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Review

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Alcohol-containing mouthwash and oral cancer risk: a review of current evidence

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Abstract

Introduction

The existence or lack of an association between the use of alcohol-containing mouthwashes and the development of oral squamous cell carcinoma remains a significantly contentious issue within the scientific community. The published literature on the topic includes both epidemiological studies assessing associations on a population level and mechanistic studies investigating the local effects of alcohol-containing mouthwashes in both *in vitro* and *in vivo* environments, as well as reviews evaluating, comparing and synthesising these results. Despite a broad base of evidence, there remains no clear academic consensus with regard to the relationship between alcohol-containing mouthwashes and oral squamous cell carcinoma. This review aims to present and evaluate the evidence for and against any association.

Conclusion

While there is a lack of consistent evidence, it is advisable for clinicians to promote the use of non-alcoholic mouthwashes in order to minimise any potential increase in risk, and discourage long-term use of high alcohol-containing products.

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Introduction

Oral squamous cell carcinoma (OSCC) is a neoplastic condition that is characterised by the malignant transformation of oral keratinocytes and represents a significant health burden, with an estimated yearly global incidence of 275,000 cases[1,2]. The major established risk factors for the development of OSCC are exposure to tobacco products, alcoholic beverages and betel nut[2]. With regard to the development of OSCC, ethanol has been recognised as the carcinogenic agent within alcoholic beverages[3]. Although not directly carcinogenic, ethanol exerts its effects through a number of secondary mechanisms, including the generation of carcinogenic acetaldehyde, induction of cytochrome P450 2E1, generation of reactive oxygen species, induction of lipid peroxidation and enhancement of the penetration of other carcinogens[4]. Ethanol is a key ingredient in a number of commercially available mouthwashes, which has led to scrutiny with regard to a possible link to the development of OSCC following regular use. This review aims to present and evaluate the evidence for and against any such association.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Epidemiological evidence

The possible existence of a relationship between the use of alcohol-containing mouthwashes and the development of OSCC was first raised by Weaver et al. in a case series published in 1979[5]. Since then there have been 15 case-control studies and one meta-analysis that have assessed mouthwash use in OSCC patients[6–22]. A number of these studies contain epidemiological evidence supportive of an association, whereas the others do not. As a result, there is no unanimous consensus as to whether use of alcohol-containing mouthwash modifies the risk of developing OSCC.

Of the available case-control studies, nine contain evidence supportive of an epidemiological association between the use of mouthwash and the development of OSCC (Table 1)[6,7,10,11,15–18,20]. A range of published results can be seen, with some showing a significant increase in OSCC risk, whereas others only show a non-significant increase in risk. Of the significant results, reported odds ratios for the development of OSCC varied from 1.1 (95% CI 1.02–1.2) for ≥ 1/daily mouthwash use as reported by Eliot et al.[20], to 5.86 (95% CI 2.91–11.77) for ≥ 2/daily mouthwash use as reported by Guha et al.[15] In studies where results were stratified by gender, greater risk was noted for women as opposed to men[6,7,10]. Mixed results were noted when studies stratified participants by tobacco and alcohol use. A greater risk of developing OSCC was found in smoking versus non-smoking mouthwash users by Winn et al.[10] and Guha et al.[15], whereas no such increase was noted by Blot et al.[6] or Eliot et al.[20] Use of alcohol was not found to affect the risk imparted by mouthwash use in any

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Table 1 Case-control studies containing evidence supportive of an association between mouthwash use and the development of oral squamous cell carcinoma

