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## Alcohol and Mouth Cancer

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### In brief

It is not alcohol but rather the first metabolite of alcohol, acetaldehyde, which is the most important carcinogen.

Patients should be made aware of their alcohol unit intake (eg consider keeping an alcohol diary or using an App).

Alcohol containing mouthwashes are essentially safe (being associated with a slightly increased risk of mouth cancer if used more than twice a day and for greater than 35 years).

### Abstract

There is now considered to be no safe limit for alcohol intake . Studies have shown that risk of mouth cancer increases with greater alcohol intake (in particular when associated with the use of tobacco). This paper reviews the role for alcohol in the aetiology of mouth cancer both in terms of how it may give rise to cancerous change and the relative risk it carries (arising from various systematic and meta-analyses reported over the last decade). Whilst obtaining a reliable alcohol history can be problematic (with under reporting frequently suspected) greater awareness of the role of alcohol in both local and systemic disease (in particular that of cancer in an ever increasing number of sites) may serve as a motivator for behaviour change within our patients. To that end patients should be aware of the alcohol content in the drinks they consume and consider recording their alcohol intake over a defined period (eg use of a diary or App over a 2 to 4 week period)

### Introduction

Alcohol, particularly in association with the use of tobacco, is recognised as an important risk factor for mouth cancer. There is also concern over increasing numbers of alcohol related admissions to hospital <sup>1</sup>. And concern over an increase in the amount of alcohol consumed ( approximately 5 years ago, Scotland consumed the equivalent of 46 bottles of vodka for every adult in the country). Scotland now consumes the equivalent of 10 litres of pure ethanol/adult/year which is approximately 2 ½ USA gallons of alcohol.<sup>1</sup> Since not all people drink alcohol, especially women, then some people are consuming huge amounts.. Faced with such a back drop, in 2016, the Chief Medical Officers for the UK finally released their report updating the guidelines , now stating that there was no safe level for alcohol intake and recommending that both men and women drink no more than 14 units per week ,with at least two days free of alcohol <sup>2</sup>. This was in part due to there being two working groups, one that looked at the evidence for effect on health and the other on behaviour. They also followed the Canadian/ Australian model of accepting a 1% lifetime risk of death from alcohol,

A standard unit of alcohol varies according to which country you reside in <sup>3</sup>. In the United Kingdom a unit is 8 g of alcohol (10 mL by volume). The number of units can be calculated by multiplying the volume consumed by the alcohol by volume (ABV) content and dividing by 1000 (or use an App such as Mydrinkaware). Hence a typical pint of beer at 4.5% ABV contains 2.5 units, a standard glass of wine (175ml) at 13.5% ABV is 2.3 units and a measure of whisky (25ml) at 40% ABV is 1 unit). In the Netherlands, it is 9.9 g. In France and Ireland, 10 g, in the USA it is 14 g and in Japan 22 g <sup>4</sup>. When comparing data between countries because of the variability in what constitutes a unit of alcohol, Tramacere et al converted the alcohol consumed into grams of alcohol using the following formula:  $0.8\text{g/ml} \times 28.35\text{ g/ounce} = 12.5\text{ g/ drink}$ <sup>5</sup>. However, there is evidence that awareness of the risk of alcohol causing cancer is not as well recognised in the general public<sup>6</sup>. Rosenberg et al<sup>6</sup> reported in 2017 that only 13% of the UK adult population knew of such a link. They postulate that one way to increase adherence to the new guideline is to raise awareness of this link. For example, cancer warnings could be added to the labels attached to alcoholic beverage<sup>7</sup> although even then it is unclear how effective these are in countries where this has been attempted. It has been suggested that they should be mandatory labelling of acetaldehyde (ACH) as well as alcohol concentrations <sup>8</sup>. Taking an alcohol history can be problematic as it may fluctuate more frequently (binge drinking at weekends rather than regular daily intake) than a smoking history, which remains fairly stable each day. For example, variation in type of beverage, alcohol by volume, acetaldehyde levels, how much they drink, how often etc. Such variables can be tricky to record or even recall by the patient. Further details regarding screening tools and the roles and responsibilities of general dental practitioners, in providing alcohol advice have recently been reviewed and described <sup>9</sup>

Alcohol use may be classified in three ways: abstinence, low to moderate intake and then heavy episodic (binge) drinking.<sup>3</sup> The WHO<sup>10</sup> defines an abstainer as someone who has not drunk alcohol in the last 12 months. Low to moderate intake equates to up to 2 drinks per day and binge drinking is greater than five drinks per day (at least 60 g pure ethanol).<sup>3</sup> In the United Kingdom, a binge drink was defined as at least six or more units for women (and eight or more units for men) in a single session (i.e. 48 g to 64 g). These factors (including potentially high concentrations of free ACH in some alcoholic drinks) lead to wide variation and exposure of the oral mucosa to ACH (the mechanism of which are reviewed later in this paper).

