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

Consumption of Alcohol and Liver 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, oesophagus) and the liver are causally related to the consumption of alcoholic beverages. In addition, IARC considered that there is sufficient evidence to conclude that cancer of the colorectum and female breast are causally related to the consumption of alcoholic beverages (IARC, 2007). Following another IARC review in 2009 (IARC 2012), IARC reaffirmed their position on the aforementioned associations.

2. In view of the recent IARC evaluation, Members agreed that an update review of the epidemiological literature on alcohol consumption and all the cancer sites was not necessary at this time. However, Members agreed that a review of the epidemiological literature published since the IARC review in 2009 should be undertaken for those cancer sites where alcohol consumption was causally associated. This review considers epidemiological studies (pooled/meta-analysis, cohort and case-control studies) published since the last IARC review on alcohol consumption and liver cancer risk.

Liver Cancer Statistics for the UK

3. Liver cancer[1] was the 18th most common cancer in the UK (2011), accounting for 1% of all new cases. It is the 14th most common cancer in males (2% of the male total), whilst it is the 19th most common in females (1%). In 2011, there were 4,348 new cases of liver cancer in the UK: 2,776 (64%) in males and 1,572 (36%) in females. The crude incidence rate shows that there are 9 new liver cancer cases for every 100,000 males in the UK, and 5 for every 100,000 females. Liver cancer incidence is strongly related to age, with the highest incidence rates being in older men and women. Liver cancer is the 14th most common cause of cancer death in the UK (2011), accounting for 3% of all deaths from cancer. There were 4,106 deaths from liver cancer in the UK in 2011: 2,440 (59%) in men and 1,666 (41%) in women, giving a male:female ratio of around 15:10.

[1] The data provided in this paragraph pertains to primary liver cancer

Liver Cancer Risk Factors

4. Increasing age and male gender increase liver cancer risk, and modifiable factors, such as smoking, hepatitis infection and heavy alcohol consumption, also play a substantial role in incidence of liver cancer. It has been estimated that around 42% of liver cancers were linked to lifestyle choices in the UK in 2010; this is proportionally higher for men (49%) than women (28%). Parkin (2011) estimated that 4.0 % of all cancers (4.6% in men and 3.3% in women) were attributed to alcohol consumption in the UK in 2010. Alcohol consumption was attributed to 9.1% of all liver cancer cases (Parkin, 2011).

Alcohol consumption and Liver cancer

5. Alcohol consumption is a risk factor for liver cancer. In earlier cohort and case-control studies and those considered in the IARC monographs (vol. 96 (2010), annex A and vol.100e (2012) annex B) on alcohol, IARC reported that liver cancer risk is causally related to the consumption of alcoholic beverages. Literature for the current review was obtained following a PubMed search and the search terms included alcohol, ethanol, drinking, consumption, liver and hepatocellular cancer. Studies published since January 2008 to April 2014 were included in the retrieval to ensure all studies published on this topic since the last IARC review to date were included.

6. Each cohort and case-control study was assessed for quality using a modified scoring scheme similar to the Newcastle-Ottawa star scoring scheme (Annex C). It was adopted to give an informal assessment of the studies and to help identify key papers for future work by the Committee on dose-response. 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 lifestyle factors like smoking, body mass index (BMI), obesity and caffeine were also extracted from the papers.

Meta- and Pooled analyses

7. Three meta-analyses and one pooled analysis have been performed since the last IARC review (Table 1). The first meta-analysis comprised of eighteen case-control studies (Li et al., 2011), the second of 20 studies (Bagnardi et al., 2013), the third of 19 cohort studies (Turati et al., 2014). The pooled analysis comprised of four cohort studies (Shimazu et al., 2011).

8. The pooled analysis of Shimazu et al. (2011) involved four population-based, prospective cohort studies encompassing 174,719 individuals (89,863 men and 84,856 women). The analysis was conducted in men and women separately. In each of the four studies included in the pooled-analysis, alcohol drinking status was exposure assessed using self-administered questionnaires at baseline. The authors noted that although the wording of the questions on alcohol varied among the studies, each study calculated alcohol intake in grams of ethanol/day as a continuous measure for regular drinkers. Intake was divided into categories by using

identical cut-points across studies and the categories were non-drinkers (never- and ex-drinker), occasional drinkers (<once/week) and regular drinkers (≥once/week: 0.1 – 22.9, 23.0 – 45.9, 46.0 – 68.9, 69.0 – 91.9, or ≥ 92.0 g/day for men; 0.1 – 22.9 or ≥ 23.0 g/day for women). Hazard ratio (HR) and 95% confidence intervals (95% CI) were calculated using the Cox proportional hazards regression and were adjusted for age at baseline, geographic area within the study area, smoking status, history of diabetes mellitus and coffee intake. The reference group in the analyses of total alcohol intake and liver cancer was the occasional drinkers group. Shimazu et al. (2010) found a U-shaped association between alcohol intake and primary liver cancer risk. In male drinkers, an increased risk of liver cancer was observed in non-drinkers (multivariate-adjusted HR = 1.70, 95% CI 1.15–2.53) compared to occasional drinkers (HR = 1.00). They also found that alcohol intake was dose-dependently associated with the risk of primary liver cancer, reporting HR of 0.88 (95% CI 0.57–1.36) for 0.1 – 22.9g/day of alcohol, 1.06 (95% CI 0.70–1.62) 23.0 - 45.9 g/day of alcohol, 1.07 (95% CI 0.69–1.66) for 46.0 – 68.9 g/day of alcohol, 1.76 (95% CI 1.08–2.87) for 69.0 – 91.9 g/day of alcohol and 1.66 (95% CI 0.98–2.82) for ≥ 92.0 g/day of alcohol for regular drinkers compared to the reference category of occasional drinkers. Only pooled analysis of three cohorts was included in the analysis for women, because there were no cases of primary liver cancer among occasional drinkers in the fourth study. A non-significant increase in liver cancer risk among non-drinkers was observed compare to occasional drinkers (multivariate-adjusted HR = 1.50, 95% CI 0.69 - 3.25). They did not observe an increased risk in women consuming 0.1 – 22.9 g/day (HR = 0.86, 95% CI 0.26 – 2.88) but drinkers consuming ≥ 23.0 g/day of alcohol had a significantly increased risk of primary liver cancer (HR = 3.60, 95% CI 1.22–10.66) compared to occasional drinkers.

9. 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 liver cancer in the Chinese population. 18 case-control studies were identified that examined the association between alcohol consumption and liver cancer. A total of 3812 cases and 10927 controls were included in their analysis. The authors noted the complexity of the definition of drinker and non-drinker. For the purposes of their meta-analysis, 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. Heterogeneity was evaluated using the Q test or the I^2 statistic. Significant heterogeneity was found ($p \leq 0.10$, $I^2 > 50\%$) between liver cancer and alcohol consumption and therefore the meta-analysis was performed using the random effects model. In their combined analysis of men and women, comparing non-drinkers with drinkers, they reported that alcohol consumption was a significant risk factor for liver cancer with an observed pooled OR of 1.56 (99% CI, 1.16–2.09, p = 0.0001). They also conducted a subgroup analysis for liver cancer after stratifying the participants by sex (male vs. female patients) and they found that alcohol consumption was a statistically significant risk factor for liver cancer in males (OR = 1.56, 99% CI, 1.01–1.62, p =0.001) but not females (OR = 1.93, 99% CI, 0.81–4.57, p = 0.05).

10. Bagnardi et al. (2013) carried out a meta-analysis to investigate the association between light drinking (defined as up to 1 drink/day) and a variety of cancers including liver cancer. They identified 20 studies that examined light drinking and

liver cancer risk (7 cohort and 13 case-control studies). Exposure assessment of alcohol consumption varied between the studies. In order to have a uniform variable of alcohol consumption for the meta- analysis, the authors calculated the amount of alcohol consumed in terms of grams of ethanol for each alcoholic beverage type for those studies, which did not provide intake in grams of ethanol per day. They found that studies usually reported alcohol exposure in intervals and therefore considered light drinking as every interval whose midpoint was ≤12.5 g per day of alcohol (or one drink per day). Where some studies reported two or more adjusted risk estimates for light drinking (e.g. 6 g/day and 12 g/day), they combined them into a single estimate using the method for pooling non-independent estimates described by Hamling et al. (2009). Summary estimates of the RR were calculated using random effects models. Non-drinkers were the reference category group. They did not find a significant association between light drinking and liver cancer (RR = 1.03, 95% CI 0.90–1.17). Stratifying the analyses based on study design, geographical area and sex revealed similar estimates across each strata. For study design they reported RRs of 1.00 (95% CI 0.85 - 1.18) for cohort studies and 1.10 (95% CI 0.86 - 1.41) for case-control studies. For geographical area, they reported RRs of 1.10 (95% CI 0.77 - 1.58) for European studies, 0.92 (95% CI 0.56 - 1.51) for North America studies and 1.02 (95% CI 0.89 - 1.17) for Asian studies. When they stratified the data based on sex, for men they observed a RR of 0.99 (95% CI 0.89 - 1.10) and for women a RR of 1.00 (95% CI 0.64 - 1.57). The authors did suggest that given the association between heavy alcoholic beverage consumption and liver cancer in other studies, the results of their meta-analysis suggest the existence of a threshold dose below which the effect of alcohol on liver cancer risk would be negligible.

