The role of alcohol in oral carcinogenesis with particular reference to alcohol-containing mouthwashes

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ABSTRACT

Worldwide, oral cancer represents approximately 5 per cent of all malignant lesions, with over 800 new intra-oral squamous cell carcinomas registered in Australia each year. Despite recent advances in therapy, the five-year survival rate remains around 50 per cent and the sequelae of treatment can be seriously debilitating. It has been long established that smoking and alcohol consumption are risk factors linked to the development of oral cancer. This review assesses the epidemiological evidence, supportive in vitro studies and mechanism by which alcohol is involved in the development of oral cancer. Further, we review the literature that associates alcohol-containing mouthwashes and oral cancer. On the basis of this review, we believe that there is now sufficient evidence to accept the proposition that alcohol-containing mouthwashes contribute to the increased risk of development of oral cancer and further feel that it is inadvisable for oral healthcare professionals to recommend the long-term use of alcohol-containing mouthwashes.

Key words: Oral cancer, alcohol, alcohol-containing mouthwash.

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INTRODUCTION

Worldwide, oral cancer represents approximately 5 per cent of all malignant lesions, with over 800 new intra-oral squamous cell carcinomas registered in Australia each year (average number of new cancers for tongue and mouth cancer between 1999 to 2003 was 881 per year; http://www.aihw.gov.au/publications/can/ca06/ca06-c02.pdf). Despite recent advances in therapy, the five-year survival rate remains around 50 per cent and the sequelae of treatment can be seriously debilitating. Cancer evolves in a series of distinct steps, each characterized by the sequential accumulation of additional genetic defects followed by clonal expansion.1 It has been long established that smoking, alcohol consumption, as well as tobacco chewing are risk factors linked to the development of oral cancer.2 Other suspected aetiological factors include viruses such as human papilloma virus and epstein barr virus, as well as Candida albicans,3 areca (betel nut) chewing, diets low in carotenoids and vitamin A4 and several measures of poor oral hygiene, including frequency of tooth brush use.5

The role of alcohol in the development of oral cancer

Epidemiological evidence

The risk of developing oral cancer has been shown to be related to both the intensity and duration of exposure to both alcohol and smoking. A case-control study estimated that the risk of developing oral cancer was approximately 50-fold greater (odd ratio [OR] 50.65; 95% CI = 19–134) in heavy smokers and drinkers than those who never smoked and never drank.6

Further, a recent prospective study by Maserejian et al. assessing associations in the development of oral premalignant lesions using a cohort of over 50 000 United States male health professionals (58 per cent of who were dentists) found that alcohol drinking was an independent risk factor for the development of these lesions, regardless of beverage type, drinking pattern or tobacco use.7 Maserejian et al. also found that an interaction between alcohol drinking and smoking was apparent by their more-than-additive joint effects.
Petti and Scully undertook an extensive study of the association between nation-based alcohol-drinking profiles and oral cancer mortality of 20 countries in Europe, Northern America and Far Eastern Asia, and showed that there were significant increases in male age standardized mortality rate associated with alcohol use, and that a high fraction of oral cancer deaths could be attributable to heavy alcohol consumption.8

In vitro studies
Laboratory studies have repeatedly shown that alcohol enhances the penetration of tobacco associated carcinogens across oral mucosa.9 Squier et al. showed that alcohol has the capacity to eliminate the lipid component of the barrier present in the oral cavity that surrounds the granules of the epithelial spinous layer,9 and short-term exposure to 15% alcohol increased the permeability of human ventral tongue mucosa.10 In this latter study, Howie et al. postulated that this is due to a disruption of the epithelial lipid molecules from their normal orderly arrangement, opening up the intercellular epithelial routes.

Chronic exposure to alcohol has been shown to cause epithelial atrophy and decreased basal cell size of the rat oesophageal mucosa.11 On the rabbit oral mucosa, short-term alcohol use resulted in varying degrees of tissue damage depending on the concentrations of alcohol, while long-term use caused both macroscopic and microscopic changes to tissue, including dysplastic changes with keratosis, increased density of the basal cell layer and increased number of mitotic figures.12

A further study by Maier et al. that assessed chronic alcohol consumption in an experimental rat model found that this caused oral mucosal atrophy with associated hyper-regeneration, and they postulated that this would enhance susceptibility of the mucosal epithelium towards chemical carcinogens.13 This hypothesis was supported in a hamster cheek pouch model of carcinogenesis where the animals' cheeks were painted with a known carcinogen and those animals that were additionally administered alcohol developed earlier and larger epithelial tumours than with chemical treatment alone.14

Thus, there appears to be sufficient evidence in laboratory animal studies to support a link between alcohol and the development of oral cancer.