Study	Cases/controls	Mouthwash usage data collected	Notable findings	Industry sponsorship
Blot et al.[6]	206/352	Frequency, history and retention time	Non-significant increase in risk among female non-smokers who used mouthwash (OR = 1.94, 95% CI 0.8–4.7)	No
Wynder et al.[7]	555/553	Frequency and history	Significant increase in risk among women (OR = 2.79, 95% CI 1.67–4.66), but not men (OR = 1.13, 95% CI 0.83–1.54), with ≥ 1/daily mouthwash use	No
Winn et al.[10]	866/1249	Alcohol content, frequency, history and reasons for use	Significant increases in risk for both men (OR = 1.4, 95% CI 1.0–1.8) and women (OR = 1.6, 95% CI 1.1–2.3) who used mouthwash. Increasing risk with increased frequency, duration and alcohol content	No
Marshall et al.[11]	290/290	History	Significant increase in risk associated with mouthwash use, no relation to duration of use	No
Guha et al.[15]	2286/1824	Frequency	Significant increase in risk associated with ≥ 2/daily mouthwash use, especially oral cavity (OR = 5.86, 95% CI 2.91–11.77). Increases in risk regardless of smoking/drinking	No
D'Souza et al.[16]	100/200	Frequency	Non-significant increase in risk associated with > 2/daily mouthwash use (OR = 3.8, 95% CI 0.9–16.5). Oropharyngeal cases only	No
Marques et al.[17]	309/468	Frequency	Significant increase in risk associated with ≥ 2/daily mouthwash use (OR = 3.3, 95% CI 1.7–6.1)	No
Macfarlane et al.[18]	356/419	Frequency	Non-significant increase in risk associated with 1/daily (OR = 1.22, 95% CI 0.65, 2.3) and ≥ 2/daily (OR = 1.7, 95% CI 0.73, 3.95) mouthwash use	No
Eliot et al.[20]	513/567	Alcohol content and frequency	Significant increase in risk associated with ≥ 1/daily mouthwash use (OR = 1.11, 95% CI 1.02–1.2)	No

study. Non-smokers/non-drinkers arguably present an ideal population for investigating possible increases in risk from alcohol-containing mouthwash use, given the lack of these two significant confounding factors. Wynder et al.[7] found an increase in the risk of this group in women who used mouthwash ≥ 1/daily (OR = 3.63, 95% CI 1.48–8.92 for non-smokers/non-drinkers compared with OR = 2.79, 95% CI 1.67–4.66 for all women), but did not find a similar increase for men. Conversely, Winn et al.[10] found that OSCC risk for both male and female mouthwash users actually decreased in the non-smoker/non-drinker population compared with the population as a whole. Of the case-control studies mentioned above, two stand out for particular reasons. Firstly, the study authored by Winn et al.[10] in 1991 included 866 cases and 1249 controls and exhibits an experimental design that is more comprehensive than other studies of the same subject matter, collecting data relating to mouthwash use including alcohol content, frequency of use, history of use and reasons for use[10]. Analysis of this data revealed significant increase in risk (after adjusting for tobacco and alcohol use) for both men (OR = 1.4, 95%

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CI 1.0–1.8) and women (OR = 1.6, 95% CI 1.1–2.3) who used mouthwash and positive dose–response relationships with increased frequency, duration and alcohol content. The second study, authored by Guha et al.[15], only collected data related to frequency of mouthwash use but had the highest pool of participants of any of the case-control studies (2286 cases and 1824 controls). In this study, significant increase in the risk of developing OSCC of the oral cavity was found to be associated with ≥ 2/daily mouthwash use (OR = 5.86, 95% CI 2.91–11.77) and a dose–response effect with increased frequency was also noted. Taken together, these two studies provide the strongest epidemiological argument for a positive link between mouthwash use and OSCC risk.

The remaining six case-control studies are not supportive of a relationship between mouthwash use and the risk of developing OSCC (Table 2)[8,9,12–14,19,21]. These studies report no association or a negative association between mouthwash use and the risk of developing OSCC. No significant differences in risk were noted when subjects were stratified according to use of tobacco and alcohol[8,13,19]. As before, two studies in particular stand out. Firstly, the study by Winn et al.[13] in 2001 consisting of 342 cases and 521 controls (a follow-up to their 1991 study) once again had a comprehensive study design that collected information related to mouthwash alcohol content, frequency of use, history of use and retention time in the mouth[13]. It was found that no increase in risk (OR = 1.0, 95% CI 0.7–1.4) was associated with mouthwash use and there were no trends related to frequency, history or retention time. Secondly, the study by Divaris et al.[19] had a large

Table 2 Case-control studies containing evidence against an association between mouthwash use and the development of oral squamous cell carcinoma