11. Turati et al. (2014) carried out a systematic review of both cohort and case-control studies and a meta-analysis of case-control studies investigating the association between alcohol consumption and liver cancer risk. The meta-analysis included 16 publications (19 cohorts): 5 publications from nested case–control studies, 10 from cohort studies and 1 from a pooled analysis of 4 cohorts, for a total of 4445 incident cases and 5550 deaths from liver cancer. For their exposure assessment, grams of ethanol were used as a measure for the analyses, defining one drink as 12.5 g of ethanol. In the analyses on amount of alcohol drinking, they used the midpoint of each category of alcohol consumption for each study. For upper, open-ended exposure categories, a 1.2-fold of its lower bound was used. The lowest category of exposure in each study (non-drinking) was used as the reference category. For their analyses, moderate alcohol drinking was defined as <3 drinks per day (~ < 37.5 g ethanol/day) and heavy drinking as ≥3 drinks per day (~ ≥37.5 g ethanol/day). Summary estimates of the RR were calculated using random effects models and for the dose–response analysis, a random-effect meta-regression model in a non-linear dose–response relationship was used. When they compared moderate drinking (<3 drinks per day) with non-drinking, they observed an overall RR of 0.91 (95% CI 0.1 – 1.02) with similar results obtained when the data was stratified based on study type (cohort studies, RR = 0.91, 95% CI, 0.81–1.03 and for nested case-control studies RR = 0.88, 95% CI, 0.81–1.02). When they compared heavy drinking (≥3 drinks per day) with non-drinking, they observed an overall RR of 1.16 (95% CI 1.01 – 1.34). However when the data was stratified based on study type, they observed a RR of 1.08 (95% CI 0.98 – 1.19) for cohort studies and a RR

of 2.63 (95% CI 1.62 – 4.28) for nested case-control studies. When the authors changed the definition of heavy drinking to ≥6 drinks/day (≥75 g ethanol/day), using the data from 6 studies, the pooled RR was 1.22 (95% CI 1.10 – 1.35). In their dose-response analysis, they observed increasing pooled RR estimates of 1.06 (95% CI, 1.02–1.11) for 12.5 g, 1.13 (95% CI, 1.04–1.24) for 25 g, 1.29 (95% CI, 1.08–1.53) for 50 g, 1.46 (95% CI, 1.13–1.89) for 75 g and 1.66 (95%CI, 1.17–2.34) for 100 g of ethanol per day, respectively. It should be noted that the authors suggested caution in interpreting the results of their study due to possible limitations of the original studies (underestimation of drinking, reverse causation (i.e. inclusion of subjects with liver diseases at baseline), and changes in drinking habits over time).

Cohort studies in the General Population (Table 2)

12. A number of cohort studies have been published since the last IARC review (2012) and these are detailed below and summarized in table 2 attached.

13. Allen et al. (2009) examined the association of demographic and lifestyle factors with liver cancer in a prospective cohort study of 1.3 million middle-aged women in the UK, recruited from 1996 to 2001. Information on each participant's lifestyle such as smoking and drinking habits was obtained by questionnaire. For the exposure assessment, one drink or unit is equivalent to 10 g alcohol. Women drinking ≤ 2 drinks per week (≤ 2.9 g ethanol/day) were the reference category. Relative risks (RR) and 95% CI were estimated using Cox proportional hazard models and adjusted for age, region of residence, socioeconomic status, body mass index, smoking, physical activity, use of oral contraceptives, and hormone replacement therapy. During the follow-up period, there were 337 cases of liver cancer. Examining the data, they found that the risk of liver cancer increased significantly when women consumed >7 drinks per week (> 10g ethanol/day) (RRs = 1.41, 1.00, 0.94, 1.20, 1.70 respectively for non-drinkers, women consuming ≤ 2 drinks/week (≤ 2.9 g ethanol/day), 3 – 6 drinks/week (4.3 - 8.6 g ethanol/day), 7 – 14 drinks/week (10 - 20 g ethanol/day), and ≥ 15 drinks/week (≥ 21 g ethanol/day), respectively). For every additional drink regularly consumed per day, Allen et al. (2009) found that the increase in incidence up to age 75 years per 1000 for women in developed countries was estimated to be about 0.7 cases for liver cancer. They also estimated that, in the United Kingdom, alcohol accounts for 22% (250 annually) of liver cancers.

14. Kim et al. (2010) examined the association between alcohol consumption and all-cause and cancer mortality in a large-scale prospective study among 1.34 million Koreans aged 49 years or more. Medical staff at local hospitals obtained information on alcohol consumption such as frequency of consumption and amount of alcohol consumed per occasion in relation to a traditional Korean alcoholic drink "Soju". Daily alcohol consumption was calculated into five categories for men (non-drinker, 1.0 - 14.9, 15.0 – 29.9, 30.0 - 89.9 and ≥ 90 g ethanol/day) and three categories for women (non-drinker, 1.0 -14.9 and ≥15 g ethanol/day). Non-drinkers were the reference category for the analysis. Relative risks and 95% CI for alcohol consumption were obtained using Cox proportional hazard regression analysis and adjustments were made for age, residence, smoking, exercise, BMI, systolic and diastolic blood pressure, fasting blood sugar, total cholesterol (only women). For

both men and women, they observed a non-statistically significant increased risk of liver cancer mortality with daily heavy alcohol consumption (RR= 1.23, 95% CI 1.01-1.51at ≥90 g ethanol/day for men and RR= 1.80, 95% CI 0.90 - 3.57 at ≥15 g ethanol/day for women) compared to non-drinkers. However, light-moderate drinking was not associated with increased liver cancer mortality. In their analysis of non-smoking men, they observed relatively low risk of liver cancer mortality at less than 90 g ethanol/day, but the risk was raised but not statistically significant with heavy alcohol consumption of ≥ 90 g/ethanol per day (RR = 1.80; 95% CI 0.90- 3.57).

15. Yi et al. (2010) examined the association between alcohol consumption and mortality risk from digestive cancers including liver cancer over a 20-year follow-up period in the Kangwha cohort of 6251 Koreans, aged 55 years or older. Information on alcohol consumption was obtained using a structured interview and study participants were divided into drinkers and non-drinkers. Participants were further divided by the amount of alcohol consumed in order to examine the dose-response relationship among subgroups. The male drinking group consisted of low alcohol consumption (< 138 g/week (< 20g ethanol/day)), moderate alcohol consumption (< 540 g/week (< 77g ethanol/day)), and high alcohol consumption (≥540 g/week (> 77g ethanol/day)), whereas the female drinking group was sub-divided into low alcohol consumption (< 12 g/week (< 2g ethanol/day)) and high alcohol consumption (≥12 g/week (≥ 2g ethanol/day)) subgroups. Relative risks and 95% CI for alcohol consumption were obtained using Cox proportional hazard regression analysis and adjustments were made for age (continuous), history of disease (ever, never), smoking habit (never, past, current smoker), ginseng intake (none, rarely, often, very often), pesticide use (user, non-user), body mass index, and education status (none, elementary school, and high school). Non-drinkers were the reference category. Yi et al. (2010) did not observe an association with alcohol consumption and increased liver cancer mortality in men or women. For example based on very few cases, the observed RR for women were 3.49 (95% CI 0.94-13.0, n=2) for consumption of <12g ethanol per week and a RR = 1.06 (95% CI 0.13-8.47, N = 1) with consumption of >12g ethanol per week compared to non-drinking women.

