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

First draft of Statement on consumption of alcoholic beverages and risk of cancer – consideration of significance to public health

1. The paper presents a first draft statement on alcohol and cancer bringing together the discussions of the Committee on alcohol and cancer from autumn 2013 to spring 2015 (Annex 1).

2. There are some sections to follow; these will either be circulated in advance of the meeting or an update provided at the meeting, while others will be updated in advance of the final draft statement.

Questions for the Committee

i). Members are asked to comment on the overall structure and content of the statement.

   a. Does the Committee wish to include a Lay or Executive Summary in the statement?

   b. A list of abbreviations has been included, would a glossary of terms also be helpful and if so please identify terms to include?

ii). Members are asked to provide detailed comments for each of the sections within the statement

COC Secretariat
June 2015

CC/2015/11 – Annex 1

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

First draft of Statement on consumption of alcoholic beverages and risk of cancer – consideration of significance to public health

First draft of statement

The attached document is a draft. It should not be cited and does not necessarily represent the views of the Committee. The final version of the statement will be published in due course on the COC website: https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc.

COC Secretariat
June 2015

Committee on CARCINOGENICITY

Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC)

Statement 2015/SX

Statement on consumption of alcoholic beverages and risk of cancer - consideration of significance to public health (First Draft)

https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc

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Committee on CARCINOGENICITY

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Statement on consumption of alcoholic beverages and risk of cancer - consideration of significance to public health (First Draft)

A Lay or Executive Summary will be added here as required

Table of Contents to be added here

Abbreviations

ABV – alcohol by volume

AC – adenocarcinoma

ADH – alcohol dehydrogenase

ALDH – aldehyde dehydrogenase

ARCAGE – alcohol-related cancers and genetic susceptibility in Europe

BRCA1, BRCA2 – breast cancer 1, breast cancer 2

CMO – Chief Medical Officer

COC – Committee on Carcinogenicity

COM – Committee on Mutagenicity

CRC – colorectal cancer

CRUK – Cancer Research UK

CYP – cytochrome P450

DH – Department of Health

ER – oestrogen receptor

g – grammes

HBV – hepatitis B virus

HCV – hepatitis C virus

HL – Hodgkin's lymphoma

HNC – head and neck cancer

HPV – human papilloma virus

IARC – International Agency for Research on Cancer

INHANCE – International Head and Neck Cancer Consortium

ml – millilitres

MTHFR – methylenetetrahydrofolate reductase

NHL – non-Hodgkin's lymphoma

PHE – Public Health England

SCC – squamous cell carcinoma

UADT(C) – upper aerodigestive tract (cancer)

Glossary of terms ***[if required]***

Committee on CARCINOGENICITY

CC/2015/SX

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Statement on consumption of alcoholic beverages and risk of cancer - consideration of significance to public health (First Draft)

Introduction

1. There are more than 200 types of cancer, each with different causes, symptoms and treatments. According to recent data from Cancer Research UK, around 331,000 new cases of cancer were diagnosed in the UK in 2011, whilst in 2012 there were around 162,000 deaths from cancer. Overall cancer incidence rates in Great Britain have increased by more than a third (23% in males, 43% in females) since the mid-1970s, with most of this rise occurring before the end of the 1990s (CRUK cancer statistics, accessed June 2015). Lifestyle choices such as alcohol consumption are known risk factors for certain types of cancer. In 2012, the Government published their Alcohol Strategy (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224075/alcohol-strategy.pdf), which led to the initiation of a Department of Health (DH) and Public Health England (PHE) evidence-based review of alcohol and alcohol guidelines. *[text will be added here about likely timescales of this review closer to the time of publication of the COC statement]*.

2. This COC statement considers the most recently published literature on alcohol consumption and cancer risk. The causal association between alcohol and cancer, even where the overall increase in risk is small, has serious public health implications due to the large number of people who consume alcohol. In addition, consumption of alcoholic beverages may be one of the few risk factors for cancer where intervention might offer some scope for reduction in cancer risk.

Previous authoritative reviews of the carcinogenicity of alcoholic beverages

COC

3. The COC reviewed the carcinogenicity of alcoholic beverages in 1995 as part of the health input to the Interdepartmental Working Group on the Sensible Drinking Message (DH, 1995).

4. In 2004, the COC published a statement on alcohol and breast cancer and concluded that it is prudent to assume that drinking alcoholic beverages may cause breast cancer in women (COC, 2004). The research considered by the Committee indicated that approximately 6% (between 3.2% and 8.8%) of breast cancers registered in the UK each year could be prevented if drinking was reduced to a very low level (i.e. less than 1 unit/week). The evidence suggested that the risk of breast cancer associated with drinking alcoholic beverages increases with prolonged consumption of alcohol. The statement also provided an evaluation of the cumulative risk of breast cancer with additional units of alcohol consumed per day above the national average of 1 unit/day.

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

International Agency for Research on Cancer

6. The World Health Organisation's International Agency for Research on Cancer (IARC) reviewed the carcinogenicity of alcoholic beverages in 1988 and concluded that cancers of the upper aerodigestive tract (oral cavity, pharynx, larynx, oesophagus) and the liver are causally related to the consumption of alcoholic beverages.

7. In 2007, IARC carried out an updated review of the epidemiological evidence on the possible association between alcoholic beverage consumption and cancer at the following anatomical sites (cancers of the oral cavity and pharynx, larynx, oesophagus, liver, breast, stomach, colon and/or rectum, pancreas, lung, urinary bladder, endometrium, ovary, uterine cervix, prostate, kidney, lymphatic and haematopoietic systems, testis, brain, thyroid, plus melanoma and other female cancers (vulva and vagina)). Their previous conclusion from 1988 that cancers of the upper aerodigestive tract (oral cavity, pharynx, larynx, oesophagus) and the liver are causally related to the consumption of alcoholic beverages was reaffirmed. In addition, in 2007 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, 2010).

8. Following a further review in 2009, IARC reported in addition to the 2007 conclusions an association between alcohol consumption and cancer of the

pancreas. The IARC working group also concluded in 2009 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 (IARC, 2012).

Consumption of alcoholic beverages in the U.K.

9. The predominant types of commercially produced alcoholic beverages consumed in the UK are beer, wine and spirits. Some beverages are a combination of alcohol types such as fortified wine, in which spirits are added to wine. Alcopops were introduced to the drinks market in the mid-1990s and are a ready-mixed alcoholic drink of either wine or spirits with a soft drink such as lemonade. The strength of alcoholic beverages is commonly expressed as *percentage* alcohol[1] by volume (ABV*)*. Typically, beer contains 4–5% ABV, wine contains about 12% ABV, and distilled spirits contain about 40% ABV. However, lower or higher ethanol content in alcoholic beverages is also possible. Estimates of the consumption of alcoholic beverages in the UK are generally reported in terms of units of alcohol or grammes (g) of ethanol consumed per day. One UK unit of alcohol is defined as 10 millilitres (ml) or 8 g pure ethanol (the specific gravity of ethanol is 0.8).The number of UK units of alcohol in a drink can be determined by multiplying the volume of the drink (in ml) by its ABV and dividing by 1000. This calculation allows a standardised comparison of the volume of pure alcohol between alcoholic beverages.