Study	Cases/controls	Mouthwash usage data collected	Notable findings	Industry sponsorship
Young et al.[8]	317/306	Yes/no only	No increase in risk among males (OR = 1.02, 95% CI 0.67–1.56) or females (OR = 0.52, 95% CI 0.25–1.10) who used mouthwash. No differences when stratified by smoking/drinking	No
Kabat et al.[9]	125/107	Frequency, history, retention time and reasons for use	No increase in risk among females (OR = 0.84, 95% CI 0.46–1.51) associated with ≥ 1/daily mouthwash use. Cases more likely to use mouthwash to cover-up tobacco and alcohol odours than food and dental odours	No
Talamini et al.[12]	132/148	Frequency	No increase in risk (OR = 1.0, 95% CI 0.4–2.4) associated > 2/weekly mouthwash use	No
Winn et al.[13]	342/521	Alcohol content, frequency, history and retention time	No increase in risk (OR = 1.0, 95% CI 0.7–1.4) associated with mouthwash use. No trend with frequency, history or retention time, however, non-significant increase (OR = 2.8, 95% CI 0.8–9.9) seen in non-smokers/non-drinkers who had used mouthwash	No
Divaris et al.[19]	1289/1361	Yes/no only	No increase in risk (OR = 0.95, 95% CI 0.80–1.13) associated with mouthwash use. No differences when stratified by smoking/drinking	No
Chang et al.[21]	317/296	Alcohol content	No difference in risk between alcohol-containing mouthwash use and no mouthwash use; insufficient statistical power	No

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number of participants with 1289 cases and 1361 controls, but collected minimal data relating to mouthwash use and found no increase in risk (OR = 0.95, 95% CI 0.80–1.13) associated with mouthwash use[19]. In addition, in 2012 Gandini et al.[22] published a meta-analysis of all known epidemiological studies examining the relationship between mouthwash use and oral cancer totalling 4484 cases and 8781 controls. After analysis, it was determined that there was no significant association between mouthwash use and OSCC (RR = 1.13; 95% CI 0.95–1.35), no significant risk associated with daily use (P = 0.11) and no significant association when it was specified that mouthwashes contained alcohol (RR = 1.0; 95% CI 0.39, 2.60)[22]. Thus it can be seen that significant epidemiological evidence exists to suggest against the existence of an association between mouthwash use and the development of OSCC.

A handful of studies have also investigated the relationship between mouthwash use and the development of oral epithelial dysplasia (a potentially malignant lesion). Morse et al.[23] in a case-control study (127 cases, 127 controls) found no evidence for a relationship, even when data were stratified by frequency of use, history of use, retention time and alcohol content. On the other hand, Dost et al.[24] found a higher proportion of dysplastic lesions in users of mouthwash, however this increase did not approach statistical significance. Overall, research on this topic is limited.

There are a number of issues with the published epidemiological literature discussed above that make it difficult to come to a true conclusion with regard to any OSCC risk imparted by use of alcohol-containing mouthwashes. Firstly, study design varies considerably between case-control studies, making overall comparisons difficult. The most significant issue is that only five out of the 16 studies discussed actually specify that the mouthwash being used contains alcohol. Given the role of exposure to ethanol in the development of OSCC, the lack of assessment of this variable is considerably important[4]. Secondly, the high incidence of alcohol and tobacco use among users of mouthwash presents a confounding influence when attempting to quantify OSCC risk given the status of tobacco and alcohol as independent risk factors for OSCC. It has been theorised that overlap from smoking and drinking has led to an overestimation of the risk imparted by alcohol-containing mouthwash use. For example, Kabat et al.[9] found that female OSCC patients were significantly more likely to use mouthwash to hide the odours of tobacco (OR = 3.3, 95% CI 1.24–8.75) and alcohol (OR = 3.25, 95% CI 1.03–10.3) than food odours (OR = 0.66, 95% CI 0.3–1.43) or dental infections (OR = 0.72, 95% CI 0.27–1.94)[9]. It remains to be seen whether there exists a cumulative or synergistic interaction between smoking and drinking and mouthwash use or whether mouthwash use merely acts as a representative for the risk imparted by tobacco and alcohol. It has also been theorised that underreporting of smoking or alcohol usage among cases may lead to the overestimation of the effect of alcohol-containing mouthwash usage[25]. However, it has rightly been pointed out that similar underreporting among controls would lead to a converse underestimation of risk[26]. As mentioned previously, non-drinkers/non-smokers may be the ideal population in which to observe any risk imparted by mouthwash use[13]. However, low levels of study participants that fit into this population frustrate these attempts. Finally, the relatively low number of participants in each study hinders any attempt to isolate any risk related to mouthwash use. Lachenmeier[27] proposed that any excess risk imparted by regular alcohol-containing mouthwash use would be relatively small, thus needing a correspondingly large epidemiological study to detect it, and that even the meta-analysis by Gandini et al.[22] (4484 cases and 8781 controls) was insufficient in terms of statistical power. Overall, the heterogeneity in design and results between epidemiological studies and reviews makes it impossible to accurately judge the relationship between use of alcohol-containing mouthwashes and the development of OSCC. Further consistently designed studies with large numbers of participants, stringent examination of all the variables related to mouthwash use, specification of ethanol content in mouthwash and detailed control for alcohol and tobacco consumption are required before a definitive relationship can be established or discredited.

