having oral cancer, 19 having oro-pharynx and 28 cases having cancer in both sites. ORs and corresponding 95% CIs were computed using unconditional multiple logistic regression models and adjusted for age, gender, area of residence, educational years and smoking habits. Garrote et al. (2002) observed a steady decline in oral cancer and oro-pharyngeal cancer risk after cessation of drinking. The results indicate that the risk falls from an OR = 1.0 in current drinkers to an OR = 0.74, 95% CI (0.31–1.80) with quitting < 10 years to an OR of 0.28, 95% CI (0.10–0.80) after 10 years or more since quitting.

27. Martinez (1969) conducted a case-control community based study of 400 patients with oesophageal, mouth and pharyngeal cancer and 1200 controls to assess the effect of dietary and environmental factors on these cancers in Puerto Rico. The original study did not offer odds ratios. Marron et al. (2010) provided the associated odds ratios following alcohol cessation for more than 20 years ago based on the information given in the original study. They reported an OR for head and neck cancer risk of 0.75 (95% CI 0.41 – 1.39) after ≥ 20 years since quitting consumption of alcohol of cessation compared to current drinkers (OR =1).

28. De Stefani et al. (2004) conducted a case-control study on risk factors for hypo-pharyngeal and laryngeal cancers in Uruguay. The study included 320 male cases and 640 male controls and was carried out from 1997-2003. ORs and corresponding 95% CIs were estimated using unconditional multiple logistic regression models and adjusted for age, residence, urban/rural status, education, body mass index, and tobacco smoking. For hypo-pharyngeal cancer, they observed an initial increase in risk in men who quit drinking up to nine years earlier (Current drinker OR = 1.0; 1-4 years since quitting OR = 1.35 (0.57-3.22); 5-9 years since quitting OR = 1.30, 95% CI 0.40-4.30) However, there was a significant reduction in hypo-pharyngeal cancer risk after 10 years or more since quitting, OR = 0.43, 95% CI 0.12-1.53 compared to current drinkers, but the risk did not reach that of never drinkers (OR = 0.16 95% CI 0.05-0.49). Similarly, for laryngeal cancer, they observed an initial increase in risk up to nine years after cessation (Current drinker OR = 1.0; 1-4 years since quitting OR = 1.94 (1.06-3.57); 5-9 years since quitting OR = 1.19 (0.48-2.94)), but there was a significant reduction in cancer risk 10 years after quitting, OR = 0.47 95% CI 0.20-1.13. This was comparable with the level of risk associated with never drinkers (OR = 0.64, 95% CI 0.39-1.04).

29. A hospital-based case-control study was conducted by Takezaki et al. (1996) in Aichi, Japan to assess the dietary factors involved in oral cancer (tongue, mouth, oro-pharynx and hypo-pharynx). They also considered the effect of alcohol and its cessation on oral cancer. ORs and corresponding 95% CIs were estimated using unconditional multiple logistic regression models and adjusted for age, sex, year of visit and smoking. 266 cases of oral cancer patients (with overlap of 141 tongue cases, 143 mouth cases, 146 oro-pharynx and 148 cases of hypo-pharynx) and a

large group of 36,527 controls (9,858 men and 26,669 women). They did not find any consistent effect of alcohol cessation on oral cancer risk when they compared the data with years since quitting drinking. They observed an initial increase in oral cancer risk 0 – 4 years since quitting drinking (OR = 2.4, 95% CI 1.1 - 5.1) compared to current drinkers (OR = 1.2, 95% CI 0.9 – 1.6); this was followed by a decrease in risk 5 -14 years since quitting drink (OR = 1.7, 95% CI 0.6 - 4.8) but not quite reduced to current drinkers level of risk. They observed a further increase in risk again after 15 + years since quitting (OR = 3.4, 95% CI 1.2 - 9.9).

30. Hayes et al. (1999) examined the effect of alcohol (and its cessation) and tobacco on oral cancer (encompassing non-salivary gland cancers of the mouth and pharynx) and salivary gland cancer risk in Puerto Rico. ORs and corresponding 95% CIs were estimated using unconditional multiple logistic regression models and adjusted for age. The study included 342 cases of oral cancer (excluding salivary gland cancers) and 521 population-based controls. Compared to recent drinkers (OR = 2.4, 95% CI 1.0 – 5.4), they observed a slight initial increase in oral cancer risk in men who quit two to nine years earlier (OR = 3.6, 95% CI 1.0 – 5.4). This decreased to the level of recent drinkers in men who had quit drinking between 10 -19 years earlier (OR = 2.7, 95% CI 1.0 – 7.0) and further decreased in those who quit twenty or more years earlier (OR = 1.3, 95% CI 0.5 – 3.6) where only a slight excess in oral cancer risk was observed compared to never drinkers (OR =1.0).

