Committee on CARCINOGENICITY

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

Statement 2015/S2

Statement on consumption of alcoholic beverages and risk of cancer

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LAY SUMMARY

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC), is a UK committee of independent experts which advises the Department of Health, the Food Standards Agency and other government departments and agencies on the likelihood of cancer of chemicals found in food, consumer products and the environment. The COC has previously looked at whether drinking alcohol in alcoholic beverages causes cancer, and in 2013 it decided to look at the new evidence.

Drinking alcohol has been shown to increase the *risk (or chance)* of getting some types of cancer. This does not mean that everyone who drinks alcohol will get cancer, but studies have shown that some cancers are more common in people who drink more alcohol.

The World Health Organisation's 'International Agency for Research on Cancer' (IARC) considers that drinking alcohol increases the risk of getting cancers of the mouth (oral cavity) and throat (pharynx), voice box (larynx), gullet (oesophagus), large bowel (colorectum) and liver, of breast cancer in women, and probably also of cancer of the pancreas. IARC made its most recent conclusions about alcohol and cancer after reviewing information that was available up to 2009.

We have reviewed new information on alcohol and cancer that has become available since the 2009 IARC review**.** There are some limitations to the conclusions that we were able to make, because of the different ways research studies record data such as whether or not someone has a particular cancer and how much alcohol a person drinks. **Overall, our findings support the view that drinking alcohol increases the risk of getting cancers of the mouth and throat, voice box, gullet, large bowel, liver, of breast cancer in women, and probably also of cancer of the pancreas.**

The available information suggests that all types of alcoholic beverage can cause cancer, with little difference in risk from different drinks (e.g. beer, wine, spirits). The risk is due to the alcohol contained in the drink. The amount of alcohol in a drink varies: a single measure of spirit generally contains about 1 unit, whilst one medium-to-large glass of wine or one pint of beer typically contain around 2-3 units of alcohol.

The new studies show that people who drink even low levels of alcohol have a greater risk of getting cancers of the mouth and throat, gullet, and of breast cancer in women than people who do not drink alcohol at all. Drinking approximately 1.5 units per day (10.5 units per week) or more increases the risk of cancers of the voice box and large bowel, whilst cancers of the liver and pancreas are more common in people who drink approximately 6 units per day (42 units per week) or more. The risk of getting these cancers increases the more alcohol a person drinks.

There is very little specific information on binge drinking (drinking large amounts of alcohol on a single occasion) and cancer. Almost all of the new studies investigated the effect of total alcohol drunk over a period such as a week or a month on cancer risk, and not the amount of alcohol drunk on a single occasion.

Scientists have identified a number of ways that alcohol can cause cancer. Both alcohol and its breakdown products can cause damage to cells, making them more likely to become cancerous. The speed at which alcohol is broken down and cleared from the body can differ between individuals due to genetic differences, and some of the new studies added to our knowledge about this. Alcohol may also interact with other cancer-causing chemicals (e.g. tobacco smoke in the mouth and throat), cause damage to liver cells leading to cirrhosis, alter levels of sex hormones (e.g. oestrogen, which may play a role in breast cancer), and alter vitamin and mineral levels (e.g. lower folate levels, which has been linked with risk of bowel cancer).

We think that it is difficult to draw firm conclusions from a small number of studies that indicate that kidney cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, and extra-hepatic bile system cancer are less common in people who drink alcohol than in non-drinkers. However, it is clear that the increased risk of other cancers as a result of drinking alcohol far outweighs any possible decreased risk of these cancers.

The effect of stopping drinking on cancer risk has been studied for some cancer types and risk decreases gradually after stopping alcohol consumption. However, it can take many years for the risk to fall to levels similar to those in people who have never drunk alcohol. Some studies show an increased risk initially, possibly due to people stopping drinking because of being unwell. Because the risk of cancer increases the more alcohol a person drinks, reducing consumption should reduce the risk of developing an alcohol-associated cancer, but we did not find any studies that had investigated this.

We looked at a number of publications estimating how many cancers occur in the UK each year as a result of people drinking alcohol. While there were some differences in how the analyses were carried out, using the two most appropriate studies produced useful estimates. **We found that 4-6% of all new cancers in the UK in 2013 were caused by alcohol consumption.**

Following our latest review we can say that:

- Drinking alcohol causes cancers of the mouth (oral cavity) and throat (pharynx), voice box (larynx), gullet (oesophagus), large bowel (colorectum), liver and the female breast. Alcohol consumption probably also has a role in cancer of the pancreas.

- People who drink even low levels of alcohol have a greater risk of getting some cancers than people who do not drink alcohol.

  Even at low levels of alcohol intake, below 1.5 units per day (10.5 units per week), there is an increased risk of the following cancer types:
  - **mouth and throat** (oral cavity and pharynx)
  - **gullet** (oesophagus)
  - **breast in women**

  At alcohol intakes above approximately 1.5 units per day (10.5 units per week), there is an increased risk of the following cancer types:
  - **voice box** (larynx)
  - **large bowel** (colorectum)

  At high levels of alcohol intake, above approximately 6 units per day (42 units per week), there is an increased risk of the following cancer types:
  - **liver**
  - **pancreas**

- The risk of getting cancer increases the more alcohol a person drinks.

- The risk of getting some alcohol-related cancers gradually decreases over time in people who stop drinking alcohol, but it can take many years for the risk to fall to levels similar to those in people who have never drunk alcohol. It is logical to assume that reducing alcohol consumption would also lead to a reduction in cancer risk.

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ABBREVIATIONS

ABV – alcohol by volume

AC – adenocarcinoma

ADH – alcohol dehydrogenase

ALDH – aldehyde dehydrogenase

ARCAGE – study on Alcohol-Related Cancers And Genetic susceptibility in Europe

BMI – body mass index

BRCA1, BRCA2 genes – genes linked with breast cancer

CI – confidence interval

CMO – Chief Medical Officer

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

COM – Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

CRUK – Cancer Research UK

CYP2E1 – cytochrome P450 2E1

DH – Department of Health

DNA – deoxyribonucleic acid

ER – oestrogen receptor

g – grammes

HBV – hepatitis B virus

HCV – hepatitis C virus

HL – Hodgkin lymphoma

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 lymphoma

OR – odds ratio

OR_{cont} – odds ratio for a continuous variable

p – probability value associated with a statistical test

PHE – Public Health England

ROS – reactive oxygen species

RR – relative risk

SCC – squamous cell carcinoma

GLOSSARY OF TERMS

Absolute risk: a measure of the association between exposure and outcome. Absolute risk difference (reduction) is the change in the risk from an exposure in relation to a comparison (reduced) exposure.

Acetaldehyde: a metabolite of ethanol.

Allele: one version of a gene at a given location (locus) along a chromosome.

Attributable fraction: a measure of the impact of a causative factor on public health; the proportion of cases of a disease among exposed persons that can be attributed to the exposure.

Binge drinking: high intake of alcohol on a single drinking occasion.

Case-control study: a study that compares individuals who have a disease or outcome of interest (cases) with individuals who do not have the disease or outcome (controls), with regard to exposures experienced in the past.

Causal association: when an exposure causes a particular outcome.

Cohort study: a study design where a group of people (a cohort) is followed prospectively with respect to development of disease outcomes and exposures of concern (risk factors) and is then compared to a non-exposed group.

Clastogenic: giving rise to or inducing chromosome breaks or other structural aberrations such as translocations.

95% confidence interval (95% CI): a range within which we can be 95% sure that the true value of the entity we are estimating lies.

Cytotoxic: toxic to cells.

Confounder or confounding variable: an extraneous variable that satisfies BOTH of the conditions defined: (1) it is a risk factor for the disease under study (2) it is associated with the study exposure but is not a consequence of exposure. For example cigarette smoking is a confounding variable with respect to an association between alcohol consumption and heart disease. Failure to adjust for a confounding variable results in distortion of the apparent magnitude of the effect of the exposure under study. (In the example, smoking is a risk factor for heart disease and is associated with alcohol consumption but is not a consequence of alcohol consumption.)

De novo: starting from the beginning; anew.

Dose-dependent: when an outcome changes as a function of the exposed dose.

Dose-response: a relationship in which a change in the amount, intensity, or duration of an exposure is associated with a change in risk of a specified outcome.

Dose-response curve: a curve plotting the relationship between the size of a dose and the response to it.

Epidemiological studies: studies designed to investigate associations, distribution, and control of disease (such as cancer) in human populations.

Ever drinker: someone who has ever consumed alcohol.

Exposure assessment methodology: how exposure (alcohol consumption) was measured, or estimated, in an epidemiology study, may include information on amount (number of drinks and the volume of the drinks), type of alcohol consumed, how often alcohol is consumed.

Gene polymorphisms: natural variations in a gene, DNA sequence, or chromosome that have no adverse effects on the individual and occur with fairly high frequency in the general population.

Genetic susceptibility (genetic predisposition): increased likelihood or chance of developing a particular disease due to the presence of one or more gene mutations and/or a family history that indicates an increased risk of the disease.

Genotoxicity: the property of a chemical or agent that causes DNA damage.

Genotype: 1] an individual's collection of genes, or 2] the two alleles inherited for a particular gene.

Heterozygous: having two different forms of a gene that controls a particular characteristic, one inherited from each parent, and therefore able to pass on either form to any children.

Incidence: a measure of the frequency with which an event, such as a new case of illness, occurs in a population over a period of time.

Interaction (effect modification): interaction occurs when the direction or magnitude of an association between two variables differs due to the effect of a third variable.

Inverse relationship: when an increase in exposure is associated with a decrease in a particular outcome, or *vice versa*.

In vitro: a Latin term used to describe effects in biological material outside the living animal or plant (literally “in glass”).

In vivo: a Latin term used to describe effects in living animals or plants (literally “in life”).

J-shaped dose-response curve: a dose-response in which an apparent improvement in an endpoint occurs at low or intermediate levels of exposure to an otherwise toxic substance.

Lifestyle factors: factors that can impact on health over which a person has control (e.g. smoking, alcohol, diet, exercise).

Meta-analysis: a method for systematically combining quantitative study data from several selected studies to develop a single conclusion that has greater statistical power.

Multiplicative effect: an effect between two components that is greater than additive.

Mutagenic/mutagenicity: the ability of a substance to cause a permanent change in the amount or structure of the genetic material in an organism or cell, which can result in a change in the observable physical, biochemical and physiological characteristics of a cell, tissue, organ or individual.

Newcastle-Ottawa star scoring scheme: a tool used for assessing the quality of non-randomised studies included in a systematic review and/or meta-analysis.

Odds ratio (OR): a measure of association that compares the odds (chance) of getting a disease in those exposed to the odds of getting a disease in those not exposed.

Pooled analysis: participant-level data from multiple studies are combined and analysed as a single dataset.

Relative risk (RR): ratio of incidence of disease in exposed individuals to the incidence of disease in non-exposed individuals.

Residual confounding: confounding that persists after attempts to adjust for the confounders measured in a study.

Risk factor: any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury.

Statistically significant: Description of a result when the P-value associated with a statistical test of a comparison meets some pre-defined criterion e.g. $P<0.05$ or 5%.

Upper aerodigestive tract: the mixed airway/gastrointestinal tract that includes the oral cavity, pharynx, paranasal sinuses, sinonasal tract, larynx, pyriform sinus, pharynx, and upper oesophagus.

Variant allele (variant genotype): an alteration in the normal sequence of a gene (collection of genes), the significance of which is often unclear until further study of the genotype and corresponding phenotype occurs in a sufficiently large population. Complete gene sequencing often identifies numerous allelic variants (sometimes hundreds) for a given gene.

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Statement on consumption of alcoholic beverages and risk of cancer

1 INTRODUCTION

There are more than 200 types of cancer, each with different causes, symptoms and treatments. According to the cancer registry data, in the UK in 2013 approximately 352,000 new cases of cancer were diagnosed and there were around 161,000 deaths from cancer. Lifestyle choices such as alcohol[1] consumption are known risk factors for certain types of cancer (CRUK, accessed 2015).

