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

Summary of epidemiology studies investigating interactive effects of alcohol intake and genetic susceptibility factors on cancer risk

Introduction

1. Following an updated review of alcohol and cancer in 2009, IARC stated that there is evidence that consumption of alcoholic beverages is causally related to cancers of the upper aerodigestive tract combined, oral cavity, pharynx, larynx, oesophagus, liver, colorectum, and female breast. In addition an association of consumption of alcoholic beverages and cancer of the pancreas was reported (IARC, 2012). The IARC working group also concluded that acetaldehyde, which is also present in alcoholic beverages, is carcinogenic to humans (Group 1), and confirmed the Group 1 classification of alcohol consumption and of ethanol in alcoholic beverages.

2. The COC reviewed new epidemiology studies on alcohol and IARC causal cancer sites published since the 2009 IARC review. A number of these studies had evaluated potential interactions of alcohol consumption with genetic risk factors, mostly relating to polymorphic genotypes in alcohol-metabolising pathways, but also to other aspects relevant to the specific cancer sites (e.g., BRCA genotypes and breast cancer, folate metabolism genotypes and colorectal cancers). At the COC meeting in April 2015, it was agreed that a paper drawing together the data on polymorphisms across the cancer sites studied would be helpful. The studies evaluating this are summarised in this document, listed by individual cancer site. In addition, the review of polymorphisms and genetic susceptibility undertaken as part of the IARC review in 2007 is included at Annex A and the IARC review in 2009 is included at Annex B.

Alcohol metabolism in humans

3. In humans, the majority of ingested alcohol is eliminated via metabolic degradation in the liver. Ethanol is first metabolised to acetaldehyde through several enzymatic and nonenzymatic mechanisms. The main enzymatic pathways involved are alcohol dehydrogenase (ADH), cytochrome P450 (CYP2E1), and catalase. Acetaldehyde is subsequently oxidized to acetate, mainly by the aldehyde dehydrogenase (ALDH) enzyme, ALDH2. Different polymorphic alleles of genes encoding the enzymes involved in these pathways encode isozymes with varying

phenotypes. For example, variations in genes encoding ADH and ALDH produce ethanol- and acetaldehyde-metabolising enzymes that vary in their activities with relation to substrate metabolism. This genetic variation may influence individual susceptibility to alcohol-related tissue damage. A detailed description of the enzymes involved in ethanol metabolism in humans can be found in IARC Monograph Volume 96 (pp. 1083-1098) (IARC, 2010).

Alcohol consumption and genetic risk factors for upper aerodigestive tract ('head and neck') cancers

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

5. A subset of 386 cases and 394 controls from this study were evaluated for the influence on alcohol- or smoking-associated upper aerodigestive tract cancer risk of homo- and heterozygosity for variants of a range of genes involved in carcinogen metabolism. The CYP1A11VS1+606T >G (rs2606345) (phase I metabolism) and ADH1CIVS6-892 A >G (rs1662058) (alcohol dehydrogenase) variants were associated with increased risk. Analysis for ADH1C indicated that, taking individuals who were homozygous or heterozygous for the common allele and light drinkers (≤2 drinks/day) as the referent group, those who were homo/heterozygous for the

[1] Oral cavity, pharynx, larynx, oesophagus

common allele who drank 3+ drinks/day had an OR of 3.71 (95% CI, 2.51-5.48), whilst those who were homozygous for the rare variant allele and drank 3+ drinks/day had an OR of 9.27 (95% CI, 4.01-21.46).