31. Castellsague et al. (2004) investigated the independent and joint effects of tobacco smoking and alcohol drinking habits on the risk of developing oral cancer, using data from a multicentre, hospital-based, case-control study in Spain. 375 cases for oral cavity or oropharynx cancers and 375 matched controls were included in the dataset. They observed an initial increase in oral cancer risk 1–2 years after quitting drinking (OR = 3.90, 95% CI 1.68–9.06) compared to current drinkers (OR = 3.52, 95% CI 1.91–6.48), cessation of alcohol significantly reduced oral cancer risk after 3 years of cessation, but only after 14 years of stopping the habit was the risk close to that of never drinkers (3–7 years since quitting alcohol OR =1.74 95% CI 0.77–3.92); 8–13 years since quitting OR = 2.28, 95% CI 0.98–5.32; ≥ 14 years since drinking OR =1.50, 95% CI 0.67–3.34).

32. Balaram et al. (2002) conducted a case-control study in three areas in Southern India to examine the effect of risk factors including alcohol on oral cavity cancer in men and women. ORs and corresponding 95% confidence intervals (CIs) were estimated using unconditional multiple logistic regression models and adjusted for age, centre, education, smoking, drinking and chewing habits. 591 oral cavity cases and 582 controls were included in the study. Compared to current drinkers (OR = 1.0 (referent)), a decreasing trend in oral cancer risk was observed (< 10 years since quitting drinking OR =0.94, 95% CI 0.43 – 2.09; ≥ 10 years since quitting drinking OR = 0.62, 95% CI 0.19 – 2.05).

33. Franceschi et al. (2000) examined data on the effect of alcohol cessation on oral cavity and pharyngeal cancer risk from two case-control studies conducted in Italy and Switzerland. The study included 754 cases of oral cavity and pharyngeal cancer and 1,775 controls. They observed an initial increase in cancer risk which peaked 7-10 years after cessation of alcohol drinking but the risk declined after this time period (Current drinker OR = 1.0; 1–3 years since quitting drinking OR = 1.2, 95% CI 0.61 –

2.38; 4 - 6 years since quitting OR = 0.82, 95% CI 0.96 – 3.46; 7 – 10 years since quitting drinking OR = 3.29 95% CI 1.49 – 7.27; \geq 11 years since quitting drinking OR = 1.91, 95% CI 0.95 – 3.84).

34. Szymanska et al. (2011) investigated the role of alcohol (and tobacco) in the development of four sites of the upper aero-digestive tract (oral cavity, oro-pharynx, hypo-pharynx and larynx) using data from a multicentre hospital-based case-control study across three different countries in Latin America (Brazil, Argentina and Cuba). A total of 2,252 cancer cases and 1,707 controls were included in the dataset. ORs were estimated by unconditional multivariate logistic regression and adjusted for sex, age, centre, education, tobacco pack-years, and fruit and cruciferous vegetable consumption. A reduction in head and neck cancer risk (oral cavity and oro-pharynx combined, $n = 1030$ cases and hypo-pharynx and larynx, $n = 997$) was observed following cessation of alcohol drinking. Compared with current drinkers (OR = 1.0), the OR for ≥ 20 years of alcohol cessation decreased to 0.42 (95% CI 0.26–0.66) for oral cavity and oro-pharynx cancer risk and to 0.55 (95 % CI 0.36–0.83) for hypo-pharynx and larynx cancer risk.

35. Takezaki et al. (2000) conducted a hospital-based case-control study in Nagoya, Japan to investigate the sub-site-specific risk factors for pharyngeal cancer. A total of 62 hypo-pharyngeal male cancer cases and 11,936 male controls were included in the study. ORs were estimated by logistic regression and adjusted for age, year and season of visit, smoking and consumption of raw vegetables. The study found that the risk of pharyngeal cancer was statistically significantly increased in ex-drinkers compared to current drinkers even after 1-9 years and 10 years or more since quitting drinking (current drinkers OR = 4.7, 95% CI 1.9 – 12.0; 1-9 years since quitting OR = 7.8, 95% CI 2.1 – 29.6; ≥ 10 years since quitting OR = 10.0, 95% CI 1.8 – 57.4).

Summary

36. Overall, the data from a number of the individual studies examining the effect of alcohol cessation on the risk of oesophageal and head/neck cancer studies demonstrated a reduction in risk following long-term cessation. However, the results were not consistent across all studies and the magnitude of effect varied between studies. In many studies, an initial increase in cancer risk was observed after cessation, followed by risk reduction after longer time periods since quitting drinking. This was particularly evident for oesophageal cancer and studies conducted in European subjects. Other studies found a decrease in risk immediately after cessation.