In 2012, it was estimated that 5.5% of all new cancers and 5.8% of cancer test worldwide were attributable to alcohol <sup>11</sup>. Alcohol is associated not only with oral cancers, but also pharynx, larynx, oesophagus, breast, liver, colorectum in males and breast in female <sup>12</sup>. In contrast, alcohol intake and risk of lymphoma, both Hodgkin and non-Hodgkin were inversely associated! <sup>12</sup>

It is 20 years since the author reviewed the mechanisms thought to be responsible for alcohol causing mouth cancer<sup>13</sup>. Advances in our knowledge will be reviewed including consideration of the role played by key enzymes in the metabolism of alcohol to acetaldehyde (ACH) (a known mutagen and carcinogen).

## **Constituent of Drinks**

Ethanol is produced by microbial fermentation of starch and grains and carbohydrates in fruit by yeast resulting in alcohol concentration around 10% in beer and 16% in wine. Distilled products (spirits) give rise to higher alcohol concentration (example vodka at 40%). Not in significant amount of free acetaldehyde can also arise, the amount of which may be influenced by the microbial flora, fermentation process and distillation technique employed. Although, it has been noted that the drink that is most frequently consumed in a particular country is the one most strongly associated with oral cancer, there is evidence that fruit based spirits (example Grappa) can contain extremely high levels of ACH (up to 1850 mg per litre or 45 mmol).<sup>8, 14, 15</sup>. This high level of intake of such spirits especially prevalent in central European countries may help explain the high incidence of alcohol-related upper aerodigestive tract cancers<sup>8</sup>

In addition, there may be volatile and non-volatile flavour compounds and impurities that may be carcinogenic (example, polycyclic aromatic hydrocarbons)<sup>16</sup>. Wine also contains phytochemicals (polyphenols derived from plant phenylalanine)<sup>3</sup>. They are divided into flavonoids, stilbenes and proanthocyanidins (also called tannins). They are thought to have health-promoting effects due to antioxidant, antimicrobial, anti-inflammatory and anticarcinogenic properties<sup>3</sup>. However, in high concentrations the antioxidant effect could become pro-oxidant leading to reactive oxygen species that might damage healthy tissue. Other new bioactive molecules have been identified in grapes and wine (example melatonin and phytosterols). Whilst it is possible they could be cancer protective their low concentration and low bioavailability are swamped by the much greater concentration of alcohol<sup>3</sup>

In regard to phytochemicals (also known as nutraceuticals) it is worth mentioning that they may be one of the reasons why a diet high in fresh fruit and vegetable could reduce cancer risk. Varoni et al<sup>3</sup> suggest that the benefit of a Mediterranean diet may arise from a synergistic effect between the phytochemicals in wine and nutraceuticals in fresh fruit and vegetable (associated with a low risk for oral cancer).

### **Mechanism by Which Alcohol May Give Rise to Cancerous Change**

Although it was reported by the International Agency for Research on Cancer (IARC) that ethanol itself was carcinogenic, the UK government committee on mutagenicity<sup>17</sup> concluded overall that there is no evidence that the ethanol molecule itself is genotoxic, mutagenic or carcinogenic unlike acetaldehyde<sup>17</sup>. Ethanol is however metabolised to ACH by alcohol dehydrogenase (which in turn is metabolised to the harmless acetate molecule by acetaldehyde dehydrogenase). Both of these enzymes exist in various isoforms. Ethanol is absorbed by the small intestine and later metabolised mainly in the liver (although as discussed later, such a capacity also exists in the oral mucosa, salivary gland and even oral microbes). When alcohol intake is high, the microsomal cytochrome P450 (CYP2E1) can also catalyse ethanol into ACH while producing reactive oxygen species<sup>18</sup>