6. Hakenewerth et al (2011) examined the association between SNPs (single nucleotide polymorphisms)/haplotypes for alcohol-related genes and alcohol exposure in subjects from a population-based case-control study of head and neck cancers in the US (Carolina Head and Neck Cancer Epidemiology Study, CHANCE). Cases[2] were identified from the central cancer registry, controls were identified from vehicle registration lists and frequency matched to cases for age, race and sex. Information on demographics, tobacco use, drinking of alcoholic beverages, diet, oral health, medical history and family history of cancer was obtained by trained interviewers. Genotypes were analysed on DNA prepared from blood or buccal cell samples. The analysis included 75 polymorphic SNPs in 12 genes: ADH1B, ADH1C, ADH4, ADH7, ALDH2, and CYP2E1 in the alcohol metabolism pathway in the upper aero-digestive tract; and CAT, SOD1, SOD2, GPX1, GPX2 and GPX4 in the oxidative stress pathway. Data were evaluated separately for African-Americans and European-Americans. Questions about alcohol use, designed to estimate lifetime history of consumption, included age of starting/stopping, years of drinking, type (beer/wine/hard liquor) and number of drinks per day/week/month/year, and drink size. Information was also collected on smoking habits (duration of smoking, ever use of non-cigarette tobacco, ever exposed to environmental tobacco smoke). Additional potential confounders considered were health insurance at reference date, oral health parameters, family history of head and neck cancer, poverty and education levels. OR for the independent effects of SNPs and alcohol, and their interactive effects, were computed using conditional logistic regression. OR for the main effects of haplotypes were computed using unconditional logistic regression. A dominant genetic model (at least one minor allele vs. referent of no minor alleles) was used, as the number of homozygous-minor-allele subjects was too small in the case of many of the SNPs. Departures from additive interaction were evaluated by computing interaction contrast ratios (ICR) and Bonferroni-corrected CI. ICR were calculated using cancer OR of subjects in three categories: (1) the highest drinking category and no minor allele (OR_{01}); (2) never-drinkers with at least one minor allele (OR_{10}); and (3) subjects in the highest drinking category and at least one minor allele (OR_{11}), compared with never-drinkers homozygous for the major allele (i.e. the referent: $OR_{00} = 1.0$). The ICR was calculated as: $ICR=OR_{11} - OR_{01} - OR_{10} + 1$. ICR significantly different from zero indicated departure from additive interaction.

7. The odds of developing head and neck cancer increased with lifetime alcohol consumption. Subjects in the lowest consumption category had reduced head and neck cancer odds compared with non-drinkers (OR=0.8; 95% CI, 0.6–1.0), mostly due to laryngeal and oral cavity tumours: OR (95% CI) = 0.7 (0.4–1.1) and 0.4 (0.2–

[2] Squamous cell carcinoma (SCC) of oral cavity, pharynx, larynx

0.9), respectively. Successively higher levels of alcohol consumption were associated with increasing odds. The middle tertile of lifetime consumption was associated with 30% higher head and neck cancer odds than never-drinkers, and the highest tertile of consumption with tripled odds.

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

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

10. Tsai et al (2014) investigated the inter-relation of alcohol consumption, oral hygiene and alcohol- and aldehyde dehydrogenase–metabolising phenotypes. This study, carried out in Taiwan, included 436 newly diagnosed head and neck[3] cancer cases aged 20-80 years and 514 hospital-based controls matched for age and sex. Information on alcohol drinking and oral hygiene habits was obtained by trained interviewer. Information on alcohol drinking included starting and quitting age (if quit for more than 6 months), type of beverage (beer, wine, hard liquor), frequency (never, monthly, weekly, daily) and quantity (number of cups, where 1 cup = 150 ml). Subjects were genotyped for alcohol dehydrogenase, *ADH1B rs1229984*: fast

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

(*2/*2), slow (*1/*2 or *1/*1), and aldehyde dehydrogenase, *ALDH2 rs671*: fast (*2/*2), slow (*1/*2), non-functional (*1/*1). Genotype combinations were also categorised into 4 sub-groups; Group 1: fast *ADH1B* /fast *ALDH2*, Group 2: fast *ADH1B*/slow or non-functional *ALDH2*, Group 3: slow *ADH1B*/fast *ALDH2*, Group 4: slow *ADH1B*/slow or non-functional *ALDH2*. Unconditional logistic regression, adjusted for sex, age, education, cigarette smoking (pack-year categories) and betel quid chewing (pack-year categories) was used to calculate OR and 95% CI for associations between head and neck cancer risk and 1] alcohol drinking, 2] oral hygiene, 3] *ADH1B*/*ALDH2* genotype sub-groups, 4] *ADH1B*/*ALDH2* genotype sub-groups by alcohol status sub-group, 5] *ADH1B*/*ALDH2* genotype sub-groups by oral hygiene status sub-group in regular drinkers.