37. Nevertheless, the data indicate a substantial time lag is required after drinking cessation until the risk is comparable to that of never-drinkers. The data from the meta-analysis and pooled analysis offer insight into the time period required for the cancer risk to return to that of a never drinker (≥ 20 years for head and neck cancers and ≥ 16.5 years for oesophageal cancers). Substantial risk reductions were achieved after 5 years of alcohol cessation for head/neck cancer risk but no equivalent value was offered for oesophageal cancer.

Questions for the committee

- 1) What are Members general comments on the data provided?
- 2) Do Members feel it is possible to quantify the potential reduction in the risk of developing oesophageal and head/neck cancer after alcohol cessation?
- 3) From the data provided, can Members estimate what time period is required for alcohol related elevated risk of oesophageal or head/neck cancer to return to that of non-drinkers?
- 4) From the data provided, can Members estimate what period of alcohol cessation would be necessary to have a significant impact on public health?
- 5) Literature is also available on the effect of alcohol cessation on other cancer sites namely liver, which IARC consider to be causally related to consumption of alcohol, and stomach, which IARC do not consider to be causally related to consumption of alcohol. Would Members like to review the studies for either or both of these sites at a future meeting?

PHE Toxicology Unit
March 2014

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Table 1. Pooled and meta-analysis studies examining drinking cessation and Oesophageal Cancer Risk							
Reference, location, name of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases/controls, n	Pooled odds ratio and confidence intervals (95% CI) ^a	Adjustment factors	Comments
Rehm et al. (2007)	Pooled Analysis	Exposure assessment varied between studies	Current Drinker Ex Drinker Years since Quitting >0–2 yr p- value 2–5 yr p- value 5–10 yr p- value 10–15 yr p- value 15 + yr p- value Never drinker p- value		1.0 (referent) 2.50 (2.23–2.80) <0.001 1.10 (1.03–1.17) <0.006 0.85 (0.78–0.92) <0.001 0.85 (0.79–0.92) <0.001 0.37 (0.33–0.41) <0.001 0.37 (0.35–0.41) <0.001	Adjusted for smoking	17.5 years was approximate time until total risk reduction They did report an increased risk following cessation
Castellsague et al. (2000) Argentina, Brazil, Paraguay & Uruguay 1986–1992 Oesophageal Squamous-cell carcinoma	4 hospital-based case control studies. 655 male cases and 1408 male controls	Information on participant's lifetime histories of smoking and alcohol consumption were obtained by interview.	Alcohol Drinking Current Drinker Ex Drinker Years since Quitting >1 – 2 years 3 - 5 years 6 - 9 years 10 - 18 years ≥ 19 years Never Drinker Trend OR per cessation year ^c P for trend	365/551 135/247 46/68 31/55 21/32 20/43 17/46 50/400	1.0 (referent) 0.7 (0.5 - 0.9) 0.8 (0.6 - 1.3) 0.7 (0.4 - 1.2) 0.7 (0.3 - 1.2) 0.6 (0.3 - 1.1) 0.4 (0.2 – 0.8) 0.3 (0.1 – 0.7) 0.96 (0.94 – 0.98) 0.001	Adjusted for age group, hospital, years of schooling, average number of cigarettes smoked per day and average amount of pure ethanol consumed per day.	This study contains the same studies as Castellsague et al (1999) above but only presents the data for men. The years since cessation of alcohol are stratified into more groups ^c Trend test performed among subjects ever exposed to that habit. 19 years was approximate time for statistically significant risk reduction They did not report an increased risk following cessation
Jarl and Gerdtham (2012)	Meta-Analysis	Exposure assessment varied between studies	Alcohol Drinking Current Drinker Ex Drinker Years since Quitting Longest time since cessation (combined from all studies)		1.00 (referent) 0.46 (0.34 – 0.63)	Adjusted for smoking	16.5 years until no elevated risk from prior alcohol consumption worldwide and 29.05 years until no elevated risk from prior alcohol consumption if only consider European studies Majority of the data presented graphically and therefore not possible to present many numbers here.