Current Government guidelines

10. Official guidance on alcohol consumption in the UK was first introduced in 1987. The current guidelines for sensible drinking, which date from 1995, state that men should not regularly drink more than 3 to 4 units of alcohol per day and women should not regularly drink more than 2 to 3 units of alcohol per day. 'Regularly' means drinking most days or every day (DH, 1995). The Government also offers guidance to women who are pregnant or trying to conceive, stating they should avoid drinking alcohol. If they do choose to drink, the guidance, to protect the baby, is to drink no more than 1 to 2 units of alcohol once or twice a week, and not to get drunk (NHS Choices, accessed 2015). In 2009, the Chief Medical Officer (CMO) of England published guidance on alcohol consumption and children http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_110258).

[May add further text here about new guidelines as appropriate]

[1] The term 'alcohol' may be used throughout the text to refer to the ethanol contained in alcoholic beverages.

Data on UK consumption

11. In UK surveys, heavy drinking is defined as exceeding twice the Government's daily recommended maximum on a single day (i.e. drinking more than 8 units on at least one day for a man and drinking more than 6 units on at least one day for a woman). Very heavy drinking is defined as exceeding three times the government's recommended limits, hence drinking more than 12 units for men and 9 units for women on at least one day. Binge drinking refers to episodic excessive drinking. In the UK, for the purposes of research and surveys, binge drinking is defined as the consumption of twice the recommended daily limit of alcohol in a day (ONS, 2015).

12. There is a wide geographic variation in overall alcohol consumption levels, both worldwide and within the EU. In the UK, alcohol consumption by adults has increased over the last 30 years, peaking in 2004 and with a subsequent downward trend. This recent decrease may be attributed to an increase in the number of abstainers: the percentage of adults reporting that they do not drink alcohol at all increased from 19% to 21% between 2005 and 2013. Evidence supports the view that men consume more alcohol than women, with the frequency of consumption increasing with age. Younger adults are more likely to drink heavily on a single occasion, however, this group also contains the fastest growing proportion of non-drinkers: there was a 40% increase from 2005 to 2013 in the number of young adults reporting that they do not drink alcohol at all, with 27% of 16–24 year-olds reporting total abstention in 2013 (ONS, 2015). It should be noted that, overall, there is substantial under-reporting of alcohol consumption, as sales data exceed consumption calculations, with greater under-reporting in heavy drinkers (Bellis, 2015).

Present COC review of alcohol and cancer risk

COC consideration of new evidence published since 2009 on alcohol consumption and cancer risk

13. The Committee considered review papers prepared by the PHE Toxicology Unit at Imperial College on the published epidemiology studies on alcohol and the following cancer sites: upper aerodigestive tract cancers (grouped), oral cavity, pharynx, larynx, oesophagus, liver, colorectum, female breast, and pancreas. For details of the literature searches underpinning these papers, see Annex A. In addition, individual meta-analyses on inverse associations of alcohol consumption with kidney cancer, Hodgkin's and non-Hodgkin's lymphoma, and extrahepatic bile system cancer were also reviewed.

Scoring scheme

14. A quality scoring scheme was adopted for all individual studies reviewed to provide an informal assessment of the studies and to help to identify key papers for potential future work on dose-response. This scoring scheme was similar to the Newcastle-Ottawa star scoring scheme and is attached as Annex B. The scoring scheme was used for the papers on upper aerodigestive tract cancers, oral cavity, pharynx, larynx, oesophagus, liver, colorectum, and female breast cancers.

Definitions of alcohol intake levels

15. In undertaking the review, the Committee noted that there was substantial variation between studies in the reporting of alcohol intake levels and the terminologies used to describe levels of alcohol intake. Amounts of alcohol intake might be reported variously, for example, as grammes, millilitres, ounces, units or drinks consumed per day, week, month or year, as drink-years or g-years. In addition, the definition of a standard drink or unit of alcohol can vary substantially between different countries (see: http://www.icap.org/table/Internationaldrinkingguidelines). For example, in the UK, one unit is considered to contain 8 g alcohol, one unit in the USA contains 14 g alcohol and in several European countries, one unit is 10 g alcohol. This can result in different levels used as benchmarks in epidemiological studies from different countries or continents. It should be noted that where alcohol intake levels have been referred to throughout the text in terms of 'drinks' (e.g., drinks/day), this refers to a standardised drink as specified in each individual study and should not be considered as equivalent between studies. In addition, many studies stratified subjects into descriptive categories of alcohol drinking levels (e.g., light, medium, heavy), but these descriptive terms are not absolute and may vary between studies. Where possible, alcohol intake levels are also reported as the equivalent in grammes of ethanol.

COM review

16. As part of this review, the COC asked its sister committee, the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM), to update its 2000 review on the evidence regarding the potential for alcoholic beverages to induce mutagenicity *in vivo*. The COM considered the available evidence to September 2014 (COM, 2015).

Alcohol and upper aerodigestive tract cancers

17. Cancers of the upper aerodigestive tract (UADT) (also often referred to as 'head and neck' cancers) traditionally comprise cancers of the oral cavity, pharynx, larynx and oesophagus. The majority of these cancers are squamous cell carcinomas (SCC) derived from the mucosal lining of these common regions. These

cancers are often combined into a single group for the purposes of epidemiological studies.

18. Tobacco smoking is the most important risk factor for upper aerodigestive tract cancers and smoking cessation results in a decrease in risk. Consumption of alcoholic beverages also increases the risk of upper aerodigestive tract cancers and a strong interaction between these two exposures has been noted. Other established risk factors for upper aerodigestive tract cancer sites include betel quid/areca nut chewing in India and Taiwan, occupational exposure to certain chemicals, poor oral health, and human papilloma virus (HPV) infection. Statistics relating to incidence and mortality for upper aerodigestive cancers are summarised in the relevant sections relating to each individual cancer type, below.

Alcohol and upper aerodigestive tract cancers (grouped)

19. In their evaluation of the carcinogenicity of alcohol in 2009, IARC stated that there is evidence that consumption of alcoholic beverages is causally related to cancers of the upper aerodigestive tract, as it is for cancers of the oral cavity and pharynx, larynx and oesophagus separately (IARC, 2012). The COC reviewed epidemiological reports on alcohol and cancers of the upper aerodigestive tract (considered as a single grouping) published since the last IARC review in 2009. Studies varied with respect to which cancer sites were included under the umbrella of 'upper aerodigestive tract' or 'head and neck' cancer, but did not include sites other than oral cavity, pharynx, larynx and/or oesophagus.

