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

Cessation of Alcohol consumption and effect on Liver 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. At the COC meeting in March 2014, members reviewed the literature on the effect of cessation of alcohol consumption on the risk of oesophageal cancer and head/neck cancers (CC/2014/04). Overall, the Committee found it difficult to quantify the possible reduction in risk of oesophageal and head and neck cancers following cessation of alcohol consumption. Based on the studies available, the time period required for risks to return to that of non-drinkers appeared to be greater than 20 years for head and neck cancers, and greater than 16.5 years for oesophageal cancers. It was not possible for the Committee to estimate a time period from cessation for which there would be a significant impact on public health. The Committee agreed that it would be helpful also to review the evidence for effect of cessation of alcohol and the risk of liver cancer, on the basis of the availability of the literature and the IARC classification for this site.

For liver cancer, a number of questions could be considered:

A) Is it possible to quantify the potential reduction in risk of developing liver cancer from alcohol cessation?
B) What time period is required for the alcohol related elevated risk of liver cancer to return 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?

Liver cancer in the UK

2. 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

[1.] Cancer statistics data presented here pertains to primary liver cancer

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.

3. 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).

Effect of alcohol cessation on liver cancer risk

4. Studies which have considered the effect of cessation of alcohol consumption on liver cancer risk were reviewed. One meta-analysis, eight cohort studies and four case-control studies were identified for review. Each cohort and case-control study was assessed for quality using a modified scoring scheme similar to the Newcastle-Ottawa star scoring scheme. It was adopted to give an informal assessment of the studies' quality and to help identify key papers for future work by the Committee on dose-response. The meta-analysis was 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. As a point of information, Jarl et al. (2010) found evidence of an effect of alcohol cessation on liver cirrhosis risk and demonstrated that from the point of alcohol cessation there was a lag time of ~20 years for men and ~23 years for women for the increased risk of liver cirrhosis to fall to that of never drinkers.

Meta-analysis (Table 1)

5. In a meta-analysis, Heckley et al. (2011) examined the effect of cessation of alcohol drinking on liver cancer risk. Four studies (2 cohort and 2 case-control studies) were included and these were Goodman et al. 1995, Donato et al. 2002, Franceschi et al. 2006 and Ozasa 2007. Estimates were calculated using a Generalised Least Square (GLS) approach. The issue of publication bias was considered using funnel plots with current drinkers as the reference category. It should be noted that the majority of the results presented in this meta-analysis was graphical or in the text. All studies observed an increased risk of liver cancer among those who recently stopped drinking compared to current drinkers. However, there was a clear decrease in liver cancer risk with longer periods of abstention, with the exception of the findings for women by Ozasa et al. (2007) which the authors note was based on a small number of cases. The findings from the meta-analysis suggest that for each year of cessation the risk of liver cancer declines by 6-7%, indicating exponential decay. They also estimated that it would take about 23 years (95% confidence interval (CI) 14 – 70 years) for the risk of liver cancer for former drinkers to fall to that of never drinkers. It is also noteworthy that the authors indicate that the results of this meta-analysis are preliminary and should be interpreted with caution due to limitations of the studies used and the statistical uncertainty.

Cohort Studies (Table 2)

6. In a 19-year follow up cohort study of 5135 Japanese male physicians, Kono et al. (1985) examined the relationship between drinking habit surveyed in 1965 and case specific mortality, focusing on cancer and cardiovascular disease. Individuals were divided into categories based on their drinking habits: ex-drinker, non-drinker, occasional drinker and daily drinker whose intake of alcohol was equivalent to < 2 or ≥ 2 go of sake (1 go of sake contains 27 ml of alcohol, ~ 20 g ethanol/day). It should be noted that the drinking status of the participants could have changed by the end of follow-up but this information was not provided in the paper. Relative risks were calculated using logistic regression analysis based on the Cox proportional hazard model adjusted for age and smoking habit and for assessing the relation with daily amount of consumption. Non-drinkers were the referent group. The study observed a non-statistically significant increased risk of liver cancer among ex-drinkers (RR= 1.4 95% CI 0.4 – 4.8) compared to non-drinkers (RR= 1.0). They did observe a statistically significant increased risk among drinkers of ≥ 2 go of sake (RR = 2.7, 95% CI 1.0 – 6.8) and a non-statistically significant increased risk among occasional drinkers (RR = 1.5 , 95% CI 0.6 – 3. 8) compared to non-drinkers.

7. Kato et al. (1992) obtained drinking and smoking habit information in a study of 1,068 Japanese patients with decompensated liver cirrhosis[2] to determine the effect of these lifestyle factors on liver cancer risk. Incidence cases of liver cancer obtained among these subjects were identified by using a cancer registry with follow up lasting 3 years. Sex- and age-adjusted relative risks (RR) and 95% confidence intervals (CI) of developing liver cancer were estimated according to several patients' characteristics, based on the Cox proportional hazards regression model. In these patients, they observed a significant inverse association between alcohol consumption and subsequent liver cancer risk, irrespective of whether the patient was a current drinker (RR = 0.41, 95% CI 0.16-1.06), occasional (RR = 0.43, 95% CI 0.15-1.24) or past drinker (RR = 0.58, 95% CI 0.32-1.04) compared to a never drinker (RR = 1.00).