Table 1 continued. Pooled and meta-analysis studies examining drinking cessation and Oesophageal Cancer Risk

Reference, location, name of study	Reference, location, name of study	Reference, location, name of study	Reference, location, name of study	Reference, location, name of study	Reference, location, name of study	Reference, location, name of study
Castellsague et al., 1999	Pooled Analysis		Alcohol Drinking	365/551	1.0 (referent)	Adjusted for age group, hospital, years of schooling and average number of cigarettes smoked per day
Argentina, Brazil, Paraguay & Uruguay	830 Cases		Current Drinker (men)			No estimate of approximate time until total risk reduction achieved
1986–1992	1779 Controls		Ex Drinker			They did not report an increased risk following cessation
Oesophageal Squamous-cell carcinoma			Years since Quitting Men			
			1–4 yr	69/105	0.90 (0.7–1.3)	
			5–9 yr	29/50	0.80 (0.5–1.4)	
			≥10 yr	37/89	0.60 (0.4–0.9)	
			p trend		0.02	
			Current Drinker (women)	40/51	1.0 (referent)	
			Ex Drinker			
			Years since Quitting Women			
			1–4 yr	12/8	1.30 (0.4–4.4)	
			5–9 yr	-	-	
			≥10 yr	8/17	0.6 (0.2–1.8)	
			p trend		0.56	
			Effect of Alcohol consumed in Men			
			Never Drinkers		1.0 (referent)	
			1-24 mls ethanol/day			
			Years since Quitting			
			0 yr		2.42	
			1–4 yr		2.11	
			5–9 yr		1.64	
			≥10 yr		1.04	
			p trend		0.12	
			24-49 mls ethanol/day			
			Years since Quitting			
			0 yr		3.60	
			1–4 yr		3.24	
			5–9 yr		2.77	
			≥10 yr		3.84	
			p trend		0.90	
			50-149 mls ethanol/day			
			Years since Quitting			
			0yr		5.93	
			1–4 yr		4.75	
			5–9 yr		3.10	
			≥10 yr		3.05	
			p trend		0.04	
			150-249 mls ethanol/day			
			Years since Quitting			
			0 yr		10.58	
			1–4 yr		5.33	
			5–9 yr		2.59	
			≥10 yr		3.80	
			p trend		0.02	
			≥249 mls ethanol/day			
			Years since Quitting			
			0 yr		17.32	
			1–4 yr		23.62	
			5–9 yr		16.56	
			≥10 yr		4.63	
			p trend		0.10	

Table 2. Studies examining the effect of alcohol cessation on oesophageal cancer risk

