

# Research Review

## EDUCATIONAL SERIES™

### Oral Healthcare in the Prevention of Oral Cancer

#### About the Expert



**Professor Lakshman  
'Sam' Samaranayake**

**BDS, DDS, DSc, FRCPath,  
FDSRCSE, FDSRCPS, FRAGDS,  
FHKCPath, FHKAM (Dent Surg)**

Professor Lakshman Samaranayake (Sam) is the Immediate Past Dean and honorary Professor of Oral Microbiomics and Infection at the University of Queensland, School of Dentistry. Prior to this he was the Dean of the Faculty of Dentistry, University of Hong Kong for a decade (now considered the No 1 Dental School in the World by QS World University Rankings). He is also an Honorary Professor at the Eastman Dental Institute, UK and many other universities in China, Saudi Arabia, India, Oman and Indonesia.

Professor Samaranayake earned his doctoral degree at the University of Glasgow, UK where he was a Consultant/ Senior Lecturer in Oral Medicine and Pathology. Then he served as a Professor at the University of Alberta, Canada, and at the Universities of Hong Kong and Queensland.

Professor Samaranayake is the author of five text books and over 450 scientific communications cited over 18,500 occasions in the literature (H-index 71). For his research, he has received many accolades including being the first from Asia to receive the Distinguished Scientist Award of the International Association for Dental Research, and the coveted King James IV Professorship of the Royal College of Surgeons of Edinburgh, UK. He has lectured in all five continents, and is the Founding Editor-in-Chief of the Journal of Investigative and Clinical Dentistry,

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This article reviews evidence for an association between oral cancer and periodontitis and the oral plaque biofilm. The existence of such an association emphasizes the importance of patients maintaining their oral health and the role of oral healthcare professionals in managing periodontitis and the biofilm as well as the detection of early oral cancer. As an adjunct to mechanical interventions, mouthwash also has a role in controlling the oral biofilm. Confounding the beneficial role of mouthwash are concerns about a putative link between alcohol-containing mouthwash use and oral cancer and the current evidence regarding this association is also reviewed. Expert commentary from Professor Lakshman Samaranayake provides a clinical practice perspective on these issues.

#### Background to oral cancer

Oral cancer is an important disease globally, accounting for 300,000 new cases in 2012 (2.1% of the world total), with two-thirds occurring in men, and 145,000 deaths (1.8% of world total).<sup>1</sup> Notably, Asia accounted for 56% of new cases of oral cancer and 67% of deaths.

At estimated age-standardized rates of 5.2 per 100,000 for males and 2.5 per 100,000 for females, the incidence of oral cancer in Asia is similar to the worldwide incidence.<sup>1</sup> However, the incidence varies across individual regions, with rates for males and females being 9.9 and 4.7 per 100,000, respectively in South-central Asia, 4.0 and 2.5 per 100,000 in South-east Asia, and 2.4 and 1.1 per 100,000 in East Asia.<sup>1</sup>

Similarly, the incidence of oral cancer varies greatly across different countries in Asia.<sup>2</sup> Compared with the world age-standardized incidence rate for oral cancer, Bangladesh, India, Sri Lanka, Pakistan, and Taiwan have higher rates while China, Hong Kong, the Philippines, Singapore, and Vietnam have lower rates. Trends also vary, with evidence of increasing incidence rates in Pakistan, Taiwan, Singapore, and Thailand and reports of decreasing rates in the Philippines and Sri Lanka.

Although the established risk factors for oral cancer, tobacco use and alcohol over-consumption, are common across Asia, betel (*paan*)-quid chewing is also common and a high oral cancer incidence is observed in Asian countries with a cultural practice of chewing quid.<sup>2,3</sup> There is also epidemiological evidence linking betel-quid chewing with oral cancer in Asian countries, including Indonesia, Malaysia, and the Philippines.<sup>3-6</sup>

#### Role of periodontitis and the oral biofilm

Researchers have investigated a possible association between periodontal disease and head and neck cancer because inflammation plays an important role in the origin and progression of cancer and periodontal disease is essentially an inflammatory disease; moreover, an anatomical relationship can exist between periodontal disease and head and neck cancer.<sup>7,8</sup>

Another pathway that has been proposed is through oral bacteria. These bacteria form biofilms (dental plaque) in the mouth that elicit the host inflammatory responses in periodontal disease.<sup>9-11</sup> They can also metabolize ethanol to produce acetaldehyde, an agent implicated in cancer causation.<sup>9,11-13</sup>

Epidemiological and biological evidence is accumulating that is supportive of periodontitis and the oral biofilm playing a role in the development of oral cancer.