16. In a pilot study of 2,260 Taiwanese men from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer–Hepatitis B Virus (REVEAL–HBV) Study Cohort, Loomba et al. (2010) examined the synergistic effects of body mass index (BMI) and alcohol consumption on hepatocellular carcinoma (HCC). Information on duration and quantity of alcohol drinking consumed by participants was obtained by interview at local research centres by research assistants. Alcohol drinkers were defined as having alcohol consumption at least 4 days per week for at least one year. Hazard Ratios (HR) and 95% CI were estimated using Cox-proportional hazards analysis to determine the hazards of incident HCC over 14 years of follow-up and estimates were adjusted for age, BMI, alcohol use, serum HBV-DNA level when applicable, smoking, serum alanine aminotransferase (ALT) level, HBeAg status, and cirrhosis at baseline visit. In their multivariate-adjusted analysis alcohol consumption was associated with statistically significant increased risk of HCC compared to non-drinkers (HR =1.54, 95% CI 1.04–2.29 for drinkers). Joint effects of alcohol use and extreme obesity (BMI, ≥30) showed that the risk of HCC was increased synergistically in alcohol users who had extreme obesity compared with those of BMI < 30 and non-drinkers of alcohol with multivariable-adjusted results indicating a HR of 3.40 (95% CI 1.24 – 9.34) for those drinkers with

BMI ≥30 kg/m^2 compared to non-drinkers with BMI <30 kg/m^2. When the results from the multivariate analysis were stratified using the WHO BMI categories for the adult Asian population (normal weight is BMI less than 23 kg/m^2, overweight is BMI of 23 to less than 25 kg/m^2, obese includes BMI of 25 to less than 30 kg/m^2, and extremely obese includes BMI of 30 kg/m^2 or greater), they observed that the risk of HCC was highest in those who drank and were extremely obese (HR = 3.21, 95% CI 1.14 – 9.06) and in those who drank for ≥ 20 years and were extremely obese (HR = 5.17, 95% CI 1.80 – 14.84). Similar results were obtained when the data was stratified into BMI quartiles, with participants in the highest quartile who drank having the highest risk of HCC (HR = 2.40, 95% CI 1.26–0.56).

17. Koh et al (2011) examined the independent effect of smoking on HCC risk, in the absence of any confounding effects of alcohol intake in the Singapore Chinese Health Study, a prospective cohort with a low prevalence of alcohol intake. In doing so, the study also offered some data on the effect of alcohol consumption on HCC in this cohort. The cohort consisted of 63 257 men and women, aged 45–74 years, recruited between 1993 and 1998 from residents of Singapore who resided in government-built housing estates, and belonging to the two major Chinese dialects, 61 321 of which were free of a history of invasive cancer at enrolment. Information on lifestyles choices such as cigarette smoking and alcohol consumption was obtained through in-person interviews conducted at enrolment. Alcohol drinkers were defined as individuals who drank any alcoholic beverage on a monthly basis or more often with one drink defined as 375 ml of beer (13.6 g of ethanol), 118 ml of wine (11.7 g of ethanol), or 30 ml of western or Chinese hard liquor (10.9 g of ethanol). Hazard ratios (HRs) and their corresponding 95% confidence Intervals (CIs), and P-values were calculated using the Cox proportional hazards regression methods and were adjusted for by dialect group, year of recruitment, the level of education, body mass index, history of diabetes and coffee drinking. During the follow-up period of 11.5 years, 394 incident cases of HCC were identified through linkage with the population-based Singapore Cancer Registry. When all adjustment factors were considered, moderate drinkers of up to two drinks daily did not show an association with HCC risk (HR = 1.01, 95% CI 0.48 –2.14) compared to non-drinkers. However, they found that consuming more than two alcoholic drinks per day was associated with a statistically significant increased risk of HCC (HR = 2.24; 95% CI 1.46–3.41) compared to non-drinkers.

18. Yang et al. (2012) investigated the effect of alcohol on overall and cause-specific mortality including liver cancer among 220 000 middle-aged men in China, with over 40 000 deaths during 15 years of follow-up in a prospective cohort study. Information on alcohol consumption was obtained by interview together with information on frequency of consumption, age at which drinking began, the type (beer, wine or spirits) and the amount of each type consumed on a typical drinking week. The total amount consumed was calculated as g of pure alcohol, based on the beverage type and amount drunk. The following alcohol content by volume (v/v): beer 4%, rice wine 15% and spirits 53% was assumed. Hazard ratios (HRs) were calculated using the Cox proportional hazards regression methods and were adjusted for smoking and education. They did not observe an statistically significant increased risk in liver cancer specific mortality with increasing alcohol consumption in this cohort of men, with adjusted HRs of 0.98, 1.13, 1.02, 1.38 and 1.21 for those who drank <140, 140–

279, 280–419, 420–699 and ≥700 g/week (equivalent to <20, 20–39, 40–59, 60–99 and ≥100 g ethanol/day), respectively, compared with non-drinkers.

19. The Korean Multicentre Cancer Cohort (KMCC) collected information from four rural and urban areas and was designed to examine the relationship between lifestyle habits, molecular genetic factors, and the risk of cancers. Using information from the KMCC, Jung et al. (2012) examined the association between alcohol consumption and all-cause and cancer-specific mortality in the Korean population. Information on alcohol consumption was obtained using a structured questionnaire Participants were divided according to their drinking status: never drinkers, past drinkers and current drinkers and their weekly alcohol consumption was categorised into five groups (non-drinkers, ≤90 g/wk, 90.01 - 252 g/wk, 252.01 - 504 g/wk, and >504 g/wk based on the quartile distribution of cases of death among current drinkers equivalent to ≤13, 13.01–36, 36.1–72.0, > 72.0 g ethanol/day). Hazard ratios (HRs) and corresponding 95% CIs were obtained using Cox proportional hazards regression models and adjusted for age, sex, body mass index, smoking habit, geographic area, and educational attainment. Reference category varied depending on analysis. When comparing drinking status, non-drinkers were the reference category. However, when they were analysing the weekly grams of ethanol, the < 90g of ethanol group of drinkers was the reference category. Among current drinkers, they did not observe a statistically significant increased association for liver cancer mortality compared to never drinkers (HR = 1.27; 95% CI 0.75 -2.15). However, for the past drinker group, significantly higher risks for mortality from liver cancer were observed (HR = 3.18; 95% CI 1.50 - 6.71) compared to never drinkers. When they compared hazard ratios for liver cancer specific mortalities according to weekly alcohol consumption, they observed increased risk in liver cancer mortality with increasing alcohol consumption compared to current drinkers of <90g ethanol/week (HR = 1.95 (95% CI 0.77 - 4.97), 1.99 (95% CI 0.72 - 5.18) and 3.50 (95% CI 1.40- 8.78) for 90.01 – 252g, 252.01 – 504g and >504.01 g ethanol/week, respectively).

20. Shih et al. (2012) examined the effect of alcohol consumption on liver cancer risk in a large multicentre cohort of the Taiwanese population. The study consisted of 2273 cases of hepatocellular cancer (1990 with viral hepatitis and 283 without), aged 20- 75 years of age and followed for an average of 10 years. Information on alcohol consumption such as age at initiation, average quantity per day, typical consumption of alcohol beverage type, frequency of consumption was obtained using a standard questionnaire and was collected pre-diagnosis. Daily alcohol intake among participants who reported ≥ 1 drink/week for ≥ 1 year was calculated based on the frequency of consumption, the alcohol content of the beverage and the average quantity consumed. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals(CI) and adjusted for age, sex, known prognosis factors, history of liver cirrhosis, status of hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus (HCV) and habitual smoking or alcohol consumption as appropriate. Never drinkers were the reference category in the analysis. For all patients combined and patients with viral hepatitis, they observed elevated risk of death due to HCC with increasing ethanol intake. For all patients combined, those who consumed 46.2–106.9 g of ethanol per day had a HR of 1.26 (95% CI 1.04 -1.52) and 107 g or more per day had a HR of 1.31 (95% CI 1.09 – 1.58) compared to never drinkers. For patients with viral hepatitis, those who

consumed 46.2–106.9 g of ethanol per day had a HR of 1.35 (95% CI 1.10–1.65) and 107 g or more per day had a HR of 1.36 (95% CI 1.12–1.66). When they calculated cumulative alcohol intake (amount of daily ethanol intake times the duration of consumption), they observed a significant increased risk of HCC-specific mortality for cumulative alcohol intake of ≥1,031 gram years in patients with viral hepatitis (HR = 1.31, 95% CI 1.07 – 1.60). They also observed an increased risk of HCC mortality for cumulative alcohol intake of ≥ 2,744.6 gram years in all patients combined (HR = 1.32, 1.10 – 1.59).

21. Further to the Loomba et al. (2010) pilot study (paragraph 16), Loomba et al. (2013) examined the synergistic effects of body mass index (BMI) and alcohol consumption on hepatocellular carcinoma (HCC) in 23,712 Taiwanese (50.3 % men and 49.7 % women) from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer–Hepatitis B Virus (REVEAL–HBV) Study Cohort. Information on alcohol consumption was as described by Loomba et al. (2010). Hazard Ratios (HR) and 95% CI were estimated using Cox-proportional hazards analysis and estimates were adjusted for age, BMI, alcohol use, serum HBV-DNA level when applicable, smoking, serum alanine aminotransferase (ALT) level, HBsAg status, and cirrhosis at baseline visit. They observed an increase in HCC incidence in those Taiwanese that consumed alcohol (HR = 2.56, 95%CI 1.96 -3.35) compared to non-drinkers. When they analysed the synergism between alcohol consumption and obesity, they found that risk of incident HCC was highest among extremely obese alcohol drinkers (HR=4.2; 95% CI 2.05 -8.28), followed by obese alcohol drinkers (HR= 1.92; 95% CI 1.21 - 3.03) and then overweight alcohol drinkers (HR = 1.91; 95% CI 1.11 - 3.29). The risk of HCC was significantly lower in participants who did not consume alcohol though they observed a HR of 1.25 (95% CI 0.68 - 2.31) in extremely obese non-drinkers. When the cohort were stratified based on the number of years they consumed alcohol, they observed that those who consumed alcohol for the longest period of time (≥20 years) and who were extremely obese were at the greatest risk of HCC (HR= 5.16; 95% CI 2.34 -11.39) when compared to non-drinker normal weight individuals.