Proposed mechanism
Acetaldehyde is a primary metabolic product of ethanol and has been shown to be mutagenic. The World Health Organization’s International Agency for Research on Cancer (IARC) produces monographs regarding the risk of various chemicals and the development of cancer. The IARC’s monographs evaluating the carcinogenic risk of acetaldehyde concluded that there was at the time (1999) inadequate evidence in humans, but sufficient evidence in experimental animals of the carcinogenic nature of acetaldehyde.15

Although the bulk of alcohol metabolism is carried out in the liver, there is good evidence to show extrahepatic metabolism of alcohol to acetaldehyde, and in particular this has been shown to occur in the oral cavity.16 Furthermore, previous research by Dong et al. showed that there was differential expression of enzymes in the oral cavity that could allow the accumulation of acetaldehyde in oral tissues.16

Experimental evidence has shown that oral microflora produce considerable quantities of acetaldehyde during social alcohol consumption and this occurred to a greater extent in individuals with a tendency to aerobic flora.17 More recently, research has shown the level of activity of alcohol dehydrogenase in a range of oral bacteria.18 This study showed significant variation between species in their ability to produce acetaldehyde with common oral bacteria, Streptococcus salivarius, S. intermedius and S. mitis producing high amounts of acetaldehyde. These authors conclude that oral streptococci may contribute significantly to the normal individual variation of salivary acetaldehyde levels after alcohol drinking and thereby also to the risk of oral cancer.16 This may in fact be the mechanism that explains the observed phenomena that individuals with poor oral hygiene have an increased risk of developing oral cancer.5

Recently, Warnakulasuriya et al. undertook an immunohistochemistry study that for the first time assessed specific alcohol-induced changes to the oral epithelium in patients with both oral cancer and dysplasia.19 This study assessed the generation and sub-cellular distribution of ethanol-induced DNA-protein alteration, particularly the presence of covalently bound intra-cellular proteins with acetaldehyde, the first metabolite of ethanol, as well as the end products of lipid peroxidation, and showed strong evidence of ethanol-induced carcinogenesis.19

The association between alcohol-containing mouthwash and oral cancer
Alcohol is used in mouthwashes principally as a solvent for other ingredients. However, at 10–12 per cent it also acts as a preservative, antiseptic and caustic agent.20 In addition to the above mentioned effects on mucosal permeability and metabolic production of acetaldehyde, studies have shown that high concentrations of alcohol in mouthrinses may have detrimental oral effects such as epithelial detachment, keratosis, mucosal ulceration, gingivitis, petechiae and oral pain.21 Bernstein et al. reported the presence of diffuse white oral mucosal lesions with long-term use of an
alcohol-containing mouthwash. Some commercially available mouthwashes and their alcohol content are outlined in Table 1.

The possibility of alcohol-containing mouthwashes contributing to the development of oral cancer is not a new proposition. In 1983, Wynder et al. undertook a retrospective analysis of patients developing oral cancer and found that the daily use of mouthwash showed a risk in females but no risk in males. Furthermore, this study reported that in non-smoking, non-drinking women, daily mouthwash use was associated with risk. A further study of 206 women with oral and pharyngeal cancers and 352 controls assessing the patterns of mouthwash use found that, among women abstaining from tobacco, the risk of developing oral cancer was almost twice as likely than non-tobacco and non-mouthwash users (OR 1.94; 95% CI = 0.8, 4.7). Blot et al. raised the possibility that mouthwash might contribute to oral and pharyngeal cancers.

Several retrospective analyses of the available literature, undertaken in 1995 and 2004 found no evidence to support a link between the use of a daily mouthwash and oral cancer development. However, these authors found that few of the available studies on mouthwash use and risk of subsequent cancer of the oropharynx adhered to basic methodological principles of case-control design.

A study undertaken in 2001 of 342 patients with oral and pharyngeal cancer and 521 population-based controls found that the use of alcohol-containing mouthwash caused an elevated, but not statistically significant, risk for oral cancer among patients who neither smoked cigarettes nor drank alcohol. These authors concluded that their evidence, in 2001, suggested a need to clarify the mechanisms of oral carcinogenesis, including the possible role of alcohol-containing mouthwashes.