#### Epidemiological evidence

Periodontal diseases are highly prevalent. The Global Burden of Disease study estimated that oral conditions affected 3.9 billion people in 2010, with severe periodontitis being the sixth most prevalent condition and affecting 11% of the global population.<sup>14</sup> Severe periodontitis was found to be a leading cause of disability in Southeast Asia.

It is well established that oral bacteria are important to the development of periodontal disease and tooth loss.<sup>9,11,15</sup> The underlying mechanism for this association is not well understood, but the oral microbiome appears to play a role. Since the identification of *Helicobacter pylori* as a causative agent in the development of gastric cancers in the early 1990s, evidence continues to emerge of an association between specific micro-organisms resident in the oral cavity and certain types of oral and gastrointestinal cancer.<sup>9,16,17</sup>

The oral microbiome is a complex and diverse multispecies community.<sup>18,19</sup> According to the polymicrobial synergy and dysbiosis model of periodontal pathogenesis, the oral microbiome usually exists in a balanced immune-inflammatory state with its host.<sup>20</sup> Under certain conditions, however, specific species of oral bacteria can disrupt this equilibrium leading to a dysbiotic microbiome. In particular, *Porphyromonas gingivalis* has been identified as an important player in the emergence of a dysbiotic microbiome and

dysregulated immune response, which ultimately leads to periodontal disease. Moreover, a range of research initiatives, including retrospective immunohistochemical analyses and prospective cohort and microbiological studies, have implicated *P. gingivalis* and *Fusobacterium nucleatum* in oral cancers and other types of gastrointestinal cancers.<sup>21-26</sup>

Another potential link between periodontitis and oral cancer is human papilloma virus (HPV) infection. Chronic periodontitis appears to facilitate the acquisition and persistence of oral HPV infection,<sup>27,28</sup> and molecular and epidemiological evidence indicating a strong etiological association between HPV and oropharyngeal cancers continues to accumulate.<sup>29,30</sup> Indeed, a rising prevalence of oropharyngeal cancer related to HPV has been demonstrated in Australia, with the prevalence increasing from 20.2% (1987-1995) to 63.5% (2006-2010) over two decades.<sup>31</sup> A similarly high rate has been reported in the US, with approximately 63% of oropharyngeal cancers having been estimated to be probably caused by HPV (1998-2003).<sup>32</sup> In Singapore, there was a steady (2% per year) increase in the incidence of potentially HPV-related oropharyngeal cancer during the period 1968-2012.<sup>33</sup>

### Mechanistic evidence

As well as epidemiological evidence of a positive association between specific species of oral bacteria and the development of oral cancers, there is also a biological basis supporting an etiological role.

Chronic inflammation, involving the tumor microenvironment, is a contributing factor in the initiation and progression of cancer.<sup>34,35</sup> *P. gingivalis* and *F. nucleatum* cause chronic infections that involve intracellular persistence within epithelial cells in addition to possessing immune disruptive activity,<sup>36</sup> with both species having been shown to be pro-inflammatory.<sup>37-40</sup> In addition to their immune-disruptive properties, both *P. gingivalis* and *F. nucleatum* can affect epithelial cell signaling that is relevant to cancer progression.