A number of review papers have also attempted to address the possible link between use of alcohol-containing mouthwashes and the development of OSCC (Table 3), focusing primarily on the previously discussed case-control studies[14,28–35]. A number of these review papers agree that the epidemiological evidence is sub-standard due to poorly designed studies and limited comparability[28,29,31]. Of the 11 available reviews, 9 conclude that current evidence does not support a link between use of alcohol-containing mouthwash and OSCC[14,22,25,28–30,32,34,35]. Of the remaining two reviews, Lachenmeier[31] concludes that as the epidemiological evidence is uncertain, there are enough concerns along with mechanistic evidence to have doubts about the safety of alcohol-containing mouthwashes, and McCullough and Farah[33] surmise that enough evidence exists to advise against their use. An interesting point raised by Lachenmeier[31] is the prevalence of industry sponsorship in reviews investigating the relationship between alcohol-containing mouthwash use and OSCC. As seen in Table 3, six out of 11 declare some form of industry

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Table 3 Reviews examining the evidence regarding an association between mouthwash use and oral squamous cell carcinoma

Study	Type	Notable conclusions	Industry sponsorship
Elmore and Horwitz[28]	Systematic review	Homogeneity of methods and results make comparison between studies difficult; available evidence does not support a causal relationship	Yes
Shapiro et al.[25]	Statistical commentary	Underreporting of tobacco and alcohol use by cases can possibly lead to an overstatement of the risk imparted by mouthwash use	Yes
Cole et al.[14]	Narrative review and dataset reanalysis	Evidence strongly suggests lack of relationship between mouthwash use and OSCC; associations in Winn et al.[10] study are arguably weaker once non-OSCC cases are removed	Yes
Carretero Pelaez et al.[29]	Narrative review	Current studies lack homogeneity; impossible to establish causative relationship with current data; no justification for addition of ethanol to mouthwashes	No
Lewis and Murray[30]	Narrative review	No association between mouthwash use and OSCC	No
Lachenmeier[31]	Narrative review	Current data raises doubts about safety of alcohol-containing mouthwashes; questionable need for ethanol in formulations; industry sponsorship is prevalent	No
Lemos and Villoria [32]	Narrative review	Evidence regarding mouthwash use and OSCC inconsistent and contradictory; alcohol-containing mouthwashes safe to use	Yes
McCullough and Farah[33]	Narrative review	Sufficient evidence to believe that alcohol-containing mouthwash use increases OSCC risk; oral health professionals should avoid recommending long-term use	No
La Vecchia[35]	Narrative review	Evidence weighs against association between mouthwash use and OSCC risk	Yes
Warnakulasuriya[34]	Narrative review	Evidence does not support causal relationship between mouthwash use and OSCC	No
Gandini et al.[22]	Quantitative meta-analysis	Data from 18 studies analysed; no statistically significant association between mouthwash use and OSCC (RR = 1.13; 95% CI 0.95–1.35) or alcohol-containing mouthwash use and OSCC (RR = 1.0, 95% CI 0.39, 2.60).	Yes

OSCC, oral squamous cell carcinoma.

affiliation or sponsorship[14,22,25,28,32,35]. Lachenmeier[31] noted that the industry supported studies had much more favourable conclusions than other independent reviews, suggesting the possibility of bias.