8. Tsukuma et al. (1993) examined risk factors for hepatocellular carcinoma in a cohort study of outpatients with chronic hepatitis or compensated liver cirrhosis at a hospital in Osaka, Japan. A total of 917 patients (548 males and 369 females), aged between 40-69 years were included in the study. Hazard rate ratios were estimated using Cox proportional regression analyses and adjusted for age, sex, stage of disease, serum alpha-fetoprotein levels, hepatitis virus markers and smoking habits. Non-drinkers were the referent group. They observed a non-statistically significant increased risk of liver cancer among ex-drinkers who consumed ≥ 80g of ethanol per day (RR= 1.66, 95% CI 0.69 – 3.96) and for ex-drinkers who consumed < 80g of ethanol per day they observed a RR of 1.46, 95% CI 0.56 – 3.79 compared to non-drinkers (RR= 1.0).

[2] Cirrhosis is divided into two stages (compensated and decompensated). Compensated cirrhosis means that the body still functions fairly well despite scarring of the liver. Decompensated cirrhosis means that the severe scarring of the liver has damaged and disrupted essential body functions. (http://umm.edu/health/medical/reports/articles/cirrhosis#ixzz35Tw3ypOx)

9. In a cohort of 36,133 residents in Hiroshima and Nagasaki, Japan, Goodman et al. (1995) examined the role played by risk factors in primary liver cancer. A self-administered survey obtained information on lifestyle including details on alcohol consumption past and present. It should be noted that men and women were surveyed differently and information on past habits were not obtained for women. The follow-up period of the study was 8.6 years and 242 cases of primary liver cancer were identified through population-based tumour registries in the two cities. The statistical analysis was performed using Poisson regression in separate and joint analyses for men and women. Relative risks (RRs) were computed after stratification on city of residence at the time of the bombing, age at the time of the bombing, attained age, liver dose of radiation, and sex. Never-drinkers were the reference category for all analyses of alcohol. They observed a greater increase risk of liver cancer among men who had quit drinking alcohol (RR = 2.33, 95% CI 1.34 – 4.07) than among current drinkers (RR = 1.11, 95% CI 0.72 – 1.70). When they examined the effect of years of cessation on liver cancer risk, they found that there was a stronger association of alcohol use with the risk of liver cancer among men who had been ex-drinkers for less than 10 years (RR = 7.87, 95% CI 3.89 – 16.0) compared with men who had been ex-drinkers for 11 -15 years (RR = 2.08, 95% CI 0.93-4.67) or more than 16 years at the time of the survey (RR = 0.96, 95% CI 0.33 – 2.77).

10. Ogimoto et al. (2004) investigated the risk of death due to liver cancer in drinkers and ex-drinkers in 66,974 eligible subjects in the Japanese Collaborative Cohort (JACC) study. They carried out a univariate analysis of data from the cohort on the effects of drinking and smoking. Information on alcohol drinking history was obtained through interview or self-administered questionnaires. Data was obtained on 1) drinking habits, 2) drinking frequency, 3) age at start of consumption, type of alcohol consumed, any changes in amount of alcohol consumed, average amount of alcohol consumed by current drinkers and 4) age of cessation of drinking and years since cessation of drinkers among ex-drinkers. Confounders included in the analysis were age, sex, past history of liver disease and collaborating institutes. Hazard ratios were obtained using Cox proportional hazard models. Never drinkers were the referent group. Among the 66,974 total subjects, those who were ex-drinkers showed elevated HRs compared to those who had never drank alcohol at the baseline, and the ratios were statistically significant except in females aged 40 – 59 years. They observed HRs of 8.11(95% CI 3.17 – 20.77) and 3.48 (95% CI 1.86 – 6.54) for ex drinking males aged 40-59 years and ex-drinking males aged 60-79 years, respectively and HRs of 0.65 (95% CI 0.27 – 1.52) and 0.75 (95% CI 0.43 – 1.31) for current drinking males aged 40-59 years and current drinking males aged 60-79 years, respectively compared to never drinkers (HR = 1.00). They observed HRs of 3.85 (95% CI 0.48 – 30.93) and 4.18 (95% CI 1.47 – 11.88) for ex drinking females aged 40-59 years and ex-drinking females aged 60-79 years, respectively, and HRs of 0.23 (95% CI 0.03 – 1.80) and 0.59 (95% CI 0.25 – 1.43) for current drinking females aged 40-59 years and current drinking females aged 60-79 years, respectively compared to never drinkers (HR = 1.00). When they examined the effect of years since cessation of drinking on hazard ratio of death from liver cancer, they observed HRs of 12.99 (95% CI 4.46 – 37.86) and 17.06 (95% CI 4.95 – 58.82) in ex-drinker males aged 40-59 years after 0-5 years and 6 - 10 years of cessation compared to never drinkers (HR = 1.00). When they examined the effect of cessation in male ex drinkers aged 60- 79 years, they observed HRs of 1.32 (95% CI 0.39 –