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 risk factors for cancer for which intervention can offer scope for reduction in cancer.

1.1 Previous reviews of alcohol and cancer

In 1995, we reviewed the carcinogenicity of alcoholic beverages across all cancer sites as part of the health input to the Interdepartmental Working Group on the Sensible Drinking Message (DH, 1995).

We also considered the possible quantitative relationship between alcohol and oesophageal cancer, as part of the 1995 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.

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[1] The term ‘alcohol’ is used throughout the text to refer to the ethanol contained in alcoholic beverages.

In 2005, we conducted a review of new data (post 1995) on the quantitative relationship between alcohol and SCC of the oesophagus. At this time, we considered that the new data strengthened the overall picture, with an increased risk apparent at intakes above 30 g ethanol (or approximately 4 units) per day (for a discussion of units of alcohol see section 1.2 below). However, it was not possible to identify a lower level of consumption below which there is no increase in risk (COC, 2005).

In 2004, we 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 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 per week (8 g ethanol/week). The evidence suggested that the risk of breast cancer associated with drinking alcoholic beverages increases with prolonged consumption of alcohol. In terms of lifetime risk, a woman drinking 2 units per day (16 g ethanol/day) was estimated to have an 8% higher lifetime risk of breast cancer than a woman drinking 1 unit per day (8 g ethanol/day).

The World Health Organisation's International Agency for Research on Cancer (IARC) reviewed the carcinogenicity of alcoholic beverages in 1987 (IARC, 1988), 2007 (IARC, 2010) and 2009 (IARC, 2012). In their latest report, IARC (2012) concluded[2] that:

> "There is *sufficient evidence* in humans for the carcinogenicity of alcohol consumption. Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver (hepatocellular carcinoma) and female breast. Also, an association has been observed between alcohol consumption and cancer of the pancreas.
> For cancer of the kidney and non-Hodgkin lymphoma, there is *evidence suggesting a lack of carcinogenicity*.
> There is *sufficient evidence* in humans for the carcinogenicity of acetaldehyde associated with the consumption of alcoholic beverages. Acetaldehyde associated with the consumption of alcoholic beverages causes cancers of the oesophagus and of the upper aerodigestive tract combined.
> There is *sufficient evidence* in experimental animals for the carcinogenicity of ethanol.
> There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.
> Alcohol consumption is *carcinogenic to humans (Group 1)*.
> Ethanol in alcoholic beverages is *carcinogenic to humans (Group 1)*.

[2] Definitions of evidence, as used in IARC Monographs for studies in humans are listed in Annex A.

Acetaldehyde associated with the consumption of alcoholic beverages is *carcinogenic to humans (Group 1)*."

In the sections below we review epidemiology studies published since the IARC review in 2009, which investigated the association of the consumption of alcoholic beverages with these cancers.

1.2 Consumption of alcoholic beverages in the UK

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 by volume (ABV*)*. Typically, beer contains 4-5% ABV, wine contains about 13% ABV and distilled spirits contain about 40% ABV (Drinkaware, 2015). 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 ABV by the volume of the drink (in mL) and dividing by 1000. This calculation allows a standardised comparison of the volume of pure alcohol between alcoholic beverages. Examples of the alcohol content of some typical alcoholic beverages are shown in Table 1.

Table 1: Typical alcohol content in grammes and UK units of different alcoholic beverages

	Typical ABV (%)	Typical volume of a drink (mL)	Ethanol content (g)	UK units of alcohol
Beer	4.5	568 (pint)	20	2.5
Wine	13	175 (glass)	18	2.3
Spirits	40	25 (single)	8	1.0

1 UK unit = 8 g ethanol

Worldwide, there is substantial variation 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 (IARD, 2015). For example, although 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.

In the UK, alcohol consumption by adults has increased over the last 30 years, peaking in 2004 and with a subsequent downward trend (see CC/2013/13 for more detail). 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. Overall, there is substantial under-reporting of alcohol consumption, as sales data exceed consumption calculations. Data from the Health Survey for England (as reported in the paper of Bellis et al., 2015) indicate an average weekly alcohol consumption in 2012 by adults in England of 13.7 units (equivalent to approximately 2 units/day, or 16 g ethanol/day), accounting for around 63% of HMRC alcohol sales data. Bellis and colleagues estimated a typical weekly intake in adults in England of 17.1 units (equivalent to approximately 2.5 units/day, or 20 g ethanol/day) in the three-quarters of survey respondents who were current drinkers, taking into account 'atypical' (e.g. festivals, holiday periods) as well as 'typical' drinking periods. These data represented around 79% of HMRC alcohol sales data (Bellis et al., 2015).

1.3 Guidance on alcohol consumption in the UK

Official guidance on alcohol consumption in the UK was first introduced in 1987. The current guidelines for lower risk drinking, which date from 1995, state that:

> "men should not regularly drink more than 3-4 units of alcohol per day and women should not regularly drink more than 2-3 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 that:

> "women should avoid drinking alcohol. If they do choose to drink, the guidance, to protect the baby, is to drink no more than 1-2 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 also published guidance on alcohol consumption and young people (DH, 2009).

In 2012, the House of Commons Science and Technology Committee recommended a review of the current lower risk guidelines. The Government response led to the initiation of a Department of Health (DH) and Public Health England (PHE) evidence-based review of alcohol and alcohol guidelines (HM Government, 2012).

2 THE 2015 COC REVIEW OF ALCOHOL AND CANCER RISK

We have reviewed epidemiology studies published since the most recent IARC review in 2009 (IARC, 2012), which evaluated the association of consumption of alcoholic beverages with the cancers listed by IARC as caused by drinking alcohol (see section 1.1). The new papers identified included cohort and case-control studies, and meta- and pooled analyses. While the cohort and case-control studies present new data, the meta- and pooled analyses include evidence from cohort and case-control studies published before 2009, as well as newer studies.

2.1 Methodology

We have considered review papers prepared by the PHE Toxicology Unit at Imperial College on the epidemiology studies published since the most recent IARC review in 2009 on alcohol and the following cancer sites: upper aerodigestive tract (combined), oral cavity and pharynx, larynx, oesophagus, female breast, liver, colorectum, and pancreas. For details of the literature searches underpinning these papers, see Annex B. A quality scoring scheme was adopted for 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 C. The scoring scheme was used for the papers on cancers of the upper aerodigestive tract (combined), oral cavity and pharynx, larynx, oesophagus, female breast, liver, and colorectum.

2.2 Findings

Based on the data available across all the studies considered for each cancer site, we have identified broad categories of intake to help in our consideration of the findings. In describing levels of alcohol consumption, we will thus use the terms ‘low’, ‘medium’ and ‘high’ to represent intakes averaging approximately <12.5 g ethanol/day (< approximately 1.5 units/day), 12.5-50 g ethanol/day (approximately 1.5-6 units/day), and >50 g ethanol/day (> approximately 6 UK units/day), respectively.

Due to the differences between countries, both in definition of a unit of alcohol (discussed in section 1.2) and in the volume of alcoholic drinks, there is much variation across all the available studies in the categories of alcohol intake used. Therefore, in selecting the cut-off values for these levels, we used the quantitative alcohol intake categories that broadly fit the available data and that were commonly used categories for some of the meta-analyses we considered. The ‘low’, ‘medium’ and ‘high’ descriptors we have given these categories are used as the most practical format for summarising overall findings from studies that we reviewed, but should be

considered in the context of current and any future UK alcohol consumption guidelines.

The results listed in the following sections are presented as risk estimates. These vary depending on the study design, with odds ratios (OR) being commonly used for case-control studies and relative risks (RR) for cohort studies. However, they can all be interpreted as assessing by how much the risk associated with alcohol consumption increases or decreases. When statistical test results, including the tests of trend (p-trend), are quoted these are based on a 95% significance level.

In drawing our conclusions for each cancer site, we have looked for consistencies in the evidence base as a whole and have accepted that there are uncertainties within studies and in extrapolating from studies.

2.2.1 Alcohol and upper aerodigestive tract cancers

Cancers of the upper aerodigestive tract (also often referred to as 'head and neck' cancers) 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 regions. These cancers are often combined into a single group for the purposes of epidemiological studies.

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 risk 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 (mainly in India and Taiwan), occupational exposure to certain chemicals, poor oral health, and human papilloma virus (HPV) infection (CRUK, accessed 2015).

2.2.1.1 Upper aerodigestive tract cancers (combined)

In its 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 (combined), as it is for cancers of the oral cavity and pharynx, larynx, and oesophagus separately (IARC, 2012). We reviewed epidemiological reports on alcohol and cancers of the upper aerodigestive tract (combined) published since the last IARC review in 2009 (for details, see discussion paper CC/2015/05). Studies varied with respect to which cancer sites were included under the umbrella of 'upper aerodigestive tract' or 'head and neck' cancer, but generally did not include sites other than oral cavity, pharynx, larynx and/or oesophagus. A dose-dependent increase in risk with alcohol intake was noted in the majority of the analyses reported. Statistically significant increased risks were consistently seen at high levels of alcohol intake, and in some studies at medium-level intakes.

A pooled analysis of case-control studies from the International Head and Neck Cancer Epidemiology Consortium (INHANCE) (Hashibe et al., 2009) indicated a statistically significant increased risk associated with ≥3 drinks/day (≥37.5 g ethanol/day) compared with never drinkers, and a strong and multiplicative combined effect of alcohol and tobacco smoking:

Drinks/day	g ethanol/day	OR	95% CI
1-2	12.5-<37.5	1.03	0.84-1.25
≥3	≥37.5	1.91	1.27-2.87
≥3+smoking	≥37.5 + smoking (>20 cigarettes / day)	14.23	8.30-24.40

The Netherlands Cohort Study (Maasland et al., 2014) showed a statistically significant association of alcohol consumption with upper aerodigestive tract cancer incidence at intakes ≥15 g ethanol/day, with a strong dose-response (RR=1.20, 95% CI 1.12-1.27, per 10 g ethanol/day increment):

g ethanol/day	RR	95% CI	
>0-<5	1.11	0.75-1.65	
5-<15	1.15	0.77-1.71	
15-<30	1.52	1.02-2.27	
≥30	2.74	1.85-4.06	(p trend <0.001)

The meta-analysis of Li et al. (2014) showed a statistically significant association of alcoholic beverage consumption with upper aerodigestive tract cancer mortality in people drinking >1 drink/day (>12.5 g ethanol/day) compared with non-/occasional drinkers:

Drinks/day	g ethanol/day	RR	95% CI
≤1	≤12.5	1.26	0.94-1.67
2-3	12.6-49.9	1.79	1.26-2.53
≥4	≥50	3.63	2.63-5.00

In summary:

- The new publications add further weight to the existing view that consumption of alcoholic beverages is causally associated with risk of upper aerodigestive tract cancers (combined). Increasing alcohol consumption increased risk in a dose-dependent manner.

- Statistically significant increased risks were generally observed at medium and high (>12.5 g ethanol/day), but not low alcohol intakes.

2.2.1.2 Oral cancer (oral cavity and pharynx)

Oral cancer as an overall term is often divided into the sub-categories of ‘oral cavity cancers’ and ‘pharyngeal cancers’. Cancers of the nasopharynx are not usually considered to come under the umbrella of oral cancer, although they are often reported in the literature with oral cancers.

In 2013, 8,580 new cases of oral cancer were diagnosed (5,713 in men and 2,867 in women) and there were 2,645 deaths from oral cancer (1,761 in men and 884 in women) in the UK.

Tobacco smoking and drinking alcohol are established risk factors for oral cancer. Infection, most commonly with human papillomavirus (HPV), is also associated with increased risk (CRUK, accessed 2015).

IARC has previously stated that alcohol causes oral cavity and pharyngeal cancer (IARC 1988, 2010, 2012). We reviewed epidemiological reports on alcohol and cancers of the oral cavity and pharynx published since the last IARC review in 2009 (IARC, 2012) (for details, see discussion paper CC/2015/02). There was a general lack of uniformity among the studies evaluated in the definitions used to describe oral cavity and/or pharyngeal cancer. We also noted that many of the studies did not take into account the human papilloma virus (HPV) status of the participants. The evidence from these studies supported an association of alcoholic beverage consumption with oral cancer (oral cavity and pharynx combined) at all levels of intake. High-level alcohol intakes were also consistently associated with risk of cancers of the oral cavity or cancers of the pharynx when considered as separate sub-categories, however the findings were more variable at medium and low levels of alcohol drinking.