Mechanistic evidence

In addition to the epidemiological studies mentioned above, there also exist a number of *in vitro* and *in vivo* studies that investigate the effects of alcohol-containing mouthwashes on human cells and in the oral cavity. Although, consistent epidemiological findings are necessary to establish a causal relationship between alcohol-containing mouthwash use and the development of OSCC, these studies may provide an insight regarding the local effects and possible carcinogenic mechanisms. As with the epidemiology, several of these studies contain findings that are notable when examined from the perspective of head and neck carcinogenesis.

The production of carcinogenic acetaldehyde by oral bacterial flora and oral epithelial cells is one of the proposed mechanisms by which ethanol exposure contributes to oral carcinogenesis[4]. Several *in vivo* studies have examined this mechanism from an alcohol-containing mouthwash perspective. Lachenmeier et al.[36] conducted a trial in healthy human volunteers to quantify the amount of acetaldehyde produced in the oral cavity following 30 s of

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exposure to 13 different alcohol-containing mouthwashes whose alcoholic concentration varied from 6.8% to 26.8% v/v. It was found that while no acetaldehyde was detectable prior to exposure, an average concentration of 52 ± 14 μM (range 11–105 μM) acetaldehyde could be detected in saliva at 2 min post-exposure. This value had been reduced to 15 ± 7 μM (range 0–37 μM) at 10 min post-exposure. As is evidenced by the range of values, a large amount of inter-individual variation was present[36].

Given that the mutagenic threshold for acetaldehyde in saliva has been theorised to lie between 50 and 150 μM, these observed levels of salivary acetaldehyde could possibly induce undesirable changes in oral epithelial cells[37]. This has been noted in a separate study where participants who rinsed with either alcohol-containing mouthwashes (11.5% or 26.9% ethanol) or alcoholic beverages (wine 14% or scotch whiskey 43% ethanol), demonstrated significantly elevated levels of acetaldehyde ranging between 43.8 and 97.0 μM 1 min after exposure[38]. Another study compared use of alcohol-containing with non-alcoholic mouthwashes and found that users of the alcoholic variant had approximately 10 times higher levels of salivary acetaldehyde at 5 min post-exposure[39]. On the other hand, two *in vivo* studies have also found that mouthwash use also has suppressive effects (compared with pure ethanol) on salivary acetaldehyde levels as it eliminates oral microbes that play a significant role in the production of acetaldehyde in the oral cavity[40,41]. It is noteworthy though that despite the significant reduction, the acetaldehyde level produced by use of the alcohol-containing mouthwash still demonstrates individual values that are within the theoretical concentration range of mutagenicity. Overall, it would appear that the antibacterial properties of alcohol-containing mouthwashes reduce the level of acetaldehyde production in the oral cavity compared with an equivalent solution of ethanol, the constituent ethanol of the mouthwash still results in an increased production of acetaldehyde to the level where mutagenic effects may occur.

In an *in vivo* study investigating the incidence of nuclear abnormalities in exfoliated buccal cells from human participants using either an alcohol-containing or non-alcoholic mouthwash twice daily for 30 days, it was found that use of the alcohol-containing mouthwash resulted in significantly higher numbers of nuclear abnormalities such as micronucleus, binucleated cells and nuclear budding, all strong markers of genotoxicity[42].

In addition to human *in vivo* studies, the effects alcohol-containing mouthwashes have also been investigated in an *in vitro* capacity. Rodrigues et al.[43] investigated the ability of three different mouthwashes to induce genetic mutations using the *Drosophila melanogaster* somatic mutation and recombination test, which is useful for modelling the human genotoxicity of environmental agents. It was found that the test mouthwash with the highest percentage of ethanol (16.8%) induced a significant number of mitotic recombinations and that the ethanol rather than the antibacterial component was responsible[43]. Furthermore, human oral epithelial cells treated *in vitro* with diluted concentrations of 26.9% ethanol-containing mouthwash demonstrated significantly greater DNA damage ($P < 0.001$) than the alcohol-free negative control group as determined by single-cell gel (Comet) assay. Short *in vitro* exposure was unable to demonstrate cellular abnormalities within the treatment timeframe compared with the genotoxic effects noted[38]. Other studies have also combined cellular models with mouthwash exposure, but have limited their investigations to toxicity following acute exposures[44–47].