Laboratory studies, by Inaba et al.<sup>41</sup> and Kunboniwa et al.,<sup>42</sup> have demonstrated epithelial cell responses to *P. gingivalis* that are consistent with carcinogenesis. These effects include inhibition of programmed cell death (apoptosis) via multiple mechanisms, inhibition of natural tumor suppression, facilitation of carcinoma cell migration and invasion, and immune evasion.<sup>42-47</sup> Similarly, laboratory-demonstrated interactions between *F. nucleatum* and epithelial cells also indicate carcinogenic potential, including elevation of cell proliferation and migration and facilitation of tumor cell invasion and immune evasion.<sup>48-50</sup> In addition, cohort studies conducted in the US and Japan suggest that *F. nucleatum* in the gut microbiome may inhibit host immunity in colon carcinogenesis.<sup>51,52</sup>

Another mechanism underlying carcinogenic potential mediated by the oral microbiome is the capacity of oral micro-organisms to metabolize alcohol to acetaldehyde.<sup>12,13,53</sup> Ethanol (alcohol) itself is not carcinogenic but some oral bacteria and yeast possess the enzyme alcohol dehydrogenase and

consequently the ability to convert ethanol in saliva to acetaldehyde, which is a recognized human carcinogen. Thus, following alcohol consumption, the oral cavity and gastrointestinal tract are directly exposed to carcinogenic acetaldehyde. Furthermore, the conversion of alcohol to acetaldehyde is likely to occur more quickly and to a greater extent in the presence of a large oral biofilm.<sup>54</sup> For example, research by Yokoyama et al. demonstrated that high acetaldehyde levels in the saliva of Japanese alcoholic men was partly attributable to increased salivary production of acetaldehyde as a result of micro-organism overgrowth and may account for their higher risk of upper aerodigestive tract cancer.<sup>55</sup> One of the factors contributing to the micro-organism overgrowth was poor oral hygiene.

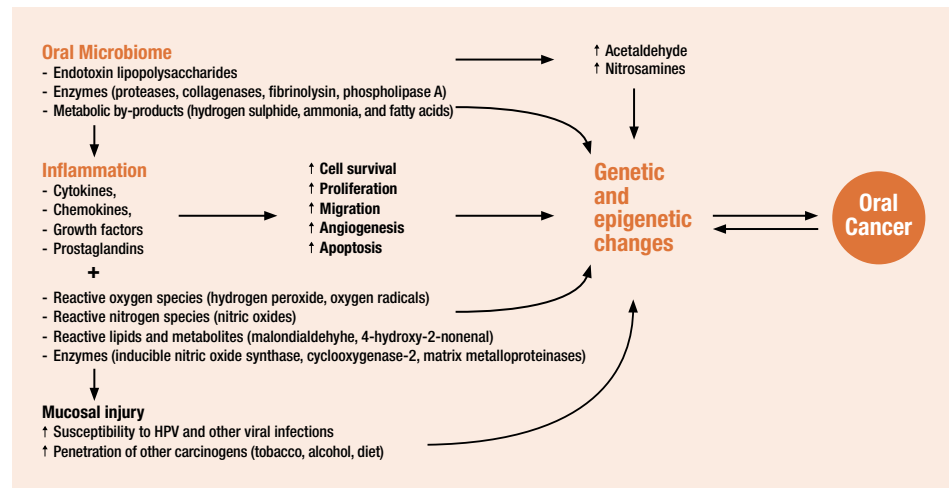


Figure 1. Depiction of the possible role of periodontitis and the oral microbiome in oral cancer.<sup>27</sup>

### Summary

A proposed model summarizing the role of periodontitis and the oral microbiome in the development of oral cancer is presented in **Figure 1**.<sup>27</sup> Periodontitis may be associated with oral cancer via the direct toxic effects of the oral microbiome and its products and/or indirectly via inflammation. Periodontitis may also lead to increased susceptibility to and persistence of oral HPV infection, which is increasingly being associated with oral cancer.

### Symptoms of Oral Cancer

According to the Australian Dental Association's Oral Cancer Facts, early detection provides a 90% chance of surviving oral cancer.<sup>56</sup> The following are signs and symptoms of oral potential malignant disorders and oral cancer to scrutinize during a patient consultation and oral examination:

- Red or white patches
- Ulcers or sores that do not heal and/or bleed easily
- Blood blisters that do not heal
- Thick or hard spots or lumps that may or may not be painful
- Roughened or crusted areas or sores
- Numbness anywhere inside the mouth
- Pain and tenderness
- Misalignment of teeth when biting down
- Pain when chewing or swallowing
- Difficulty swallowing or moving the jaw
- Difficulty moving the tongue
- Changes in speech such as slurring or lack of clarity
- Loose teeth and/or sore gums
- Altered taste
- Swollen lymph glands.