4.52), 4.90 (95% CI 2.02 – 11.87), 5.73 (95% CI 1.92 – 17.13) and 2.99 (95% CI 1.00 – 8.92) after 0-5 years, 6 - 10 years, 11 – 15 years and > 16 years of cessation compared to never drinkers (HR = 1.00). In females aged 40 – 59 years, data was only available for those who had given up drinking 6 -10 years ago and the observed HR was 26.36 (95% CI 3.18 – 218.82). HRs were not calculated for the other years due to the small numbers in those datasets. When they examined the effect of cessation in female ex drinkers aged 60- 79 years, they observed HRs of 3.79 (95% CI 0.51 – 27.86), 6.57 (95% CI 0.89 – 48.55), 7.87 (95% CI 1.06 – 58.58) and 5.59 (95% CI 0.76 – 40.97) after 0-5 years, 6 - 10 years, 11 – 15 years and > 16 years of cessation compared to never drinkers (HR = 1.00). The authors noted that this study did not consider the effect of confounders such as smoking or virus infection and further analysis was needed to take account of these.

11. Nakaya et al. (2005) investigated the association between alcohol consumption and the risk of total cancer in a cohort of 21,201 Japanese men. The study included individual data for liver cancer risk among ex-drinkers. Information on alcohol consumption such as drinking status (never, former, or current drinker), was obtained using a self-administered questionnaire. Cox proportional-hazards regression was used to estimate relative risk of liver cancer and data were adjusted for age (in years); cigarette smoking (never smoked, smoked in the past, currently smoking 1–19 cigarettes per day, or currently smoking 20–29, or 30 or more cigarettes per day); education (in school until age 15 years or younger, 16–18, or 19 years or older); daily consumption of orange and other fruit juice, spinach, carrot or pumpkin, and tomato (less than 1 day per week, 1 or 2 days per week, 3 or 4 days per week, or daily). Never drinkers were the reference category in their analysis. A total of 48 cases of liver cancer was diagnosed during follow-up. They observed an increased risk of liver cancer in ex-drinkers (RR = 6.6; 95% CI 1.8–24.2) compared to current drinkers (2.7; 95% CI 0.8– 8.9) and the reference category never drinkers (RR =1.00).

12. Ozasa (2007) investigated the effect of alcohol consumption on mortality in the large Japanese Collaborative Cohort (JACC) study. This study is a follow up study to Ogimoto et al. (2004) described in paragraph 10. This study consisted of over 125,000 participants from 45 different areas in Japan. Information on alcohol consumption and other lifestyle choices were obtained by self-administered questionnaires. Hazard ratios (HR) and 95% CI were calculated using Cox proportional hazard models and adjusted for age, sex and area of residence. Never or rare drinkers were used as the referent group. They observed statistically significant increased risk of death from liver cancer in both male and female ex-drinkers (HR = 3.16, 95% CI 2.32 – 4.31 for males and HZ = 2.89, 95% CI 1.51 – 5.53 for females). They also observed a persistent increased risk of death from liver cancer following cessation (< 5 years, HR = 3.79, 95% CI 2.24 – 6.42 for men and HR = 1.58, 95% CI 0.22 – 11.4 for females; 5-15 years since quitting HR = 4.56, 95% CI 2.83 – 7.33 for males and HR = 7.53, 95% CI 3.04 – 18.7 for females; 15 + years since quitting, HR = 2.43, 95% CI 1.23 – 4.79 for males and HR = 1.92, 95% CI 0.26 – 13.8 for females).

13. In a large multicentre cohort, Shih et al. (2012) examined the effects of cessation of alcohol consumption on liver cancer risk in a 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 frequency of consumption and years since cessation 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) status and habitual smoking or alcohol consumption as appropriate. In a multivariable regression model, ex-drinkers who quit drinking ≥10 years before the hospital admission compared to continuing drinkers showed a decreased risk of death from HCC (HR = 0.74, 95% CI 0.56–0.98).

Case-Control Studies (Table 3)

14. Tanaka et al. (1992) carried out a case-control study examining the role played by hepatitis B virus (HBV), cigarette smoking and alcohol consumption in hepatocellular cancer (HCC) risk in Japan. A total of 204 Japanese patients with HCC were included as eligible cases and the controls were hospital-based comprising of 410 persons (aged 40-69 years). Information on alcohol consumption was obtained by interview and drinkers were defined as those who had drunk at least 1 or more units of alcoholic beverages per day, once a week or more, for at least 1 year. Among the drinkers, those who had stopped drinking 1 or more years prior to the interview were considered ex-drinkers. RRs and their 95% CIs were estimated by modelling the data through unconditional logistic regression and were controlled for possible confounding factors such as sex and age. 50 out of the 68 ex-drinkers among the cases reported that they had given up alcohol due to their pre-existing liver disease. In light of this information, the authors combined current and ex-drinkers together and calculated a combined RR compared to non-drinkers. RR for those who had ever drunk was not significantly elevated (sex- and age-adjusted RR = 1.3, 95% CI 0.9 - 2.0) compared to non-drinkers.