Oral cavity and pharynx (combined): Meta-analyses reported by Tramacere et al. (2010) and Bagnardi et al. (2013; 2015) showed a statistically significant positive association between alcohol consumption and cancer of the oral cavity and pharynx (combined) at all levels of alcohol consumption, compared with non-/occasional drinkers:

Drinks/day	g ethanol/day	RR	95% CI	
≤1	≤12.5	1.21	1.10-1.33	
≥4	≥50	5.24	4.36-6.30	(Tramacere et al. 2010)

	g ethanol/day	RR	95% CI	
	≤12.5	1.13	1.00-1.26	
	≤50	1.83	1.62-2.07	
	>50	5.13	4.31-6.10	(Bagnardi et al. 2015).

Two Latin American case-control studies reported statistically significant positive associations for ever drinking and increasing cumulative exposure of alcohol and the risk of cancer of the oral cavity and oropharynx (combined) (Szymańska et al., 2011; Ferreira Antunes et al., 2013).

Oral cavity: 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. Risk was consistently elevated at high levels of alcohol consumption, while evidence for a positive association was less consistent at

lower alcohol drinking levels. Most of the pooled and meta-analyses reported statistically significant positive associations. The pooled analysis of Lubin et al. (2010) from the INHANCE consortium showed statistically significant association at low and high (but not medium) levels of alcohol intake compared with the referent of 0.01-<1 drinks/day (0.1-<12.5 g ethanol/day):

Drinks/day	g ethanol/day	OR	95% CI	
1-2.9	12.5-<37.5	1.26	1.0-1.6	
3.0-4.9	37.5-<62.5	1.29	0.9-1.8	
5.0-10.0	62.5-125	1.87	1.2-3.9	(p trend <0.01)

A subsequent breakdown by gender showed a statistically significant increased risk only at high alcohol intake in men (OR=1.75, 95% CI 1.1-2.8 for 5-10 drinks/day) (Lubin et al., 2011). A meta-analysis reported by Turati et al. (2010) showed statistically significant association of alcohol drinking with oral cavity cancer at both the low and high intake categories evaluated compared with non-/occasional drinkers, with a clear dose-response:

Drinks/day	g ethanol/day	RR	95% CI
≤1	≤12.5	1.17	1.01-1.35
≥4	≥60	4.64	3.78-5.70

Conversely, the pooled analysis of Hashibe et al. (2009) from the INHANCE consortium did not observe a statistically significant increased risk of cancer of the oral cavity at any level of alcohol intake compared with never drinkers:

Drinks/day	g ethanol/day	OR	95% CI
1-2	12.5-<37.5	0.88	0.65-1.20
≥3	≥37.5	1.05	0.62-1.77

It is unclear whether missing data for alcohol frequency categories leading to reduced number of cases and controls may have contributed to this. With regard to sub-types within the oral cavity, the findings from a French case-control study (Radoï et al., 2013) and an international meta-analysis (Turati et al., 2010) suggest that the tongue, and possibly the floor of the mouth, may present specific target sites within the mouth.

Pharynx: A statistically significant positive association between alcohol consumption and cancer of the pharynx was reported in the majority of studies. All of the pooled or meta-analyses reported a statistically significant positive association at high levels of alcohol intake, however, as with studies of oral cavity cancers, there was less consistent evidence of an association at lower levels of alcohol drinking. The pooled analysis of Hashibe et al. (2009) from the INHANCE consortium found a statistically significant increased risk of pharyngeal cancer from alcohol intakes of ≥3 drinks/day (≥37.5 g ethanol/day), compared with never drinkers:

Drinks/day	g ethanol/day	OR	95% CI
1-2	12.5-<37.5	1.26	0.92-1.73
≥3	≥37.5	2.94	1.73-5.02

The pooled analysis of Lubin et al. (2010) from the INHANCE consortium showed a statistically significant association at all intake levels compared with a referent category of 0.01-<1 drinks/day (0.1-<12.5 g ethanol/day):

Drinks/day	g ethanol/day	OR	95% CI	
1-2.9	12.5-<37.5	1.2	1.0-2.9	
3.0-4.9	37.5-<62.5	2.30	1.7-3.1	
5.0-10.0	62.5-125	3.67	2.6-5.3	(p trend <0.01)

A subsequent breakdown of these data showed statistically significant increased risks at all intake levels for oro-pharyngeal cancer and in the medium- and high-level intake categories for hypo-pharyngeal cancer (Lubin et al., 2011). The meta-analysis by Turati et al. (2010) showed statistically significant association of alcohol drinking with pharyngeal cancer at high but not low alcohol intakes compared with non- or occasional drinkers:

Drinks/day	g ethanol/day	RR	95% CI
≤1	≤12.5	1.23	0.87-1.73
≥4	≥60	6.62	4.72-9.29

In summary:

- The new publications add further weight to the existing view that consumption of alcoholic beverages is causally associated with risk of cancers of the oral cavity and pharynx (combined). Increasing alcohol consumption increases risk in a dose-dependent manner. Statistically significant increased risks were observed at low, medium and high levels of alcohol intake.

- The new publications add further weight to the view that consumption of alcoholic beverages is causally associated with the risk of cancer of the oral cavity. Statistically significant increased risks were consistently observed at high alcohol intakes (>50 g ethanol/day), but findings were more variable at medium and low intakes.

- The new publications add further weight to the view that consumption of alcoholic beverages is causally associated with the risk of cancer of the pharynx. Statistically significant increased risks were consistently observed at high alcohol intakes (>50 g ethanol/day), but findings were more variable at medium and low intakes.

2.2.1.3 Laryngeal cancer

Cancer of the larynx accounted for 2,315 new cancer diagnoses (1,915 in men and 400 in women) in 2013 in the UK and 843 deaths (667 in men and 176 in women) from laryngeal cancer occurred in the same period.

Major risk factors for laryngeal cancer are tobacco smoking and drinking alcohol – in particular, the combination of smoking and drinking regularly, which we discussed in our statement on mixtures (COC, 2010). 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 (CRUK, accessed 2015).

IARC has stated that alcohol causes cancer of the larynx (IARC, 2012). We reviewed epidemiological reports on alcohol and cancer of the larynx published since the last IARC review in 2009 (for details, see discussion paper CC/2015/03). The majority of the new publications described pooled and meta-analyses. An association of alcohol drinking with laryngeal cancer was noted in the majority of the analyses reported, with statistically significant increased risks seen consistently at high intakes and in some studies at medium-level intakes.

The pooled analysis by Lubin et al. (2010) using data from the INHANCE consortium showed a statistically significant increased risk of laryngeal cancer at intakes of 5-10 alcoholic drinks/day (62.5-125 g ethanol/day) compared with the referent category of 0.01-<1 drinks/day (0.1<12.5 g ethanol/day), but not at lower levels:

Drinks/day	g ethanol/day	OR	95% CI	
1-2.9	12.5-<37.5	1.05	0.8-1.4	
3.0-4.9	37.5-<62.5	1.08	0.7-1.6	
5.0-10.0	62.5-125	1.64	1.0-2.6	(p trend <0.01)

A meta-analysis reported by Islami et al. (2010) indicated increased risk at alcohol intakes >1 drink/day (>12.5 g ethanol/day) compared with non-/occasional drinkers, but not at lower intakes:

Drinks/day	g ethanol/day	RR	95% CI
>0-1	>0-<12.5	0.88	0.71-1.08
>1-<4	>12.5-<50	1.47	1.25-1.72
≥4	≥50	2.62	2.13-3.23

The RRs estimated by the model for selected amounts of daily alcohol consumption were: 1.20 (95% CI 1.15-1.25), 1.45 (95% CI 1.33-1.57), 1.72 (95% CI 1.52-1.90), 2.04 (95% CI 1.76-2.36), and 3.77 (95% CI 2.93-4.86) for 12.5, 25, 37.5, 50, and 100 g ethanol/day, respectively (Islami et al., 2010). Meta-analyses by Bagnardi and colleagues (Bagnardi et al., 2013; 2015) also indicated increased risk of laryngeal cancer associated with alcohol intakes >12.5 g ethanol/day, but not at lower levels, compared with non-/occasional drinkers:

g ethanol/day	RR	95% CI
≤12.5	0.87	0.68-1.11
≤50	1.44	1.25-1.66
>50	2.65	2.19-3.19.

In summary:

- The new publications add further weight to the existing view that consumption of alcoholic beverages is causally associated with risk of laryngeal cancer.

- Statistically significant increased risks were consistently observed at medium and high (>12.5 g ethanol/day) but not low alcohol intakes.

2.2.1.4 Oesophageal cancer

In 2013, 8,779 new diagnoses (5,848 in men and 2,931 in women) of oesophageal cancer were made in the UK, and 7,750 deaths occurred due to oesophageal cancer (5,275 in men and 2,475 in women).

The majority (over 80%) of oesophageal cancers fall into one of two sub-types: 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 oesophagus. 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 pre-cancerous condition called Barrett's oesophagus (CRUK, accessed 2015).

IARC has stated that consumption of alcoholic beverages is causally related to squamous cell carcinoma (SCC) of the oesophagus, and that increasing alcohol consumption increases risk in a dose-dependent manner (IARC, 2012). IARC reported that there is a substantial body of evidence that alcoholic beverage consumption is not associated with adenocarcinoma (AC) of the oesophagus (IARC, 2012). We evaluated epidemiological literature published since the 2009 IARC review (for details, see discussion paper CC/2015/04). Evaluations generally showed a positive association between drinking alcohol and oesophageal cancer, although one large-scale evaluation from the European ARCAGE study did not find a statistically significant association (Marron et al., 2012). Many studies evaluated risk by oesophageal cancer sub-type (AC or SCC), indicating a clear association of alcohol drinking at all intake levels with oesophageal SCC, supporting the IARC conclusion. For oesophageal AC, the new publications also supported the IARC view that drinking alcoholic beverages is not associated with oesophageal AC.

Oesophageal SCC: Several pooled- or meta-analyses indicated a positive, causal association between drinking alcohol and oesophageal SCC, with association at all

levels of alcohol intake, and a clear dose-response observed. The pooled analysis of Rota et al. (2010), using mostly data from European populations, showed a strong, non-linear dose-response with RRs of 2.81 (95% CI 1.79-4.40) for 25 g ethanol/day, 5.11 (95% CI 2.63-9.94) for 50 g ethanol/day, and 11.00 (95% CI 4.61-26.24) for 100 g ethanol/day, respectively, compared with non-drinkers. The meta-analysis of Bagnardi et al. (2015) also indicated a statistically significant association at all levels of alcohol drinking compared with non-/occasional drinkers, and a clear dose-response:

g ethanol/day	RR	95% CI
≤12.5	1.26	1.06-1.50
≤50	2.23	1.87-2.65
>50	4.95	3.86-6.34

Individual cohort and case-control studies evaluated also provided further evidence for a causal association between alcohol consumption and oesophageal SCC.

Oesophageal AC: Studies indicated no positive association of alcohol consumption with oesophageal AC at any of the intake levels evaluated. A meta-analysis of studies worldwide showed a clear absence of association between alcohol drinking ('drinkers' versus 'non-drinkers') and risk of oesophageal AC (RR= 0.87, 95% CI 0.74-1.01) and gastric cardia AC (RR=0.89, 95% CI 0.76-1.03) (Tramacere et al., 2012a). A pooled analysis from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON) (mostly US-based studies) (Freedman et al., 2011) also showed no positive association of alcohol drinking and risk of oesophageal AC or oesophago-gastric junction AC at any alcohol intake level, compared with non-drinkers:

AC of:		Oesophagus		Oesophago-gastric junction	
Drinks/day	g ethanol/day	OR	95% CI	OR	95% CI
>0-<0.5	>0-<7.0	0.86	0.65-1.13	0.83	0.68-1.00
0.5-<1.0	7.0-<14.0	0.63	0.41-0.99	0.78	0.62-0.99
1-<3	14-<42	0.81	0.60-1.09	0.77	0.62-0.94
3-<5	42-<70	0.86	0.59-1.24	0.93	0.73-1.19
5-<7	70-<98	0.93	0.66-1.31	0.95	0.69-1.32
≥7	≥98	0.97	0.68-1.36	0.77	0.54-1.10
		p trend 0.21		p trend 0.88	

The individual cohort and case-control studies published also indicated a lack of a causal association between alcohol consumption and oesophageal AC.