20. A dose-dependent increase in risk with alcohol intake was noted in the majority of the analyses reported. A pooled analysis of case-control studies from the International Head and Neck Cancer Epidemiology Consortium (INHANCE) indicated significantly increased risk associated with drinking ≥ 3 drinks/day (equivalent to approximately 37 g ethanol/day) and a strong and multiplicative combined effect of alcohol and tobacco smoking (Hashibe et al., 2009). Analyses from two large studies – the Netherlands Cohort Study (Maasland et al., 2014) and the Europe-based ARCAGE Study (Marron et al., 2012) – indicated that the increased risk of upper aerodigestive tract cancer associated with alcohol intake was not significantly different by breakdown for different types of alcoholic drinks, supporting the hypothesis that the carcinogenic effects are due to a common ingredient or metabolite (ethanol or acetaldehyde).

21. The Committee concluded that the recently available epidemiological studies on alcohol consumption and upper aerodigestive cancer risk added weight to the existing view that alcohol consumption is causally associated with the risk of upper aerodigestive tract cancers.

Oral cavity and pharynx

22. 'Oral cancer' as an overall term represents a group of cancers that includes cancers of the lip, tongue mouth, oropharynx, piriform sinus, hypopharynx, and other ill-defined sites of the lip, oral cavity and pharynx that are considered as part of the pharynx. Cancers of the nasopharynx are usually considered as part of other head and neck sites although they are often reported in the literature with oral cancers. The CRUK website notes that "There is no standard definition of oral cancer and different studies report data using different combinations of ICD codes so caution needs to be used when making comparisons between analyses." (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oral-cancer#heading-Four).

23. Oral cancer was the 16th most commonly diagnosed cancer in the UK in 2011, accounting for 2% of all new cases. It was the 12th most commonly diagnosed cancer in males (4,510 men, 3% of male cancers) and the 16th most commonly diagnosed in females (2,257 women, 1% of female cancers). Overall, around one-fifth of oral cancers in the UK are diagnosed in people ≥ 75 years old (around 15% for males, 29% for females), whilst the 50–74 age group contributes around 70% of cases in men and around 60% of cases in women. Oral cancer incidence rates in the UK have risen by a third in the last decade. Around 2,100 people died of oral cancer in 2012 in the UK, of whom around two-thirds were men and around three-quarters were ≥ 60 years old. Oral cancer mortality rates have increased by around 10% in the last decade (CRUK cancer statistics, accessed June 2015).

24. Tobacco smoking and drinking alcohol are established risk factors for oral cancer. Infection with the human papillomavirus (HPV) and some other infections are also associated with increased risk.

25. IARC have previously stated that alcohol causes oral cavity and pharyngeal cancer. The COC reviewed epidemiological reports on alcohol and cancers of the oral cavity and pharynx published since the last IARC review in 2009 (IARC, 2012). The Committee noted that there was a general lack of uniformity among the studies evaluated in the definitions used to describe oral cavity/pharyngeal cancer, and that many of the studies did not take into account the human papilloma virus (HPV) status of the participants.

26. A statistically significant positive association between alcohol consumption and cancer of the oral cavity (as a whole) was reported in the majority of studies, regardless of study type (5 meta-analyses, 2 cohort and 6 case-control studies), and the risk in these studies was consistently elevated at the highest levels of alcohol consumption. There was less consistent evidence of a positive association at lower alcohol drinking levels although one cohort (Shanmugham et al. 2010) and two case-control studies (US/French) (Hakenewerth et al., 2011; Radoi et al., 2013) provided evidence of significantly negative associations at lower levels of intake. There were

no clear indications from the reported evidence that consumption of a specific type of alcoholic beverage is associated with an increased risk of cancer of the oral cavity. With regard to subtypes within the oral cavity, the findings from a French case-control study (Radoi et al. 2013) and an international meta-analysis (Turati et al. 2010) suggested that the tongue (and possibly the floor of the mouth) may present specific target sites within the mouth.

27. All studies evaluated (3 meta-/pooled analyses, 1 cohort and 1 case-control study) showed a statistically significant positive association between alcohol consumption and risk of cancer of the pharynx. Similar to the oral cavity, there was no consistent evidence of an association at lower levels of alcohol drinking, and no consistent evidence that consumption of a specific type of alcoholic beverage is associated with a particularly elevated risk of cancer of the pharynx. With regard to cancer subtypes within the pharynx, all studies reported significant positive associations for alcohol drinking and risk of cancer of the oropharynx (Turati et al. 2010; Lubin et al. 2011; Smith et al., 2010; Hakenewerth et al., 2011). This risk was found to be elevated in North American and European women compared to their male counterparts, although there was no significant association with cumulative exposure (drink-years) for either sex (Lubin et al., 2011). The same studies reported similar and stronger associations for cancer of the hypopharynx. Cancer arising in the 'orohypopharynx' was investigated in a Dutch cohort study that observed a significant positive association with heavy alcohol consumption (Maasland et al. 2014). There was no strong evidence to suggest that alcohol consumption was associated with the risk of cancer of the nasopharynx.

28. Three international meta-analyses provided data on the risk of cancer of the oral cavity and pharynx (combined) and alcohol consumption (Tramacere et al 2010; Bagnardi et al. 2013; 2015). These analyses showed a statistically significant positive association between alcohol consumption and cancer of the oral cavity and pharynx (combined) at all levels from light (≤ 1 drink/day or 12.5 g ethanol/day) to heavy (≥ 4 drinks/day or > 50 g ethanol/day) levels of consumption, with a clear dose-response. Finally, two Latin American case-control studies reported significant positive associations for ever drinking and increasing cumulative exposure of alcohol and the risk of cancer of the oral cavity and oropharynx (combined) (Szymanska et al., 2011; Ferreira-Antunes et al., 2013).

29. The Committee concluded that there was consistent evidence of an association of alcohol consumption with these oral cancer sites (apart from the nasopharynx) and a dose-response effect. This supported and added weight to the existing conclusions.

Larynx

30. Laryngeal cancer is approximately four times more common in men than women. In 2011, 2,360 people were diagnosed with laryngeal cancer in the UK, of

whom around 1,900 were men and 400 were women – around 1% and 0.3%, respectively, of cancers diagnosed in men and women, a rate of around 6 per 100,000 males and 1 per 100,000 females in the population. Incidence of laryngeal cancer increases with age, with around three-quarters of diagnoses in the period 2009-2011 being made in people ≥ 60 years old. There were around 780 deaths from laryngeal cancer in the UK in 2012, representing 0.7% and 0.2% of all cancer-related deaths in men and women, respectively (CRUK cancer statistics, accessed June 2015).