### Role of oral healthcare professionals

With periodontitis and the oral biofilm having been implicated as a risk factor for oral cancer, it is perhaps not surprising that regular dental check-ups have been demonstrated to be associated with a reduced risk of oral cancer,<sup>57,58</sup> and poor oral health and a lack of regular dental visits to be associated with an increased risk of oral cancer.<sup>57,59</sup> Hence, patients visiting their oral healthcare professional regularly is likely to be an effective preventative strategy for oral cancer.

Dental check-ups provide the opportunity to reduce the biofilm and manage periodontal disease and to reinforce patient self-administered oral hygiene practice. The importance of professional plaque removal in combination with oral hygiene instruction in the primary prevention of periodontitis has recently been emphasised.<sup>60,61</sup>

ARCAGE, a large European epidemiological study, demonstrated that poor oral health is an independent risk factor for upper aerodigestive tract cancer.<sup>57</sup> Patients with aerodigestive tract tumors were interviewed about their oral health and dental care behaviors, in addition to their lifestyle factors, other medical conditions, and socioeconomic status. People with the poorest oral health (complete denture wearers and persistent gum bleeding) more than doubled their risk of mouth and throat cancer compared with those with the best oral health, even when adjusted for the confounding factors of smoking and alcohol consumption.

The ARCAGE study also observed that people with the poorest dental care (those who hardly ever brushed their teeth or visited the dentist) more than doubled their risk (adjusted for smoking and alcohol consumption) of mouth and throat cancer compared with those with the best dental care.<sup>57</sup> Other epidemiological studies have also demonstrated an association between poor patient oral hygiene practices (low frequency of dental visits, tooth brushing, and use of dental floss and mouthwash) and oral cancers, also after adjusting for alcohol and tobacco usage.<sup>58,59,62</sup> A positive association between poor oral hygiene and oral cancer has been demonstrated in case-control studies in Indian populations.<sup>63,64</sup>

Evidence for both poor oral health and poor dental care being associated with an increased risk of oral cancer emphasizes the importance of the role of dental healthcare professionals in helping to reduce the risk of oral cancer via control of the oral biofilm and reinforcement of patient oral hygiene practice, including regular dental check-ups.

Dental check-ups also provide the opportunity for oral healthcare professionals to screen for pre-cancerous and cancerous lesions on a regular basis whilst performing routine oral examinations in practice.<sup>65</sup> Two recent studies that evaluated the oral mucosal screening and referral attitudes of Australian dentists,<sup>66</sup> and those of oral health therapists and dental hygienists,<sup>67</sup> demonstrated an unambiguous understanding of the importance of screening and the need to be alert to oral mucosal changes. However, lack of training, time, confidence, and financial incentives were perceived as barriers to mucosal screening. In Indonesia, a nasopharyngeal cancer awareness programme was found to be an effective tool for improving the knowledge of primary healthcare workers,<sup>68</sup> suggesting that an oral cancer awareness campaign might also be effective in oral healthcare professionals. Overall, these findings indicate the requirement for further and/or improved oral healthcare professional education and training for oral cancer screening and referral.<sup>66,67,69</sup>

The FDI World Dental Federation policy statement on oral cancer (adopted on 24<sup>th</sup> September 2015, Bangkok, Thailand) acknowledges that oral healthcare professionals play a key role in educating patients about risk factors and how to avoid them.<sup>70</sup> This role extends to the early detection of oral cancers via the examination of hard and soft tissues, both inside and outside the mouth, in all patients. The FDI recommends the provision of specific training for the early recognition, referral, treatment, and post-treatment management of oral cancer.

Oral healthcare practitioners should also be knowledgeable about the association of HPV with oropharyngeal cancers, and they should be prompt in referring patients with suggestive symptoms for evaluation.<sup>29</sup> Oral healthcare practitioners playing an important role in increasing patients' knowledge of HPV, oropharyngeal cancers, and HPV vaccines has also been advocated.