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

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

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

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

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

Oropharyngeal cancer

16. Matsuo et al. (2012) conducted a hospital-based Japanese case-control study to investigate the interaction between folate and alcohol and to evaluate the potential effect modification by aldehyde dehydrogenase 2 (ALDH2) genotype in oral and pharyngeal cancer (OPC) risk. Data relating to alcohol exposure and risk of OPC and its modification by ALDH2 genotype are summarised here. Cases were patients histologically diagnosed with OPC between Jan 2001 to Dec 2005 at Aichi Cancer Centre hospital. OPC included cancers of the oral cavity, oropharynx and hypopharynx according to ICD codes. Malignant neoplasms of the lip, salivary glands and nasopharynx were not included. Randomly selected controls comprised outpatients from the Aichi Cancer Centre hospital between Jan 2001 to Dec 2005 who were medically and radiologically confirmed not to have cancer or history of cancer. Controls were age- and sex matched to cases at a ratio of 3:1. Details of alcohol consumption, such as quantity and types of beverages drunk (i.e. Japanese sake, beer, shochu, whiskey, and wine converted into a Japanese sake equivalent) were obtained at study entry via self-administered questionnaire. Alcohol intake was based on the assumption that 1 drink = 180 ml sake (contains 23 g ethanol) = large bottle beer (633 ml), two shots whisky (57 ml), 2.5 glasses wine (200 ml) and 1 unit = 12.5 g ethanol. Drinking groups were defined as either being intermediate (< 4 units/day) or high (≤ 4 units/day). Never drinkers were the referent category. A total of 409 (296 male, 113 female) cases were included in the analysis, comprising 257 oral cavity; 72 oropharyngeal; 80 hypopharyngeal cancer cases, with 1227 controls (888 male, 339 female). DNA samples were available for approximately 60% of study participants (251 cases and 759 controls), and were genotyped for ALDH2 Glu504Lys. This allele encodes a catalytically inactive subunit such that individuals experience a marked elevation in blood acetaldehyde after alcohol ingestion and also have higher susceptibility to upper aerodigestive tract cancer (UATC) compared to the ALDH2 Glu/Glu genotype, due to decreased acetaldehyde elimination rate. The ALDH2 genotypes detected among participants were: Glu/Glu (encodes a catalytically active subunit): 103 cases, 372 controls; and Lys+: 148 cases, 387 controls. Average daily intake of folate was estimated from responses to FFQs after calculating the sums of their intakes in the single food items as estimated from a food composition table according to the indicated portion size, multiplied by the food frequency. ORs and 95% CIs were calculated by multiple logistic regression models and adjusted for age, occupation, BMI, smoking, non-alcoholic energy intake, and smoking.

17. There was a significantly positive association between alcohol and OPC risk. Compared to never drinkers (n=113 cases, 454 controls) consumption of ≤ 4 units/day was associated with a significantly increased risk of OPC (OR= 2.67 (1.83-3.88) p for trend <0.001). With regard to the interactive effect of ALDH2 genotype and alcohol (stratified according to folate intake) the effect of alcohol was only significantly elevated in heavy-drinking ALDH2 Lys allele carriers (not in ALDH2

Glu/Glu), and the risk of OPC was further increased in those with low-intermediate folate intake (< 243.5 µg/day) compared to those with high folate intake (≥ 78.4 µg/day). Compared to never drinkers with high folate intake (n=11 cases, 75 controls), ORs for OPC in high drinkers were 11.9 (3.95-36.1) in those with low folate intake, and 4.36 (1.04-18.2) in those with high folate intake. P value = 0.001 for a 3-way interaction term for genotype, folate and alcohol consumption.