15. Donato et al. (2002) investigated the relationship between alcohol habits and HCC in both men and women in a hospital-based case-control study in the Brescia province of Italy. The study involved 464 cases and 824 controls. All cases and controls were interviewed about their history of alcohol drinking habits. Odd ratios and their 95% CI were computed as estimates of the relative risks with unconditional logistic regression analysis by the maximum likelihood method. Sex, age, area of residence, and HBsAg and HCV RNA were included in regression models as possible confounders. In their analysis when never drinkers were used as the referent group they observed an increased OR for former male drinkers of 8.5 (95% CI 3.3 -22.3) and an increased OR of 2.8 (95% CI 1.0 – 7.9) for former female drinkers compared to ORs of 2.7 (95% CI 1.1 – 6.8) and 0.9 (95% CI 0.3 – 2.3) for current male and female drinkers, respectively. In additional analysis, using current drinkers as the referent group, they reported that an increased liver cancer risk was observed in those who had recently quit drinking; 0 - 5 years since quitting OR= 5.0, 95% CI 2.9 – 8.6 and 6–10 years since quitting OR= 4.0, 95% CI 2.2 – 7.4. After this time, liver cancer risk decreased with longer periods of abstention but the OR did not reach 1.0; 11 - 15 years since quitting OR = 1.6, 95% CI 0.6 – 4.5 and > 15 years

since quitting OR = 1.4, 95% CI 0.6 – 3.1. For women, they did not observe a clear pattern of risk for time since stopping because of the small number of quitters.

16. Sakamoto et al. (2006) carried out a hospital based case-control study to examine the modifying effects of alcohol consumption and polymorphisms on liver cancer risk in the city of Saga, Japan. Due to the prevalence of hepatocellular cancer patients with chronic liver disease (CLD), two different controls were recruited for the study, 1) hospital controls and 2) patients with CLD without hepatocellular cancer. The study included 226 liver cancer cases, 275 hospital based controls and 381 CLD patients without HCC controls. Information on lifestyle choices including details on alcohol consumption were obtained by interview. Never drinkers were defined as those who had never drunk or had drunk less than once per week and/or for less than 1 year and past drinkers were defined as those who quit alcohol use 1 or more years prior to the interview. Never drinkers were the referent group in the analysis. Unconditional logistic regression models were used to estimate the ORs of HCC and their 95% CIs for alcohol consumption adjusted for potential confounders including sex, age, smoking habit, and HBsAg and anti-HCV status. They found that ex-drinkers had an increased OR for HCC cases (OR = 5.3, 95% CI 1.6 – 18.6) compared with hospital controls, but not statistically significantly increased when compared to CLD patient controls (OR = 1.3, 95% CI 0.7 – 2.2). They observed slightly elevated ORs for current drinkers with HCC regardless of control (OR = 2.9, 95% CI 1.2 - 7.4 compared to hospital based controls and OR = 1.8, 95% CI 1.0 – 3.0 compared to CLD patient controls).

17. Franceschi et al. (2006) carried out a hospital-based case-control study in two areas of Italy (the province of Pordenone and the town of Naples in the South) to investigate the effect of a number of factors including alcohol consumption on liver cancer risk. The study included 229 cases of liver cancer and 431 controls. The questionnaire obtained information on drinking status (never, former, or current drinker), weekly number of drinks of the five most common alcoholic beverages or groups of beverages, age at starting and duration of the habit. Never drinkers were individuals who had abstained from alcohol drinking throughout life. Former drinkers were individuals who had abstained from alcohol drinking for at least 12 months. Odds ratios (OR), % attributable risks, and corresponding 95% CI were computed using unconditional multiple logistic regression and adjusted for age, gender, study centre, years of education and, when mentioned, HBsAg and anti-HCV positivity. Drinking cessation was reported by 51.5% of liver cancer cases but only 11.1% of controls. They found an association with drinking cessation and increased liver cancer risk (OR = 3.98; 95% CI, 1.74 - 9.09) for former drinkers compared to an OR of 0.84 (95% CI 0.39-1.83) for current drinkers. When they examined the effect of years since cessation of drinking on the odds ratio for liver cancer, they observed ORs of 6.34 (95% CI 1.92 – 21.04) and 2.56 (95% CI 0.96 – 6.82) in former drinkers < 5 years and ≥ 5 years of cessation compared to never drinkers (OR = 1.00).

Summary

18. Overall, the data from a number of the individual studies examining the effect of alcohol cessation on the risk of liver cancer studies demonstrated a reduction in risk but only after long-term cessation. However, the results were not consistent across all studies and the magnitude of effect varied between studies. In some studies, an

initial increase in cancer risk was observed after cessation, followed by risk reduction after longer time periods since quitting drinking. 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 offered insight into the time period required for the liver cancer risk to return to that of a never drinker (≥ 20 years).