## Role of mouthwash

As an adjunct to the mechanical control of oral biofilm, there is a clear benefit of a significant reduction of both dental plaque and gingivitis associated with the use of mouthwash formulations containing either chlorhexidine or essential oils.<sup>71-73</sup> Hence, by contributing to a reduction in periodontitis and the oral biofilm, mouthwash use has the potential to also help to reduce the risk of oral cancer. However, with many available mouthwash formulations containing alcohol, there have been concerns that some mouthwashes could contribute to an increased risk of oral cancer via the carcinogenic effects of alcohol.

## Mouthwash use and oral cancer concerns

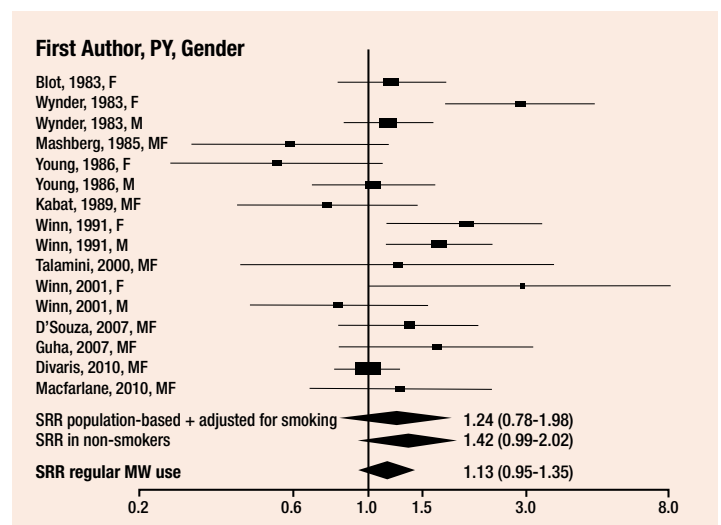
Given that the consumption of large quantities of alcohol, especially with concomitant smoking, is a proven risk factor for the development of oral cancer, and that alcohol can be metabolized in the mouth to acetaldehyde, a recognized carcinogen, research has been directed at assessing whether there is any cancer risk associated with rinsing the mouth with alcohol-containing mouthwashes.

### Epidemiological evidence

A possible link between the use of alcohol-containing mouthwash and a higher risk of oral cancer has been a subject of research since the late 2000s.<sup>74</sup> In 2008, McCullough and Farah concluded that it was inadvisable for oral healthcare professionals to recommend the long-term use of alcohol-containing mouthwashes based on an assessment of the available relevant literature at the time.<sup>75</sup>

Following the McCullough and Farah article, there has been a literature review by La Vecchia in 2009.<sup>76</sup> La Vecchia critically assessed ten case-control studies published during the previous 30 years that investigated a possible relationship between mouthwash use and oral cancer risk. It was observed that three of the ten case-controlled studies reported relative risks above unity but that the other seven studies reported no consistent association. Moreover, only a few studies included information on different types of mouthwash, and addressed the issue of alcohol-containing mouthwash. La Vecchia concluded therefore that a link between mouthwash use, specifically alcohol-containing mouthwash, and oral cancers was not supported by the published epidemiological evidence.