Oesophageal cancer

18. Tanaka et al. (2010) conducted a case-control and genome-wide association study in Japan to investigate the environmental and genetic risk factors for oesophageal SCC (squamous cell carcinoma). There were 1,071 cases, patients newly diagnosed with oesophageal SCC, aged between 35 and 85, and identified from six hospitals between 2000-2008; 2,762 healthy controls without previous cancer history were recruited from Kyushu University Hospital (and related hospitals) during the same time period. All controls were enrolled after receiving an upper gastrointestinal endoscopy test to ensure they had no disease. From the genome-wide association study, two SNPs were identified as being highly associated with oesophageal SCC: risk alleles of rs1229984 (from chromosome 4 of the ADH1B gene) and rs671 (from chromosome 12 of the ALDH2 gene) were highly associated with oesophageal SCC (OR 4.08, 95% CI 3.27- 5.09, $p=4.43x10^{-40}$ for rs1229984, and OR 3.54, 95% CI 3.04- 4.14, $p=5.53x10^{-62}$ for rs671). Next, the study authors estimated the genetic risk of specific genotypes of rs671 and rs1229984. For rs671, the genotype GG was taken to be genetic risk no.=0, while the genotype AG/AA was a genetic risk no.=1. For rs1229984, the genotype of genetic risk no.=0 was AA/AG, while genotype GG was a genetic risk no.=1. If both risk genotypes were present, then the genetic risk no.=2. Environmental risk was estimated separately, with an environmental risk no.=0 for a non-drinker and non-smoker, an environmental risk no.=1 for an ever-drinker and non-smoker or a non-drinker and ever-smoker, and an environmental risk no.=2 for an ever-drinker and ever-smoker. For an ever-drinker and non-smoker, there was a significant association with risk of oesophageal SCC with an OR of 3.5 (95% CI 2.1-5.8), based on 67 cases and 170 controls. The genetic and environmental risks were then combined. For an ever-drinker and non-smoker with no genetic risk factors, the OR of oesophageal SCC was 1.5 (95% CI 0.7-3.3), suggesting that without the genetic factors, alcohol consumption was not significantly associated with risk of the disease. However, when either of the genetic risk genotypes was present, the OR rose to 12.1(95% CI 5.5-26.6), with a p value <0.001 for the interaction of genetic risk with alcohol consumption. The combination of smoking with drinking and the presence of either genetic risk factor further increased the OR to 62.1(95% CI 30.3-127.4), based on 612 cases and 309 controls, strongly suggesting that, if the genetic risk factors are present, drinking significantly increases the risk of disease.

19. A case-control study was performed by Ding et al (2010) in China to investigate the relationship between alcohol dehydrogenase-2 (ADH2) and aldehyde dehydrogenase-2 (ALDH2) genetic polymorphisms, alcohol consumption and susceptibility to oesophageal cancer. There were 221 cases, histopathologically diagnosed as having oesophageal cancer, between January 2005 and December 2006. There were 191 population-based controls, recruited from healthy residents in the villages or towns in which the patients lived. Alcohol drinkers with the ALDH2 A allele showed a significantly increased risk of oesophageal cancer compared with drinkers with the ALDH2 G/G genotype (OR 3.08, 95% CI 1.65–5.78) or non-drinkers with any genotype (OR 3.05, 95% CI 1.49–6.25). Furthermore, drinkers with the ALDH2 A allele and a cumulative amount of alcohol consumption =2.5 kg*years were at a significantly higher risk of developing oesophageal cancer (OR 11.93, 95% CI 3.17–44.90) compared with individuals with ALDH2 G/G genotypes and a cumulative amount of alcohol consumption <2.5 kg *years. Regarding the relationship between the ADH2 genotype, drinking habit and oesophageal cancer risk, the study results did not indicate any significant associations. When looking at interactive effects of the genotypes, drinkers carrying both ALDH2 A and ADH2 G alleles and with a cumulative amount of alcohol consumption =2.5 kg*years, compared to individuals carrying ALDH2 G/G and ADH2 A/A alleles and with a cumulative amount of alcohol consumption of <2.5 kg* years, showed a significantly elevated risk of oesophageal cancer (OR 53.15, 95% CI 4.24-666.84). However, this result was based on information from only 13 cases and 1 control. Overall, the authors concluded that to help lower their risk for oesophageal cancer, persons carrying the ALDH2 A allele should be encouraged to reduce their consumption of alcohol.

20. Talukdar et al (2013) conducted a case-control study on a population of North East India, in the Assam and Mizoram states, which they reported as having a high incidence of oesophageal cancer, with an age-adjusted rate of around 17/100,000 to 27/100,000 in the population. The aim of the study was to investigate the interaction of various habits-related factors, including alcohol consumption, and polymorphism of GSTM1/GSTT1 genes, and the effect of promoter hypermethylation in four tumour suppressor genes. The GSTM1 and GSTT1 genes are involved in metabolising carcinogens, in particular several of the carcinogenic compounds present in tobacco. In the population studied, cigarette smoking and betel quid chewing were common. The authors also included alcohol as one of the risk factors. There were 112 histopathologically confirmed oesophageal SCC patients from different cancer hospitals of NE India, recruited during January 2011 to October 2012. Oral swabs from 130 age and gender matched healthy controls were also collected; no other details are provided on controls. Cases and controls with family history of oesophageal or other cancers were excluded. Genotyping of the GSTM1 and GSTT1 genes was performed by PCR, and promoter methylation status of 4 tumour suppressor genes (TSG), p16, DAPK, GSTP1 and BRCA1, was determined by Methylation Specific PCR. A methylation index (MI) was calculated, as the ratio of the number of methylated promoters to the total number of promoters under study.