In summary:

- The new publications add further weight to the existing view that consumption of alcoholic beverages is causally associated with risk of squamous cell carcinoma (SCC) of the oesophagus. Increasing alcohol consumption

increases risk in a dose-dependent manner. Statistically significant increased risks were observed at low, medium and high alcohol intakes.

- The new publications add further weight to the existing view that consumption of alcoholic beverages is not associated with adenocarcinoma (AC) of the oesophagus.

2.2.2 Alcohol and female breast cancer

Breast cancer accounted for 53,339 new diagnoses of cancer in women in the UK in 2013. In the same year, 11,470 deaths occurred in women due to breast cancer. Breast cancer does also occur in men, however we are focussing on female breast cancer in our review because male breast cancer is much less common (333 new diagnoses[3] and 96 deaths[4]) and no association with alcohol consumption has been established.

Risk of breast cancer depends on many factors, including age, genetics (including BRCA1 and BRCA2 gene mutations) and exposure to risk factors. Female breast cancer is linked to various lifestyle factors including oestrogen exposure, being overweight and alcohol consumption. IARC and the World Cancer Research Fund cite the following factors for which there is convincing evidence of association with breast cancer: alcoholic beverages, diethylstilboestrol, 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 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 (CRUK, accessed 2015).

We previously evaluated research published to June 2003 on alcohol consumption and breast cancer, and concluded that drinking alcoholic beverages may result in breast cancer in women (COC, 2004). The research considered indicated that approximately 6% (3.2% to 8.8%) of breast cancers registered in the UK each year could be prevented if drinking alcohol was reduced to less than 1 unit/week (8 g ethanol/week). We noted that this implied that consuming 1 alcoholic drink per day (at the time equivalent to approximately 1 unit/day) has a measurable effect. IARC also concluded that alcohol consumption is causally associated with breast cancer (IARC, 2010; 2012). We reviewed new reports published since the 2009 IARC evaluation (for details, see discussion paper CC/2014/19). Compared to some of the other cancer sites we reviewed, there were many more new cohort and case-control

[3] 2013 data for England and Scotland and yearly average data (2009-2013) for Northern Ireland. No data available for Wales

[4] 2013 data for England, Wales and Scotland and yearly average data (2009-2013) for Northern Ireland.

studies, as well as a number of new meta-analyses. Most of the meta-analyses observed a positive association (Brennan et al., 2010; Seitz et al., 2012; Trentham-Dietz et al., 2014; Bagnardi et al., 2015), as did the majority of cohort and case-control studies.

The meta-analysis of Bagnardi et al. (2015) indicated a statistically significant increased risk at all alcohol consumption levels compared with non-/occasional drinkers, with a clear dose-response:

g ethanol/day	RR	95% CI
≤12.5	1.04	1.01-1.07
≤50	1.23	1.19-1.28
>50	1.61	1.33-1.94

The large meta-analysis of Seitz et al. (2012) indicated an RR of 1.04 (95% CI, 1.02-1.07) associated with alcohol intake of ≤1 drink/day (≤12.5 g ethanol/day) compared with non-drinkers. Since the last IARC review, more studies have been published that evaluated the relationship between alcohol and type of breast cancer (ductal or lobular) or receptor status. Ductal and lobular carcinomas account for approximately 90% and 10%, respectively, of invasive breast cancers in women in the UK. Most of the results showed similar effects for either sub-type (Kotsopoulos et al., 2010; Chen et al., 2011; Newcomb et al., 2013), but one showed a slightly stronger positive association for lobular tumours (Li et al., 2010) and another showed no association for ductal carcinoma *in situ* (Kabat et al., 2010). There is increasing evidence to indicate a stronger association between alcohol consumption and ER-positive than ER-negative tumours (Li et al., 2010; Kabat et al., 2010), however risks are increased for tumours with either receptor status. We note that there were some limitations in terms of disease ascertainment, exposure assessment methods and lack of adjustment for confounders in some of the studies. There were a number of new studies on breast cancer mortality and recurrence. Overall, there was inconsistency across these studies, and therefore we are uncertain of the effect of alcohol consumption on recurrence and mortality.

In summary:

- The new evidence is consistent with the existing view that alcohol consumption is causally associated with female breast cancer. Increasing alcohol consumption increases risk in a dose-dependent manner.

- Overall, the new publications indicate a statistically significant increased risk at low, medium and high alcohol intakes.

2.2.3 Alcohol and liver cancer

In 2013, there were 5,373 new diagnoses of liver cancer (3,466 in men and 1,907 in women) in the UK and 4,846 deaths due to liver cancer (2,934 in men and 1,912 in women).

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 (CRUK, accessed 2015). Dietary exposure to aflatoxins from crops such as corn and peanuts is a risk factor that is present mostly in developing countries (WCRF, 2015).

IARC has stated that alcohol consumption is causally associated with liver cancer (IARC, 1988, 2010, 2012). We reviewed epidemiological literature published since the 2009 IARC review that reported evaluations of the association of alcohol intake with liver cancer (for details, see discussion paper CC/2014/12). A consistently positive association was observed between alcoholic beverage consumption and liver cancer at high intakes.

The meta-analysis of Bagnardi et al. (2015) showed an association of alcohol consumption with increased risk of liver cancer at intakes >50 g ethanol/day, but not at lower levels, compared with non-/occasional drinkers:

g ethanol/day	RR	95% CI
≤12.5	1.00	0.85-1.18
≤50	1.08	0.97-1.20
>50	2.07	1.66-2.58

The meta-analysis of Turati et al. (2014) indicated a statistically significant increased risk at alcohol intake ≥37.5 g ethanol/day compared with non-drinkers:

Drinks/day	g ethanol/day	RR	95% CI
<3	<37.5	0.91	0.81-1.02
≥3	≥37.5	1.16	1.01-1.34

Dose-response analysis from this study indicated a linear relationship between alcohol intake and liver cancer risk with RRs (95% CI) of 1.06 (1.02-1.11) for 12.5 g ethanol/day, 1.13 (1.04-1.24) for 25.0 g ethanol/day, 1.29 (1.08-1.53) for 50 g ethanol/day, 1.46 (1.13-1.89) for 75 g ethanol/day, and 1.66 (1.17-2.34) for 100 g ethanol/day. A statistically significant increased risk of liver cancer associated with high levels of alcohol drinking was also seen in the majority of individual cohort studies reviewed and in one nested case-control study.

In considering the new evidence on alcohol consumption and liver cancer risk, we noted that the majority of studies had been carried out in Asian populations. For liver cancer in particular, this gave rise to additional uncertainty in applicability of the findings to the UK population as a result of confounding by liver cancer arising from hepatitis. This was a particular concern as not all studies either established hepatitis status of the participants at the start or controlled for hepatitis in the analysis. In addition, some of the studies were designed to investigate hepatitis rather than alcohol. It is not clear whether this would affect relative risk estimations, while it would be important in terms of absolute risk. Other factors were also noted, such as differences in the types of alcohol consumed in these studies compared to the UK and the deficiency in the alcohol dehydrogenase 2 (ADH2) enzyme in Asian populations, but these were an uncertainty across all the cancer sites. An apparent J-shaped dose-response curve was identified in some analyses, with increased risk seen in non-drinkers compared with low-level alcohol consumption. We consider that it is difficult to suggest a plausible mechanism for this, that there are shortcomings in the data, and that it would be difficult to investigate the size of the effect with the methods available.

In summary:

- The new evidence is consistent with the existing view that alcohol consumption is causally associated with liver cancer. A consistently positive, statistically significant association was observed at high intakes.

2.2.4 Alcohol and colorectal cancer

Colorectal ('bowel') cancer accounted for 41,075 new cancer diagnoses in 2013 in the UK (22,943 in men and 18,132 in women). In the same year, 15,954 deaths were caused by colorectal cancer (8,658 in men and 7,296 in women).

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, and smoking. Some medical conditions, such as inflammatory bowel diseases may also be associated with increased risk. Dietary fibre and physical activity are associated with reduced risk of colorectal cancer (CRUK, accessed 2015).

IARC has stated that there is sufficient evidence to conclude that consumption of alcoholic beverages is causally related to cancer of the colorectum (IARC, 2010; 2012). We reviewed epidemiological evaluations on alcohol and colorectal cancer published since the 2009 IARC review (for details, see discussion paper CC/2014/20). Overall, the findings were variable, with the majority of individual new cohort and case-control studies showing no statistically significant positive

association between alcohol consumption and colorectal cancer, but pooled- and meta-analyses, which also include older studies, showing associations at high and in some cases medium intake levels.

Pooled analyses from the US Nurses' Health Study and Health Professionals Follow-up Study (Cho et al., 2012; Nan et al., 2013) revealed RRs around 1.35 for individuals consuming ≥30 g ethanol/day compared with non-drinkers, whilst evaluation of lower intake categories in the study of Cho et al. did not show a statistically significant increased risk:

g ethanol/day	RR	95% CI	
0.1-<5	1.16	0.87-1.54	
5.0-<10	1.08	0.91-1.28	
10-<15	1.26	0.96-1.66	
15-<30	1.11	0.92-1.33	
≥30	1.36	1.10-1.68	(p-trend 0.14)

Further analysis by Cho and colleagues indicated that the increased risk at intakes ≥30 g ethanol/day was statistically significant in subjects with (RR=2.02, 95% CI 1.30-3.13) but not without (RR=1.23, 95% CI 0.96-1.57) a family history of colorectal cancer. Meta-analyses by Fedirko et al. (2011) and Bagnardi et al. (2013; 2015) showed increased risk of colorectal cancer, compared with non-drinkers, associated with alcohol intakes >12.5 g ethanol/day but not at levels below this:

g ethanol/day	RR	95% CI	
≤12.5	0.99	0.95-1.04	
≤50	1.17	1.11-1.24	
>50	1.44	1.25-1.65	(Bagnardi et al. 2015)

Drinks/day	g ethanol/day	RR	95% CI	
≤1	≤12.5	1.0	0.95-1.05	
2-3	>12.5-<50	1.21	1.13-1.28	
≥4	≥50	1.52	1.27-1.81	(Fedirko et al. 2011)

An alternative analysis by Fedirko et al. (2011) showed RRs of 1.07 (95% CI 1.04-1.10), 1.18 (95% CI 1.12-1.25), 1.38 (95% CI 1.28-1.50), and 1.82 (95% CI 1.41-2.35) for 10, 25, 50, and 100 g ethanol/day, respectively.

In summary:

- Most of the evidence from the new meta-analyses is consistent with the existing view that alcohol consumption is causally associated with colorectal cancer. However, the majority of the new cohort and case-control studies published since 2009 showed no statistically significant positive association.
- The positive associations were observed at medium and high (>12.5 or >30 g ethanol/day) but not low alcohol intakes.

2.2.5 Alcohol and pancreatic cancer

Pancreatic cancer accounted for 9,389 new cancer diagnoses in the UK in 2013 (4,706 in men and 4,683 in women) and caused 8,524 deaths (4,234 in men and 4,290 in women).

Tobacco is a major risk factor for pancreatic cancer and body fatness is cited by IARC as a 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 (CRUK, accessed 2015).

IARC (2012) concluded that there is accumulating evidence that high alcohol intake (≥30 g/day) is associated with a small increased risk of cancer of the pancreas, but could not exclude the possibility that residual confounding by smoking may partly explain this association. We reviewed epidemiological evaluations on alcohol and pancreatic cancer published since the 2009 IARC review (for details, see discussion paper CC/2014/02). Overall, the new publications supported the conclusion of IARC that low-to-medium levels of alcohol consumption are not associated with increased pancreatic cancer risk, but high levels may increase risk.