22. Schwartz et al. (2013) examined the effect of alcohol consumption and one-carbon metabolite (folate, cysteine, vitamin B6, riboflavin, vitamin B12, and methionine) intake on liver cancer incidence and liver disease mortality in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study conducted in Finland. A total 27,068 persons were included in the cohort and 194 cases of liver cancer were identified from the Finnish Cancer registry. In addition, they examined the effects of alcohol consumption and one-carbon metabolism on liver cancer development in a nested case-control study. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models and estimates were adjusted for study arm, age, education, BMI, diabetes and smoking. In their cohort analysis, they found that increasing alcohol intake was associated with increased risk of liver cancer (p-trend = 0.02) with a significant increased risk in the highest consumption group of > 20.33 grams/day (HR 1.52, 95%CI 1.06–2.18). When they conducted their nested case-control study to examine the effect of alcohol consumption on liver cancer risk, they did not find a significant association between alcohol intake and liver cancer risk (HR = 0.92 (0.40- 2.14) for those consuming 4.15 – 13.80 grams/day of alcohol and a HR of 1.24 (0.54- 2.85)

for those consuming > 13.80g/day of alcohol compared to those consuming <4.15 grams/day.

23. Fan et al. (2013) and a previous study by Liang et al. (2010) estimated the cancer burden which is attributable to alcohol drinking in China. The population attributable fraction (PAF) was calculated using relative risks (RR) obtained from large-scale studies and meta-analysis. Pei et al. (2008) carried out a meta-analysis using data from Chinese studies for alcohol consumption and liver cancer (published in Chinese; unretrieved for this CoC paper) and the derived RR were used by Fan et al. (2013) and Liang et al. (2010). Information on the prevalence of alcohol consumption among the participants was obtained using data from two national surveys representative of the Chinese population. Both papers reported the same data/results. Pei et al. (2008) reported elevated liver cancer risks for both men and women who consumed alcohol compared to non-drinker (RRs = 1.87). Using this information from Pei et al., they report that the proportion of liver cancers attributable to alcohol drinking was 15.7 % overall (23.4 % in men and 2.2 % in women).

24. Persson et al. (2013) investigated the association of alcohol consumption and folate intake, both independently and together on HCC incidence and liver disease mortality in the US NIH-AARP Diet and Health cohort study of 494,743 participants. A total of 435 cases of HCC were identified. Information on alcohol consumption was obtained using a self-administered questionnaire and information such as frequency of consumption per day and types and quantities of various alcoholic beverages were retrieved in the survey. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models and estimates were adjusted for sex, race, education, diabetes, smoking, and body mass index (BMI). Individuals consuming <1drink/day were the reference category. Examining the independent effect of alcohol on HCC risk, they observed a statistically significant increased risk of HCC for individuals consuming more than 3 drinks/day with a HR of 1.92 (95% CI 1.42–2.60) compared to those drinking up to one drink per day. They also observed that non-drinkers were also at higher risk of both developing HCC (HR: 1.71; 95%CI: 1.37–2.14) compared to those drinking up to one drink per day.

Cohort studies in special populations (Table 3)

25. Saieva et al. (2012) evaluated the general and cancer mortality in a cohort of 2,272 subjects (1,467 men and 805 women) with alcohol addiction residing in Tuscany (Central Italy) followed from April 1985 to September 2001. The participants in the cohort were identified by the patient's voluntary self-referral to the alcohol centre for a baseline examination. Following admission, all participants underwent a CAGE test[2], used to make a diagnosis of alcoholism. Obtaining test scores of 2 or 3 indicated a high index of suspicion of alcohol dependency while a test score of 4 indicated alcohol-related problems. All subjects reported a high score in the CAGE test and were diagnosed as alcoholics according to their status of alcohol dependence. Mortality rates were provided by the regional mortality registry, which collects and codes individual death certificates. Standard Mortality Ratios (SMR)

[2] CAGE test is a diagnostic tool used by health workers to assess alcohol abuse

were estimated by dividing the number of observed (O) deaths by the number of those expected (E) for liver cancer and the 95% confidence intervals (CI) were calculated based on the assumption of a Poisson distribution for deaths observed in the follow-up period. They observed a 13 fold increased risk of mortality from liver cancer in the cohort compared to the general population (SMR = 13.5; 95 % CI 9.2 - 19.8) with a significant excess of mortality observed for liver cancer when the analysis was stratified by gender (SMR = 13.9, (95% CI 9.2 - 20.9) and SMR = 11.2 (95% CI 3.6 - 34.6) for males and females, respectively).

Case-control studies in the General Population (Table 4)

29. Three case-control studies were identified in the literature that have been published since the last IARC review was undertaken in 2009 including two nested case-control studies and one hospital based study. These are detailed below and summarized in table 4 attached.

30. Ohishi et al. (2008) conducted a nested case-control study among the Adult Health Study cohort of Hiroshima and Nagasaki in Japan. The study included 224 cases and 644 controls. Information on lifestyle factors including details on alcohol consumption was obtained using self-administered questionnaires. This information was either obtained in 1965 during attendance at the Health Study examination or in 1978 by mail survey. Never drinkers were used as the reference category in the study. In their analysis on the role of alcohol consumption in liver cancer risk, they observed an increased risk in liver cancer with increasing alcohol consumption with RRs of 1.27 (95% CI 0.56 – 2.87), 1.02 (95% CI 0.34 – 3.05), 4.36 (95% CI 1.48 – 13.0) for >0 - <20 g ethanol/d, ≥ 20 - < 40g ethanol/day and ≥ 40g ethanol/day respectively. Using continuous alcohol consumption (per 20g ethanol/day) as a variable, the risk of HCC was significant with a multivariate adjusted RR of 1.73 (95% CI 1.19 – 2.52). They also estimated the population attributable fractions based on the multivariate analysis and the proportion of liver cancer cases that was attributable to ≥ 40g ethanol per day was 17.4% for the present study.

31. Trichopoulos et al. (2011) carried out a nested case-control study using data collected in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, conducted from 1992 -2006. The study consisted of 115 cases of hepatocellular carcinomas and 229 control subjects. Information on alcohol consumption was obtained by self-questionnaire at enrolment for the original EPIC cohort study. Consumption was stratified into none-low, moderate or high consumption (for men, high: ≥40 g/d, moderate: 10 to <40 g/d, low: 0 to <10 g/d; for women, high: ≥20 g/d, moderate: 5 to <20 g/d, low: 0 to <5 g/d; 12 g of ethanol correspond approximately to one glass of alcoholic beverage). Odds ratios (OR) and associated 95% confidence intervals (CI) were estimated using conditional logistic regression models and were adjusted for age, date, time of day at blood collection, study centre, education, BMI, smoking, coffee, chronic HBV infection, chronic HCV infection, and, for women only, menopausal status and exogenous hormones. None - low drinkers were the referent category in the study. They did not observe any increased risk of liver cancer with moderate consumption of alcohol (OR = 0.48 95% CI 0.24 to 0.97 for all subjects). However, high or heavy drinking was associated with an increased risk of liver cancer but the association was not statistically significant (OR = 1.77, 95% CI = 0.73 - 4.27 for all subjects). They also calculated the

population attributable fractions (as percentages) and the proportion of liver cancer cases that was attributable to heavy drinking was 10.2% (95% CI = -8.6% to 22.5%) for the present study.

32. Ha et al. (2012) examined various risk factors including alcohol consumption associated with HCC in a large case–control study of US patients with underlying liver diseases. A total of 1,037 patients were included in the study, 259 cases and 778 controls. Information on alcohol consumption was obtained by self-reporting at interview. Information was obtained on average consumption per day and total number of years of alcohol consumption. ORs and 95% CI were estimated using both univariate and multivariate logistic regression with the multivariate analysis adjusted for age, sex, cirrhosis status, Asian versus non-Asian, alpha-fetoprotein levels, cumulative cigarette use, heavy alcohol consumption, etiology of liver diseases, and diabetes mellitus. They observed similar alcohol consumption frequency (never, occasional, daily drinker) between case and control patients. They also reported similar alcohol use duration, cumulative amount of alcohol consumed between the two groups. In their dose-response analysis, there was no significant dose–response correlation between cumulative alcohol consumption and HCC (Heavy alcohol use >50 g/day OR = 0.8, 95% CI 0.5–1.3). Similar drinking habits of both the cases and controls may be the reason no significant association between alcohol and liver cancer risk was observed, according to the authors.