Logistic regression analysis of the risk factors for oesophageal SCC was performed. The major risk factors for oesophageal SCC were tobacco chewing and smoking, and the effect of alcohol was not seen to be a significant association: OR 1.23, 95% CI 0.67-2.46. Considering the genes themselves, the risk of oesophageal SCC was significantly higher for GSTT1 null variants only, among the cases. When the effect of alcohol as a risk factor for oesophageal SCC was considered together with TSG promoter methylation, cases who were alcohol drinkers with promoter methylation were seen not to have significant risk of oesophageal SCC, whereas alcohol-drinking cases with a zero methylation index had increased ORs for all 4 tumour suppressor genes, suggesting that alcohol consumption is not associated with promoter hypermethylation. When all cases with zero methylation were considered together, alcohol drinkers had an OR of 2.47, 95% CI 1.00-6.04, of developing oesophageal SCC compared to controls. An MDR (Multifactor Dimensionality Reduction) analysis was performed to detect gene-gene and gene-environment interactions. The best predictive models of interaction between environmental and genetic parameters up to four orders of interaction are described in the paper. The best model for a 2nd order interaction was tobacco chewing and alcohol consumption (OR 5.01,95% CI 2.54-9.88), and for occurrence of oesophageal SCC without promoter hypermethylation, the best model suggested an interaction of betel quid chewing, alcohol consumption and null GSTT1, with an OR of 9.88, 95% CI 3.67-26.54. Thus, alcohol was seen to be a risk factor when combined with other risk factors. However, the number of cases and controls was small, drinkers were not categorised by quantity or type of alcohol consumed, and the study relates to a very specific population with prevalence of tobacco and betel quid chewing, so that results may not be generalisable to other populations.

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

when compared with non-drinking CYP2C19*3 GG genotypes. However, the number of cases and controls was small, and there was no quantification of the amount of alcohol that drinkers consumed.

22. Wang et al (2011) conducted a case-control study in China to evaluate the contribution of ADH1B and ALDH2 polymorphisms to the risk of oesophageal SCC in Chinese females. Alcohol dehydrogenase-1B (ADH1B) and aldehyde dehydrogenase-2 (ALDH2) are key enzymes for elimination of ethanol and acetaldehyde, and it is thought that genetic variation in the ability to metabolise alcohol might be associated with oesophageal cancer risk. The authors describe that the homodimer of ADH1B encoded by ADH1B*1/*1 has only 1/100 and 1/200 of the ethanol oxidising capacity of the isozymes encoded by ADH1B*1/*2 and ADH1B*2/*2, respectively. The ALDH2*2 allele is also prevalent in east Asians and encodes a catalytically inactive subunit, and ALDH2*2 allele carriers experience unpleasant flushing responses after drinking small amounts of ethanol. There were 81 Chinese female cases, recruited from the hospital of the Armed Police College of Medicine from June 2009 to December 2010. All were newly diagnosed with primary oesophageal cancer. There were 162 controls, randomly selected from people who requested general health examinations in the same hospital during the same period and who were confirmed to have no malignancy, digestive diseases or chronic diseases and also no prior history of malignancy. The controls were matched with cases by age within five years. Alcohol drinking was categorised into former, never and current drinking. Individuals who had quit drinking for more than one year were considered as former drinkers, and individuals who drank more than 200 ml beer, 125 ml wine and 50 ml white spirit per month and for at least 6 months were regarded as current drinkers. Current drinkers were divided into three groups: 1-20 g/d alcohol (light drinking), 21-40 g/d alcohol (moderate drinking) and >40 g/d alcohol (heavy drinking). When compared with the ADH1B*2/*2 genotype, subjects with ADH1B*1/*2 had an OR of 1.47, 95% CI 0.84-2.58 for risk of oesophageal SCC, while those with ADH1B*1/*1 had an increased risk with an OR of 2.36, 95% CI 1.14-5.79. For ALDH2, the ALDH2*1/*2 genotype was significantly associated with increased SCC risk compared with ALDH2*1/*1, OR 3.24, 95% CI 1.45-5.36. When the risk of SCC was stratified by quantity of alcohol drinking (never, light, moderate or heavy), no significant associations were found across the genotypes.