19. We did not find any UK study that examined the effect of alcohol cessation and liver cancer risk. The majority of the studies identified for this review were of Asian origin and only two studies (Donato et al. (2002) and Franceschi et al. (2006)) were of European origin. These two studies were included in the meta-analysis of Heckley et al. (2011) as the case-control studies. It should be noted that there are limitations in terms of disease ascertainment, exposure assessment methods and failure to consider confounding factors such as hepatitis in some of the studies. It should also be borne in mind that the reason for quitting alcohol drinking was not explored in the majority of studies. Ex-drinkers may be suffering from liver disease or another condition that may result in bias in the cessation group.

Questions for the committee

1) What are members general comments on the data provided?
2) Do members consider it is possible to quantify the potential reduction in the risk of developing liver cancer after alcohol cessation?
3) From the data provided, can members estimate what time period is required for alcohol related elevated risk of liver 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?

References

Cancer Research UK (2012). http://www.cancerresearchuk.org/cancer-info/cancerstats/

Cancer Research UK. Lifetime risk was calculated by the Statistical Information Team at Cancer Research UK, 2012.

Donato F, Tagger A, Gelatti U, Parrinello G, Boffetta P, Albertini A, Decarli A, Trevisi P, Ribero ML, Martelli C et al: Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 2002, 155(4):323-331.

Franceschi S, Montella M, Polesel J, La Vecchia C, Crispo A, Dal Maso L, Casarin P, Izz F, TommaSi LG, Chemin I et al: Hepatitis viruses, alcohol, and tobacco in the etiology of hepatocellular carcinoma in Italy. Cancer Epidemiology Biomarkers & Prevention 2006, 15(4):683-689.

Goodman MT, Moriwaki H, Vaeth M, Akiba S, Hayabuchi H, Mabuchi K: Prospective cohort study of risk factors for primary liver cancer in Hiroshima and Nagasaki, Japan. Epidemiology 1995, 6(1):36-41.

Heckley GA, Jarl J, Asamoah BO, G-Gerdtham U. How the risk of liver cancer changes after alcohol cessation: a review and meta-analysis of the current literature. BMC Cancer. 2011 13;11:446.

Jarl J, Gerdtham UG, Ludbrook A, Petrie D. On measurement of avoidable and unavoidable cost of alcohol: an application of method for estimating costs due to prior consumption. Int J Environ Res Public Health. 2010;7(7):2881-95

Kato I, Tominaga S, Ikari A: The risk and predictive factors for developing liver cancer among patients with decompensated liver cirrhosis. Jpn J Clin Oncol 1992, 22(4):278-285.

Kono S, Ikeda M, Tokudome S, Yoshimura T, Nishizumi M, Kuratsune M: Alcohol and cancer in male Japanese physicians. J Cancer Res Clin Oncol 1985, 109(1):82-85.

Nakaya N, Tsubono Y, Kuriyama S, Hozawa A, Shimazu T, Kurashima K, Fukudo S, Shibuya D, Tsuji I. Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. Eur J Cancer Prev. 2005;14(2):169-74.

Ogimoto I, Shibata A, Kurozawa Y, Nose T, Yoshimura T, Suzuki H, Iwai N, Sakata R, Fujita Y, Ichikawa S et al: Risk of death due to hepatocellular carcinoma among drinkers and ex-drinkers. Univariate analysis of JACC study data. Kurume Med J 2004, 51(1):59-70.

Ozasa K: Alcohol use and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007, 8 Suppl:81-88.

Parkin DM. Cancers attributable to consumption of alcohol in the UK in 2010. BJC 2011;105 Suppl 2:S14-8.

Sakamoto T, Hara M, Higaki Y, Ichiba M, Horita M, Mizuta T, Eguchi Y, Yasutake T, Ozaki I, Yamamoto K et al: Influence of alcohol consumption and gene polymorphisms of ADH2 and ALDH2 on hepatocellular carcinoma in a Japanese population. International Journal of Cancer 2006, 118(6):1501-1507.

Shih WL, Chang HC, Liaw YF, Lin SM, Lee SD, Chen PJ, Liu CJ, Lin CL, Yu MW. Influences of tobacco and alcohol use on hepatocellular carcinoma survival. Int J Cancer. 2012; 131(11):2612-21.

Tanaka K, Hirohata T, Takeshita S, Hirohata I, Koga S, Sugimachi K, Kanematsu T, Ohryohji F, Ishibashi H: Hepatitis B virus, cigarette smoking and alcohol consumption in the development of hepatocellular carcinoma: a case-control study in Fukuoka, Japan. *Int J Cancer* 1992, 51(4):509-514.

Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, Nakanishi K, Fujimoto I, Inoue A, Yamazaki H et al: Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993, 328(25):1797-1801.