A pooled analysis by Michaud et al. (2010) showed no statistically significant association of alcohol intakes at levels up to ≥60 g ethanol/day with pancreatic adenocarcinoma incidence, compared with the referent group (>0-<5 g ethanol/day):

g ethanol/day	OR	95% CI	
0	1.19	0.97-1.48	
>0-<5	1.00	(ref)	
5-<10	1.00	0.78-1.28	
10-<15	1.15	0.85-1.54	
15-<30	1.08	0.83-1.40	
30-<45	1.36	0.99-1.88	
45-<60	0.86	0.54-1.37	
≥60	1.38	0.86-2.23	(p trend 0.11)
ORcont[5]	1.03	0.97-1.10	

The pooled analysis of Lucenteforte et al. (2012) showed some statistically significant associations at very high alcohol intakes compared with abstainers or occasional drinkers (<1 drink/day):

[5] per 15 g ethanol/day

Drinks/day	g ethanol/day	RR	95% CI	
0-1	0-<12	1	(ref)	
1-2	12 - <24	1.02	0.76-1.37	
2-3	23.6 - <36	0.91	0.73-1.15	
3-4	36 - <47	0.93	0.69-1.26	
4-5	47 - <59	1.26	0.99-1.61	
5-6	59 - <71	1.14	0.86-1.50	
6-7	71-<83	1.59	1.16-2.20	
7-8	83 - <95	1.30	0.81-2.09	
8-9	95 - <107	1.25	0.74-2.10	
≥9	≥107	1.60	1.16-2.22	(p trend 0.302)

The meta-analysis of Bagnardi et al. (2015) indicated a statistically significant increased risk of pancreatic cancer associated with alcoholic beverage intake at >50 g ethanol/day compared with non- or occasional drinkers, but this was not observed at lower intake levels:

g ethanol/day	RR	95% CI
≤12.5	0.95	0.89-1.01
≤50	1.03	0.97-1.09
>50	1.19	1.11-1.28

The exact role of alcohol consumption in pancreatic cancer remains unclear, as other risk factors are involved. However, where smoking status was considered separately, the new evaluations indicate that there may be an effect of alcohol on pancreatic cancer independent of the effect of smoking.

In summary:

- Evidence from the new publications supports the conclusion that low and medium levels of alcohol consumption are not associated with increased pancreatic cancer risk, but high intakes (>50 g ethanol/day) may be associated with a small increase in risk. The exact role of alcohol consumption remains unclear.

- Studies where smoking status was considered separately were suggestive of an effect of alcohol on pancreatic cancer independent of the effect of smoking.

2.3 Conclusions

In reviewing new epidemiological publications on the association of alcoholic beverage intake and specific cancers we noted limitations of some of the studies, including uncertainties in disease ascertainment and exposure assessment methodologies, lack of consistency between studies in reporting alcohol intake

levels, and lack of differentiation between never drinkers and former or ex-drinkers, given that many studies used a non-drinker category.

Our findings and conclusions based on the new publications for each of the cancer types evaluated are summarised in Table 2.

Table 2: Summary of findings from epidemiological data published since the last IARC review in 2009 on cancer sites considered to be associated or causally associated with alcoholic beverage consumption.

Cancer site	**IARC opinion (IARC, 2012)**	**New publications - COC conclusions**
Upper aerodigestive tract (combined)	Consumption of alcoholic beverages is causally related to cancer of the upper aerodigestive tract. Increasing alcohol consumption increases risk in a dose-dependent manner, and does not vary by beverage type or sex.	Studies add further weight to the view that consumption of alcoholic beverages is causally associated with risk of upper aerodigestive tract cancers. Increasing alcohol consumption increases risk in a dose-dependent manner. Statistically significant increased risks were generally observed at medium and high (>12.5 g ethanol/day) but not low alcohol intakes.
Oral cavity and pharynx	Consumption of alcoholic beverages is causally related to cancer of the oral cavity and pharynx. Increasing alcohol consumption increases risk in a dose-dependent manner, and does not vary by beverage type or sex.	Studies add further weight to the view that consumption of alcoholic beverages is causally associated with risk of cancers of the oral cavity and pharynx (combined). Increasing alcohol consumption increases risk in a dose-dependent manner. Statistically significant increased risks were observed at low, medium and high levels of intake. Studies add further weight to the view that consumption of alcoholic beverages is causally associated with the risk of cancer of the oral cavity. Statistically significant increased risks were consistently observed at high alcohol intakes (>50 g ethanol/day), but findings were more variable at medium and low intakes. Studies add further weight to the view that consumption of alcoholic beverages is causally associated with the risk of cancer of the

Cancer site		IARC opinion (IARC, 2012)	New publications - COC conclusions
			pharynx. Statistically significant increased risks were consistently observed at high alcohol intakes (>50 g ethanol/day), but findings were more variable at medium and low intakes.
Larynx		Consumption of alcoholic beverages is causally related to cancer of the larynx. Increasing alcohol consumption increases risk in a dose-dependent manner, and does not vary by beverage type or sex.	Studies add further weight to the view that consumption of alcoholic beverages is causally associated with risk of laryngeal cancer. Statistically significant increased risks were consistently observed at medium and high (>12.5 g ethanol/day) but not low alcohol intakes.
Oesophagus	Oeso-phageal squamous cell carcinoma (SCC)	Consumption of alcoholic beverages is causally related to squamous cell carcinoma (SCC) of the oesophagus. Increasing alcohol consumption increases risk in a dose-dependent manner, and does not vary by beverage type or sex.	Studies add further weight to the existing view that consumption of alcoholic beverages is causally associated with risk of squamous cell carcinoma (SCC) of the oesophagus. Increasing alcohol consumption increases risk in a dose-dependent manner. Statistically significant increased risks were observed at low, medium and high alcohol intakes.
	Oeso-phageal adeno-carcinoma (AC)	There is a substantial body of evidence that alcoholic beverage consumption is not associated with adenocarcinoma (AC) of the oesophagus.	Studies add further weight to the view that consumption of alcoholic beverages is not associated with adenocarcinoma (AC) of the oesophagus.
Female breast		Consumption of alcoholic beverages is causally associated with the occurrence of cancer of the female breast. Cancer risk increases proportionately according to the amount of alcohol consumed, with an increase in risk up to 12% for each additional drink consumed regularly each day (equivalent to about 10 g/day). Risk does not appear to vary significantly by beverage type or smoking status. It is unclear whether the risk of female breast cancer associated with alcoholic beverage consumption varies by use of hormone-replacement therapy or by tumour	Studies are consistent with the view that alcohol consumption is causally associated with female breast cancer. Increasing alcohol consumption increases risk in a dose-dependent manner. Statistically significant increased risk was observed at low, medium and high alcohol intakes.

Cancer site	IARC opinion (IARC, 2012)	New publications - COC conclusions
	receptor status.	
Liver	Consumption of alcoholic beverages is causally related to hepatocellular carcinoma.	Studies are consistent with the view that alcohol consumption is causally associated with liver cancer. A consistently positive association was observed between alcoholic beverage consumption and liver cancer at high intakes.
Colorectum	Consumption of alcoholic beverages is causally related to cancer of the colorectum. Most of the evidence suggests that the association is with both cancer of the colon and rectum and is similar in men and women, but data are not entirely consistent. There is some evidence that risk may only be increased at high levels of intake (> 30 g/day). There is consistent evidence that risk does not differ by beverage type. The evidence is inconsistent as to whether the risk associated with consumption of alcoholic beverages differs by smoking or folate intake status.	Overall, new evidence is consistent with the view that alcohol consumption is causally associated with colorectal cancer. The majority of individual cohort and case-control studies showed no statistically significant positive association between alcohol consumption and colorectal cancer, whilst some of the meta-analyses showed associations at medium and high (>12.5 or >30 g ethanol/day) but not low levels of alcohol intake.
Pancreas	Accumulating evidence that high alcohol intake (≥ 30 g/day) is associated with a small increased risk for cancer of the pancreas, but the possibility of residual confounding by smoking cannot be excluded. It is unclear whether the risk associated with heavy alcohol consumption differs by beverage type, smoking status or body mass index.	Studies support the conclusion that low and medium levels of alcohol consumption are not associated with increased pancreatic cancer risk, but high intakes (>50 g ethanol/day) may be associated with a small increase in risk. Studies where smoking status was considered separately were suggestive of an effect of alcohol on pancreatic cancer independent of the effect of smoking.

2.3.1. Comparison of findings from the new publications with those of the IARC review in 2009

We consider that the new epidemiological papers published since the most recent IARC review in 2009 (IARC, 2012) add further weight to the view that consumption of alcoholic beverages is causally associated with risk of cancers of the upper aerodigestive tract including the oral cavity and pharynx, larynx and oesophageal

squamous cell carcinoma (SCC), and the female breast, the liver, and the colorectum.

The new information on alcohol consumption and pancreatic cancer risk also supports the conclusion made by IARC in 2009 that there is accumulating evidence that consumption of alcoholic beverages at high levels is associated with increased risk of cancer of the pancreas.

The new evidence supports the opinion of IARC that consumption of alcoholic beverages is not associated with oesophageal adenocarcinoma (AC).

The new publications support the opinion of IARC that risk of cancer does not depend on the type of alcoholic beverage consumed. A number of studies evaluated cancer risks associated with drinking specific beverage types (e.g., wine, beer, or spirits). Overall, it was not possible to identify any specific beverage type that had a specific effect at any of the cancer sites considered.

2.3.2 Levels of alcohol consumption associated with risk of cancer

In looking at the new evaluations, we have identified that for some cancers intake of alcohol at all levels of consumption increases risk, whereas at other cancer sites there is only good evidence of an effect of alcoholic beverage consumption above certain levels of intake:

- At **low, medium and high levels of alcohol intake,** there is a statistically significant increased risk at the following cancer sites:
    - oral cavity and pharynx (combined)
    - oesophagus (squamous cell carcinoma)
    - female breast
- At **medium and high levels of alcohol intake** (i.e. generally at intakes >12.5 g ethanol/day, or > approximately 1.5 UK units/day), there is a statistically significant increased cancer risk for the following cancer sites:
    - larynx
    - colorectum
- **At high levels of alcohol intake** (i.e. generally at intakes >50 g ethanol/day, or > approximately 6 UK units/day) there is a statistically significant increased cancer risk for the following cancer sites:
    - liver
    - pancreas

3 EVIDENCE FOR THE EFFECTS OF BINGE DRINKING ON CANCER RISK

At the start of our review, we recognised the growing interest in the effects of drinking large amounts of alcohol over a short time period, or 'binge drinking' (HM Government, 2012). The UK Opinions and Lifestyle Survey (ONS, 2015), similar to the predecessor surveys, considers people to have binged if they consumed more than 8 units (>64 g ethanol) for men or 6 units (>48 g ethanol) for women (i.e. more than double the current guidelines) on their heaviest drinking day in the last week. We decided, where possible, to specifically investigate whether the new publications (see section 2.1) provided data on whether binge drinking affects cancer risk.

The vast majority of the studies reviewed evaluated the effect of total alcohol intake on cancer risk, without necessarily identifying any specific pattern of drinking amongst the participants. The surveys used in the epidemiology studies would often use a questionnaire-based approach to estimate exposure and then either use a weekly intake (which if not already done we averaged to a daily intake) or the heaviest drinking day in the last week without evaluating on how many days the participant had consumed alcohol.