Alcohol consumption and genetic risk factors for breast cancer

23. A number of genes associated with hereditary susceptibility to breast cancer have been identified and include *BRCA1*, *BRCA2*, *TP53*, *PTEN/MMAC1*, and *STK11.* Germline mutations in *BRCA1* are associated with early-onset breast cancer and ovarian cancer, and mutations in *BRCA2* are associated with multiple cases of breast cancer in families and are also associated with male breast cancer, ovarian cancer, prostate cancer, melanoma, pancreatic cancer, and fallopian tube cancer.

Cohort studies

24. LeCarpentier et al. (2011) examined the effect of alcohol consumption on breast cancer risk in a French cohort of 1,337 women including 863 BRCA1 mutation carriers and 474 BRCA2 mutation carriers. Details of alcohol consumption, such as number of glasses per week were recorded and categorised as 0, 1-5, 6-10, and >10 at the age of 20 and at the time of interview. HRs and 95% CI were estimated using Cox proportional hazard regression models and adjusted for parity, menopausal status, gene and number of years of smoking interruption. When the analyses were stratified by tobacco use (never smokers and ever smokers), they observed no increased risk of breast cancer with alcohol consumption in current drinkers compared to never drinkers. For all women, they reported an HR = 1.10, 95% CI 0.76-1.61 for never smokers and an HR = 0.89, 95% CI 0.53-1.52 for ever smokers. For those carrying the BRCA1 mutation, they observed an HR = 1.02, 95% CI 0.65-1.60 for never smokers and an HR = 0.90, 95% CI 0.49-1.68 for ever smokers. Similarly no associations were observed for all women and BRCA1 carriers with increasing dose of alcohol and breast cancer risk. However, the HR was higher among BRCA2 carriers who were current drinkers compared to never drinkers (HR =1.21, 95% CI 0.68-2.15).

Case-control studies

25. McCarty et al. (2012) assessed the modifying effects of ADH1B, ADH1C and CYP2E1 on the association between alcohol intake and breast cancer incidence. This case-control study comprised 2,111 women (1,041 breast cancer cases and 1,070 controls) enrolled in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. Information on alcohol intake was obtained using a food frequency questionnaire such as frequency and serving size of beer, wine and spirits. RRs and 95% CI were estimated using Cox proportional hazard ratios, adjusted for age, race, ethnicity, age at menarche, parity, age of first live birth, family history of breast cancer, and personal history of benign breast disease. Compared to non-drinkers, they observed an increase in breast cancer risk with increasing alcohol consumption, with HR of 1.31 (95% CI 1.01-1.71) for women consuming >0-0.99 drinks/day (>0-9.99 g/day), 1.54 (95% CI 1.04-2.28) for women consuming 1.00-1.99 drinks/day (10g-19.9g/day), 1.75 (95% CI 1.02-3.00) for women consuming 2.00-2.99 drinks/day (20-29.8 g/day) and 2.00 (95% CI 1.11-3.61) for women consuming 3 or more drinks/day (>30 g/day). Stratifying by ADH1B genotype, they observed for the GG genotype statistically significant associations between all levels of alcohol intake and breast cancer risk (HR = 1.29 (95% CI 0.97-1.72) for women consuming >0-0.99 drinks/day, 1.66 (95% CI 1.09-2.52) for women consuming 1.00-1.99 drinks/day, 1.88 (95% CI 1.07-3.29) for women consuming 2.00-2.99 drinks/day and 2.22 (95% CI 1.19-4.13) for women consuming 3 or more drinks/day. However for the GA and AA genotypes, no associations between alcohol intake and breast cancer risk were observed with some indications of a decreased risk at higher levels

of alcohol consumption compared to non-drinkers. When they examined the data stratifying by ADH1C genotypes, they found the association between alcohol intake at all levels and breast cancer risk was similar across all genotypes. For CYP2E1, small sample size of CT and TT genotypes made interpretation of the results difficult.

26. Dennis et al. (2010) investigated the role played by alcohol on breast cancer risk in 3,850 women with either the BRCA1 or BRCA2 mutation in a case-control study. Information on alcohol consumption such as current drinking status, quantity and beverage type were obtained using a self-administered questionnaire. Non-drinkers were the reference category in the study. ORs and 95% CI were estimated using conditional logistic regression analysis and adjusted for ethnicity, menopausal status, oral contraceptive use, HRT use, smoking, oophorectomy, BMI and parity.