31. Major risk factors for laryngeal cancer are tobacco smoking and drinking alcohol – in particular, the combination of smoking and drinking regularly. Other potential risk factors include poor diet, human papilloma virus (HPV) infection, medical conditions such as HIV/AIDS, previous cancers, some occupational and/or environmental exposures, and family history of head and neck cancer.

32. IARC has previously stated that alcohol causes cancer of the larynx. The COC reviewed epidemiological reports on alcohol and cancer of the larynx published since the last IARC review carried out in 2009 (IARC, 2012). The majority of new studies were pooled- and meta-analyses. A pooled analysis using data from the International Head and Neck Cancer Epidemiology (INHANCE) consortium (European and American populations) showed statistically increased risk of laryngeal cancer at intakes of 5-10 alcoholic drinks/day (125 g ethanol/day) but not at lower levels (Lubin et al., 2010). A meta-analysis of studies published worldwide indicated increased risk in moderate (>1 – <4 drinks/day or > 12.5 – 50 g ethanol/day) and heavy (≥ 4 drinks/day or ≥ 50 g ethanol/day), but not light (≤ 1 drink/day or ≤ 12.5 g ethanol/day) drinkers (Islami et al., 2010). Two meta-analyses by Bagnardi and colleagues, which included studies from Europe, North America and Asia, also indicated increased risk of laryngeal cancer associated with moderate (the interval with midpoint ≤ 50 g ethanol/day) and heavy (the interval with midpoint > 50 g ethanol/day), but not light (the interval with midpoint ≤ 12.5 g ethanol/day) alcohol intakes (Bagnardi et al., 2013; Bagnardi et al., 2015).

33. Overall the Committee concluded that the new evidence added further weight to the causal relationship between alcohol and cancer of the larynx, with increased risk noted in moderate and heavy drinkers (i.e. at levels > 12.5 g ethanol/day) but not in light drinkers. It was noted that the combination effect with smoking was marked.

Oesophagus

34. Oesophageal cancer was the 13th most commonly diagnosed cancer in the UK in 2011, accounting for 3% of all new cancer cases, of which approximately two-thirds were in men. It was the 8th most commonly diagnosed cancer in males (5,582 cases, around 18 per 100,000 male population) and the 14th most common in females (2,750 cases, around 9 per 100,000 female population). Incidence of oesophageal cancer is strongly related to age, with 83% of the cases diagnosed in

the period 2009-2011 occurring in people aged ≥ 60 years. Oesophageal cancer was the 6th most common cause of cancer death in the UK in 2012, accounting for 5% (7,701 persons) of all deaths from cancer (17 and 8 deaths per 100,000 male and female population, respectively) (CRUK cancer statistics, accessed June 2015).

35. The majority of oesophageal cancers fall into one of two subtypes: squamous cell carcinoma (SCC) or adenocarcinoma (AC). Oesophageal SCC, which accounted for more than a quarter (28%) of oesophageal cancers diagnosed in England in 2008-2010, is found more commonly in the upper third and middle of the oesophagus, developing from the squamous cells that make up the inner lining of the oesophagus. Oesophageal AC, which accounted for just over one-half (55%) of all oesophageal cancers diagnosed in England in 2008-2010, derives from mucous-producing glandular cells and occurs mostly in the lower third of the oesphagus. Tobacco use increases the risk of both SCC and AC oesophageal cancer. Oesophageal SCC has also been strongly linked with alcohol consumption. By comparison, research has indicated that oesophageal AC is linked with excess body weight and long-term acid reflux, which can lead to a precancerous condition called Barrett's oesophagus (CRUK, 2015).

36. IARC previously stated that there was sufficient evidence to conclude that cancer of the oesophagus is causally related to the consumption of alcohol, and this position was reaffirmed after their 2009 review of alcohol and cancer (IARC, 2012). The COC evaluated epidemiological literature published since the 2009 IARC review to gain further insights into this association. Studies covered a variety of geographical regions, including the UK, Europe and the United States. A number of the studies reported on oesophageal cancer by subtype, and the evidence reviewed supported the view that oesophageal SCC is linked with alcohol consumption, whereas oesophageal AC is linked with other risk factors but not causally related to alcohol intake. The meta-analyses and pooled analysis that reported on oesophageal cancer or oesophageal SCC all indicated a positive, causal association between drinking alcohol and the disease, with a dose-response observed. The one pooled analysis that reported on oesophageal AC did not find evidence for an association with alcohol consumption (Tramacere et al., 2012). The individual cohort and case-control studies evaluated also provided further evidence for a causal association between alcohol consumption and oesophageal cancer or oesophageal SCC, but not oesophageal AC. A large-scale evaluation from the Europe-based ARCAGE study did not find a significant association between drinking alcohol and oesophageal cancer, although the analysis was not divided into the subtypes of SCC and AC (Marron et al., 2012). A Brazilian (Szymanska et al., 2011) and a US (Navarro Silvera et al., 2011) study observed a significant association of alcohol drinking with oesophageal SCC, whilst an Australian study (Pandeya et al., 2013) reported an association with heavy drinking.

37. The Committee concluded that the evidence available since the last IARC review added further weight to the causal association between alcohol and oesophageal SCC. A clear dose-response was observed, and effects were evident with light drinking as well as moderate and heavy drinking. There was no evidence of an association between alcohol consumption and oesophageal AC.

Alcohol and female breast cancer

38. Breast cancer is currently the most common cancer in women in the UK, accounting for 30% of all new cancers diagnosed in 2011 (49,936 cases, around 155 per 100,000 women). Female breast cancer incidence is strongly related to age, with around 80% of the cases diagnosed in the period 2009-2011 occurring in women ≥ 50 years old, and around a quarter in women ≥ 75 years old. In 2010, in the UK, the lifetime risk of developing breast cancer was 1 in 8 for women. Breast cancer was the 2nd most common cause of cancer death among women in the UK in 2012, accounting for 15% (11,716 women) of female deaths from cancer – around 36 per 100,000 women in the population (CRUK cancer statistics, accessed June 2015).

39. Risk of breast cancer depends on many factors, including age, genetics (including BRCA1 and BRCA2 gene mutations) and exposure to risk factors. It has been estimated that around 27% of female breast cancers in the UK are linked to lifestyle factors, which include oestrogen exposure, being overweight and obesity, alcohol, and some occupational exposures. IARC and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) cite the following factors for which there is convincing evidence of association with breast cancer: alcoholic beverages, diethylstibestrol, oestrogen-progestogen contraceptives and menopausal therapy, X- and gamma radiation, body fatness and adult attained height. They also note other risk factors for which there is probable evidence, including digoxin, oestrogen menopausal therapy, ethylene oxide, shift-work, tobacco smoking, height, weight and body-fat factors, and dietary fat intake. Breastfeeding and physical activity are associated with reduced risk of breast cancer.