One of the studies we reviewed did report consideration of the effect of binge drinking on pancreatic cancer risk in men, where binge drinking was defined as the irregular consumption of >5 drinks/day (>70 g ethanol/day), analysed separately from the usual drinking pattern. This case-control study also looked at how often binge drinking occurred, and over how many years binge drinking had occurred (Gupta et al, 2010)., There was a statistically significant increased risk of pancreatic cancer increased in men with a 'usual' alcohol intake above 22 drinks per week compared with men consuming <1 drink/month:

Drinks/week	g ethanol/day	RR	95% CI
22-35	>42-70	1.9	1.0-3.7
>35	>70	2.2	1.1-4.6

For men with a lifetime history of binge drinking at least once per month, the RR was 3.5 (95% CI 1.6-7.5) versus men consuming <1 drink/month. Risk was associated with increasing average number of drinks consumed during a drinking session and also with increasing number of years of binge drinking. Even where frequency of binge drinking was once a month or less, it was still associated with elevated risk (OR=4.3, 95% CI 1.8-10) compared with a lifetime alcohol consumption of none or <1 drink/month.

Based on the Gupta paper, there does seem to be potential for an effect of binge drinking on lifetime risk of cancer, in this instance pancreatic cancer, but further evidence is required for the different cancer sites and from more studies to determine whether there is a specific effect of binge drinking over and above that of total lifetime alcohol consumption.

We note that there are a number of similar, but not identical, definitions of binge drinking available (NHS choices, Alcohol Concern, and Public Health Agency, Northern Ireland), which consider both number of units but also the time frame over which drinking occurs. The definition of binge drinking used by the ONS (ONS, 2015), that people have binged if they consumed more than double the current guidelines of 8 units (64 g ethanol) for men or 6 units (48 g ethanol) for women on their heaviest drinking day in the last week, is essentially the same means by which heavy drinking appears to us to be identified, and therefore there may be some overlap between effects reported as associated with heavy drinking and those that may be associated with binge drinking. In addition, we also note the recent paper on atypical and special occasion drinking compared to national survey information (Bellis et al., 2015).

We consider that, while there is an overlap between binge drinking and regular heavy drinking, it would be helpful if both survey data on consumption trends and epidemiology studies express clearly their definition of binge drinking, how it has been assessed and the intake category it is being compared to.

To evaluate the potential effects of binge drinking on cancer risk, we recommend agreement of a clear and measureable definition of binge drinking. It would also be helpful if studies provide clear data on the following aspects: background average drinking level, without binge sessions; the time frame of individual binge drinking sessions (hours or based on a day's consumption or over a couple of days); amount of alcohol consumed to classify as a binge; frequency of binge episodes; number of years of binge drinking; and how long ago binge drinking may have stopped.

In summary:

- There is very little evidence from the new publications regarding the effect of drinking large amounts of alcohol on a single occasion ('binge drinking'). Most of the new evaluations looked at the effect of total alcohol intake over a period such as a week or a month on cancer risk, and not the amount of alcohol consumed per drinking episode.

4 INTERACTION BETWEEN ALCOHOL AND GENOTYPE IN CANCER RISK

In its latest evaluation of alcohol and cancer, IARC noted that there is sufficient epidemiological evidence showing that people who are deficient in the oxidation of acetaldehyde to acetic acid and subsequently acetate have a substantially increased risk of developing alcohol-related cancers, in particular of the oesophagus and the upper aerodigestive tract (IARC, 2012). IARC noted that the available epidemiological data suggest a positive association between the alcohol dehydrogenase (ADH) genotype ADH1B*1/*1 and cancer of the oesophagus, and cancers of the upper aerodigestive tract combined, with insufficient data to draw

conclusions regarding this genotype for other cancer sites. IARC considered that there were insufficient data to draw conclusions regarding the ADH1C genotype and cancer at any site. Regarding the aldehyde dehydrogenase genotype, ALDH2, IARC noted that there is evidence for a contribution of heterozygous ALDH2 genotype to the development of alcohol-related cancer in the upper aerodigestive tract, oesophagus and oropharyngolarynx, particularly the hypopharynx, and that there are some data suggestive of association of heterozygous ALDH2 genotype with individual sub-sites of the oral cavity, oropharynx and larynx, but that evidence for other cancers was inconclusive. The IARC evaluation cautioned that data regarding genetic susceptibility can be difficult to interpret and require careful evaluation, particularly when identified susceptibility genes have no or unknown functional characterisation (IARC, 2012). It was noted that for polymorphisms affecting alcohol or acetaldehyde metabolism people may be heterozygotes for some of the alleles encoding more or less active forms that could both promote and inhibit the development of cancer. Also, heterozygotes for some alleles that enhance alcohol oxidation or inhibit acetaldehyde metabolism may avoid drinking alcohol and so be protected from the harmful effects. It is, thus, essential when looking at these gene polymorphisms and cancer to control for differences in alcohol drinking.

With respect to the potential mutagenicity of alcohol or its metabolites, the UK independent advisory Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) recently concluded that, overall, studies investigating genetic polymorphisms in key enzymes involved in ethanol metabolism have suggested that the ALDH2-deficient genotype is likely to contribute to the overall mutagenic potential of alcohol, whilst at present data are inconsistent or lacking for genetic polymorphisms of other enzymes (COM, 2016).

Amongst the new epidemiological studies that we reviewed, a small number of these evaluated cancer risk associated with variant genotypes and alcoholic beverage consumption. The findings support the conclusions of IARC that variations in ADH1B and ALDH2 genotypes may affect risk of upper aerodigestive tract and oesophageal cancers (Ding et al., 2010; Tanaka et al., 2010; Hakenewerth et al., 2011; Tsai et al., 2014) and that ALDH2 genotypes also affect oral cavity and pharyngeal cancer risk (Matsuo et al., 2012). In addition, an analysis from the European ARCAGE study indicated an association between homozygosity for an ADH1C variant and alcohol-associated upper aerodigestive tract cancer (Canova et al., 2010). A few studies suggested association among ADH1B and ADH1C genotypes and alcohol intake and risk of breast (Benzon Larsen et al., 2010; McCarty et al., 2012) or colorectal (Bongaerts et al., 2011; Ferrari et al., 2012) cancers. One study in Korea showed an interaction between alcohol consumption and MTHFR genotype in colorectal cancer risk (Kim et al., 2012).

In summary:

- The new publications indicate some evidence for alcohol consumption and genotype interactions in cancer risk for ADH1B, ALDH2 and ADH1C genes and upper aerodigestive tract cancers, ADH1B and ADH1C genes and breast or colorectal cancers, and the MTHFR gene and colorectal cancer.

5 BURDEN – ALCOHOL ATTRIBUTABLE RISK

As part of this review, the Committee looked at a number of publications estimating the burden of cancer attributable to alcohol in the UK, by applying relative risk data from epidemiological studies to UK survey data, and other papers discussing methodological aspects of undertaking such estimates. As these papers provided estimates based on recent data, we agreed to review the approaches used, rather than undertake our own *de novo* estimation.

Of the five papers considered which made estimates of burden of cancer attributable to alcohol consumption in the UK, four considered all the 6 cancer sites for which IARC concluded alcohol consumption has a causal association. The last paper focused on oral cavity and pharyngeal cancer. The approaches by the different authors used broadly similar methodology to calculate the alcohol attributable fraction. The main differences were choice of:

- The relative risk estimates from epidemiological studies, and
- The alcohol consumption data from surveys, including whether and how this was adjusted to address the differences between reported consumption from the surveys and alcohol sales data.

The estimated alcohol attributable fractions for each of the papers are given in Table 3 (see next page) with the relative risk and alcohol consumption estimates used in each.

Table 3: Overall alcohol attributable fractions for the UK or England determined in the literature by cancer site along with the sources of data for the risk ratios and alcohol consumption levels used

	All age alcohol attributable fractions by sex (%)									
	Parkin, 2011		Jones and Bellis, 2014		Schutze et al, 2011		Jones et al, 2008		Meier et al, 2013	
	M	F	M	F	M	F	M	F	M	F
Oral cavity and pharynx	37	17	42	34	45	30	45	26	47 to 60	28 to 35
Oesophagus	25	11	58	43			25	12	-	-
Larynx	27	12	37	24			28	14	-	-
Colorectal	16	7	16	12	14	5	4	2	-	-
Liver	11	5	15	11	33	13	13	6	-	-
Breast	-	6	-	13	-	5	-	6	-	-
	Source of, and approximate exposure-response (excess risk per g alcohol per day)									
Oral cavity and pharynx	Corrao et al., 2004: ~0.019; 0.04 at 50 g/d		Tramacere et al., 2010: 0.029 at 10 g/d; 0.045 at 50 g/d		Inter-nal: 1.4 $x10^{-2}$	Inter-nal: 2 $x10^{-2}$	Corrao et al., 2004		Tramacere et al., 2010	
Oesophagus	Corrao et al., 2004: ~0.013; 0.019 at 50 g/d		Islami et al., 2011: ~0.05				Corrao et al., 2004		-	-
Larynx	Corrao et al., 2004: ~0.014; 0.02 at 50 g/d		Islami et al., 2010: 0.017 at 10; 0.27 at 100				Corrao et al., 2004		-	-
Colorectal	Various: 0.008		Fedirko et al., 2011: ~0.007		Inter-nal: 4 $x10^{-3}$	Inter-nal: 3 $x10^{-3}$	Corrao et al., 2004: 0.002 at 30 (col); 0.003 at 30 (rect)		-	-
Liver	Corrao et al., 2004: 0.006		Corrao et al., 2004		Inter-nal: 1.1 $x10^{-2}$	Inter-nal: 7.5 $x10^{-3}$	Corrao et al., 2004		-	-
Breast	-	Hama-jima et al., 2002: 0.007	-	Hama-jima et al., 2002	-	Inter-nal: 4 $x10^{-3}$	-	Hama-jima et al., 2002	-	-
Mean alcohol consumption (g/d)	23.6	11.6	32.9	17.3	35.2	17.6	22.5	12.6	-	-

In considering the available attributable fractions, we noted that the Jones and Bellis (2014) paper was an update of the Jones et al. (2008) paper and therefore we decided to focus on the more recent paper.

One paper from the European Prospective Investigation into Cancer and Nutrition (EPIC) (Schütze et al, 2011), gave attributable fractions that were somewhat different to the others. This was because: 1) the relative risk data came only from the EPIC study, whereas the other studies used similar values for the relative risk (depending on the data available at the time of the analysis); 2) the consumption data came from WHO rather than the UK Office for National Statistics, which was

used in the other studies, with varying adjustment to account for under-reporting in surveys compared to sales data. While the Schütze et al. (2011) paper came from the well regarded EPIC study, due to the different data used and because of the number of assumptions made in the analysis, we did not use the results from this paper in our estimation of number of alcohol attributable cancers below.

The Meier et al (2013) paper focussed on oral cavity and pharyngeal cancer and investigated the effects of different approaches to adjusting survey data to bring it more in line with sales data. Therefore, we did not use these data in our estimation of number of alcohol attributable cancers.

A number of aspects that could be adjusted for, and sensitivity analyses that had been undertaken, were reviewed by the Committee and further information is available in the discussion papers considered (CC/2014/18 and CC/2015/07).

Only one of the papers (Parkin, 2011) took account of any latency period for induction of alcohol-related cancer, by using consumption data from the period 10 years earlier. While this addresses the possibility that risk of cancer relates more closely to earlier rather than current consumption, it is likely that the relative risks in epidemiology studies encompass some variation in habits over time and also relate to recent rather than lifetime drinking (Darnton 2015, personal communication).

There is a mismatch between self-reported alcohol consumption from surveys and data on alcohol sales, with sales data indicating higher per capita consumption. A number of the papers estimating the UK attributable fraction by applying relative risks from epidemiological studies to UK survey data adjust the alcohol consumption survey data to reflect this discrepancy with sales data in their analyses. The paper by Meier et al (2013) focused on investigating the effects of different approaches to adjusting survey data to bring it more in line with sales data using oral cavity and pharyngeal cancer as an example. However, Parkin (2011) suggests that the under-reporting of alcohol consumption in surveys can similarly be considered to occur from self-reporting of alcohol consumption in the epidemiology studies from where the relative risk estimates can be derived and thus adjusting for this may be inappropriate. Parkin did not therefore adjust his estimates which are substantially lower than other estimates (Table 3). In contrast, Jones and Bellis (2014) do adjust the alcohol consumption rates to take account of under-reporting. In doing so, they note that adjustment for under-reporting based on per capita consumption brings further assumptions, such as that under-reporting is evenly distributed across different population groups, e.g. age and sex groups, and that it applies evenly across the different alcohol consumption levels. Overall, we recognise the need for some adjustments to be made, but there needs to be recognition of the uncertainties associated with uprating and the further assumptions that it brings. Therefore, in this analysis we have considered one paper that does adjust (Jones and Bellis, 2014) and one paper that does not adjust (Parkin, 2011) for under-reporting of alcohol consumption in estimating the alcohol attributable fraction.