Reference, location, year of study, Cancer type	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases/controls, n	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments
Bosetti et al., 2000 Italy & Switzerland 1992–1999 Oesophageal Squamous-cell carcinoma	404 cases (356 men, 48 women) 1,070 Controls (878 men, 192 women)	Information on lifestyle habits were collected by trained interviewers using a structured questionnaire	<u>Alcohol Drinking</u> Current Drinker Ex Drinker Years since Quitting 1–5 yr 6–14 yr >15 yr Never drinker	347/870 20/25 24/19 5/22 7/133	1.0 (referent) 0.85 (0.41–1.75) 1.72 (0.83–3.57) 0.53 (0.15–1.85) 0.31 (0.14–0.69)	Adjusted for age, sex, study centre, years of education, and amount of alcohol and tobacco consumption.	No estimate of approximate time until total risk reduction achieved, but some risk reduction achieved after 15 years cessation. Study observed an increased risk following cessation
Castelletto et al., 1994 Argentina 1986–1989 Oesophageal Squamous-cell carcinoma	131 cases 261 controls	Information on lifestyle habits by a social worker	<u>Alcohol Drinking</u> Current Drinker Ex Drinker Years since Quitting 2–7 years ≥8 years Never Drinkers	96/157 12/26 11/19 12/59	2.9 (1.4 – 6.0) 2.0 (0.7 – 5.5) 2.5 (0.9 – 7.2) 1.0	Adjusted for age, sex, hospital, education and average number of cigarettes/day	No estimate of approximate time until total risk reduction achieved . They did not report an increased risk following cessation,
De Stefani et al., 1990 Uruguay 1985–1988 Oesophageal Squamous-cell carcinoma	261 cases (199 males and 62 females) and 522 hospital based controls	Information on lifestyle habits were obtained by trained interviewers using a standard questionnaire	<u>Alcohol Drinking</u> Current Drinkers Ex Drinker Years since Quitting 1–9 years ≥10 years Never Drinker <i>p</i> for trend	 	1.0 (referent) 0.78 (0.48–1.26) 0.46 (0.23- 0.92) 0.48 (0.29–0.81) 0.001	Adjusted for age, residence, and amount of cigarettes per day	14 years was approximate time until total risk reduction was achieved They did report an increased risk following cessation.
Martinez, 1969 Puerto Rico 1966 Epidid carcinoma of Oesphagus	Total of 179 oesophageal cancers cases (120 in males and 59 in females)	Information on lifestyle habits were obtained by trained interviewers	<u>Alcohol Drinking</u> Current Drinkers Ex Drinker Years since Quitting ≥ 10 years Never Drinker	 	1.0 (referent) 0.38(0.17–0.83) 0.54 (0.32 – 0.92)		Original paper did not provide odd ratios. Jarl and Gerdtham (2012) calculated ORs and confidence intervals based on the data provided in the original paper. Rehm et al. (2007) also calculated ORs but did not present 95% CIs in their paper 15 years was approximate time until total risk reduction was achieved They did report an increased risk following cessation in female subjects only.
Rolon et al., 1995 Paraguay 1988–1991 Not specified	131 cases 381 controls	Information on lifestyle habits were obtained by trained interviewers	<u>Alcohol Drinking</u> Current Drinker Ex Drinker Years since Quitting 1–5 years 6–14 years 15+ years Never Drinker Years since Quitting 1–5 years 6–14 years 15+ years Never Drinker	80/134 28/25 4/9 3/11 16/202 28/25 4/9 3/11 16/202	12.4 (6.1 – 25.4) ^a 7.7 (3.6 – 16.5) ^b 5.6 (1.3-23.8) ^a 8.9 (2.3-34.8) ^a 23.4 (9.9-54.9) ^a 12.4 (6.1-25.4) ^a 1.0 4.3 (0.9-20.4) ^b 7.0 (1.6-30.7) ^b 13.5 (5.4-33.7) ^b 1.00 (referent)	^a adjusted for design variables age group, sex, and hospital group. ^b adjusted for design variables and lifetime cigarette consumption.	No estimate of approximate time until total risk reduction achieved. They did report an increased risk following cessation
Szymanska et al. 2011 Latin America Squamous cell carcinoma of oesophagus	171 cases 1,707 controls	Information on lifestyle habits were obtained by trained interviewers using structured questionnaire	<u>Alcohol Drinking</u> Current drinker Ex Drinker Years since Quitting 2–4 5–9 10–19 ≥ 20	77/184 28/30 15/37 18/39 9/30	1.00 (referent) 2.15 (1.10–4.21) 0.89 (0.43–1.85) 0.75 (0.36–1.55) 0.46 (0.19–1.16)	Adjusted by sex, age, centre, education, tobacco pack-years, and fruit and cruciferous consumption; alcohol-grams per day	
Vioque <i>et al.</i> 2008 Spain 1995 -1999 Oesophageal Cancer	202 Cases 455 Controls	Information of lifestyle habits were obtained by face to face interview by trained interviewers	<u>Alcohol Drinking</u> Current Drinker Ex Drinker Years since Quitting <5 years ≥5 years	148/235 16/12 22/37	1.0 (referent) 3.60 (1.34–9.69) 1.71 (0.86–3.41)		No estimate of approximate time until total risk reduction achieved They did report an increased risk following cessation
Ozasa, 2007 Japan 1988 to 2003 Squamous-cell carcinoma of the oesophagus	127,477 participants (54,032 men and 73,445 women) registered in the study. Of these, 110,792 subjects (46,465 men and 64,327 women) were eligible for follow-up	Information on alcohol consumption was obtained using a self-administered questionnaire	<u>Alcohol Drinking</u> Ex Drinker Years since Quitting <5 years 5–15 years 15+ years Never drinker	 	1.66 (0.51–5.36) 1.22 (0.34–4.43) 0.46 (0.06–3.64) 0.44	Hazard ratios were adjusted for age and area of study	No estimate of approximate time until total risk reduction achieved They did report an increased risk following cessation

[illegible]