In vivo studies in animals investigating the effects on the oral mucosa of long-term topical exposure to alcohol-containing mouthwashes are non-existent. However, several animal studies that utilise pure ethanol in similar concentrations to commercially available mouthwashes do exist. In one study, rats were fed a diet containing 6.6% v/v ethanol for 6 months, which induced several changes in the epithelium of the floor of mouth and tongue including basal cell nuclear enlargement, basal cell hyperplasia and irregular epithelial stratification[48]. A similar study with rats (with a diet of 6.4% w/v ethanol for 5 months) found changes such as hyperproliferation of the oesophageal epithelium[49].

Overall, mechanistic evidence from these *in vivo* and *in vitro* studies suggests that the metabolism of the ethanol in alcohol-containing mouthwashes can produce a significant amount of acetaldehyde in the oral cavity even up to a level where genetic damage may occur. Information relating to the effects of alcohol-containing mouthwash on animal and cellular models is rare, especially any chronic effects related to repeated exposures as most studies focussed on acute toxic effects only. Greater investigation with both cellular and animal models is required to characterise the events and pathways by which genetic damage may occur through chronic exposure to alcohol-containing mouthwashes.

Unifying hypothesis

Field cancerisation, with particular reference to the oral cavity, refers to the theory that exposure of environmental carcinogens to the mucosal surface induces undesirable molecular changes within the entirety of the mucosa. This results in a cellular 'field' that is more susceptible to the development of malignant foci at multiple sites[50]. With regard to OSCC, these environmental risk factors have been identified as tobacco,

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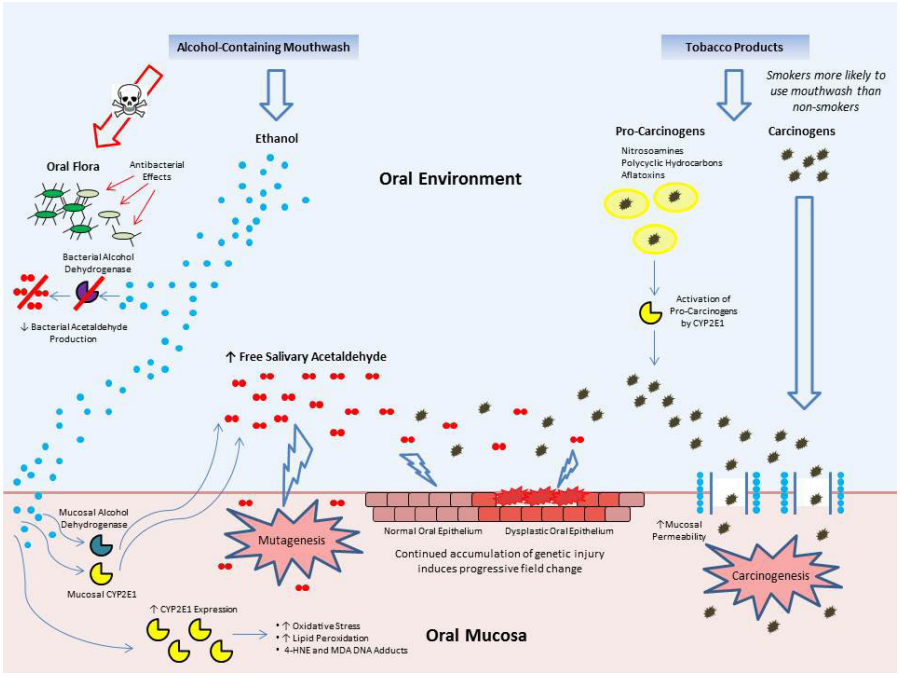

Figure 1: Hypothetical model of pathways leading to oral mucosal carcinogenesis following alcohol-containing mouthwash use.