Overall Summary

33. IARC has previously reported that alcohol consumption is causally associated with liver cancer. However, it was possible to draw some further conclusions from the new studies presented in this update review of the literature published since 2009. Taking the data from the meta- and pooled- analyses considered here, Bagnardi et al. (2013) did not find a significant association between light drinking (<12.5g ethanol/day or 1 drink per day) and liver cancer. Similarly, in the dose response analysis of Turati et al. (2014) consumption of 12 g ethanol/day gave an estimated excess liver cancer risk of 6% (RR = 1.06) compared to an excess risk of 29 %, 46% and 66% at 50, 75 and 100 g ethanol/day. Heavy drinking was associated with increased liver cancer risk.

34. It should be noted that there are some limitations in terms of disease ascertainment and the exposure assessment methods in some of the studies, reflected in their lower star quality rating. When considering the results, the study population is also an important factor. Consideration of the role played by genetic polymorphisms in alcohol metabolising enzymes in different populations and also the role played by confounders such as viral hepatitis and its interaction with alcohol are important.

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 liver cancer risk?
2) Do the studies reviewed here add further weight to the existing view that alcohol consumption is causally associated with liver cancer risk?
3) Several studies suggest U-shaped curves in terms of alcohol consumption and liver cancer risk. What are member's views on this?

4) Do members think there is sufficient data (both from the IARC review and this current paper) to come to a conclusion about the amount of alcohol and nature of drinking i.e. cumulative per week, daily intake, type of alcohol and liver cancer?
5) The Committee intends to calculate the burden of cancer attributable to alcohol consumption in due course. From the data presented here and in the IARC monographs 96 and 100e, can members highlight the relevant studies to take this work forward?
6) Since the last COC meeting, a star scoring scheme has been developed and adopted to assess the quality of the cohort and case-control studies. Do members think this is a helpful addition to the ongoing reviews?

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Table 1.Pooled and meta-analysis studies examining Alcohol Consumption and Liver Cancer Risk, published since 2009

Reference, location, name of study	Description (No. in analysis)	Exposure assessment	Exposure categories	No. of cases/ controls, n	Pooled odds ratio and confidence intervals (95% CI)[a]	Adjustment factors	Comments
Li et al. (2011) China	Meta analysis of 18 case control Chinese studies (3812 cases and 100927 controls)	Varied	**Drinking Status** *Men and Women* Non-drinker Drinker P trend *Men* Non-drinker Drinker P trend *Women* Non-drinker Drinker P trend		 1.00 1.56 (1.16, 2.09) 0.0001 1.00 1.56 (1.01–1.62, 0.001 1.00 1.93 (0.81–4.57) 0.05	*None mentioned*	99% CI used in statistical analysis
Shimazu et al. 2011 Pooled analysis of 4 cohort studies (1) JPHC I (2) JPHC II (3) JACC (4)MIYAGI	Meta-analysis Japan Cases 804 (605 Men and 199 Women)	Varied	***Drinking Status*** ***Men*** Non-drinkers Occasional drinkers (<1/week) Current drinkers, alcohol intake (g/day) 0.1–22.9 23.0–45.9 46.0–68.9 69.0–91.9 ≥92.0 Alcohol intake as a continuous variable (per 10 g/day)[1] Nondrinkers Occasional drinkers (<1/week) Current drinkers, alcohol intake (g/day) 0.1–22.9 23.0–45.9 46.0–68.9 69.0–91.9 ≥92.0 Alcohol intake as a continuous variable (per 10 g/day) ***Women*** Nondrinkers Occasional drinkers (<1/week)	 228 29 82 107 76 54 29 228 29 82 107 76 54 29 175 7	***Age, area adjusted HR*** 1.69 (1.14–2.51) 1.00 (Referent) 0.88 (0.57–1.36) 1.13 (0.75–1.72) 1.16 (0.75–1.80) 1.98 (1.22–3.23) 1.91 (1.13–3.23) 1.03 (1.01–1.05) ***Multivariate adjusted HR*** 1.70 (1.15–2.53) 1.00 (Referent) 0.88 (0.57–1.36) 1.06 (0.70–1.62) 1.07 (0.69–1.66) 1.76 (1.08–2.87) 1.66 (0.98–2.82) 1.02 (1.00 -1.04) ***Age, area-adjusted HR*** 1.50 (0.69–3.25) 1.00 (Referent)	Multivariate adjusted for geographic area (in the JPHC I, JPHC II and JACC), age, history of diabetes mellitus, smoking status, and coffee intake	Reference category was Occasional drinker

Table 1 continued. Pooled and meta-analysis studies examining Alcohol Consumption and Liver Cancer Risk							
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls, n**	**Pooled odds ratio and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
Shimazu et al. 2011 Pooled analysis of 4 cohort studies (1) JPHC I (2) JPHC II (3) JACC (4) MIYAGI	Meta-analysis Japan Cases 804 (605 Men and 199 Women)	Varied	***Drinking status*** Current drinkers, alcohol intake (g/day) 0.1–22.9 >23.0 Alcohol intake as a continuous variable (per10 g/day) ***Women*** Nondrinkers Occasional drinkers (<1/week) Current drinkers, alcohol intake (g/day) 0.1–22.9 >23.0 Alcohol intake as a continuous variable (per 10 g/day)	 8 9 175 7 8 9 	***Multivariate-adjusted HR*** 0.88 (0.25–3.05) 4.09(1.40-11.90) 1.17 (1.01–1.35) 1.50 (0.69–3.25) 1.00 (Referent) 0.86 (0.26–2.88) 3.60(1.22-10.66) 1.11 (0.96–1.29)	Multivariate adjusted for geographic area (in the JPHC I, JPHC II and JACC), age, history of diabetes mellitus, smoking status, and coffee intake	Reference category was Occasional drinker
Bagnardi et al. (2013)	Meta-analysis of 20 studies (7 cohorts and 13 case-controls)	Varied	**Drinking Status** Non-drinker Light-drinker ***Stratified Results*** *Study design* Cohort Case–control *Geographical area* Europe North America Asia *Sex* Men Women	(2034 cases 2592 controls)	 1.0 1.03 (0.90-1.71) 1.00 (0.85- 1.18) 1.10 (0.86- 1.41) 1.10 (0.77- 1.58) 0.92 (0.56- 1.51) 1.02 (0.89- 1.17) 0.99 (0.89- 1.10) 1.00 (0.64- 1.57)	Age, Sex, Liver Disease, BMI or Diabetes	Light alcohol drinking = up to 1 drink/day (up to 12.5 g alcohol/day)
Turati et al. (2014)	4445 incident cases and 5550 deaths from liver cancer	Varied	**Drinking Status** **Moderate drinking (<3 drinks per day)** *Men & Women* Drinker Non-drinker *Men* Drinker Non drinker *Women* Drinker Non-drinker		 0.91(0.81 - 1.02) 1.00 0.90 (0.76–1.07) 1.00 0.89 (0.71–1.12) 1.00		

Table 1 Continued. Pooled and meta-analysis studies examining Alcohol Consumption and Liver Cancer Risk							
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls, n**	**Pooled odds ratio and confidence intervals (95% CI)[a]**	**Adjustment factors**	**Comments**
Turati et al. (2014)	4445 incident cases and 5550 deaths from liver cancer	Varied	**Drinking Status** **Heavy drinking (≥3 drinks per day)** **Combined men and Women** Drinker Non drinker **Men** Drinker Non drinker **Dose-response analysis g ethanol/day** 12 25 50 75 100		 1.16 (1.01–1.34) 1.00 1.14 (0.96–1.34) 1.00 1.06 (1.02–1.11) 1.13 (1.04–1.24) 1.29 (1.08–1.53) 1.46 (1.13–1.89) 1.66 (1.17–2.34)		