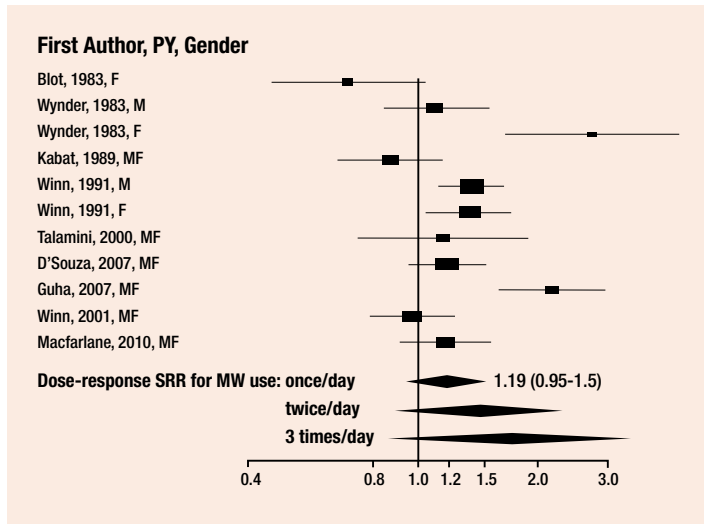
La Vecchia's critical review of the literature was followed in 2012 by a comprehensive meta-analysis of epidemiological studies of mouthwash and oral cancer risk undertaken by Gandini et al.<sup>74</sup> Notably, their analysis included studies of mouthwash containing >25% alcohol (ethanol content in alcohol-based mouthwashes is typically 5-27%). After conducting a systematic literature search, Gandini and colleagues selected only studies with sufficient data to allow adequate estimation of the relative risk and 95% confidence intervals for the meta-analysis. The quantitative analysis of a total of 18 published studies of mouthwash use and oral malignancy revealed no statistically significant associations between mouthwash use and risk of oral cancer (**Figure 2**). This finding is consistent with that of systematic literature reviews of the relationship between mouthwash use and oral cancer.<sup>71</sup> Moreover, Gandini and colleagues' analysis did not show a significant trend in risk of oral cancer with increasing daily use of mouthwash and no association between use of alcohol-containing mouthwash and oral cancer risk (**Figure 3**).<sup>74</sup> The latter finding is consistent with that of a previous meta-analysis that also found no connection between use of alcohol-containing mouthwash and oral cancer among nine epidemiological studies.<sup>77</sup>



**Figure 2.** Forest plot showing no significant association between regular mouthwash use and oral cancer based on 12 epidemiological studies published between 1983 and 2010 that were available for the main meta-analysis by Gandini et al.<sup>74</sup>

Abbreviations: F = females; M = males; MW = mouthwash; PY = publication year; SRR = summary relative risk (with 95% Confidence Intervals)

Also, following the McCullough and Farah article, there has been a comprehensive literature review on mouthwash efficacy and safety by Boyle et al., which was published in 2014.<sup>71</sup> This review also addressed the issue of mouthwash use and oral cancer and, in particular, the effects of confounding factors, including other sources of acetaldehyde inside the oral cavity, and its total exposure to acetaldehyde. These authors concluded that the evidence indicates that mouthwash use does not increase the risk of oral cancer, even with the use of mouthwash containing a high percentage of alcohol.



**Figure 3.** Forest plot showing no significant association between increasing mouthwash use and oral cancer based on 9 epidemiological studies published between 1983 and 2010 that were evaluable for the dose-response meta-analysis by Gandini et al.<sup>74</sup>

Abbreviations: F = females; M = males; MW = mouthwash; PY = publication year; SRR = summary relative risk (with 95% Confidence Intervals)

An interesting observation in the 2014 ARCAGE epidemiological study, which assessed the association of mouthwash use and upper aerodigestive tract cancer, was a 3-fold higher risk for oral cancer in a sub-group of people who used mouthwash  $\geq 3$  times per day versus those who did not use mouthwash.<sup>57</sup> However, rinsing  $\geq 3$  times per day is not considered normal use. For example, in a UK study that determined patterns of mouthwash use in the general population, only 25% of participants reported using mouthwash once per day with the remainder reporting less than once-daily use.<sup>78</sup> Moreover, in the ARCAGE study, <2% of cases and controls reported using mouthwash >3 times daily. It is also relevant that an increased risk of oral cancer was not found among people who used mouthwash <3 times per day in the ARCAGE study.<sup>57</sup>

The ARCAGE investigators also acknowledged some limitations of their study.<sup>57</sup> It did not distinguish between mouthwash that contained alcohol and mouthwash without alcohol and some participants could have used mouthwash to mask bad breath caused by smoking and alcohol consumption. The investigators also acknowledged that more data is required before definitive conclusions can be made.