ethanol and betel quid. Within this model, regular topical exposure to alcohol-containing mouthwash could theoretically have several effects from a carcinogenic viewpoint (Figure 1). A brief exposure has already been shown to induce a sharp rise in the level of salivary acetaldehyde to a point where there is the potential for mutagenic events to occur[36–38]. As noted, the antibacterial action of alcohol-containing mouthwashes does reduce the contribution to salivary acetaldehyde by oral flora; however, use of an alcohol-containing mouthwash generates significantly higher levels of salivary acetaldehyde compared with a non-alcoholic mouthwash, even after 2 weeks of twice-daily use, after which the oral flora would be thoroughly suppressed[39]. This demonstrates that even in the relative absence of contributing bacteria, ethanol in mouthwashes drives increased salivary acetaldehyde. In addition to the direct generation of a carcinogen, ethanol also has indirect effects such as increased mucosal permeation, and induction of cytochrome P450 2E1, which act to enhance the actions of tobacco-related carcinogens evidenced by a greater than multiplicative increase in OSCC risk associated with concurrent smoking and drinking[4,51]. This is likely to be relevant to alcohol-containing mouthwash use, as mouthwash users who smoke are at greater risk of developing OSCC than non-smoking users[10,15]. These combined effects may result in continued mutagenic events within an already sensitised field, promoting continued epithelial transformation. The effects of alcoholic beverages in this respect have already been seen, as it has recently been shown that continued consumption of alcoholic beverages after the development of OSCC significantly increases a patient's risk of developing a second primary OSCC presumably from continued transformation within the sensitised field[52].

It is possible to identify several groups of alcohol-containing mouthwash users who could theoretically be at higher risk with chronic use of high alcohol-containing mouthwash. Firstly, subjects who smoke and use alcohol-containing mouthwash are regularly exposed to both tobacco carcinogens and ethanol, the synergy of which has been highlighted above. Epidemiological studies have also shown that current and past smokers are more likely to use mouthwash[6,7,9,10,20]. Secondly, use of alcohol-containing mouthwash by patients with oral epithelial dysplasia has the potential for concern, as continued exposure to ethanol may act to facilitate progression towards malignancy. Patients with oral epithelial dysplasia tend to be smokers, and the oral epithelium in these patients is already transformed, placing them at heightened risk of further cellular and molecular damage should they engage in chronic use of alcohol-containing mouthwash. It is also possible that the discovery of an oral lesion by a patient may act as the motivating factor for mouthwash use, which would place the patient at increased risk of further damage to an existent lesion.

Although, there is still controversy regarding the possible effects imparted by alcohol-containing mouthwash use, in the meantime it is reasonable for clinicians to take steps to mitigate against any possible risk. As mentioned previously, ethanol is the ingredient in mouthwashes that has led to increased scrutiny, and in response to this, a number of ethanol-free antibacterial mouthwashes have become available on the general market, particularly in recent years following renewed calls for cessation of their regular use. Studies have shown that these formulations are as effective and have been shown to have a lower incidence of adverse effects than their ethanol-containing counterparts[53–60]. Given this, in our opinion it is the responsibility of health practitioners to educate patients about the presence of ethanol in mouthwashes with the aim of minimisation of any possible

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risk brought about by their use, particularly given the questionable need for the addition of ethanol to these products in the first instance.

Conclusion

There is currently an overall lack of general consensus with regard to the existence of a relationship between the use of alcohol-containing mouthwashes and the development of OSCC. This is largely due to poor design and lack of comparability between epidemiological studies and limited *in vivo* and *in vitro* mechanistic studies, particularly those investigating the effects of repeated exposures. Overall, the current analysis of the literature reveals a need for further consistently designed epidemiological studies with greater participant numbers, and mechanistic studies investigating cellular and molecular events and pathways through which genetic damage may occur following acute and chronic exposure to alcohol-containing mouthwashes. As there is a lack of consistent evidence, it is also advisable for clinicians to promote the use of non-alcoholic mouthwashes in order to minimise any potential increase in risk, and discourage long-term use of high alcohol-containing products.

Abbreviation list

OSCC, oral squamous cell carcinoma.

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