Table 3. Pooled and meta-analysis studies examining drinking cessation and Head and Neck Cancer Risk							
Reference, location, name of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases/controls, n	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments
Ahmad-Kiadaliri et al. 2013 9 studies included were: Altieri et al., 2002; Balaram et al., 2002; Castellsague et al., 2004; De Stefani et al., 2004; Garrote et al., 2001; Marron et al., 2009; Martinez, 1969; Szymanska et al., 2011; Takezaki et al., 1996	9 case- control studies were included in the meta-analysis (4 estimates for laryngeal and 8 estimates for pharyngeal cancers)	Exposure assessment varied across the studies	<u>Laryngeal Cancer</u> Never Drinker Current Drinker <u>Pharyngeal Cancer</u> Never Drinker Current Drinker		1.00 (referent) 0.53 (0.37–0.75) 1.00 (referent) 0.47 (0.31– 0.70)		13 studies were included in the systematic review but only 9 were included in the meta-analysis Excluded from the meta-analysis were 1) Takezaki et al. (2000) as it did not present sufficient data for meta-analysis, 2) Rehm et al. (2007) as it was a meta-analysis including some of the other studies identified for inclusion, 3) Franceschi et al. (2000) and 4) Hayes et al. (1999) to avoid giving too much weight to these two specific samples as they were included in the pooled analysis of Marron et al. (2010). The risk of developing laryngeal cancer and pharyngeal cancer was 47% and 53% lower for never drinkers than for current drinkers, respectively. Alcohol-related elevated risk of laryngeal and pharyngeal cancer would last 36 (95% CI: 11–106) years and 39 (95% CI 13–103) years after drinking cessation, respectively. Majority of data was presented graphically in paper
Marron et al. 2010	8 case control studies used in Pooled Analysis 9167 cases 12593 controls	Exposure assessment varied slightly across the studies but the questionnaire were conceptually similar	<u>Alcohol Status</u> <u>Head and Neck</u> Current drinkers Cessation of alcohol drinking >1–4 years 5–9 years 10–19 years ≥ 20 years Never drinkers p trend <u>Oral Cavity</u> Current drinkers Cessation of alcohol drinking >1–4 years 5–9 years 10–19 years ≥ 20 years Never drinkers p trend <u>Oropharynx/ Hypopharynx</u> Current drinkers Cessation of alcohol drinking >1–4 years 5–9 years 10–19 years ≥ 20 years Never drinkers p trend <u>Larynx</u> Current drinkers Cessation of alcohol drinking >1–4 years 5–9 years 10–19 years ≥ 20 years Never drinkers p trend	4668/5915 564/505 575/576 790/802 591/762 1602/3693 1131/5715 132/504 149/576 174/801 155/763 737/ 3674 1703/5915 213/505 240/576 340/802 221/763 406/3693 1103/4961 141/353 112/358 199/553 157/514 243/	1.00 (Ref) 0.99 (0.69–1.43) 0.90 (0.62–1.30) 0.94 (0.75–1.18) 0.60 (0.40–0.89) 0.74 (0.51–1.06) 0.05 1.00 (Ref.e) 0.81 (0.61–1.07) 0.77 (0.52–1.15) 0.66 (0.47–0.92) 0.45 (0.26–0.78) 0.65 (0.36–1.16) 0.05 1.00(Ref) 1.04 (0.73–1.48) 0.95 (0.61–1.49) 1.15 (0.92–1.43) 0.74 (0.50–1.09) 0.65 (0.42–1.02) 0.18 1.00 (Ref.c,e) 1.16 (0.82–1.63) 0.88 (0.65–1.19) 0.93 (0.64–1.36) 0.69 (0.52–0.91) 0.69 (0.43–1.09) 0.28	Adjusted for age, sex, race/ethnicity, study centre, education level, tobacco pack years and drinking frequency	Results presented in this table are based on overall risk. Data available in study on the effect of cessation stratified by frequency of alcohol consumption.
Rehm et al 2007 Martinez, 1969 Altieri et al. 2002 Balaram et al. 2002 De Stefani et al. 2004 Castellsague et al. 2004 Franceschi et al. 2000 Garrote et al. 2001 Hayes et al.1999	Pooled Analysis 8 studies included 3075 cases 6061 controls	Exposure assessment varied	<u>Alcohol Status</u> Current Drinker Ex Drinker Years since quitting >0–5 yr p-value 5–10 yr p-value 10–16 yr p-value 16+ yr p-value Never drinker p-value		1.0 (referent) 1.12 (1.06–1.19) <0.001 1.26 (1.18–1.35) <0.001 0.67 (0.63–0.73) <0.001 0.72 (0.65–0.78) <0.001 0.46 (0.43–0.48) <0.001	Adjusted for smoking	