A point mutation in the aldehyde dehydrogenase 2 (ALDH2) gene results in deficient activity in the ACH metabolising enzyme giving rise to increased ACH exposure. Although the liver is regarded as the main area for alcohol metabolism, the oral mucosa can also metabolise alcohol. However, the conversion to the relatively harmless acetate molecule is very limited due to lack of ALDH enzyme in these oral cell types, thus irrespective of whether the individual has an ALDH2 active (or deficient) isoform of the enzyme, the drinking of alcohol (and its derivatives from other sources) can result in the accumulation of mutagenic concentrations of ACH in saliva<sup>8</sup>. The oral bacteria and yeast (such as candida albicans and other candida species) obtain alcohol from alcoholic beverages, foods and local conversion of sugars to ethanol and ACH. Salivary ACH is mainly of microbial origin<sup>8</sup>. The use of chlorhexidine mouthwash for three days prior to moderate alcohol intake decrease the levels of salivary acetaldehyde significantly compared to those that did not use chlorhexidine, pointing to a significant role for the oral bacteria in acetaldehyde production<sup>8</sup>. For a detailed analysis of the effect of drinking alcohol on ACH levels the reader is referred to the work of Salaspuro<sup>8</sup>

The most important exogenous source for ACH exposure are alcohol containing drinks, tobacco, non-alcoholic drinks that may contain ACH and in food.<sup>8</sup> However, it is bacteria that play a major role in local formation of ACH in the mouth. The rise in salivary acetaldehyde lasts as long as ethanol is available to the bacteria and yeast. ACH accumulates after alcohol intake to two times higher concentration in saliva of Acetaldehyde Dehydrogenase 2 (ALDH2) deficient compared to ALDH2 active patient. This deficiency is frequently found in Chinese/Japanese<sup>4</sup> but appears rare within the Indian population where it was not associated with oral cancer risk<sup>19</sup>. The same was also true for ADH1B, ADH1C and ADH17<sup>19</sup>. ACH causes DNA strand breaks, DNA adducts and chromosome aberrations. Mutagenic levels of ACH are estimated to occur at 40 to 100  $\mu\text{M}$ . This can be achieved by sipping diluted vodka within 20 to 40 minutes<sup>8</sup>. Furthermore, the microbes associated with premalignant and oral cancer sites have been shown to have high ACH activity in vitro<sup>8</sup> example Prevotella, Candida, and Streptococcal species. It has been suggested that candida albicans may affect the biofilm giving rise to more anaerobes which may increase local ACH concentration<sup>8</sup>. (This may also be influenced by alcohol, tobacco and poor oral hygiene habits). Since oral mucosal cells have only 6% ADH activity of the liver and have no ALDH enzyme, microbes are the most significant local cause for increased ACH levels.<sup>8</sup> When drinking alcohol, the oral mucosa is exposed to microbial ACH via saliva (up to 260  $\mu\text{M}$ ) which continues for as long as alcohol is consumed. Furthermore, alcohol that has been absorbed into the blood find its way to the salivary glands where the oral microbes oxidise it to ACH (systemic source).<sup>8</sup> The ADH enzyme encode by ADH-1C1 allele metabolises ethanol to ACH 2.5 times faster than the ADH-1C2 allele.<sup>8</sup> In heavy alcohol drinkers, this polymorphism is associated with increased risk for upper aerodigestive tract cancers<sup>8</sup>. However, the slow ADH enzyme might lead to increase microbial derived ACH exposure to the oral mucosa if the reduced activity ADH results in a blood and salivary alcohol level that falls more slowly<sup>8</sup>.

### **How Might Alcohol Give Rise to Mouth Cancer?**

The following reasons have been put forward to explain the association between alcohol and carcinogenesis<sup>8, 16, 18</sup>.