Table 1. Pooled and meta-analysis studies examining alcohol cessation 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
Heckley et al (2011) **4 studies** Goodman et al. 1995 Donato et al. 2002 Franceschi et al. 2006 Ozasa 2007	Meta-analysis	Exposure Varied	Drinking Status Current Drinker Ex-Drinker	Not given	Not Given	Not given	The findings of the meta-analysis suggest that for each year of cessation the risk of liver cancer declines by about 6-7% and they estimated tgat it would take 23 years (95%CI 14-70 years) for the risk of live cancer of quitters of alcohol to fall to that of never drinkers.

Table 2. Cohort studies examining the effect of alcohol cessation on liver cancer risk								
Reference, location, year of study, Cancer type	**Cohort description (No. in analysis)**	**Exposure assessment**	**Exposure categories**	**No. of subjects in each category of liver cancer cases versus controls**	**Pooled odds ratio and confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Rating for Quality**
Kono et al. 1986 Japan 1965-1977	Prospective cohort 5,135 Japanese male physicians 25 cases of liver cancer 25-70 years	Self-administered questionnaire on drinking and smoking habits	**<u>Drinking status</u>** Non drinkers Ex Drinkers Occasional Drinkers Daily Drinker <2 go[#]/day >2 go[#]/day		1.0 1.4 (0.4 – 4.8) 1.5 (0.6 – 3.8) 2.0 (0.8 - 5.1) 2.7 (1.0 - 6.8)	Age and Smoking	[#]Go = conventional unit of go is a 180 ml drink and 1 go of sake contains 27 ml alcohol.	5
Kato et al. 1992 Japan 1987-1990	Prospective cohort 1,845 cohort members with de-compensated liver cirrhosis, 122 cases of liver cancer ≥ 16 years follow up	Interview based questionnaire on drinking and smoking	**<u>Drinking status</u>** Never Past Occasional Current	46/435 19/222 4/ 65 5/ 88	1.00 0.58 (0.32-1.04) 0.43 (0.15-1.24) 0.41 (0.16-1.06)	Age and sex	**Period until classified as a former drinker = 0 year**	6
Tsukuma et al. 1993 Japan 1987–1991	917 patients with chronic hepatitis or compensated cirrhosis (548 men and 369 Women) 54 liver cancer cases at 3 years follow up	Interview based questionnaire on lifestyle factors including drinking	**<u>Drinking status</u>** Non drinkers Occasional Drinkers Former drinker < 80 g ethanol/day ≥80 g ethanol/day		1.00 0.77 (0.20–2.99) 1.46 (0.56–3.79) 1.66 (0.69–3.96)	Age, sex, stage of disease, serum alpha-fetoprotein, HBsAg, anti-HBc, anti-HCV, smoking		6
Goodman et al. 1995 Japan 1978– 1989	36,133 residents of Horoshima and Nagasaki (Atomic bomb survivors) 242 liver cancer cases (156 men and 86 women)	Self-adminsitered survey received by mail	Drinking Status Men Never-drinker Ever-drinker Ex-drinker Years since Quitting ≤ 10 years ago 11–15 years ago ≥ 16 years ago Current drinker	No of liver cancer cases 25 126 25 12 8 4 100	1.00 1.11 (0.72–1.70) 2.33 (1.34– 4.07) 7.87 (3.89– 16.0) 2.08 (0.93– 4.67) 0.96 (0.33–2.77) 0.98 (0.63–1.52)	Sex, age, residence, age at the time of bombing, radiation dose to the liver	Original cohort designed to examine the association between exposure to atomic bomb radiation and disease. Results only available for men due to the low numbers in the female categories	6