40. In 2004, the COC evaluated all the available published research to June 2003 on alcohol consumption and breast cancer, and concluded that drinking alcoholic beverages may result in breast cancer in women. Research considered by the Committee indicated that approximately 6% (3.2% to 8.8%) of breast cancers registered in the UK each year could be prevented if drinking was reduced to less than 1 unit/week. It was noted that this implies that 1 drink/day has a measurable effect. Following their evaluation in 2007, IARC also reported that alcohol consumption is causally associated with breast cancer (IARC, 2010) and this position was reaffirmed in 2009 (IARC, 2012).

41. The COC reviewed new data published since the 2009 IARC evaluation. It was noted that the meta-analyses did not all observe a positive association. Three studies reported an increased risk: Trentham-Dietz et al., 2014 – a combined analysis of 5 population-based case-control studies in the US; Seitz et al., 2012 – a meta-analysis of data on light alcohol drinking and breast cancer risk using data from 70 case-control and 43 cohort studies identified by database search; and Brennan et al. (2010) – a systematic review and meta-analysis of cohort and case-control studies to determine the effect of dietary patterns including alcohol drinking patterns on breast cancer risk. One Chinese study (Li et al., 2011) reported a decreased risk and another Chinese study (Gou et al., 2014) observed no association between breast cancer risk and alcohol consumption. The large meta-analysis of Seitz et al. (2012) indicated a modest but significant 4% increase in risk of breast cancer associated with light drinking (≤ 1 drink/day or ≤ 12.5 g ethanol/day). Overall, the Committee concluded that this new evidence is consistent with the view that alcohol consumption is causally associated with breast cancer.

42. It was noted that since the last IARC review, more studies had been reported that had evaluated the relationship between alcohol and breast cancer as a breakdown by type of breast cancer (ductal or lobular) or receptor status. The Committee found that the data were conflicting for tumour type. The cohort study of Li et al. (2010) observed a statistically significant increase in lobular but not ductal breast cancer risk with increasing alcohol consumption. Regarding oestrogen receptor (ER) status, there was increasing evidence to indicate a stronger association between alcohol consumption and ER-positive than ER-negative tumours, however, risks were increased for tumours with either receptor status. It was noted that there were some limitations in terms of disease ascertainment, exposure assessment methods and lack of adjustment for confounders in some of the studies.

Alcohol and liver cancer

43. Liver cancer was the 18th most commonly diagnosed cancer in the UK in 2011, accounting for 1% of all new cancer cases. It was the 14th most common cancer in males (2% of the male total) and the 19th most common in females (1% of the female total). There were 4,348 new cases of liver cancer, of which around two-thirds were in males (2,776 cases; around 9 per 100,000 male population) and one-third in females (1,572 cases; around 5 per 100,000 female population). Liver cancer incidence is strongly related to age. In the UK between 2009-2011, around 43% of cases were diagnosed in people ≥ 75 years old and 81% of cases in people ≥ 65 years old. Liver cancer was the 12th most common cause of cancer death in the UK in 2012, accounting for 3% of all deaths from cancer – 2,675 men (9 per 100,000 male population) and 1,839 women (6 per 100,000 female population) (CRUK cancer statistics, accessed June 2015).

44. It has been estimated that 42% (49% in males and 28% in females) of liver cancer cases in the UK are associated with lifestyle factors, including tobacco smoking (23%), infections (16%), and alcohol consumption (9%). An estimated 90% of liver cancer cases in developing countries and 40% in developed countries are caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infections. Oral contraceptives, ionising radiation, some occupational exposures, being overweight and obesity have been cited as possible risk factors. Diseases with a genetic aetiology that can increase the risk of liver cancer include haemochromatosis and Wilson's disease. Dietary exposure to aflatoxins from crops such as corn and peanuts is a risk factor that is present mostly in developing countries.

45. IARC has previously stated that alcohol consumption is causally associated with liver cancer (IARC, 1988, 2010, 2012). The COC reviewed epidemiological literature published since the 2009 IARC review that reported evaluations of the association of alcohol intake with liver cancer. Considering the data from pooled and meta-analyses, the Committee noted that the meta-analysis of Bagnardi et al. (2013) did not find a significant association between light drinking (1 drink/day or < 12.5 g ethanol/day) and liver cancer. The dose-response analysis of Turati et al. (2014) indicated that consumption of 12.5 g ethanol/day gave an estimated excess liver cancer risk of 6%, whilst excess risks of 13%, 29%, 46% and 66% were observed for intakes of 25, 50, 75 and 100 g ethanol/day, respectively. These data clearly indicate that heavy drinking is associated with increased liver cancer risk. The Committee considered the biological plausibility of the apparent J- or U-shaped dose-response curve for alcohol and liver cancer reported in some of the studies. Overall, the Committee concluded that it was difficult to suggest a plausible mechanism for a U-shaped dose-response curve, that there were shortcomings in the data and that it would be difficult to investigate the size of the effect with the methods available.

46. The Committee highlighted the predominance of studies in Asian populations and discussed the applicability of these studies to the UK population. The higher incidence of liver cancer related to hepatitis in Asian countries and the fact that studies did not always adjust for hepatitis in the analysis were noted. It was not clear whether this would affect relative risk estimations, while it would be important in terms of absolute risk. In addition, it was noted that some of the studies were designed to investigate hepatitis rather than alcohol. The deficiency in alcohol dehydrogenase 2 (ADH2) in Asian populations was noted and it was not known what the prevalence of this deficiency is in the UK population but it was thought to be rare. It was also noted that the Asian population in the UK is not dominated by the (predominantly East Asian) populations studied in the literature. Finally, the difference in the types of alcohol consumed in Asia compared to types consumed in the UK, and the impurities within the alcohol, was also highlighted as limiting the applicability of the data to the UK population.

Alcohol and colorectal cancer

47. Colorectal ('bowel') cancer was the 3rd most commonly diagnosed cancer in men and the 3rd most commonly diagnosed cancer in women in the UK in 2011, with 41,581 new cases, of which 56% were in males (23,171 cases, around 58 per 100,000 male population) and 44% in females (18,410 cases; around 38 per 100,000 female population). Colorectal cancer incidence rates have increased by 6% over the last decade. Incidence is strongly related to age, and 95% of cases occur in people ≥ 50 years old. Colorectal cancer was the 2nd most common cause of cancer death in the UK in 2012, accounting for 16,187 deaths, of which 8,795 were men (21 per 100,000 male population) and 7,392 were women (13 per 100,000 female population) (CRUK cancer statistics, accessed June 2015).

48. CRUK note that the risk of colorectal cancer is related to age, genetics and exposure to specific risk factors. It has been estimated that slightly more than half of colorectal cancers in men and women in the UK are attributable to lifestyle factors, including consumption of red and processed meats, being overweight or obese, alcohol consumption, smoking, and ionising radiation. Fibre consumption and physical activity are protective. Asbestos exposure and some medical conditions, such as inflammatory bowel diseases, can also be associated with increased risk.