Table 2. Cohort studies examining the effect of alcohol consumption on liver cancer risk								
Reference, location, year 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**	**Star Rating for Quality**
Allen et al. 2009 Million Women Study UK 1996/2001 – 2006 (7.2 years)	Cohort consisted of 1 280 296 UK women, aged > 49 years 337 Cases of liver cancer	Self administered questionnaire	**<u>Drinking status</u>** Women Non Drinkers ≤ 2 drinks/w 3 – 6 drinks/w 7 – 14 drinks/w ≥ 15 drinks/w	 114 83 58 59 23	 1.41 (1.16 -0.72) 1.00 (0.80 -1.24) 0.94 (0.72-1.21) 1.20 (0.93-1.55) 1.70 (1.12 -2.56)	Age, region, socioeconomic status, BMI, smoking, physical activity, OC, HRT	RRs and 95% CIs for different categories of alcohol consumption compared with non-drinkers were derived from the 95% floated CIs provided by the authors ≤ 2 drinks/week = ≤ 2.9 g ethanol/day, 3 – 6 drinks/week = 4.3 - 8.6 g ethanol/day), 7 – 14 drinks/week = 10 - 20 g ethanol/day, ≥ 15drinks/week = ≥ 21 g ethanol/day	6 stars
Kim et al. 2010 KNHIC HEC 2000 Korea 2001–2005 (5 years)	Cohort consisted of 1,341,393 Korean men and women aged 40-69 years old 1680 liver cancer cases (1506 men and 174 women)	Interview based	**<u>Drinking status</u>** *<u>Men</u>* *<u>g ethanol/d</u>* Non-drinker 1.0 -14.9 15.0 – 29.9 30.0 - 89.9 ≥ 90 *<u>Non-smoking men</u>* *<u>g ethanol/d</u>* non-drinker 1.0 -14.9 15.0 – 29.9 30.0 - 89.9 ≥ 90 *<u>Women</u>* *<u>g ethanol/d</u>* non-drinker 1.0 -14.9 ≥15		 1.00 0.92 (0.8 –1.05) 0.95 (0.82- 1.11) 1.10 (0.93 -1.30) 1.23(1.01-1.51) 1.00 0.64 (0.49-0.84) 0.91 (0.67-1.22) 1.09 (0.77-1.55) 1.72 (1.15-2.58) 1.00 0.74 (0.44-1.22) 1.80 (0.90- 3.57)	Age, residence, smoking, exercise, BMI, systolic and diastolic blood pressure, fasting blood sugar, total cholesterol (only women); stratified by sex	Subjects with liver diseases at baseline and those who died in the same year of the medical examination were excluded	8 stars
Yi et al. 2010 Kangwha Cohort Study Korea 1985–2005 (20.8 years)	Cohort consisted of 6291 Korean men and women aged 55 years and older 55 liver cancer deaths (36 Men 19 Women)	Information on alcohol consumption was obtained using a structured interview	**<u>Drinking Status</u>** **<u>Men</u>** Non-drinkers Drinkers **<u>Women</u>** Non-drinkers Drinkers **<u>Men</u>** Non-drinker Low Moderate High **<u>Women</u>** Non-drinker Low High	 13 8 8 8 5 2 1	 1.00 0.83 (0.41-1.65) 1.00 2.13 (0.65-6.98) 1.00 0.91 (0.38–2.22) 0.94 (0.38–2.28) 0.79 (0.31–2.01) 1.00 3.49 (0.94-13.0) 1.06 (0.13-8.47)	Age, education, BMI, smoking, history of chronic diseases, ginseng, pesticide use. Stratified by sex	Alcohol consumption **<u>Men</u>** Low = <138g/week Moderate = <540g/week High = ≥540g/week **Women** Low = <12g/week High = ≥12g/week	8 stars

Table 2 continued. Cohort studies examining the effect of alcohol consumption on liver cancer risk

Reference, location, year 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	Star Rating for Quality
Loomba et al. 2010 Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer–Hepatitis B Virus (REVEAL–HBV) Study Cohort 14 years follow up, up to June 2004	Cohort consisted of 2260 Taiwanese men 135 liver cancer cases	Interview at local research centers by well-trained research assistants according to a structured question-aire	**Drinking Status** Non-drinkers Drinker **BMI** *Non-drinker* <30 kg/m^2 ≥30 kg/m^2 *Drinker* <30 kg/m^2 ≥30 kg/m^2 **WHO BMI category[b]** *Non-drinker* Normal weight Overweight Obese Extremely obese *Drinker* Normal weight Overweight Obese Extremely obese **Year of alcohol consumption** ***0 Years*** Normal weight Overweight Obese Extremely obese ***1–19 Years*** Normal weight Overweight Obese Extremely obese ***≥20 Years*** Normal weight Overweight Obese Extremely obese **BMI Quartiles[c]** *Non Drinker* Quartile 1 Quartile 2 Quartile 3 Quartile 4 *Drinker* Quartile 1 Quartile 2 Quartile 3 Quartile 4 **BMI Quartiles Year of alcohol consumption** *0 years* Quartile 1 Quartile 2 Quartile 3 Quartile 4 *1-19 years* Quartile 1 Quartile 2 Quartile 3 Quartile 4 *≥20 Years* Quartile 1 Quartile 2 Quartile 3 Quartile 4		1.00 1.54 (1.04–2.29) Ref 0.64 (0.16–2.63)[a] 1.64 (1.12–2.40)[a] 3.40 (1.24–9.34)[a] Ref 0.78 (0.45–1.35)[a] 1.04 (0.65–1.67)[a] 0.62 (0.15–2.59)[a] 1.17 (0.58–2.34)[a] 2.50 (1.36–4.59)[a] 1.38 (0.74–2.55)[a] 3.21 (1.14–9.06)[a] Ref 0.79 (0.45–1.36)[a] 1.05 (0.65–1.68)[a] 0.62 (0.15–2.55)[a] 0.79 (0.75–4.23)[a] 1.76 (0.62–4.98)[a] 1.63 (0.58–4.58)[a] - 0.74 (0.23–2.41)[a] 2.16 (0.91–5.13)[a] 1.31 (0.62–2.78)[a] 5.17(1.80-14.84)[a] Ref 0.79 (0.45–1.42)[a] 1.17 (0.68–2.02)[a] 0.81 (0.44–1.50)[a] 1.42 (0.58–3.47)[a] 1.78 (0.85–3.71)[a] 1.16 (0.56–2.39)[a] 2.40 (1.26–0.56)[a] Ref 0.79 (0.44–1.42)[a] 1.18 (0.69–2.03)[a] 0.82 (0.44–1.50)[a] 1.94 (0.67–5.62)[a] 1.85 (0.55–6.20)[a] 1.65 (0.57–4.83)[a] 1.23 (0.37–4.10)[a] 1.16 (0.27–4.91)[a] 1.24 (0.43–3.64)[a] 0.78 (0.29–2.10)[a] 3.29 (1.60–6.76)[a]	Adjusted for age, BMI, alcohol use, serum HBV-DNA level when applicable, smoking, serum alanine aminotransferase [ALT] level, HBeAg status [yes/no], and cirrhosis at baseline visit. [a]BMI analysis with alcohol were adjustment for age, serum ALT level, serum HBV–DNA level, and cirrhosis at entry.	[b]WHO BMI categories: normal weight is BMI less than 23 kg/m^2, overweight is BMI of 23 to less than 25 kg/m^2, obese includes BMI of 25 to less than 30 kg/m^2, and extremely obese includes BMI of 30 kg/m^2 or greater. [c]Participants are classified into quartiles of BMI: quartile 1 (lowest BMI: referent group) and quartile 4 (highest BMI category).	8 stars

Table 2 continued. Cohort studies examining the effect of alcohol consumption on liver cancer risk

Reference, location, year 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	Star Rating for Quality
Koh et al. 2011 Singapore Chinese Health Study Singapore 1993/1998–2007 (11.5 years)	Cohort consisted of 63,257 men and women, aged 45–74 years 394 liver cancer cases		**Drinking Status** Non-drinkers Less than daily Daily drinkers ≤ two drinks/day ≥two drinks/day Non-drinkers Less than daily Daily drinkers ≤ two drinks/day ≥two drinks/day	 308 55 31 7 24 308 55 31 7 24	[a] Hazard ratios 1.00 0.76 (0.57 –1.02) 1.58 (1.09 –2.30) 0.87 (0.41-1.84) 2.09 (1.37 –3.19) [b] Hazard ratios 1.00 0.79 (0.59 –1.06) 1.75 (1.20 –2.54) 1.01 (0.48 –2.14) 2.24 (1.46 –3.41)	[a] Hazard ratios were adjusted for gender, age at recruitment year of recruitment dialect group, and the level of education. [b] Hazard ratios were further adjusted for body mass index, diabetes mellitus, and cups of coffee.	1 alcoholic drink was converted in 12.8 g of ethanol per day, based on the definition of one drink reported in the paper	8 stars
Yang et al. 2012 China 45 areas randomly selected (23 urban and 22 rural areas) Follow-up 1990/1991–2006 (15 years)	Cohort consisted of 22000 Chinese men 1115 liver cancer deaths	Interview by trained health workers on lifestyle factors	**Drinking Status** **Men** All-drinkers Non-drinkers **Amount drunk (ethanol g/wk)** <140 140–279 280–419 420–699 ≥700	No. of deaths 412 703 62 108 103 79 60	**HR (95% CI)** 1.12 (0.98–1.28) 1.00 (0.91–1.09) 0.98 (0.76–1.25) 1.13 (0.94–1.37) 1.02 (0.84–1.25) 1.38 (1.11–1.73) 1.21 (0.92–1.09)	Adjusted for Education and smoking		7 stars
Jung et al (2012) Korean Median Follow up 9.3 years	Cohort consisted of 16 320 participants 20 years or older Korean Multi-center Cancer Cohort		**Drinking Status** Non-Drinker Past Drinker Current drinker **Weekly consumption** g ethanol/week Never drinker Current Drinkers < 90 90.01 - 252 252.01 - 504 >504.01	 34 11 40 45 8 10 8 11	 1.0 3.18 (1.50 -6.71) 1.27 (0.75 -2.15) 1.74 (0.80, 3.76) 1.0 1.95 (0.77- 4.97) 1.99 (0.72- 5.18) 3.50 (1.40- 8.78)	Drinking status analysis was adjusted for age, sex, body mass index, smoking habit, geographic area, and educational attainment Weekly grams of ethanol analysis was adjusted for age, sex, body mass index, and smoking habit.		7 stars