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

Reference, location, year of study, Cancer type	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of subjects in each category of liver cancer cases versus controls	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Ogimoto et al. 2004 Japan 1988 - 1999	Cohort of 66,974 residents in 45 areas throughout Japan (28343 men and 38631 women) Death	Both interview and self-administered questionnaire was adopted to obtain information on alcohol consumption.	**Drinking Status**	No of subjects		Collaborating institute	Univariate analysis	5
			Males 40 – 59 Years					
			Never drinker	2,707	1.00			
			Ex-drinker	592	8.11 (3.17– 20.77)			
			Current drinker	13,416	0.65 (0.27– 1.52)			
			Males 60 – 79 Years					
			Never drinker	2,550	1.00			
			Ex-drinker	1,085	3.48 (1.86– 6.54)			
			Current drinker	7,993	0.75 (0.43– 1.31)			
			Females 40 -59 Years					
			Never drinker	16,256	1.00			
			Ex-drinker	335	3.85 (0.48– 30.93)			
			Current drinker	5,937	0.23 (0.03– 1.80)			
			Females 60 -79 Years					
			Never drinker	12,816	1.00			
			Ex-drinker	297	4.18 (1.47–11.88)			
			Current drinker	2,990	0.59 (0.25–1.43)			
			Age at Cessation of drinking					
			Males 40 – 59 Years					
			Never drinker	2,707	1.00			
			Aged 30 yrs or less	51				
			30 - <45 yrs	180	4.86 (1.01-23.47)			
			45 -<60 yrs	294	14.45 (5.20- 40.14)			
			60 or greater	0	-			
			Males 60 – 79 Years					
			Never drinker	2,550	1.00			
			Aged 30 yrs or less	25	-			
			30 - <45 yrs	106	1.24 (0.16-9.39)			
			45 -<60 yrs	308	4.83 (2.13 – 10.91)			
			60 or greater	153	1.92 (0.43 – 8.57)			
			Females 40 -59 Years					
			Never drinker	16,256	1.00			
			Aged 30 yrs or less	18	-			
			30 - <45 yrs	129	-			
			45 -<60 yrs	138	10.49(1.33 – 82.90)			
			60 or greater	0	-			
			Females 60 -79 Years					
			Never drinker	12,816	1.00			
			Aged 30 yrs or less	0	-			
			30 - <45 yrs	26	11.41 (1.55-83.71)			
			45 -<60 yrs	88	6.46 (1.53- 27.35)			
			60 or greater	43	7.74(1.05-57.15)			
			Years since cessation of drinking					
			Males 40 – 59 Years					
			Never drinker	2,645	1.00			
			0 -5 years	232	12.99 (4.46-37.86)			
			6 -10 years	100	17.06 (4.95-58.82)			
			11-15 years	50	-			
			16 or more years	94	-			
			Males 60 – 79 Years					
			Never drinker	2,496	1.00			
			0 -5 years	393	1.32 (0.39-4.52)			
			6 -10 years	210	4.90(2.02-11.87)			
			11-15 years	122	5.73 (1.92 – 17.13)			
			16 or more years	204	2.99 (1.00 -8.92)			
			Females 40 -59 Years					
			Never drinker	15,896	1.00			
			0 -5 years	148	-			
			6 -10 years	52	26.36(3.18-218.82)			
			11-15 years	27	-			
			16 or more years	36	-			
			Females 60 -79 Years					
			Never drinker	12,562	1.00			
			0 -5 years	81	3.79 (0.51-27.86)			
			6 -10 years	46	6.57 (0.89-48.55)			
			11-15 years	34	7.87 (1.06-58.58)			
			16 or more years	58	5.59 (0.76-40.97)			