1. Polymorphisms within the ADH and ALDH enzymes vary the amount of ACH and the time it remains presents. For example, ADH-1C1 allele metabolises alcohol two and a half times faster than the ADH-1C2 allele.<sup>18</sup>
2. ACH disrupts DNA synthesis and repair, binding to protein and interfering with enzymes responsible for DNA repair.
3. ACH can also bind to DNA creating DNA adducts that can give rise to mutations (these can also be formed by reactive oxygen species (ROS)).
4. Reactive oxygen species can lead to lipid peroxidation products which can form DNA adducts.
5. ROS can also give rise to upregulation of Vascular Endothelial Growth factor (VEGF), a mediator of tumour angiogenesis and metastases.
6. ROS mediated increases in metalloproteinases (example MMP2) can give rise to breakdown of extracellular matrix potentially aiding metastasis. The oral microbial oxygenation of ethanol can create ACH levels at much higher levels in saliva than that seen in blood.<sup>7</sup>
7. Ethanol may act as a solvent for other carcinogens acting upon the oral mucosa especially when pooling in the so called non-keratinising sites of floor of mouth/ventral tongue.
8. Both ethanol and ACH alter methyl transfer inducing DNA hypomethylation which might alter the expression of oncogenes and tumor suppressor genes.
9. Ethanol can decrease levels of retinoic acid due to increased metabolism by the cytochrome P4502E1 system. Retinoids (vitamin A and its derivatives) induce cellular growth, differentiation and apoptosis and hence can potentially protect against carcinogenesis. Excess alcohol interferes with retinoid metabolism.
10. There is also the possibility of ethanol induced immunodeficiency, which might impede the host response to inhibiting tumour development
11. Alcohol may give rise to a reduction in folate absorption (which may also occur as a result of malnutrition). Although folic acid is necessary for making DNA and RNA its reduction may be associated with cancer. It is possible that ethanol could dissolve the extracellular lipid layer of the oral mucosa that seeks to protect the epithelium. The permeability of the (thinner) so called 'non-keratinised' sites eg ventral tongue where oral cancer is more frequent, is much greater than the (thicker) keratinised oral sites eg dorsal tongue<sup>20</sup>.
12. It is also possible that chronic alcohol intake, giving rise to sialosis of the parotid gland, could result in decreased saliva flow and therefore decreased efficiency for clearing carcinogens presents in the mouth.
13. Systemic effects include alcohol damage to the liver which is then less able to deal with potentially carcinogenic substances.

### **Risk of Oral Cancer arising from Use of Alcohol**

A few of the larger studies have been chosen to review our understanding of the risk associated with alcohol use in the aetiology of mouth cancer and to guide advice on alcohol intake.

### **INHANCE Study report<sup>21</sup>.**

The INHANCE consortium (International Head and Neck Cancer Epidemiology) consisted of 35 studies who pulled their data resulting in 25,500 patients with head and neck cancer and 37,100 controls. Alcohol drinking amongst none users of tobacco was only a significant risk amongst heavy drinkers (three or more drinks per day versus none drinkers, (Odds ratio ,OR= 2.04 95%CI 1.29-3.21). The benefit to stopping alcohol drinking was only evident after 20 years! The risk of head and neck cancer revealed a risk of 5.44(95%CI 3.1-9.2) for beer drinkers imbibing greater than 30 drinks per week. A risk of 3.63(95%CI 2.2-5.8) for spirit only drinkers taking greater than 30 drinks per week and a risk of 6.3(95%CI 2.2-18.6) for wine only drinkers with greater than 30 drinks per week. Greater harm arose more quickly for higher intake compared to those who drank fewer drinks but over a greater time period (in contrast to that seen for non-drinking tobacco users).

Tramacere et al (2010), Peluchi et al (2011) <sup>5, 22</sup>

A meta-analysis of data published up to September 2009 was reviewed. They listed 43 case controls and two cohort studies (17085 cases of oropharyngeal cancer). The pooled relative risk(RR) was 1.21(95%CI 1.1-1.3) for less than one drink per day rising to 5.2(95%CI 4.3-6.3) for heavy alcohol use (at least four drinks per day). The dose risk analysis resulted in relative risk of 1.29 for 10 g of ethanol per day, 3.2 for 50 g of ethanol per day and 8.6 for 100 g of ethanol per day. They conject that there was under reporting of alcohol intake to help explain the increased risk with light drinking. The risk of oral cancer is increased by 20% by low (less than one drink per day) alcohol intake <sup>22</sup>

### **Additional INHANCE Study Report <sup>23</sup>**

This paper considered 4,759 head and neck cancer cases within five studies within the International Head And Neck Cancer Epidemiology consortium. The overall survival for oral cavity cancer (1,404 cases) revealed only a very slight increase in hazard ratio for drinkers at 1.08 (95%CI 0.8-1.4) compared to that of non-drinkers (1.0).

Goldstein et al (2010) <sup>24</sup>

Cohort and case control studies between 1988 and 2009 were reviewed. The adjusted relative risks were 9.2 for > 60 g (> four drinks) per day in Europe and 3.24 in USA. Although, a strong dose response relationship was found in three studies, there were two studies in which risk lowered at low alcohol intake. Alcohol was also associated with the development of second primary cancers in the mouth. The dominant drink in each population carried the greatest risk. For example, wine in Italy, hard liquor in Brazil.