For the reasons discussed in this section, we have used the all-age overall attributable fractions from Parkin (2011) and Jones and Bellis (2014) and applied these to the 2013 Cancer Registry incidence statistics, to estimate the alcohol attributable number of cancers (Table 4, see next page). Using the attributable fractions from Parkin (2011) results in an estimate of 4% of all new cancers in the UK in 2013 being attributable to alcohol consumption, while using the Jones and Bellis (2014) attributable fractions results in an estimate of 6% of new cancers being attributable to alcohol consumption.

In summary:

- We looked at available papers assessing the burden of alcohol consumption on cancer incidence in the UK in order to get a general idea of the involvement of alcohol in cancer burden. The evaluations used broadly similar approaches and most used similar datasets to underpin the calculations, but there were differences in adjustment of the data. As a result we did not consider it necessary to undertake our own *de novo* estimation.

- Of the adjustments made, the most common was to account for the under-reporting of alcohol consumption in surveys as compared to alcohol sales, and though this also introduces uncertainty, we conclude that some adjustment is appropriate.

- Findings from the two most appropriate studies on UK populations indicate that 4-6% of all new cancers in the UK in 2013 were caused by alcohol consumption.

Table 4: Alcohol attributable numbers of cancers diagnosed in 2013 by cancer site

	Males					Females					Total		
		Parkin, 2011		Jones & Bellis, 2014			Parkin, 2011		Jones & Bellis, 2014			Parkin, 2011	Jones & Bellis, 2014
	Cancers diagnosed 2013 in the UK	Attributable fraction (%)	Attributable number	Attributable fraction (%)	Attributable number	Cancers diagnosed 2013 in the UK	Attributable fraction (%)	Attributable number	Attributable fraction (%)	Attributable number	Cancers diagnosed in 2013 in the UK	Attributable number	Attributable number
Oral cavity & pharyngeal cancer	5,713	37	2,114	42	2,399	2,867	17	487	34	975	8,580	2,601	3,374
Laryngeal cancer	1,915	27	517	37	709	400	12	48	24	96	2,315	565	805
Oesophageal cancer	5,848	25	1,462	58	3,392	2,931	11	322	43	1,260	8,779	1,784	4,652
Female breast cancer						53,339	6	3,200	13	6,934	53,339	3,200	6,934
Liver cancer	3,466	11	381	15	520	1,907	5	95	11	210	5,373	476	730
Colorectal cancer	22,943	16	3,671	16	3,671	18,132	7	1,269	12	2,176	41,075	4,940	5,847
Oral cavity, pharyngeal, laryngeal, oesophageal, female breast, liver & colorectal cancers combined (%)	39,885		8,145 (20%)		10,691 (27%)	79,576		5,421 (7%)		11,651 (15%)	119,461	13,566 (11%)	22,342 (19%)
Total of all cancers and percentage of alcohol attributable cancers	179,093		5%		6%	172,485		3%		7%	351,578	4%	6%

6 EVALUATION OF SOME INDIVIDUAL META-ANALYSES REPORTING POTENTIAL INVERSE RELATIONSHIPS BETWEEN ALCOHOL AND SOME CANCER TYPES

We reviewed some individual meta-analyses published since the most recent IARC review of alcohol and cancer in 2009, which evaluated the relationship between alcoholic beverage intake and the risks of kidney cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and extra-hepatic bile system cancer. These individual publications were reviewed because they came to our attention due to the suggestion that alcohol consumption results in reduced risk for these cancers. They were not identified in the same way as the information on the cancer sites above in section 2, nor have any further literature searches been carried out to identify other available data on these cancer sites. These data are summarised in Table 5.

6.1 Kidney

In 2013, there were 11,023 new cases (6,885 in men and 4,138 in women) of kidney cancer and 3,785 deaths (2,335 in men and 1,450 in women) from kidney cancer in the UK.

IARC (2012) concluded that there is no causal association between consumption of alcoholic beverages and cancer of the kidney. We reviewed two meta-analyses published since the latest IARC evaluation that showed an inverse relationship between alcohol consumption and renal cell carcinoma risk. The meta-analysis of Song et al. (2012) indicated a combined RR of 0.73 (95% CI 0.67-0.79) for top versus bottom alcohol intake categories. The meta-analysis of Bellocco et al. (2012) showed a negative association between alcohol consumption and renal cell carcinoma for low and medium alcohol intakes, whilst results were not statistically significant for high intakes, compared with non-drinkers:

g ethanol/day	RR	95% CI
0.01-14.49	0.90	0.83-0.97
12.5-49.9	0.79	0.71-0.88
≥50	0.89	0.58-1.39

We note that in the small number of studies included in these meta-analyses that considered high levels of alcohol consumption, the negative association levelled off at intakes of 20-25 g ethanol/day.

We discussed the possible mechanisms by which alcohol might reduce the risk of kidney cancer. While it is 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.

6.2 Non-Hodgkin lymphoma and Hodgkin lymphoma

There were 13,395 new cases (7,253 in men and 6.142 in women) of non-Hodgkin lymphoma (NHL) and 1,951 new cases (1.097 in men and 854 in women) of Hodgkin lymphoma (HL) in the UK in 2013. In the same year, there were 4,666 deaths (2,559 in men and 2,107 in women) from NHL and 294 deaths (164 in men and 130 in women) from HL.

IARC (2012) concluded that there is evidence suggesting a lack of carcinogenicity of alcoholic beverages and NHL, noting that the results from some cohort studies and very large case-control studies showed an inverse association or no association. IARC (2012) did not state a conclusion regarding alcohol consumption and HL, but did note that there is a consistent inverse association in case-control studies investigating ever-alcohol consumption and risk for HL. We reviewed two meta-analyses (one for NHL and one for HL) published since the most recent IARC evaluation that suggested a decrease in risk of these cancer types among people consuming alcohol as compared with non-drinkers. The meta-analysis of Tramacere et al. (2012b) showed an overall RR for NHL of 0.85 (95% CI 0.79-0.91) and that of Tramacere et al. (2012c) an overall risk for HL of 0.70 (0.60-0.81) in drinkers versus non-drinkers. However, breakdown by study type tended to show significant findings for case-control but not cohort studies. A statistically significant dose-response was not observed for either cancer type and the authors suggested caution in interpretation of the findings.

We have concerns about the consistency of the classification of cancers of this type and the confounding effect of diverse lymphoma types. In addition, there is no immediately obvious mode of action that could explain the association.

6.3 Extra-hepatic bile system cancer

There were 1,932 new cases (835 in men and 1,097 in women) of extra-hepatic bile system cancer England and Scotland[6] in 2013, and 790 cancer deaths (269 in men and 521 in women) in England, Wales and Scotland[7].

IARC (2012) noted that it is not possible to draw any conclusion concerning the consumption of alcoholic beverages and risk of cholangiocarcinoma (which includes intra- and extra-hepatic bile system cancers). We reviewed a meta-analysis published since the last IARC evaluation that showed an inverse association of alcohol consumption and extra-hepatic bile system cancer. This is a rare cancer site with a large number of potential risk factors. The meta-analysis of Kan et al. (2011)

[6] Wales and Northern Ireland data not available
[7] Northern Ireland data not available

showed an overall OR for extra-hepatic bile system cancer of 0.82 (95% CI 0.72-0.94) for alcohol drinkers versus non-drinkers. The OR was increased in high-level drinkers (≥80 g ethanol/day) versus non-drinkers, but the results were not statistically significant (OR=1.58, 95% CI 0.97-2.57). The authors noted that there may be a threshold of alcohol consumption for risk of extra-hepatic bile system cancer, though this would need to be verified.

6.4 Conclusions on studies reporting potential inverse effects

A summary of the IARC conclusions for these cancer sites and our conclusions based on these individual papers is presented in Table 5.

Table 5: Summary of findings from some individual epidemiological meta-analyses published since the last IARC review in 2009, reporting inverse associations of alcoholic beverage consumption with some cancer types.

Cancer site	IARC opinion (IARC, 2012)	COC observations
Kidney	There is no causal association between the consumption of alcoholic beverages and cancer of the kidney.	Two meta-analyses (Song et al., 2012; Belloco et al., 2012) indicated an inverse association between alcohol consumption and renal cell carcinoma risk. There was no consistent dose-response.
Non-Hodgkin lymphoma (NHL)	There is evidence suggesting a lack of carcinogenicity of alcoholic beverages and non-Hodgkin lymphoma. The results from some cohort studies and very large case-control studies have shown an inverse association or no association. In general there is no difference in findings for specific beverage types.	The meta-analysis of Tramacere et al. (2012b) indicated a decrease in risk of non-Hodgkin lymphoma in people consuming alcohol compared with non-drinkers. A statistically significant dose-response was not observed.
Hodgkin lymphoma	There is a consistent inverse association in case-control studies investigating ever-alcohol consumption and risk for Hodgkin lymphoma, with no significant different between alcoholic beverage types.	The meta-analysis of Tramacere et al. (2012c) indicated a decrease in risk of Hodgkin lymphoma in people consuming alcohol compared with non-drinkers. A statistically significant dose-response was not observed.
Extrahepatic bile system	It is not possible to draw conclusions regarding the consumption of alcoholic beverages and the risk of cholangiocarcinoma *(i.e. intra- and extra-hepatic bile system cancer)*.	The meta-analysis of Kan et al. (2011) indicated an inverse association of alcohol consumption and extra-hepatic bile system cancer. Compared with non- or low-level drinkers, risk was reduced for moderate drinkers but increased for heavy drinkers.

We note that one of the limitations across all these studies is the comparison category. In some instances the non-drinker is the comparator, though it is possible that this would include people who stopped drinking as a result of their diagnosis. It is also possible that the characteristics of the people in the non-drinker category are different to those in the drinking category, which could confound the results. Finally, in some studies the comparison group is non- and low-intake drinkers, making it difficult to comment on the effect of low-level alcohol consumption.

We note that associations such as those suggested by these meta-analyses are sometimes stated as showing a protective effect, in this instance of alcohol consumption for these cancers. However, we have not reviewed any mechanistic information which might explain any protection. Although the meta-analyses may be suggestive of an inverse relationship with lower levels of alcohol consumption, the underlying mechanisms are unclear, thus limiting the interpretation of these findings. Any positive effects are outweighed by the risks associated with alcohol consumption.

In summary:

- Overall, it is difficult to draw any firm conclusions from these meta-analyses on inverse effects of alcohol consumption for these cancers, which nevertheless support the conclusions of IARC that alcohol consumption is not causally associated with these cancers.

7 EFFECT OF CESSATION OF ALCOHOL CONSUMPTION ON CANCER RISK.

As part of our review of alcohol and cancer risk, we felt that it was important to consider risk reduction strategies. Therefore, we reviewed the available evidence on the impact of cessation of alcohol consumption on cancer risk for the cancer sites where IARC has concluded that alcohol consumption has a causal association.

Evidence on the effect of cessation of alcohol consumption was only identified for upper aerodigestive tract cancers and liver cancer (for further information, see discussion papers CC/2014/04 and CC/2014/13). 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 is not always clear why people stopped drinking, but potential reasons include health concerns or deteriorating health, which could influence the results, especially for the years immediately after cessation of alcohol consumption. 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.

Overall, the data from a number of studies examining the effects of alcohol cessation on the risk of upper aerodigestive tract and liver cancers demonstrate a reduction in risk following long-term abstention. However, the results are not consistent across all studies and the magnitude of effect varies 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. This apparent increase in cancer risk immediately after cessation of alcohol consumption may be a consequence of cessation by people who were already becoming ill, i.e. the sick-quitter phenomenon. This is clearly different to the benefits of smoking cessation, where the risk starts to decrease shortly afterwards.