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

Reference, location, year of study, Cancer type	Cohort description (No. in analysis)	Exposure assessment	Exposure categories	No. of subjects in each category of liver cancer cases versus controls	Pooled odds ratio and confidence intervals (95% CI)	Adjustment factors	Comments	Star Rating for Quality
Nakaya et al. 2005 Japan 1990– 97	21, 201 Men residents in 14 municipalities of Miyagi 48 liver cancer cases	Self-administered questionnaire on various health habits, including alcohol consumption	**Drinking status** Never Former Current	 3 10 35	 1.00 6.6 (1.8–24.2) 2.7 (0.8– 8.9)	Age, smoking, education, daily consumption of orange and other fruit juice, spinach, carrot or pumpkin, and tomato		8 stars
Ozasa 2007 Japan	Prospective Japanese Collaborative Cohort study	Information on alcohol consumption was obtained by self-administered questionnaires	**Drinking Status** **Alcohol Drinking Males** Non Drinkers or Rare Drinkers Ex-drinkers *Females* Non Drinkers or Rare Drinkers Ex-drinkers ***Years since drinking ceased*** *Males* < 5 years 5 – 15 years 15 + years *Females* < 5 years 5 – 15 years 15 + years		 1.00 0.89 (0.69 – 1.15) 3.16 (2.32 – 4.31) 1.00 0.83 (0.57- 1.21) 2.89 (1.51 – 5.53) 3.79 (2.24 – 6.42) 4.56 (2.83 – 7.33) 2.43 (1.23 – 4.79) 1.58 (0.22 – 11.4) 7.53 (3.04 – 18.7) 1.92 (0.26 – 13.8)	Age and centre	Period until classified as a former drinker = 0 years	1 star
Shih et al. 2012	2,273 HCC cases (1990 with viral hepatitis and 283 without), aged 20–75 years Average 10 years follow up	Standard questionnaire on lifestyle factors	**Drinking Status** **All patients (n = 2273)** Never drinkers Ex-drinkers Current drinkers **Patients without viral hepatitis (n = 283)** Never drinkers Ex-drinkers Current drinkers **Patients with viral hepatitis (n = 1990)** Never drinkers Ex-drinkers Current drinkers **Years since quitting** Continuing drinker Never drinkers **Ex-drinker** <5 years 5–9 years ≥10 years	 1500[a]/934[b] 263[a]/187[b] 508[a]/365[b] 162[a]/68[b] 27[a]/19[b] 94[a]/50[b] 1338[a]/866[b] 236[a]/168[b] 414[a]/315[b] 414[a]/315[b] 1338[a]/866[b] 84[a]/57[b] 69[a]/50[b] 83[a]/61[b]	 1 (Referent) 1.05 (0.89–1.25) 1.23 (1.08–1.41) 1 (Referent) 1.44 (0.81–2.57) 1.31 (0.86–2.01) 1 (Referent) 1.03 (0.87–1.23) 1.26 (1.10–1.45) 1 (Referent) 0.79 (0.69–0.91) 0.83 (0.63–1.10) 0.92 (0.68–1.25) 0.74 (0.56–0.98)	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 3. Case-Control studies examining the effect of alcohol cessation on liver cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Quality**
Tanaka et al. 1992 Japan 1985-1989	Cases 204 HCC patients aged 40–69 (168 men, 36 women); residents of Fukuoka or Saga Prefecture, Japanese nationality, enrolled from Kyushu University Hospital; 40% histologically confirmed enrolled in 1985–89	Controls 410 residents (291 men, 119 women) of Fukuoka city who visited a public health center near Kyushu University Hospital between January 1986 and July 1989 for a health examination; matched on age, sex	In-person interview	Drinking status *Men and Women* Non-drinker Past Drinker *Men* Non-drinker Past Drinker *Women* Non-drinker Past Drinker	 1.0 (reference) 1.3 (0.9 - 2.0) 1.0 (reference) 2.2 (0.9 - 5.8) 1.0 (reference) 1.2 (0.7 - 1.9)	Sex, age	Period until classified as a former drinker = 1 year 50 out of the 68 ex-drinkers among the cases reported that they had given up alcohol due to their pre-existing liver disease. In light of this information, the authors combined current and ex-drinkers together and calculated a combined RR compared to non-drinkers.	5
Sakamoto et al. 2006 Japan 2001 - 2004	Hospital-based case-control study 209 cases (141 men and 68 women)	Study contained two different controls 275 Hospital controls (180 men and 95 women) 381 patient controls with chronic liver disease (CLD) but without liver cancer (298 patients with chronic patients and 83 patients with liver cirrhosis)	Interview based questionnaire on lifestyle factors including drinking	**Drinking status** Never drinker (78/156) Former drinker (50/17) Current drinker (81/102) Never drinker (78/196) Former drinker (50/74) Current drinker (81/111)	Based on Hospital controls 1.0 5.3 (1.6–18.6) 2.9 (1.2–7.4) Based on CLD controls 1.0 1.3 (0.7– 2.2) 1.8 (1.0– 3.0)	Adjusted for sex, age, smoking, HBsAg, and anti-HCV	For data analysis, never drinkers were defined as those who had never drunk or had drunk less than once per week and/or for less than 1 year Past drinkers were those who quit alcohol use 1 or more years prior to the interview	6
Franceschi et al. 2006 Pordenone and Naples, Italy, 1999–2002 (1999–2002)	Cases 279 cases, aged 43–84 years; diagnosed with HCC without treatment; 78.2% histologically confirmed; enrolled from hospitals and cancer institutes in Naples and Pordenone,	Controls 431 hospital based controls; 40–83 years old; admitted for reasons other than alcohol and tobaccorelated use or hepatitis; distribution matched on age, sex	Questionnaire	**Alcohol drinking** Never Former Current **Years since cessation** <5 years >5 years	 1.00 3.98 (1.74-9.09) 0.84 (0.39-1.83) 6.34 (1.92-21.04) 2.56 (0.96-6.82)	Gender, age, center, education, HBV, HCV markers	Period until classified as a former drinker = 1 year Alcohol drinking (cases/controls) Never (20/66) Former (118/48) Current (91/317) Years since cessation <5 years (46/11) >5 years (72/37)	5

Table 3 continued. Case-Control studies examining the effect of alcohol cessation on liver cancer risk								
Reference, location, period	**Characteristics of cases**	**Characteristics of controls**	**Exposure assessment**	**Exposure category**	**Relative Risk confidence intervals (95% CI)**	**Adjustment factors**	**Comments**	**Star Quality**
Donato et al. 2002 Italy 1995-2000 Hosptial based case-control study	464 cases 40-75 years	824 controls	Interview based questionnaire on drinking history	**<u>Drinking status</u>** ***Males*** Never Drinkers Ex drinkers Current Drinkers ***Females*** Never Drinkers Ex drinkers Current Drinkers **<u>Years since Quitting</u>** ***Males*** Current Drinkers 1 – 5 years 6 -10 years 11 – 15 years >15 years ***Females*** Current Drinkers 1 – 5 years 6 -10 years 11 – 15 years >15 years	 1.00 8.5 (3.3 -22.3) 2.7 (1.1 – 6.8) 1.00 2.8 (1.0 – 7.9) 0.9 (0.3 – 2.3 Reference 5.0 (2.9-8.6) 4.0 (2.2-7.4) 1.6 (1.6-4.5) 1.4 (0.6-3.1) Reference 3.0(0.6-15.2) 2.7 (0.5-13.6) 1.9 (0.2 – 19.2) 8.6 (1.3-56.0)	Sex, age, area of residence, and HBsAg and hepatitis C virus RNA	Period until classified as a former drinker = 1 year	7