

Are alcohol containing mouthwashes safe?

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IN BRIEF

- Dentists need to be aware that there is a hypothetical risk for the development of oral cancer from repeated use of alcohol containing mouthwashes.
- The existing evidence to support or refute such an association has been the subject of two recent conflicting reviews.
- This paper critically evaluates the two reviews and further explores the data on the efficacy of the addition of alcohol to mouthwashes.

Alcohol (ethanol) is a constituent of many proprietary mouthwashes. Some studies have shown that regular use of such mouthwashes can increase the risk of developing oral cancer. Recently, the evidence has been reviewed by two separate authors. The conclusions from these reviews are conflicting. In this paper, we reconsider the epidemiological evidence linking alcohol containing mouthwashes with an increased risk of oral cancer. The evidence is considered in terms of sample size, strength of association, confounding variables and data collection. In addition, clinical studies comparing alcohol *versus* non-alcohol mouthwashes are evaluated. The evidence suggests that the alcohol component of mouthwashes affords little additional benefit to the other active ingredients in terms of plaque and gingivitis control. In view of this outcome and the hypothetical risk of oral cancer, it would seem prudent that members of the dental team advise their patients accordingly.

INTRODUCTION

Many proprietary mouthwashes contain alcohol (ethanol) and in some, the concentration of ethanol can be as high as 26%.¹ Two recent reviews^{2,3} have considered whether alcohol containing mouthwashes increase the risk of the development of oral cancer. The conclusions from these reviews are conflicting, with one stating 'there is now sufficient evidence to accept the proposition that alcohol containing mouthwashes contribute to the increase of the development of oral cancer',² while the other states that 'critical review of the published data revealed that a link between mouthwash use, specifically alcohol containing mouthwash and oral cancers, is not supported by epidemiological evidence.'³

The reviews were published in 2008 and 2009 and for the most part have quoted the same evidence to support their conclusion. In this paper we shall look critically at both

reviews and the interpretation of the evidence and hopefully provide readers with an opinion on the safety or otherwise of alcohol containing mouthwashes.

EPIDEMIOLOGICAL EVIDENCE

Epidemiological studies are complex and aspects such as sample size, strength of association, confounding variables and data collection bias can be rightfully challenged. By contrast, arguments can also be made for the exploitation of specific aspects of interest (reporting bias). This is obviously a controversial topic which can lead to different courses of clinical action. Dentistry often deals with such issues and dentists have to make ethical decisions on clinical protocols and material based on less than ideal types of scientific evidence.

Our aim is to guide the reader through a clear pathway which provides relevant information for reflection and leads to an informed decision. Scientific evidence will be explored in light of the most recent reviews so that we can empower all members of the dental team with the best clinical advice on the use of mouthwashes.

Centre for Evidence Based Dentistry (CEBD)

The CEBD suggests the following step-wise approach for dealing with clinical

problems: question formulation, verification of latest evidence, critical appraisal and value assessment of evidence and clinical indication. Epidemiological studies have different weights on the evidence they provide. Additional information from *in vivo* studies, especially those that investigate the possible mechanism of alcohol toxicity to the oral mucosa, may complement the epidemiological evidence and provide possible benefits and risks for clinical use of alcohol containing mouthwashes. All of this information is then evaluated to ascertain whether the benefits of alcohol containing mouthwashes outweigh the risk of damage to the oral mucosa.

QUESTION FORMULATION

Do the clinical benefits of an alcohol containing mouthwash in the prevention of plaque related oral diseases outweigh the possible safety issues? The significant safety issue is developing oral squamous cell carcinoma. This raises the further question, is alcohol containing mouthwash a justifiable clinical treatment course to encourage patients to take?

WEIGHTING EPIDEMIOLOGICAL EVIDENCE

In an attempt to answer the questions set out above via an evidence-based approach,

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the epidemiological evidence needs to be quantified. The criteria for quantifying epidemiological evidence are shown in Table 1.

Neither of the review papers can be classified as systematic reviews as they have not included a randomised clinical trial (RCT) and do not follow strict reviewing protocols. Although this is a criticism, it should be identified that a RCT to show an association between oral cancer and alcohol containing mouthwash use would be difficult to carry out. Oral cancer is a chronic disease, can take many years to develop and an RCT will require a large follow-up population.

The possible risk association between alcohol containing mouthwashes and oral cancer is considered from five directly relevant case control studies (type IV evidence). In such studies, subjects were selected on the basis of whether they do (cases) or do not have a particular disease (controls). Information is then determined based on the calculated odds ratios (OR). It is important to differentiate here the fact that risk in another type of study (cohort study) is derived from risk ratios (RR), which are determined by a different mathematical formulation. The terms OR and RR have been used interchangeably in the literature evaluated and our assumption is that the calculation appropriate for case control studies was carried out, regardless of how it has been reported.