There is also a need for caution because most studies were case-control studies with small numbers of subjects included, especially at longer time points.

The evidence on cessation of alcohol consumption shows that it takes a long time for risks to fall to the level of the never drinker. The time period required for risks of upper aerodigestive tract and liver cancers for former drinkers to fall to those of never drinkers appears to be in the range of 20 years or more.

We considered whether it would be possible to comment on the impact of reducing alcohol consumption rather than complete cessation on cancer risk, but no data were identified to assess this. However, it is plausible that there would be a benefit of reducing consumption, as the risk of cancer at the sites assessed tends to be lower at lower alcohol intake.

In summary:

- The effect of long-term abstention from alcohol on cancer risk has been investigated for upper aerodigestive tract and liver cancers. These studies indicated a reduction in risk following long-term abstention, although risks may take many years, in the range of 20 years, to fall to the level of never drinkers.

- While there are no studies investigating reducing alcohol consumption, it is plausible that reducing consumption would lead to a reduction in cancer risk.

8 POTENTIAL MECHANISMS BY WHICH ALCOHOL MAY INCREASE THE RISK OF CANCER

IARC (2012) concluded that ethanol is the principal ingredient that renders alcoholic beverages carcinogenic, and that in the body ethanol is converted by ADH and CYP2E1 enzymes to acetaldehyde, which is cytotoxic, genotoxic, mutagenic and clastogenic, and has been shown to be carcinogenic in experimental animals.

Evidence for the key roles of ethanol and acetaldehyde is strengthened by the associations observed between different forms of cancer and polymorphisms in ethanol and acetaldehyde metabolism (see Section 4). Potential ethanol-related mechanisms of carcinogenesis include oxidative stress (which has been associated with ethanol-induced carcinogenesis in many organs, such as breast, liver and pancreas), cirrhosis (hepatocellular injury leading to enhanced fibrogenesis in the liver), interactions with tobacco smoke (especially for oro-pharyngeal and oesophageal cancers), effects on sex hormones (such as increased oestrogen and androgen levels associated with alcohol intake in women that may contribute to the development of breast cancer) and effects on folate metabolism (e.g. the association of alcoholic beverage consumption, folate deficiency and colorectal cancer). A role of acetaldehyde has been demonstrated by associations of inactive ALDH alleles with oesophageal cancer in East Asian populations and of ADH1B polymorphisms and upper aerodigestive tract cancers (IARC, 2012).

In our previous evaluation of the association of alcohol and breast cancer, we concluded that it is not known precisely how drinking alcohol can lead to breast cancer. The most likely explanation is that drinking alcohol can produce biochemical effects in the liver (such as changes to oestrogen metabolism and effects on growth factors) which, if alcohol drinking is prolonged (i.e. over decades), could lead to breast cancer (COC, 2004).

As part of this review we asked 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 May 2014 on the mutagenicity of alcohol and its primary metabolite, acetaldehyde, from *in vitro* and *in vivo* studies and studies in humans following consumption of alcoholic beverages (see MUT/2014/05). Studies investigating genotoxic and mutagenic effects arising from the consumption of alcoholic beverages in humans did not consistently account for relevant confounding factors (e.g. smoking, BMI, or nutritional intake). Other quality issues limited the reliability of the study findings (e.g. small sample sizes, poor exposure assessments). The COM acknowledged the emergence of additional studies on DNA adduct formation in humans, and studies reporting the influence of polymorphisms in enzymes involved in alcohol metabolism, particularly in relation to induction of micronuclei. However, it considered that the poor quality of most of these studies prevented any useful conclusions from being drawn. The COM noted that a number of studies have implicated the formation of acetaldehyde-specific DNA adducts and inter-strand DNA crosslinks as upstream events in the genotoxicity of alcohol. However, the poor reliability of data available from *in vivo* studies on the genotoxicity of ethanol and from studies in humans meant it was not possible to draw any definitive conclusions on the genotoxicity of alcohol *per se*. Acetaldehyde is widely accepted as being genotoxic *in vitro* and *in vivo*, when administered directly. It was agreed that the recent *in vitro* data on acetaldehyde added further strong

evidence for the genotoxicity of this compound, particularly with regard to generation of acetaldehyde-specific DNA adducts and induction of micronuclei in mammalian cells at concentrations of acetaldehyde realistically achievable from alcoholic beverage consumption. It was concluded that acetaldehyde remains the metabolite of most concern with respect to the genotoxic effects of alcohol. However, there is uncertainty as to whether such effects occur as a result of its production *in vivo* following metabolism of ethanol. Studies examining the potential mutagenic mechanisms of ethanol and acetaldehyde were evaluated. Data suggest that multiple modes of action contribute to the overall genotoxicity of ethanol.

The COM also considered a paper reviewing the hypothesis that associates the mutagenic and carcinogenic mode of action of alcohol in the liver with the generation of reactive oxygen species (ROS) and the role of CYP2E1 in this process (see MUT/2015/02). Alcohol consumption can result in the formation of ROS in the liver either via inflammatory-mediated processes or oxidative metabolism. ROS have the potential to generate lipid peroxidation products, which in turn may yield mutagenic, exocyclic DNA etheno adducts (e.g. N6-etheno-2'-deoxyadenosine, εdA; N4-etheno-2'deoxycytidine, εdC). Ethanol consumption also results in the induction of CYP2E1, primarily in the liver but also in extra-hepatic tissues such as the oesophagus and intestine. It is suggested that this induction enhances the metabolism of alcohol to acetaldehyde and the generation of ROS, and accordingly increases the associated likelihood of adduct formation. A correlation between CYP2E1 levels and DNA etheno adducts has been demonstrated in animal models and in humans. However, an association between specific CYP2E1 alleles and alcoholic liver damage or alcohol-induced carcinogenesis in humans is not well defined. Overall the COM agreed that the hypothesis that alcohol-induced oxidative stress is of importance in the pathogenesis of alcohol-induced liver injury and carcinogenesis was plausible. There is some evidence to support this premise in humans following alcohol consumption. However, more work would be required in this complicated area before definitive conclusions could be drawn (COM, 2015).

In summary:

- Ethanol is the principal ingredient that renders alcoholic beverages carcinogenic. There are probably several different mechanisms by which ethanol causes cancer, and different mechanisms may be involved in the development of different cancer types. These include metabolism to acetaldehyde, oxidative stress, damage to cells in the liver leading to cirrhosis, interaction with other chemicals such as tobacco smoke, effects on sex hormones, and effects on vitamins and minerals in the body.

9 SUMMARY

1. The World Health Organisation's International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence in humans for the

carcinogenicity of alcohol consumption. IARC last reviewed the carcinogenicity of alcoholic beverages in 2009, concluding that alcohol consumption causes cancers of the oral cavity and pharynx, larynx, oesophagus (squamous cell carcinoma), colorectum, liver (hepatocellular carcinoma) and female breast, and that an association has been observed between alcohol consumption and cancer of the pancreas (IARC, 2012).

2. We have carried out an updated review of epidemiological evaluations published since the IARC review in 2009, which investigated the association of the consumption of alcoholic beverages with these cancers. The findings reported in these new publications add further weight to the view that consumption of alcoholic beverages is causally associated with risk of cancers of the oral cavity and pharynx, larynx, oesophagus (squamous cell carcinoma), female breast, liver, and colorectum. The new evidence adds further weight to the conclusion of IARC that alcohol consumption is associated with cancer of the pancreas, though the role of alcohol in pancreatic cancer is unclear. The new evidence also supports the opinion of IARC that consumption of alcoholic beverages is not associated with oesophageal adenocarcinoma.

3. The new publications show a statistically significant increase in cancer risk:

- At **low, medium and high** levels of alcohol intake for cancers of the oral cavity and pharynx (combined), oesophagus (squamous cell carcinoma) and female breast
- At **medium and high** levels of alcohol intake (i.e. generally at intakes >12.5 g ethanol/day, or > approximately 1.5 UK units/day) for cancers of the larynx and colorectum
- At **high** levels of alcohol intake (i.e. generally at intakes >50 g ethanol/day, or > approximately 6 UK units/day) for cancers of the liver and pancreas.

4. We note limitations of some of the studies that we reviewed, including uncertainties in disease ascertainment and exposure assessment methodologies, lack of consistency between studies in reporting alcohol intake levels, and lack of differentiation between never drinkers and former or ex-drinkers in ‘non-drinker’ reference categories.

5. There is very little evidence from the new publications regarding the effect of drinking large amounts of alcohol on a single occasion. Most of the new evaluations looked at the effect of total alcohol intake over a period such as a week or a month on cancer risk, and not the amount of alcohol consumed per drinking episode.

6. The new publications support the conclusion that all types of alcohol increase the risk of cancer. This is consistent with the hypothesis that it is the ethanol in alcoholic beverages, and the associated acetaldehyde, that is carcinogenic, and this is further supported by new publications that reported association of the risk of some

alcohol-associated cancers with specific variants of genes encoding enzymes involved in alcohol and acetaldehyde metabolism.

7. We looked at a number of publications estimating the burden of cancer attributable to alcohol in the UK and others discussing methodological aspects of undertaking such estimates. We conclude that the available papers assessing the burden of alcohol consumption on cancer incidence in the UK use broadly similar approaches and most use similar datasets to underpin the calculations, but there are differences in adjustment of the data. As a result we did not consider it necessary to undertake our own *de novo* estimation. Of the adjustments made, the most common was to account for the under-reporting of alcohol consumption in surveys as compared to alcohol sales. Using the two most appropriate available studies produces estimates that 4-6% of all new cancers in the UK in 2013 were caused by alcohol consumption.

8. We also discussed the findings of five individual meta-analyses that indicate that alcohol consumption results in reduced risk for some cancers. Several factors limit the drawing of firm conclusions from these studies. However, we conclude that they support the opinion of IARC that alcohol consumption is not likely to be causally associated with kidney cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, or extra-hepatic bile system cancer.

9. To assess whether the risk of cancer from drinking alcohol can be reduced, we performed a search for all published studies that investigated the effects of alcohol cessation on cancer risk. Data were identified for upper aerodigestive tract and liver cancers. These studies indicated a reduction in risk following long-term abstention, although risks took several years, in some cases 20 years or more, to fall to the level of never drinkers. Some studies showed an initial increase in risk after cessation, followed by decreased risk in the longer term, which may be an effect of cessation by people who were already becoming ill.

10 CONCLUSIONS

The findings of new epidemiology evaluations published since the most recent IARC review in 2009 add further weight to the view that consumption of alcoholic beverages is causally associated with risk of cancers of the oral cavity and pharynx, larynx, oesophagus (squamous cell carcinoma), female breast, colorectum, and liver. Alcohol consumption is also associated with cancer of the pancreas, although it is not clear whether this is a causal association.

The new publications show:

- At **low, medium and high alcohol intakes**, a statistically significant increased risk at the following cancer sites:
    - oral cavity and pharynx (combined)
    - oesophagus (squamous cell carcinoma)
    - female breast
- At **medium and high alcohol intakes** (i.e. generally at intakes >12.5 g ethanol/day, or > approximately 1.5 UK units/day), a statistically significant increased cancer risk at the following cancer sites:
    - larynx
    - colorectum
- At **high levels of alcohol intake** (i.e. generally at intakes >50 g ethanol/day, or > approximately 6 UK units/day), a statistically significant increased cancer risk for the following cancer sites:
    - liver
    - pancreas.

COC
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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.

Definitions of evidence, as used in IARC Monographs for studies in humans (IARC, 2012)

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories. In some instances, these categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is sufficient evidence is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition,

the possibility of a very small risk at the levels of exposure studied can never be excluded.

References

IARC (2012). Personal Habits and Indoor Combustions. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; Volume 100E. Available here: http://monographs.iarc.fr/ENG/Monographs/vol100E/mono100E.pdf (accessed 23/06/2015)

Annex B

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 C

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 exposed 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 an 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	

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