27. Among women with a *BRCA1*-mutation, the odds ratio for breast cancer associated with current alcohol consumption was 0.82 (95% CI 0.70–0.96), and a significant trend of decreasing risk of breast cancer with increasing drinks per week was observed (OR = 0.77, 95% CI 0.67-0.94 for 0-3 drinks/week (0-4.3 g/day), 0.98, 95% CI 0.73-1.32 for 4-9 drinks/week (5.7-12.9 g/day), 0.55, 95% CI 0.33-0.91 for = 10 drinks/week (= 14 g/day), p-trend = 0.03) compared to a non-drinker. The association was not appreciably modified by age at diagnosis or BMI. Among *BRCA1* carriers, consumers of wine exclusively had a reduced risk of breast cancer compared to non-drinkers (OR = 0.64, 95% CI 0.47-0.87), whereas women who did not consume wine exclusively had a risk of breast cancer that was similar to that of non-drinkers (OR = 0.89, 95% CI 0.70-1.12). A significant decreasing trend in the risk of breast cancer was seen with increasing weekly alcohol consumption for consumers of wine exclusively, but not for the other sub-groups of types of alcohol consumed.

28. Among women with a *BRCA2*-mutation, the odds ratio associated with current alcohol consumption was estimated to be 1.00 (95% CI 0.71-1.41). The association between the number of drinks consumed per week and breast cancer risk was not significant (OR = 0.97, 95% CI 0.67-1.41 for 0-3 drinks/week, 1.04 95% CI 0.67-1.63 for 4-9 drinks/week, 1.16, 95% CI 0.55-2.45 for = 10 drinks/week, p-trend = 0.72), nor was it modified by restricting to pairs in which both the case and control consumed alcohol, by age at diagnosis, or by BMI. Among women with a *BRCA2* mutation, the odds ratios for breast cancer associated with exclusive and non-exclusive wine consumption compared to no alcohol consumption were 1.01 (95% CI 0.61-1.69) and 0.88 (95% CI 0.53-1.48), respectively.

Nested case-control studies

29. Benzon Larsen et al. (2010) examined the modifying effect of various alcohol dehydrogenase (ADH) enzyme polymorphisms on breast cancer risk in a Danish case-control study of 809 post-menopausal women. Information on alcohol intake, such as frequency, beverage type and drinking patterns were obtained using both

food frequency questionnaires and lifestyle questionnaires. Incident rate ratios (IRRs) were determined using conditional logistic regression analysis and adjusted for parity, age of first birth, length of school education, duration of HRT use and BMI. They observed that the variant allele carriers of ADH1B Arg48 His were at a lower risk of breast cancer (IRR = 0.78, 95% CI 0.48-1.26) than the homozygous wild type allele carriers. Homozygous variant allele carriers of ADH1C Arg272Gln were at a 1.27 (95% CI 0.94-1.73) higher risk and heterozygous carriers were at a 1.09 (95%CI 0.87-1.36) higher risk of breast cancer than homozygous wild-type allele carriers although none of the associations were of statistical significance. They also reported that for both heterozygous and homozygous carriers of the variant allele of ADH1C Arg272Gln, alcohol intake was associated with a 1.12-fold (95% CI 1.01-1.24) and 1.19-fold (95% CI 1.01-1.39) higher risk per 10 g alcohol consumed per day. Alcohol intake was not associated with breast cancer among the homozygous wild-type carriers.

Alcohol consumption and genetic risk factors for colorectal cancer

30. Bongaerts et al. (2011) examined associations between alcohol consumption, the ADH1C genotype, and risk of CRC within the Netherlands Cohort Study on diet and cancer. In subjects who reported to have consumed equal amounts of total alcohol both 5 years before baseline and at baseline, drinkers of > 30 g/d with the ADH1C*2/*2 genotype were associated with an increased risk of CRC relative to abstainers with the ADH1C*1/*1 genotype, but the increase was not statistically significant (RR = 1.91, 95% CI: 0.68-5.43). The risk estimate in this exposure group increased slightly when compared with light drinkers of >0.5 - <5 g/d with the ADH1C*1/*1 genotype (RR = 2.32, 95% CI: 0.80-6.72) but the interaction term was not statistically significant (P > 0.05). In subjects who reported to have consumed equal amounts of total alcohol both 5 years before baseline and at baseline, drinkers of >30 g of alcohol per day were non-statistically significantly associated with an increased risk of CRC relative to abstainers (RR = 1.38; 95% CI: 0.80-2.38). This risk estimate for high-level drinkers became stronger when compared with light drinkers (RR = 1.74; 95% CI: 1.01-2.00). As the main effect of genotype, they observed that the ADH1C*2/*2 genotype was associated with a 42% increase in risk of CRC when compared with the ADH1C*1/*1 genotype. They concluded that both genotype and alcohol consumption were associated with an increased risk of CRC.