49. In 2007, IARC considered that there was sufficient evidence to conclude that cancer of the colorectum is causally related to the consumption of alcoholic beverages (IARC, 2010) and this was reaffirmed in their 2009 review (IARC, 2012). The COC reviewed epidemiological studies on alcohol and colorectal cancer published since the 2009 IARC review. The Committee highlighted uncertainties and limitations of the data, relating for example to the use of categorical groups and the appropriateness of reference categories. A meta-analysis by Fedirko et al. (2010) showed evidence for an increased risk of colorectal cancer associated with moderate (> 1 drink/day or > 12.5 g ethanol/day) and heavy, but not light (≤ 1 drink/day or ≤ 12.5 g ethanol/day), alcohol consumption. This meta-analysis included many of the studies that had been reviewed previously by IARC. A pooled analysis by Nan et al. (2013) found a significantly increased risk of colorectal cancer in individuals consuming > 30 g ethanol/day compared with non-drinkers, however no difference between the two groups was observed after the introduction of food fortification with folate. The Committee considered that findings were generally variable, with the majority of individual cohort and case-control studies showing no statistically significant positive association between alcohol consumption and colorectal cancer, but some of the meta-analyses showing associations at > 1 drink/day or > 30 g/day.

Alcohol and pancreatic cancer

50. Pancreatic cancer was the 10th most commonly diagnosed cancer in the UK in 2011, accounting for 3% of all new cancers. It was the 13th most common cancer in

men (4,328 cases, 14 per 100,000 male population) and the 9th most common cancer in women (4,445 cases, 14 per 100,000 female population). Pancreatic cancer incidence is strongly related to age, with almost one-half of cases being diagnosed in people ≥ 75 years old and 95% of cases in people ≥ 50 years old. Pancreatic cancer was the 5th most common cause of cancer death in the UK in 2012, accounting for 4,279 male deaths (14 per 100,000 male population) and 4,383 female deaths (14 per 100,000 female population). In 2010, in the UK, the lifetime risk of developing pancreatic cancer was 1 in 73 for men and 1 in 74 for women (CRUK cancer statistics, accessed June 2015).

51. Tobacco is a major risk factor for pancreatic cancer and body fatness is cited by IARC as a convincing risk factor. Probable risk factors are cited as alcohol, ionising radiation, excess abdominal fat, red meat and attained height. Some other factors that have been associated with pancreatic cancer risk include certain medical conditions (e.g., pancreatitis, diabetes), genetic conditions such as Peutz-Jeghers syndrome, and hepatitis B virus (HBV) and *H. pylori* infections.

52. In their 2009 review, IARC concluded that high alcohol intake is associated with a small increased risk of pancreatic cancer (IARC, 2012). The COC reviewed epidemiological studies on alcohol and pancreatic cancer published since the 2009 IARC review. The Committee noted that the exact role of alcohol consumption in pancreatic cancer remains unclear, as other risk factors are involved. However, the Committee concurred that the available new evidence supports the conclusion of IARC in 2009 that low-to-moderate alcohol consumption (up to 30 g/day) is not associated with increased pancreatic cancer risk. Heavier drinking (> 30 g/day) may, however, increase pancreatic cancer risk.

53. In their conclusion on pancreatic cancer and alcohol, IARC acknowledged the possibility of residual confounding due to smoking. In studies where smoking status was considered separately, the COC noted that the data were suggestive of an effect of alcohol on pancreatic cancer independent of the effect of smoking.

54. It was also noted that recent evidence has included data on drinking patterns, such as daily drinking, binge drinking and volume consumed over a week. One case-control study in the US (Gupta et al., 2010) found an association of alcohol consumption with pancreatic cancer in men but not women, with increased risk ranging from 1.5 to 6.0-fold based on dose, duration and pattern of alcohol consumption reported. In men, a history of binge drinking (defined as consumption of ≥ 5 drinks/day or ≥ 70 g alcohol/day) conferred a 3.5-fold increased risk, and the risk increased with increasing average number of drinks consumed during the binging episode and with frequency of binge drinking each month.

55. Overall, the Committee concluded that the new evidence supports the conclusion of IARC in 2009 that high alcohol intake is associated with a small increase in risk of pancreatic cancer.

Alcohol and other cancers

56. The COC reviewed some individual meta-analyses reporting inverse associations between alcohol and risk of kidney cancer, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, and extrahepatic bile system cancer.

Kidney

57. The COC considered two meta-analyses that both showed an inverse relationship between alcohol consumption and renal cell carcinoma risk (Song et al., 2012, Bellocco et al., 2012). Although the data provided evidence of an inverse relationship, it was not clear what mechanisms could be involved. It was suggested that the development of tumours might be influenced by altered fluid consumption impacting on urine production. The Committee did note that in the small number of studies that considered heavy drinking, the risk reduction levelled off at intakes of 20–25 g alcohol/day. The Committee concluded that the studies indicated an inverse association between alcohol consumption and renal cell carcinoma risk, but that there was no consistent dose-response.

Non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL)

58. Two meta-analyses (one for NHL and one for HL) suggested a decrease in risk of these cancer types among people consuming alcohol as compared with non-drinkers but a significant dose-response was not observed for either cancer type (Tramacere et al., 2012a, 2012b). The authors of the meta-analyses themselves suggested caution in interpretation of the findings. The Committee raised concerns about the consistency of the classification of cancers of this type and commented that this was confounded by the heterologous tumour pathology. It was queried whether these findings could be artefactual, as there was no immediately obvious mode of action that could explain the association. Overall, it was concluded that, although based on only a few cases, the finding was very consistent and thus could not be discounted.

Extrahepatic bile system cancer

59. The COC also considered a meta-analysis showing an inverse association of alcohol consumption and extrahepatic bile system cancer (Kan et al., 2011). The Committee noted that this was a rare cancer site with a large number of potential risk factors. The adjusted odds ratio as compared with non- or low-level drinkers was 0.8 for moderate drinkers and 1.58 for heavy drinkers, suggesting that this may represent an alcohol-associated cancer exhibiting a threshold for effect. It was concluded that this study suggested an inverse relationship at moderate consumption levels compared with non- or low-level drinkers, but it is unclear what mechanisms might be involved.

Effect of cessation of alcohol consumption on cancer risk

60. The COC reviewed the available evidence on the effect of cessation of alcohol consumption on the risk of upper aerodigestive tract and liver cancers. It was noted that much of the evidence was based on case-control studies and relied on subjects providing a history of their exposure rather than on prospective follow-up of a cohort of people. It was not always clear why people had stopped drinking, but potential reasons included health concerns or deteriorating health, which could influence the results, especially for the years immediately after cessation of alcohol consumption. It was noted that the comparison groups varied between studies, in some cases comprising people who had never consumed alcohol, whilst in other studies comparison was made with current drinkers.