The adjusted OR's were 1.66 (for one to two drinks per day) 2.30 (for three to four drinks per day) and 5.5 (for at least five drinks per day). No apparent association was observed for duration of alcohol use and risk of head and neck cancer in none users of tobacco. A meta-analysis of these studies estimated relative risk of 1.21 for one or less drinks per day, 1.75 for 25 g per day, rising to 6.01 for 100 g per day. Compared with current drinkers, reduced risk kicked in after 10 years of alcohol cessation in this analysis.

### **Other Sources of Acetaldehyde and Ethanol**

ACH exposure can arise in food in three ways; naturally, due to production processes or additive flavourings. Milk product such as yogurt can contain ACH in concentrations above mutagenic level (40 to 100  $\mu$ M). However exposure time to this form of ACH is much shorter than with alcohol. Not all the alcohol that is used in cooking foods evaporates such that it can be retained in the food. ACH is also found in tobacco and has also been reported in electronic cigarettes<sup>25</sup>. During smoking, salivary ACH levels raised rapidly remaining so for as long as smoking continues. A mean level of 261  $\mu$ M (11.5 mg /L) has been reported<sup>8</sup> Those who smoke greater than three to five cigarettes per day (but do not drink) have a two-fold (OR) risk for head and neck cancer<sup>26</sup>. The act of smoking can alter the oral microflora which may select from microbes that produce AHC. When combined with drinking a seven-fold increase in local ACH exposure within saliva was reported<sup>27</sup>

### **Use of Alcohol Containing Mouthwashes (MW)**

The INHANCE study involved the greatest number of patients,<sup>21, 28</sup> They found that ever use of MW had a slightly increased risk for mouth cancer (Odds ratio (OR) 1.11 95% CI 1.00-1.23). Infact risk only really increased beyond 35 years of use (OR 1.28 95% CI, 1.06-1.56) and for use more than once per day (OR 1.26 95% CI 0.98-1.62).<sup>21</sup> Prior to that risk actually appeared to drop for use between 1 and 15 years OR 0.95 95% CI 0.78-1.16) although use up to once a day carried OR for mouth cancer of 1.20 (95% CI 1.00-1.44) The Alcohol Related Cancers and Genetic Susceptibility in Europe (ARCAGE) study (1,963 head and neck cancer cases and 1,993 controls) found the strongest association with cancer to be with frequent mouthwash used (3+ times per day)(OR 3.53 95% CI 1.65-7.57) for oral cavity cancer (but this was only 36 cases and 16 controls)<sup>29</sup> They note that since alcohol use amongst never smokers appears to have little or no risks for head and neck cancer that any risk associated with alcohol in mouthwash maybe solely seen in smoker. For mouthwash use, no greater than twice a day the OR dropped to 1.1 (95% CI 0.86-1.44) compared to >2/day(OR 3.53). From these studies it would appear that MW use once a day doesn't confer a clinically significantly increased risk of developing oral cancer but that risk does increase with time (and beyond 35 years of use). To that end the move towards a reduced or zero alcohol content MW is to be welcomed.

### **Conclusion**

Thus the oral mucosa, salivary glands and oral microbes contribute to ACH production and add to that present in the drinks and foods consumed by the individual and thus potentially have a role in oral carcinogenesis. Further work is required in, for example,



characterising the complex interplay between exogenous factors (such as alcohol and tobacco) that may influence the oral microbes in the natural history of the oral cancerous lesion. At what stage, if any, do the microbes play a crucial role and what characteristics protect those in which such change does not arise. Although there is a risk associated with the consumption of alcohol in non smokers , the risk rises considerably with heavy alcohol use or concurrent tobacco habits. Patients should be aware of the alcohol content in the drinks they consume (examples are given above). They should consider recording their alcohol intake over a defined period (eg over a 2 to 4 week period) and drink within the recommended guidelines of 14 UK units of alcohol spread out over a week , with at least 2 days free of alcohol .Whilst the evidence for the latter may be less important for those drinking within guidelines, it does encourage lower overall lifetime alcohol consumption and reduces the risk of psychological dependence.

### **Declaration of interests**

The author is a member of the Medical Advisory Panel for Drinkaware..

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