31. Ferrari et al. (2012) carried out a nested case-control study (1,269 cases matched to 2,107 controls by age, sex, study centre and date of blood collection) within the EPIC study to evaluate the impact of rs1229984(A) *(*ADH1B), rs1573496 *(*ADH7*)* and rs441 *(*ALDH2*)* polymorphisms on CRC risk. These polymorphisms were chosen because investigations in central European populations had indicated that they are associated with the risk of upper aerodigestive tract cancer and that the association is potentially modifiable by the level of alcohol consumption. Using the wild-type variant of each polymorphism as reference category, CRC risk estimates

were calculated using conditional logistic regression, with adjustment for matching factors. Total alcohol and wine intakes were significantly higher in cases than controls but beer and spirit intakes were not. Individuals carrying one copy of the rs1229984(A) *(*ADH1B) allele (fast metabolisers) showed an average daily alcohol intake of 4.3 g/day lower than subjects with two copies of the rs1229984(G) allele (slow metabolisers) (P<0.01). None of the polymorphisms was associated with risk of CRC. Heavy alcohol intake was more strongly associated with CRC risk among carriers of the rs1573496(C) allele, with odds ratio equal to 2.13 (95% CI: 1.26-3.59) compared with wild-type subjects with low alcohol consumption (*P*diff=0.07).

32. Kim et al. (2012) investigated the association between folate and alcohol intake, methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, and CRC risk in Koreans. 787 cases and 656 controls were recruited from 2 university hospitals. The controls had been hospitalized during the same period as the cases for a wide spectrum of non-neoplastic conditions. Cases had significantly lower BMI, number of patients with a positive family history for CRC, and were more likely to be current smokers and drinkers. MTHFR 677T homozygotes were at a lower risk of CRC (OR = 0.60, 95% CI: 0.46-0.78 for TT compared with CC/CT). High folate intake was associated with reduced CRC risk (OR = 0.64, 95% CI: 0.49-0.84 for high compared with low intake), and high alcohol consumption was associated with increased risk of CRC (OR = 1.76, 95% CI: 1.26-2.46 for higher compared with low intake). When the effects of alcohol consumption on the association between MTHFR C677T genotype and CRC were studied, a positive association was found between alcohol and CC/CT genotype (OR = 1.87, 95% CI: 1.29-2.71) for high vs. low alcohol consumption, but not for alcohol and TT genotype (OR = 0.89, 95% CI: 0.51-1.54). This association was stronger in patients with colon cancer than in patients with rectal cancer. Tobacco use alone, without alcohol consumption, was not shown to influence the probability of CRC presenting at a younger age. In the whole population studied, there was no significant difference in the number of CRC cases presenting at stage 2A or greater. However, in younger patients (<70 years of age), the current use of both alcohol and tobacco significantly increased the probability of presenting with a higher stage CRC, when compared to those patients never using either.

Summary

33. Since the most recent review of alcohol and cancer by IARC in 2009 (IARC, 2012), a number of epidemiological analyses have been published that have evaluated potential interactions of alcohol consumption with individual genetic risk factors. Many of these analyses have focussed on polymorphic genotypes in alcohol-metabolising pathways. Increased cancer risk with alcohol consumption in association with certain alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH) and/or cytochrome P450 (CYP) genotypes was reported from some studies on upper aerodigestive tract, breast, and colorectal cancers. One study in Korea

showed an interaction of alcohol consumption and MTHFR genotype in colorectal cancer risk. It should be noted that many of these studies have been carried out in Eastern Asian populations, in whom there are substantial differences in the proportions of different genotypes in comparison with European populations and hence, the applicability of these studies to the mostly Caucasian population in the UK may be limited. Furthermore, particular dietary habits and different types of alcohol consumed in different countries may result in study findings not being generalizable to other populations.

Questions for Members:

i. A short summary of this paper has been included in the draft statement in CC/2015/11. Taking in to account the findings in this paper and from the IARC reviews in the Annexes, is it possible to draw any specific conclusions on genetic polymorphisms and susceptibility to be included in the statement?

COC Secretariat
June 2015

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