Table 2 continued. Cohort studies examining the effect of alcohol consumption on liver cancer risk

Reference, location, year 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	Star Rating for Quality
Shih et al. 2012 Taiwan 1997 –2004 Average 10 years follow up	Cohort consisted of 2,273 participants with hepatocellular cancer (1990 with viral hepatitis and 283 without), Aged 20–75 years 1,488 liver cancer deaths	Standard question-naire on lifestyle factors	**Drinking Status** **All patients (n = 2273)** Never drinkers Ex-drinkers Current drinkers ***Daily intake (g)*** <19.5 19.5–46.1 46.2–106.9 ≥107 ***Cumulative alcohol intake (gram-years)*** <365.5 365.5–1030.9 1031.0–2744.6 >2744.6 **Patients without viral hepatitis (n = 283)** Never drinkers Ex-drinkers Current drinkers ***Daily intake (g)*** <19.5 19.5–46.1 46.2–106.9 ≥107 ***Cumulative alcohol intake (gram-years)*** <365.5 365.5–1030.9 1031.0–2744.6 >2744.6 **Patients with viral hepatitis (n = 1990)** Never drinkers Ex-drinkers Current drinkers ***Daily intake (g)*** <19.5 19.5–46.1 46.2–106.9 ≥107 ***Cumulative alcohol intake (gram-years)*** <365.5 365.5–1030.9 1031.0–2744.6 >2744.6	 1500[a]/934[b] 263[a]/187[b] 508[a]/365[b] 189/135 192 132 187 137 193 139 190[a]/130[b] 191[a]/134[b] 189 /137[b] 190[a]/141[b] 162[a]/68[b] 27[a]/19[b] 94[a]/50[b] 23[a]/15[b] 22[a]/15[b] 39[a]/21[b] 36[a]/17[b] 23[a]/14[b] 22[a]/14[b] 33[a]/17[b] 42[a]/23[b] 1338[a]/866[b] 236[a]/168[b] 414[a]/315[b] 166[a]/120[b] 170[a]/117[b] 148[a]/116[b] 157[a]/122[b] 167[a]/116[b] 169[a]/120[b] 156[a]/120[b] 148[a]/118[b]	 1 (Referent) 1.05 (0.89-1.25) 1.23 (1.08–1.41) 1.03 (0.86–1.25) 1.11 (0.92–1.34) 1.26 (1.04–1.52) 1.31 (1.09–1.58) 1.05 (0.87–1.27) 1.11 (0.92–1.35) 1.20 (0.99–1.46) 1.32 (1.10–1.59) 1 (Referent) 1.44 (0.81–2.57) 1.31 (0.86–2.01) 1.23 (0.68–2.23) 1.98 (1.07–3.66) 1.07 (0.60–1.91) 1.36 (0.74–2.49) 1.51 (0.84–2.74) 1.58 (0.84–2.97) 0.94 (0.51–1.73) 1.37 (0.80–2.36) 1 (Referent) 1.03 (0.87–1.23) 1.26 (1.10–1.45) 1.02 (0.84–1.25) 1.05 (0.86–1.29) 1.35 (1.10–1.65) 1.36 (1.12–1.66) 1.02 (0.83–1.25) 1.08 (0.88–1.32) 1.31 (1.07–1.60) 1.36 (1.11–1.67)	Adjusted for age at recruitment, sex, maximum tumor size, number of lesions, serum a-fetoprotein levels, cigarette smoking, history of liver cirrhosis and status of HBsAg and anti-HCV.	[a] Cases [b]HCC Deaths	7 stars

Table 2 continued. Cohort studies examining the effect of alcohol consumption on liver 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**	**Star Rating for Quality**
Loomba et al. (2013) Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer–Hepatitis B Virus (REVEAL–HBV) Study Cohort Median follow up 11.6 years	Cohort consisted of 23712 Taiwanese men and women 305 liver cancer cases	interview at local research centers by well-trained research assistants according to a structured questionn aire	**All subjects** **Drinking Status** Non-drinkers Drinker **BMI** *Non-drinker* <30 kg/m^2 ≥30 kg/m^2 *Drinker* <30 kg/m^2 ≥30 kg/m^2 **WHO BMI category** *Non-drinker* Normal weight Overweight Obese Extremely obese *Drinker* Normal weight Overweight Obese Extremely obese **Year of alcohol consumption** ***0 Years*** Normal weight Overweight Obese Extremely obese ***1–19 Years*** Normal weight Overweight Obese Extremely obese ***≥20 Years*** Normal weight Overweight Obese Extremely obese		Unadjusted HR 1.00 2.56 (1.96- 3.35) Mutivariate analysis 1.00 (Referent) 1.17 (0.65 -2.11) 1.46 (1.07-1.98) 3.82 (1.94 -7.52) 1.00 (Referent) 1.14 (0.82 -1.60) 1.07 (0.79 -1.46) 1.25 (0.68 -2.31) 1.22 (0.72 -2.07) 1.91 (1.11 -3.29) 1.92 (1.21 -3.03) 4.12 (2.0 - 8.28) 1.00 (referent) 1.14 (0.82 -1.60) 1.07 (0.79 -1.46) 1.26 (0.69 -2.33) 1.74 (0.84 -3.62) 2.15 (0.86 -5.34) 1.62 (0.75 -3.54) 2.50(0.61-10.23) 0.89 (0.4 -1.93) 1.44 (0.66 -3.13) 2.05 (1.19 -3.55) 5.16 (2.3 -11.39)	Adjusted for age, BMI, alcohol use, serum HBV-DNA level when applicable, smoking, serum alanine aminotransf erase (ALT) level, HBeAg status, and cirrhosis at baseline visit.		8 stars
Schwartz et al. (2013) Finland Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study.	Cohort consisted of 27,068 male smokers 194 cases of liver cancer		**Drinking Status** *Alcohol Intake (grams/day)* <5.33 5.33–20.44 >20.44	 53 /8869 64/9055 77/8968	 1.00 (Referent) 1.20 (0.83-1.73) 1.52 (1.06 -2.18)	Adjusted for study arm, age, education, BMI, diabetes and smoking.		5 stars
Fan et al. (2013) China 15 years lag time	Liver cancer deaths in 2005 was 339,308	Data on alcohol extracted from National survey in 1991	**Drinking Status** Men and Women Non-drinker Drinker		 1.00 1.87	None mentioned in paper	CI not given in paper. Data taken from paper in Chinese, unretrieved)	3 stars

Table 2 continued. Cohort studies examining the effect of alcohol consumption on liver cancer risk								
Reference, location, year 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**	**Star Rating for Quality**
Persson et al. 2013 NIH-AARP Diet and Health Study United States Follow up Median = 6.3 years	Cohort consisted of 494,743 participants (Men and Women) 435 cases of HCC	Self-administered questionnaire	**Drinking Status** Alcohol consumption (drinks/day) None <1 1–3 >3	 148 172 52 59	 1.71 (1.37–2.14) 1.00 (Referent) 0.97 (0.71–1.32) 1.92 (1.42–2.60)	Adjusted for age, sex, race, education, smoking, BMI, diabetes	Reference category was changed from drinkers of <1 drink per day to non-drinkers	6 stars

Table 3. Cohort studies in special populations examining the effect of alcohol consumption on liver cancer risk								
Reference, location, name of study	**Description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of cases/ controls, n**	**Standard Mortality Ratios (SMR) and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	Star Quality
Saieva et al. (2012) Italy Median Follow up 9.6 years	2272 participants (alcoholics) 1,467 men 805 women	Alcoholism was diagnosed by physician using the scoring scheme of the CAGE test*	Males Observed Males Expected Female observed Females expected All observed All expected	23 1.66 3 0.27 26 1.93	13.9 (9.2 - 20.9) 11.2 (3.6 - 34.6) 13.5 (9.2 - 19.8)		A Cage test is used to make a diagnosis of alcoholism. Scores of 2 or 3 = high index of suspicion. Score of 4 = alcohol-related problems. All subjects reported a high score at CAGE test and have been diagnosed as alcoholics according to their status of alcohol dependence	4 stars