However, a most recent and extensive study by Guha et al. has shown a significant link between the daily use of an alcohol-containing mouthrinse and development of oral cancer. This international, multicentre, case-control study of 3210 patients with head and neck cancer and 2752 controls found that self-reported daily mouthwash use (OR 3.40; 95% CI = 1.96, 5.89) is a significant risk factor for the development of head and neck cancer independent of tobacco use and other alcohol consumption. When only cancers of the oral cavity, pharynx and larynx were considered (not including other head and neck cancers, such as the oesophagus where one might presume mouthwash use would have little effect because it is not normally swallowed) then the use of an alcoholic mouthwash twice daily increased the chance of acquiring cancer by over nine times (OR 9.15) for current smokers, over five times for those who also drank alcohol (OR 5.12) and almost five times for those who never drank alcohol (OR 4.96). These authors did not know the type of mouthwash being used nor its alcohol content, however the most common mouthwash in the countries from which the data were drawn, possibly with up to 80 per cent of the market share, contained levels of alcohol over 20%. These authors postulate that the observed increase in risk of cancer among alcohol abstainers indicated that the alcohol content of certain mouthwashes (up to 30 per cent) may be a causal agent for head and neck cancers.

### CONCLUSIONS

There is now sufficient evidence to accept the proposition that developing oral cancer is increased or contributed to by the use of alcohol-containing mouthwashes. Whilst many of these products may have been shown to be effective in penetrating oral microbial biofilms in vitro and reducing oral bacterial load, it would be wise to restrict their use to short-term therapeutic situations if needed. Perhaps the use of mouthwashes that do not contain alcohol may be equally effective. Further, mouthrinses should be prescribed by dentists, like any other medication. There may well be a reason for the use of alcohol-containing mouthrinses, but only for a particular situation and for a limited and controlled period of time. As such, patients should be provided with written instructions for mouthwash use, and mouthwash use should be restricted to adults for short durations and specific, clearly defined reasons. It is the opinion of the authors that, in light of the evidence currently available of the

<table>
<thead>
<tr>
<th>Mouthwash</th>
<th>Ethanol concentration (%)</th>
</tr>
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<tbody>
<tr>
<td>Listerine Antiseptic</td>
<td>26 v/v</td>
</tr>
<tr>
<td>Listerine Teeth Defence</td>
<td>22 v/v</td>
</tr>
<tr>
<td>Listerine Cool Mint</td>
<td>22 v/v</td>
</tr>
<tr>
<td>Listerine Tartar Control</td>
<td>22 v/v</td>
</tr>
<tr>
<td>Listerine Citrus Fresh</td>
<td>22 v/v</td>
</tr>
<tr>
<td>Listerine Smooth Mint</td>
<td>21.6 v/v</td>
</tr>
<tr>
<td>Cepacol Mint</td>
<td>15 v/v</td>
</tr>
<tr>
<td>Cepacol</td>
<td>14 v/v</td>
</tr>
<tr>
<td>Savacol Original</td>
<td>11.5 w/v</td>
</tr>
<tr>
<td>Savacol Freshmint</td>
<td>9.5 w/v</td>
</tr>
<tr>
<td>Listerine Whitening</td>
<td>8 v/v</td>
</tr>
<tr>
<td>Difflam Solution</td>
<td>7.5 w/v</td>
</tr>
<tr>
<td>Difflam-C Solution</td>
<td>7 w/v</td>
</tr>
<tr>
<td>Neutrafluor 220</td>
<td>7 w/v</td>
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<tr>
<td>Plax</td>
<td>6 w/v</td>
</tr>
<tr>
<td>Peroxyl</td>
<td>5.5 w/v</td>
</tr>
<tr>
<td>Neutrafluor 900</td>
<td>5 w/v</td>
</tr>
<tr>
<td>Curasept</td>
<td>0</td>
</tr>
<tr>
<td>Dentyl</td>
<td>0</td>
</tr>
<tr>
<td>Biotene</td>
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</tr>
<tr>
<td>Oral B</td>
<td>0</td>
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<tr>
<td>Amosan</td>
<td>0</td>
</tr>
<tr>
<td>Neutrafluor 220 Ethanol Free</td>
<td>0</td>
</tr>
<tr>
<td>Fluorocare 200</td>
<td>0</td>
</tr>
</tbody>
</table>
association of alcohol-containing mouthwashes with the development of oral cancer, it would be inadvisable for oral healthcare professionals to recommend the long-term use of alcohol-containing mouthwashes.

CONFLICTS OF INTEREST
The authors declare that they do not have any financial, commercial or personal relationship with any company or other party that could inappropriately influence or bias the views expressed in this review.

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