61. Overall, the data from a number of the individual studies examining the effects of alcohol cessation on the risk of upper aerodigestive tract and liver cancers demonstrated a reduction in risk following long-term abstention. However, the results were not consistent across all studies and the magnitude of effect varied between studies. In some studies, an initial increase in risk or a trend to an initial increase in risk was observed, followed by decreased risk in the longer term, while other studies found a decrease in risk immediately after cessation. The observation of an initial increase in risk following cessation was particularly evident for oesophageal cancer and studies conducted in European subjects. The Committee suspected that this apparent increase in cancer risk immediately after cessation of alcohol consumption may be an effect of cessation by people who were already becoming ill – i.e. the sick-quitter phenomenon. The Committee also expressed the need for caution because most studies were case-control studies with small numbers of subjects included, especially at longer time points. It was noted that the evidence on cessation of alcohol consumption showed that it takes a long time before risks return to the level of the non-drinker. The time period required for risks to return to those of non-drinkers appeared to be in the range of 20 years or more for upper aerodigestive tract and liver cancers. This is clearly different to the benefits of smoking cessation, where the risk starts to decrease shortly afterwards. It did indicate that it could be important to communicate with younger people about the benefits of limiting alcohol intake at a young age on subsequent cancer risk.

62. It was not possible to estimate a time period following cessation where a significant impact on public health would be evident. The Committee made the observation that reducing alcohol intake is likely to be more achievable than giving up completely. However, no data were identified assessing the impact of reducing alcohol intake on the risk of cancer.

Evidence for the effects of binge drinking on cancer risk

63. The vast majority of the studies reviewed by the COC did not specifically assess the effect of binge drinking, but instead evaluated the effect of total alcohol intake on cancer risk. One study in the US had assessed the effects of binge drinking on pancreatic cancer risk (Gupta et al., 2010). In this study, a history of binge drinking (≥ 5 drinks/day or ≥ 70 g alcohol/day) was associated with a 3.5-fold increased risk of pancreatic cancer in men, and the risk increased with increasing average number of drinks consumed during the binging episode and with frequency of binge drinking each month.

Evidence for effects of different alcohol types affecting the risk of cancer

64. The recent IARC review concluded that all types of alcohol increase the risk of cancer, and the COC concurs with this. Where available, the Committee considered data on different types of alcoholic beverage. Overall it was not possible to identify any specific beverage type that had a specific effect at any of the cancer sites considered.

Potential mechanisms by which alcohol consumption may increase the risk of different cancers

This section will follow later and will include the COM conclusions when statement is finalised (COM, 2015)

Interaction of alcohol and genetic polymorphisms in cancer risk

65. A number of epidemiological studies published since the 2009 IARC review evaluated potential interactions of alcohol consumption with individual genetic risk factors, mostly relating to polymorphic genotypes in alcohol-metabolising pathways.

66. 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 was noted that many of the studies reporting on genotype/alcohol interactions in cancer risk were carried out in Eastern Asian populations, in whom there are substantial differences in the proportions of different genotypes in comparison with European populations. 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 generalisable to other populations.

67. Consideration of the role played by genetic polymorphisms in alcohol metabolising enzymes in different populations was also concluded to be important in liver cancer, although individual studies on this were not reviewed.

Burden – alcohol attributable risk

This section will follow later

Conclusions of current review

- The COC evaluated new epidemiology studies and analyses published since the 2009 review by IARC on alcohol and the following cancer sites: upper aerodigestive tract cancers (grouped), oral cavity, pharynx, larynx, oesophagus, liver, colorectum, female breast, and pancreas. In addition, individual meta-analyses on inverse associations of alcohol consumption with kidney cancer, Hodgkin's and Non-Hodgkin's lymphoma, and extrahepatic bile system cancer were also reviewed. The Committee noted limitations of some of the studies, including disease ascertainment and exposure assessment methodologies, lack of consistency between studies and/or countries as to how much alcohol was considered to be low, moderate and heavy consumption, and lack of differentiation between never drinkers and former or ex-drinkers, given that many studies had used a non-drinker category. It was noted that many of the studies reviewed had been performed in Asian (particularly Eastern Asian) populations and that these results may not be directly relevant to the predominantly Caucasian population in the UK.

- Recently available epidemiological studies on alcohol consumption and upper aerodigestive cancer risk added weight to the existing view that alcohol consumption is causally associated with cancers in the upper aerodigestive tract. Risk for cancers of the oral cavity or pharynx (considered separately) was consistently elevated at the highest levels of alcohol consumption, but there was less consistent evidence of a positive association at lower alcohol drinking levels. Meta-analyses that considered oral cavity and pharyngeal cancers combined showed a statistically significant positive association with alcohol consumption at all levels from light (≤ 1 drink/day or 12.5 g ethanol/day) to heavy (≥ 4 drinks/day or > 50 g ethanol/day) levels of consumption, with a clear dose-response. Increased risk of laryngeal cancer was noted in moderate and heavy drinkers (i.e. at intakes above 12.5 g ethanol/day) but not in light drinkers (≤ 12.5 g ethanol/day), and a marked combination effect with smoking was noted. Studies added further weight to the causal association between alcohol and oesophageal SCC (squamous cell carcinoma) with a clear dose-response observed and effects evident with light drinking as well as moderate and heavy drinking. There was no evidence

of an association between alcohol consumption and oesophageal AC (adenocarcinoma).

- Overall, new evidence was consistent with the view that alcohol consumption is causally associated with breast cancer, although not all the new studies found a positive association. The large meta-analysis of Seitz et al. (2012) indicated a modest but significant 4% increase in risk of breast cancer associated with light drinking (≤ 1 drink/day or ≤ 12.5 g ethanol/day). There was increasing evidence to indicate a stronger association between alcohol consumption and ER-positive than ER-negative tumours, however, risks were increased for tumours with either receptor status.

- New data clearly indicated that heavy drinking is associated with increased liver cancer risk. The dose-response analysis of Turati et al. (2014) indicated that consumption of 12.5 g ethanol/day gave an estimated excess liver cancer risk of 6%, whilst excess risks of 13%, 29%, 46% and 66% were observed for intakes of 25, 50, 75 and 100 g ethanol/day, respectively. The meta-analysis of Bagnardi et al. (2013) did not find a significant association between light drinking (< 1 drink/day or 12.5 g ethanol/day) and liver cancer.

- New data on alcohol consumption and colorectal cancer risk were variable. A meta-analysis by Fedirko et al. (2010) showed evidence for an increased risk associated with moderate (> 1 drink/day or > 12.5 g ethanol/day) and heavy, but not light (≤ 1 drink/day or ≤ 12.5 g ethanol/day), alcohol consumption. A pooled analysis by Nan et al. (2013) found a significantly increased risk of colorectal cancer in individuals consuming > 30 g alcohol/day compared with nondrinkers, although no difference between the two groups was observed after the introduction of food fortification with folate.