Some studies also refer to 'excess risk', which can introduce ambiguity in the terminology. Excess risk should be defined as the difference between the proportion of subjects in a population with oral cancer who were exposed to alcohol containing mouthwashes and the proportion of subjects with oral cancer who were not exposed. In the context of the literature on this subject, 'excess risk' seems to refer to statistically significant risk/odds ratio beyond 1.0.

LATEST REVIEWS

Two reviews have already been highlighted and these will be considered in further detail.

Review 1: 'The rate of alcohol in oral carcinogenesis with particular reference to alcohol containing mouthwashes.'²

The review initially suggests an increased risk from alcohol containing

mouthwashes in the development of oral cancer. This suggestion is based upon case control studies which examined the smoking-alcohol association in general, with no stratification of alcohol containing mouthwash use.^{4,5} The findings shown in a nation-based alcohol profile and oral cancer mortality correlation study failed to indicate that the weight of this association is not as strong as the one from case control studies.⁶

The main conclusion of this review is based upon the evidence provided by Guha *et al.*,⁷ which uses data obtained from two multi-centred case control studies. Nevertheless, a particularly relevant finding from this study⁷ curiously was not mentioned, weakening the review further. The information related to self reported use of more than twice a day mouthwash indicated that it increased the chance of developing oral squamous cell carcinoma by almost six fold (OR 5.86; 95% CI = 2.91, 11.77) when compared to those patients who reported never having used mouthwash products.

Lack of more in-depth explanation on existing evidence of association (or lack of association) gives the impression that the most conclusive epidemiological evidence should be derived solely from the most recent published study. The laboratory studies quoted in this review, at best, explore the link between alcohol and oral cancer as a facilitating factor rather than a causal or risk factor. A more balanced view on existing association between alcohol containing mouthwashes from case control studies would have increased the credibility of the conclusion from this paper. The review lacked depth of analysis on key issues, which brings into question the validity of its conclusions.

Review 2: 'Mouthwash and oral cancer risk: an update.'³

This second review paper concluded that alcohol containing mouthwash use was not associated with an increased risk of oral squamous cell cancer. The author highlighted the lack of a dose response relationship. This review focused on the only two papers that specifically looked at alcohol containing mouthwashes as a risk for oral cancer. The studies were conducted by the US National Cancer Institute (NCI) and the findings of the first study⁸ were published in 1991. The second study⁹ was

Table 1 Criteria for quantifying epidemiological evidence

Type I	A least one good systematic review (including at least one randomised clinical trial)
Type II	At least one good randomised clinical trial
Type III	Well designed interventional studies without randomisation
Type IV	Well designed observational studies (case control and cohort studies)
Type V	Descriptive studies (correlational studies, cross sectional surveys), case reports, case series, influential reports and expert opinion

published in 2001 and a re-analysis of the 1991 data by authors not involved in the original study, followed in 2003.¹⁰

The 1991 study showed a statistically significant increase in risk of oral cancer associated with regular mouthwash use and suggested that the risk varied in proportion to dose, duration and frequency of mouthwash usage and alcohol concentration. The authors concluded that regular use of a mouthwash with high alcohol content contributes to oral cancer risk. The re-analysis of the same data¹⁰ divided the cases of oropharyngeal cancers into mucosal (true cases) and non-mucosal (pseudo cases). The re-analysis concluded that regular use of a mouthwash was associated more strongly with the pseudo cases than the true cases in women and there was a weak dose response relationship between mouthwash use and oropharyngeal cancer in pseudo cases. In men, the association between mouthwash use and true disease was confirmed, but considered weak evidence. The re-analysis also commented that such weak associations might reflect the use of mouthwashes by 'smokers' and 'drinkers' to conceal breath odours, as suggested by previous studies.¹¹⁻¹⁴ One outcome of the 2003 re-analysis that was not commented upon was that women classified as 'true cases', those who had started to use mouthwashes before the age of 20 showed a significantly higher risk of oropharyngeal cancer as compared to controls (RR = 2.3).

The 2001 NCI study reported no overall increased risk of oral cancer associated with mouthwash use.

The conclusion of the second review does not appear to provide a balanced view of the analysis of the data. The opposing

Table 2 Comparative studies which have compared alcohol containing and alcohol-free mouthwashes on various oral health parameters