Table 4. Case-Control studies examining the effect of alcohol consumption on liver cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)[b]**	**Adjustment factors**	**Comments**	**Star Quality**
Ohishi et al 2008 Nested Case-control study based on the Adult Health Study longitudinal cohort from Hiroshima and Nagasaki Japan	**Cases** Total = 224 (136 men and 88 women)	**Controls** Total = 644 (387 men, 257 women)	Self-administered questionnaire on various lifestyle factors	**Drinking status** g ethanol/d Never >0 - <20 (37/130) ≥ 20 - < 40 (20/64) ≥ 40 (45/68) Continuous (per 20 g of ethanol/day)	1.00 1.27 (0.56-2.87) 1.02 (0.34 -3.05) 4.36(1.48-13.0) 1.73 (1.19-2.52)	Adjusted for hepatitis virus infection, continuous alcohol consumption, smoking habit, coffee drinking, BMI diabetes mellitus, and radiation dose to the liver	Nested Case-control study	7 stars
Trichopoulos et al. 2011 Nested case–control study based on the EPIC Cohort Europe 1992–2006 (9 years)	115 Cases (80 Men and 35 Women)	229 Controls (159 Men and 70 Women)	Self-administered questionnaire on lifestyle factors including drinking habits	**Drinking status** Ethanol intake at baseline, g/d None to low Moderate High None to low Moderate High None to low Moderate High	**All Subjects** 1.00 0.48 (0.24 to 0.97) 1.77 (0.73 to 4.27) **Males** 1.00 0.41 (0.17 to 0.98) 1.17 (0.40 to 3.40) **Females** 1.00 0.57 (0.14 to 2.42) 7.10 (0.69 to 73.38)	Adjusted for age, date, time of day at blood collection, study centre, education, BMI, smoking, coffee, chronic HBV infection, chronic HCV infection, and, for women only, menopausal status and exogenous hormones.	None to Low: Men (0 to <10) g/d and Women (0 to <5) g/d; Moderate: Men (10 to <40) g/d and Women (5 to <20) g/d; High: Men, (≥40) g/d and Women (≥20) g/d.	7 stars
Ha et al. 2012 Hospital based case control study US	Cases Total = 259 (211 men, 48 women)	Controls Total = 778 (477 men, 301 women)	Interview based	**Drinking status** Heavy alcohol use (>50 g/day) P value Heavy alcohol use (>50 g/day) P value	**Univariate Analysis** 0.9 (0.6–1.2) 0.90 **Multivariate Analysis** 0.8 (0.5–1.3) 0.38	Multivariate analysis were adjusted for age, sex, cirrhosis status, Asian versus non-Asian, AFP, cigarette use, heavy alcohol consumption, diseases, diabetes		5 stars
Schwartz et al. (2013) Finland Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort	Nested Case-Control 95 men cases	103 controls	Self-administered questionnaire	**Drinking status** Alcohol Intake (grams/d) <4.15 4.15-13.80 >13.80	1.00 (Referent) 0.92 (0.40- 2.14) 1.24 (0.54- 2.85)	Adjusted for study arm, age, education, BMI, diabetes, smoking, HBV and HCV.	**Alcohol intake** <4.15 g/day 26 cases and 34 controls 4.15 -13.80 g/day 24 cases and 35 controls 13.80 g/day 45 cases and 34 controls	5 stars

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Consumption of Alcohol and Liver Cancer Risk – Monograph 100e (pages 386-388)

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Scoring scheme for cohort and case-control studies

Cohort Studies: Alcohol and Cancer - Scoring System to assess study quality			
Cancer Site			
Study Title			
Author			
Study Design			**Star Rating**
1	Representatives of the exposed cohort	a) Truly representative of the average _____(describe) in the community b) Somewhat representative of the average in the community c) Selected group of users eg nurses, volunteers d) No description of the derivation of the cohort	
2	Selection of the non-exposed cohort	a) Drawn from the same community as the exposed cohort b) Drawn from a different source c) No description of the derivation of the non exposes cohort	
3	Ascertainment of exposure	a) Secure record (eg surgical records) b) Structured interview c) Written self-report d) No description	
4	Demonstration that outcome of interest was not present at the start of study	a) Yes b) No	
Comparability			**Star Rating**
1	Comparability of cohorts on the basis of the design or analysis	a) Study controls for _____ (select the most important factor) b) Study controls for any additional factor _____ (this criteria could be modified to indicate specific control for a second important factor)	
Outcome			**Star Rating**
1	Assessment of outcome	a) Independent blind assessment b) Record linkage c) Self-report d) No description	
2	Was follow-up long enough for outcomes to occur	a) Yes (select and adequate follow up period for outcome of interest) b) No	
3	Adequacy of follow up of cohorts	a) Complete follow-up – all subjects accounted for b) Subjects lost to follow up unlikely to introduce bias – small number lost - ___% (select an adequate %) follow up, or description provided of those lost c) Follow up rate __ % (select and adequate %) and no description of those lost d) No statement	
			Total Star Score

continued Cohort Studies - Additional Details of study			
Author			
Susceptibility to biases			
1.	Non-differential measurement error		
2.	Dependent/differential measurement error		
3.	Selection bias (baseline or follow-up		
4.	Inadequate control of confounding		
5.	Biased control selection		
6.	Poor data on modifier		
7.	Other (specify): _____		
Additional common topics			
1.	Implausible temporal relationship		
2.	Dose-response implausible		
3.	Effects only in subgroups		
4.	Errors in analysis or statistical inference		
5.	Crude versus adjusted implausible		
6.	Inadequate statistical power		
7.	Multiple comparisons		
8.	Lack of generalizability		
9.	Other (specify): _____		
Alcohol consumption data		**Yes**	**No**
Did the study contain any information on the following			
1.	Dose –response analysis		
2.	Frequency and duration of alcohol consumption		
3.	Different drinking patterns (light, heavy, binge)		
4.	Alcohol-free days		
Did the study consider beverage type individually (ie beer, wine, spirits)?			
In relation to Alcohol consumption, did the study stratify or consider the interaction with		**Yes**	**No**
Smoking			
Obesity/BMI			
Caffeine			

Case-Control Studies: Alcohol and Cancer - Scoring System to assess study quality

Cancer Site	
Study Title	
Author	

Study Design			**Star Rating**
1	Is the case definition adequate?	a) Yes, with independent validation b) Yes, e.g. record linkage or based on self-reports c) No description	
2	Representativeness of the cases	a) Consecutive or obviously representative series of cases b) Potential for selection biases or not stated c) No description	
3	Selection of controls	a) Community controls b) Hospital controls c) No description	
4	Definition of controls	a) No history of disease (endpoint) b) No description of source	
Comparability			**Star Rating**
1	Comparability of cases and controls on the basis of the design or analysis	a) Study controls for _____ (select the most important factor) b) Study controls for any additional factor - _____(this criteria could be modified to indicate specific control for a second important factor)	
Exposure			**Star Rating**
1	Ascertainment of exposure	a) Secure record b) Structured interview where blind to case/control status c) Interview not blinded to case/control status d) Written self-report or medical record only e) No description	
2	Same method of ascertainment for cases and controls	a) Yes b) No	
3	Non-response rate	a) Same rate for both groups b) Non-respondents described c) Rate difference and no designation	
		Total Star Score	

continued Case –Control Studies - Additional Details of study			
Author			
Susceptibility to biases			
1.	Non-differential measurement error		
2.	Dependent/differential measurement error		
3.	Selection bias (baseline or follow-up)		
4.	Inadequate control of confounding		
5.	Biased control selection		
6.	Poor data on modifier		
7.	Other (specify): _____		
Additional common topics			
1.	Implausible temporal relationship		
2.	Dose-response implausible		
3.	Effects only in subgroups		
4.	Errors in analysis or statistical inference		
5.	Crude versus adjusted implausible		
6.	Inadequate statistical power		
7.	Multiple comparisons		
8.	Lack of generalizability		
9.	Other (specify): _____		
Alcohol consumption data		**Yes**	**No**
Did the study contain any of the following information			
1.	Dose –response analysis		
2.	Frequency and duration of alcohol consumption		
3.	Different drinking patterns (light, heavy, binge)		
4.	Alcohol-free days		
Did the study consider beverage type individually (ie beer, wine, spirits)?			
In relation to Alcohol consumption, did the study stratify or consider the interaction with		**Yes**	**No**
Smoking			
Obesity/BMI			
Caffeine			