Table 4. Case-Control studies examining drinking cessation and Head and Neck Cancer Risk							
Reference, location, name of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases/controls, n	Pooled odds ratio and confidence intervals (95% CI) ^a	Adjustment factors	Comments
Talamini et al., 2002 Italy & Switzerland 1992–2000 Squamous-cell carcinoma of larynx	527 cases 1297 controls	Information was collected on lifestyle habits by ad hoc trained interviewers	Alcohol drinking Status Current drinkers Never drinkers Ex-drinkers Time since cessation (years) < 10 years ≥ 10 years	448/1075 19/135 60/87 35/54 24/33	1.8 (1.0–3.3) 1.0 (referent) 2.8 (1.4–5.5) 2.3 (1.2–4.3) 2.4 (1.0–6.1)	Adjusted for age, sex, study centre, education and smoking habit	Same dataset as Altieri et al 2002, but used never drinkers as their referent group
Altieri et al., 2002 Italy & Switzerland 1992–2000 Squamous-cell carcinoma of larynx	527 cases 1297 controls	Information was collected on lifestyle habits by ad hoc trained interviewers	Alcohol drinking Status Current drinkers Never drinkers Ex-drinkers Time since cessation (years) 1–5 years 6–19 years ≥ 20 years P value for trend test	448/1075 19/135 60/87 30/39 24/33 5/15	1.0 (referent) 0.56 (0.31–0.99) - 1.24 (0.69–2.24) 1.29 (0.68–2.47) 0.53 (0.15–1.94) 0.82	Adjusted for age, sex, study centre, education and smoking habit.	Same dataset as Talamini et al 2002, but used current drinkers as the referent group, also greater stratification of the data on years since quitting
De Stefani et al., 2004 Uruguay 1997–2003 Squamous-cell carcinoma of larynx And hypopharynx	320 male cases 640 male controls	Information was collected on lifestyle habits using social worker interviewers	Alcohol drinking Status <u>Hypo-pharynx</u> Current Drinkers Years since quit drinking 1–4 5–9 10+ Never drinkers <u>Larynx</u> Current Drinkers Years since quit drinking 1–4 5–9 10+ Never drinkers	66/361 8/34 4/19 3/35 4/191 159/361 27/34 9/19 8/35 32/191	1.0 1.35 (0.57–3.22) 1.30 (0.40–4.30) 0.43 (0.12–1.53) 0.16 (0.05–0.49) 1.0 1.94 (1.06–3.57) 1.19 (0.48–2.94) 0.47 (0.20–1.13) 0.64 (0.39–1.04)	Adjusted for age, residence, urban/rural status, education, body mass index, and tobacco smoking	
Szymanska et al. 2011 Larynx Hypo-pharynx Oro-pharynx Oral Cavity	2,252 total cancer cases 997 cases of Larynx and Hypo-pharynx 1,030 cases of oro-pharynx and oral Cavity 1,707 controls	Information on lifestyle habits were obtained by trained interviewers using structured questionnaire	Alcohol Status <u>Oral cavity + oropharynx</u> Current drinkers Ex Drinker Years since quitting 2–4 5–9 10–19 ≥20 <u>Hypopharynx and larynx</u> Current drinkers Ex Drinker Years since quitting 2–4 5–9 10–19 ≥20	669/692 95/96 82/101 70/116 36/80 601/779 72/106 64/108 89/124 48/91	<u>Oral cavity + oropharynx</u> 1.00 (ref) 0.81 (0.57–1.14) 0.63 (0.45–0.90) 0.50 (0.35–0.71) 0.42 (0.26–0.66) <u>Hypopharynx and larynx</u> 1.00 (ref) 0.83 (0.58–1.18) 0.57 (0.40–0.82) 0.74 (0.54–1.04) 0.55 (0.36–0.83)	Adjusted by sex, age, centre, education, tobacco pack-years, and fruit and cruciferous consumption; alcohol-grams per day	
Balaram et al., 2002 India 1996–1999 Oral cavity (not specified)	591 Total Cases (309 male and 282 female cases) 582 Controls (292 males and 290 females)	Information on lifestyle habits were obtained by trained social workers	Alcohol Status Current drinkers Ex Drinker Years since quitting < 10 years ≥ 10 years p value for trend	84/44 49/27 16/7	1.0 (referent) 0.94 (0.43–2.09) 0.62 (0.19–2.05) 0.55	Adjusted for age, center, education, smoking, drinking and chewing habits	