Study	Agents	Number of subjects	Model/Design	Duration	Outcome
Quiryren <i>et al.</i> 2001 ²¹	*CHX 0.2% + alcohol CHX 0.12% + alcohol CHX 0.12% + sodium fluoride **CPC 0.05%	16	Randomised, double-blind four way crossover study of experimental gingivitis model No mechanical plaque control for 11 days Plaque scored after 7 and 11 days of treatment	11 days with 3 week washout period between treatments	CHX 0.2% + alcohol, CHX 0.12% + alcohol and CHX 0.12% + CPC were equi-effective anti-plaque and anti-inflammatory agents over the 11 day observation period All three products were significantly superior to CHX 0.12% + sodium fluoride
Leyes Borrajo <i>et al.</i> 2002 ²²	CHX 0.12% + alcohol (11%) CHX 0.12% no alcohol placebo	96	Parallel, double-blind study to evaluate mouthwashes with respect to plaque and gingival bleeding	28 days with evaluation at 14 and 28 days	Both CHX rinses resulted in significant differences in plaque, gingivitis and papilla bleeding index when compared to placebo No differences between the two CHX rinses
Van Strydonck <i>et al.</i> 2005 ²³	CHX 0.2% + alcohol CHX 0.12% no alcohol + 0.05% CPC	40	Single-blind randomised two group parallel design using the 3 day plaque development model	3 days	No significant differences between treatment groups with respect to plaque accumulation Subjects preferred the taste of the non-alcoholic CHX + 0.05% CPC solution
Almerich <i>et al.</i> 2005 ²⁴	Hydroalcoholic triclosan 0.15% + zinc chloride Aqueous triclosan 0.15% + zinc chloride	30	Double-blind crossover design using the 21 day experimental gingivitis model	21 days with a 14 day washout period	The development of both gingivitis and plaque indices showed no significant differences between treatment groups The alcohol containing mouthwash produced a larger number of unwanted oral effects
Arweiler <i>et al.</i> ²⁵	CHX 0.2% + alcohol CHX 0.2% with anti-discolouration system, no alcohol Placebo	21	Crossover design x 3 with a 0-day washout period between treatment	4 days	The CHX 0.2% with alcohol showed superiority in the inhibition of plaque regrowth and reducing bacterial vitality when compared to the CHX solution without alcohol, but containing an anti-discolouration additive
Lorenz <i>et al.</i> 2006 ²⁶	CHX 0.2% no alcohol CHX 0.2% no alcohol + NaF 0.055% CHX 0.2% with alcohol	90	Investigator blind, randomised study of parallel design	21 days with examinations at 0, 7, 14 and 21 days	No difference in efficacy between the three CHX preparations with respect to plaque inhibition and gingival inflammation

*Chlorhexidine
**Cetylpyridinium

arguments were not considered. Results from previous case control studies^{12,14,15} were not mentioned and epidemiological evidence from case control studies showing no association between alcohol containing mouthwashes and oral cancer were scant.

SAFETY AND EFFICACY OF ALCOHOL CONTAINING MOUTHWASHES

The incorporation of ethanol into mouthwashes serves several purposes: it is a solvent for other active ingredients, has antiseptic properties and acts as a preservative. Ethanol is easy to produce and relatively cheap.

In vitro studies have demonstrated that alcohol enhances the mucosal penetration of the various carcinogens found in tobacco.¹⁶ Alcohol on its own does cause damage to the oral mucosa and includes epithelial atrophy and decrease in basal cell size atrophy with associated hyper-regeneration.¹⁷

The prime metabolite of alcohol is acetaldehyde, which is mutagenic and animal studies have shown this substance to be carcinogenic.¹⁸ While the bulk of the metabolism of alcohol is carried out in the liver, there is evidence that alcohol metabolism could occur in the oral cavity and that various bacteria in plaque can metabolise alcohol to acetaldehyde. This may support the only theory for why patients with poor oral hygiene are at an increased risk of oral cancer.

In addition to the possible risk of oral cancer, alcohol containing mouthwashes are also reported to have other adverse effects on oral structures and functions. These include burning mouth, drying of the oral mucosa, softening effects on composite filling materials and mucosal pain.^{19,20}

The concern over the alcohol content of mouthwashes has led to the development of alcohol-free preparations. Various studies have been completed comparing

the active mouthwash ingredient incorporated into an alcohol-free preparation with alcohol mouthwash, but a full systematic review has yet to be carried out. However, relevant studies obtained via a Medline search are listed in Table 2 and show that alcohol containing mouthwashes afford little or no advantage in terms of efficacy over the alcohol-free competitors.

CONCLUSION

Two review papers^{2,3} have reviewed the evidence suggesting alcohol containing mouthwashes as a risk for the development of oral cancer and also cancer of the mucosal surfaces of the upper aerodigestive tract. The conclusion from these two reviews is conflicting. Both papers have been selective in the studies that they have reviewed on this topic and their interpretation of the data. There is evidence to show an association between use of an alcohol containing mouthwash and oral cancer. However, this evidence

is weak and inconclusive. A robust randomised controlled trial would be necessary to answer the question of whether alcohol containing mouthwashes increase the risk of developing oral cancer. The feasibility and justification for such a trial is likely to raise ethical and logistical questions.

Against this background there is overwhelming evidence that mouthwashes are of value in reducing bacterial plaque and gingivitis and are useful adjuncts to mechanical methods of plaque removal. The comparative studies between alcohol containing and alcohol-free mouthwashes have for the most part shown that the alcohol content adds little in the way of efficacy to the product. Besides this, alcohol containing mouthwashes may be also avoided on the basis of cultural preferences. Therefore, as the benefit of alcohol in a mouthwash is negligible and it may carry a risk of oral cancer which is difficult to quantify, is there any value in members of the dental team prescribing/recommending alcohol containing mouthwashes to their patients?

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