- New evidence supported the conclusion of IARC in 2009 that low-to-moderate alcohol consumption (up to 30 g/day) is not associated with increased pancreatic cancer risk, but heavier drinking (> 30 g/day) may be associated with a small increase in risk. The exact role of alcohol consumption in pancreatic cancer remains unclear, as other risk factors are involved. Studies where smoking status was considered separately were suggestive of an effect of alcohol on pancreatic cancer independent of the effect of smoking.

- An inverse relationship between alcohol consumption and cancer risk was observed for some cancer types. Two meta-analyses showed an inverse relationship between alcohol consumption and renal cell carcinoma risk, however there was no consistent dose-response and it was not clear what mechanisms could be involved. Two meta-analyses suggested a decrease in risk of non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) in people consuming alcohol as compared with non-drinkers, but a significant dose-response was not observed for either cancer type. There were concerns

about the consistency of the classification of cancers of this type and confounding by the heterologous tumour pathology. There is no immediately obvious mode of action that could explain the association. Overall, it was concluded that, although based on only a few cases, the finding was very consistent and thus could not be discounted. One meta-analysis showed an inverse association of alcohol consumption and extrahepatic bile system cancer, a rare cancer site. Compared with non- or low-level drinkers, risk was reduced for moderate drinkers but increased for heavy drinkers, suggesting that this may represent an alcohol-associated cancer exhibiting a threshold for effect. It is unclear what mechanisms might be involved.

- Overall, data from studies examining the effects of alcohol cessation on the risk of upper aerodigestive tract and liver cancers demonstrated a reduction in risk following long-term abstention. Results were not consistent across all studies and the magnitude of effect varied between studies. In some studies an initial increase in risk or a trend to an initial increase in risk was observed, followed by decreased risk in the longer term. This was particularly evident for oesophageal cancer in studies conducted in European subjects. This may be an effect of cessation by people who were already becoming ill. The time required for risk to return to that of a never-drinker after cessation of alcohol consumption was generally observed to be in the range of 20 years or more.

- The vast majority of the studies did not specifically assess the effect of binge drinking, but instead evaluated the effect of total alcohol intake on cancer risk. However, one study in the US found that a history of binge drinking (≥ 5 drinks/day or ≥ 70 g alcohol/day) was associated with increased risk of pancreatic cancer in men, and the risk increased with increasing average number of drinks consumed during the binging episode and with frequency of binge drinking each month.

- New data supported the conclusion that all types of alcohol increase the risk of cancer. It was not possible to identify any particular beverage type that has a specific effect at any of the cancer sites considered.

- New data were reported indicating interactions between alcohol consumption and individual genotypes in cancer risk. The majority of these studies had focussed on polymorphic genotypes for genes related to alcohol-metabolising pathways.

COC
Date 2015

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Annex A

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

STATEMENT ON CONSUMPTION OF ALCOHOLIC BEVERAGES AND RISK OF CANCER.

Strategy and keywords/terms used in literature search.

Literature searches were performed using Pubmed for all epidemiological studies relating to alcohol and site-specific cancers published between January 2008 and the time of presentation of each paper to the Committee. This time frame ensured that all studies published since the last IARC review, were identified. Reference lists from all relevant studies, reviews and meta-analyses published on the alcohol–cancer association were also checked to identify additional studies. Non-English-language publications were excluded. Publications that had been reviewed by IARC in 2009 were also excluded.

Upper aerodigestive tract cancers (grouped)

Papers were included from the searches for oral cavity and pharyngeal, oesophageal and laryngeal cancers where data for the cancers were combined.

Oral cavity and pharyngeal cancers

Search terms were ethanol, alcohol, drinking, consumption, alcoholic beverages, beer, wine, spirits, liquor, oral cavity cancer, pharyngeal cancer, mouth cancer, lip cancer, tongue cancer, carcinoma, risk. Search Publication dates: January 2008 – December 2014.

Oesophageal cancer

Search terms were ethanol, alcohol, drinking, consumption, alcoholic beverages, beer, wine, spirits, liquor, oesophagus, oesophageal cancer, carcinoma, risk. Search Publication dates: January 2008 – December 2014.

Laryngeal cancer

Search terms were ethanol, alcohol, drinking, consumption, alcoholic beverages, beer, wine, spirits, liquor, larynx, laryngeal cancer, carcinoma, risk. Search Publication dates: January 2008 – December 2014.

Breast cancer

Search terms were ethanol, alcohol, drinking, consumption, alcoholic beverages, beer, wine, spirits, liquor, female, breast cancer, risk. Search Publication dates: January 2008 – September 2014.

Pancreatic cancer

Search terms were ethanol, alcohol, drinking, consumption, alcoholic beverages, beer, wine, spirits, liquor, pancreas, pancreatic cancer, risk. Search Publication dates: January 2008 – January 2014.

Liver cancer

Search terms were ethanol, alcohol, drinking, consumption, alcoholic beverages, beer, wine, spirits, liquor, hepatocellular, liver cancer, risk. Search Publication dates: January 2008 – April 2014.

Colorectal cancer

Search terms were ethanol, alcohol, drinking, consumption, alcoholic beverages, beer, wine, spirits, liquor, colon, rectum, colorectal cancer, risk. Search Publication dates: January 2008 – September 2014.

Annex B

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

STATEMENT ON CONSUMPTION OF ALCOHOLIC BEVERAGES AND RISK OF CANCER.

The Newcastle-Ottawa scale for assessment of study quality.

Assessment of the quality of the cohort studies and case-control studies reviewed for the Committee's work on alcohol and cancer was carried out using a modified version of the Newcastle-Ottawa Scale (NOS) (resulting from collaboration between the Universities of Newcastle, Australia and Ottawa, Canada). Pooled and meta-analyses were not scored.

The NOS uses a 'star system' in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively (Wells et al, accessed 2015).

The alcohol quality assessment considered three specific areas: 1) study design, 2) alcohol consumption data collection methods, and 3) data analysis. For many of the cancer sites reviewed, smoking was considered the most important confounder with other factors such as BMI, caffeine intake etc. also being important. For ease of reviewing the causal sites where a large number of papers had been identified (breast and oesophageal cancer studies), the cohort studies and case-control studies were further divided into two categories: a) those examining cancer incidence, and b) those examining cancer mortality. Within each section, the studies were reported by geographic region (UK, Europe, US, and other regions) and, within each region, in order of their modified Newcastle-Ottawa (NO) score, beginning with the highest scoring study.

The template for the NOS scoring used for the COC review is given on the next page.

References

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M & Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 23/06/2015)

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	

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

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			

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