Table 4 continued. Case-control studies examining drinking cessation and Head and Neck Cancer Risk							
Reference, location, name of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases/controls, n	Pooled odds ratio and confidence intervals (95% CI) ^a	Adjustment factors	Comments
Castellsague et al., 2004 Spain 1996 – 1999 Oral cancer including oral cavity and oro-pharyngeal 1996–1999 Oral cavity & oropharynx (not specified)	375 cases 375 controls	Information on lifestyle habits were obtained by trained interviewers using structured questionnaire	Alcohol Status Current drinker Ex Drinker Years since quitting alcohol drinking 1–2 years 3–7 years 8–13 years ≥ 14 years Unknown P value for trend	251/197 28/18 22/30 20/23 19/31 0/1	3.52 (1.91–6.48) 3.90 (1.68–9.06) 1.74 (0.77–3.92) 2.28 (0.98–5.32) 1.50 (0.67–3.34) – 0.003	Adjusted for center, gender, age group, years of schooling and average number of cigarettes smoked per day	
Franceschi et al., 2000 Italy & Switzerland 1992–1997 Oral cavity & pharynx (combined)	754 Total cases 344 cases of oral cavity (274 men and 70 women) 410 cases of pharyngeal cancer (364 men and 46 women) 1775 controls (1254 men and 521 women)		Alcohol drinking Status Current Drinker Ex Drinker Years since quitting alcohol drinking 1–3 years 4 - 6 years 7 – 10 years ≥ 11 years P value for trend	 27/35 37/26 36/15 26/34	 1.0 (referent) 1.21 (0.61 – 2.38) 1.82 (0.96 – 3.46) 3.29 (1.49 – 7.27) 1.91 (0.95 – 3.84) 0.21	Adjusted for age, gender, centre, interviewer, education, smoking habits and drinking status	
Garrote et al., 2001 Cuba 1996–1999 Oral cavity & oropharynx (not specified)	200 total cancer of oral cavity and pharyngeal cancer (143 men and 57 women) Of the 200 cases, 153 were oral cancer, 19 were oro-pharynx and 28 cases had cancers in both sites 200 controls in total (136 men and 64 women)	Information on lifestyle habits were obtained by a dentist during a hospital visit	Alcohol drinking Status Current drinker Ex Drinker Years since quitting alcohol drinking <10 years ≥10 years P for trend test	81/60 21/18 14/16	1.0 (referent) 0.74 (0.31–1.80) 0.28 (0.10–0.80) 0.03	Adjusted for gender, age, area of residence, education and smoking and drinking habits	
Hayes et al. (1999) Puerto Rico 1992 – 1995 Oral cavity Pharynx Salivary gland	342 cases of mouth and pharynx cancers 25 cases of salivary glands cancers 521 controls	Information on lifestyle habits were obtained by trained interviewers using structured questionnaire	Alcohol drinking Status <u>Men</u> Recent use (< 2 years) Ex-drinkers Time since cessation (years) 2-9 years 10-19 years 20 + years <u>Women</u> Recent use (< 2 years) Ex-drinkers Time since cessation (years) 2-9 years 10-19 years 20 + years	163/216 60/47 20/46 34/40 15/22 6/4 4/4 5/4	2.4 (1.0-5.4) 3.6 (1.5-9.0) 2.7 (1.0-7.0) 1.3 (0.5-3.6) 1.2 (0.4-3.4) 1.0 (0.2-5.4) 0.9 (0.2-4.8) 1.1 (0.2-6.4)	Adjusted for age and lifetime tobacco use	
Martinez, 1969 Puerto Rico 1966 Mouth and Pharynx	153 cases of mouth cases (115 males and 38 females), 68 cases of pharyngeal cancer (55 males and 13 females)	Information on lifestyle habits were obtained by trained interviewers using structured questionnaire	Alcohol drinking Status Current drinker Ex Drinker Years since quitting alcohol drinking ≥ 20 years		1.00(referent) 0.75 (0.41 – 1.39)		Original paper did not provide odd ratios. Marron et al. (2010) calculated ORs and confidence intervals based on the data provided in the original paper. ORs for Martinez (1969) also calculated by Rehm et al. (2007) but only OR and not 95% CI presented in paper

Table 4 continued. Case-control studies examining drinking cessation and Head and Neck Cancer Risk						
Reference, location, name of study	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases/controls, n	Pooled odds ratio and confidence intervals (95% CI) ^a	Adjustment factors
Takesaki et al. (1996) Japan 1988 - 1993 Oral Cancers including Tongue Mouth Oro-pharynx Hypo-pharynx	189 male and 77 female cases 9858 male and 26,669 females controls	Information on lifestyle habits were obtained by a self-administered questionnaire	Alcohol Status Current drinkers Ex Drinker Years since quitting 0 – 4 years 5 -14 years 15 + years	138/13811 9/320 4/180 4/62	1.2 (0.9 – 1.6) 2.4 (1.1 - 5.1) 1.7 (0.6 - 4.8) 3.4 (1.2 - 9.9)	Adjusted for age, sex, year of visit and smoking
Takesaki et al. (2000) Hypo-pharynx	62 male cases of hypo-pharyngeal cancer and 11,936 male controls	Self-administered questionnaire was used to obtain information on lifestyle habits and a trained interviewer check all responses	Alcohol Drinking Current Drinker Ex Drinker Years since Quitting 1–9 years ≥10 years Never Drinker		4.7 (1.9 – 12.0) 7.8 (2.1 – 29.6) 10.0 (1.8 – 57.4) 1.0	Adjusted for age, year and season of visit, smoking (never, former, current) and consumption of raw vegetables.