## Mechanistic evidence

A possible role of mouthwash use in the etiology of oral cancer should also be considered in the wider context of the biology of the mouth and the biology of oral carcinogenesis.<sup>74</sup> With regard to alcohol-containing mouthwash, an effect of alcohol on the development of cancer is likely to depend dose and duration of exposure and inter-individual variability.<sup>71</sup>

In their comprehensive literature review on the efficacy and safety of mouthwash, Boyle et al.<sup>71</sup> raised the following points relevant to discussion of a biological mechanism linking alcohol in mouthwash with oral cancer via its metabolism to acetaldehyde:

- Ethanol is metabolized by alcohol dehydrogenase to acetaldehyde, a genotoxic compound, which is subsequently metabolized by aldehyde dehydrogenase to acetic acid.<sup>71</sup>

- There is substantial evidence that acetaldehyde derived from the metabolism of ethanol in alcoholic beverages contributes to the causation of esophageal tumors in people who are deficient in aldehyde dehydrogenase.<sup>71</sup> For example, the inactive form of aldehyde dehydrogenase-2 (ALDH2), which is a primary enzyme for the elimination of acetaldehyde that is prevalent in East Asian populations, has been linked to upper aerodigestive tract cancer susceptibility in Chinese men and women.<sup>79,80</sup>
- Acetaldehyde is a naturally-occurring substance and is a product of normal metabolism and it is unclear whether acetaldehyde concentrations detected in human studies may result in DNA damage in cells of the oral cavity.<sup>71</sup>
- Common sources of acetaldehyde are cigarettes, alcoholic beverages, and certain foods; the contribution from alcohol-based mouthwash use is <1% of daily dose.<sup>71</sup>
- Exposure from alcohol-containing mouthwash is less than that from alcoholic beverage consumption, which has been estimated to cause 1% of oral cancer in humans.<sup>71</sup>
- Use of alcohol-containing mouthwash is likely to have a negligible effect on the cumulative lifetime exposure to acetaldehyde from common foods.<sup>71</sup>
- Mouthwashes with concentrations of up to 27–28% alcohol, even when used twice daily every day, would have a negligible impact on cumulative lifetime exposure to acetaldehyde derived from consuming certain foods and fermenta.<sup>71</sup>

With regard to specific investigations of acetaldehyde exposure from mouthwash use, Moazzez et al., in their 2011 randomized controlled study in healthy volunteers, showed a rapid increase in acetaldehyde in saliva after rinsing with ethanol solutions or alcohol-containing mouthwashes but the levels were transient, decreasing to undetectable levels within 10 minutes (versus 3-4 hours with moderate drinking of alcoholic beverages).<sup>81</sup> Interestingly, they also observed that the lowest level of acetaldehyde was from one of the mouthwash brands tested and the highest level was from a 21.6% ethanol solution, possibly suggesting acetaldehyde suppression properties of mouthwash. In a related investigation, Koschier et al. measured the influence of ethanol and ethanol-containing mouthwash on mucosal permeability using an *in vitro* oral buccal mucosal construct.<sup>82</sup> Their results showed no effect of alcohol-containing mouthwash on mucosal permeability after a typical daily rinsing pattern and no apparent absorption of acetaldehyde. Investigators who used a human oral mucosal model in an earlier investigation also found that alcohol-containing mouthwashes did not significantly affect tissue viability.<sup>83</sup>

In a 'real world' investigation of alcohol exposure via mouthwash use, a UK study was carried out to develop and validate a mouthwash use questionnaire to determine the lifetime exposure to alcohol from mouthwash use in the general population.<sup>84</sup> As well as confirming that the questionnaire was a valid and reliable tool to investigate mouthwash use and to measure alcohol exposure from mouthwash, the study observed that life-time exposure from alcohol in mouthwash was relatively small for most of the study participants with 79% having rinsed for less than one year with an alcohol-equivalent of one glass of wine per day. To give this level of exposure some context, the consumption of 1.5L of wine per day was associated with an increased risk of developing upper aerodigestive tract cancers in an assessment of dose-response relationships between alcohol consumption and risk of head and neck cancers,<sup>85</sup> which suggests that the exposure of the oral cavity to ethanol from mouthwash use is substantially lower than that from consumption of alcoholic beverages. Indeed, whereas social drinking potentially exposes the oral mucosa to long durations of alcohol exposure (one hour or longer), the exposure from normal use of mouthwash is much shorter (30-60 seconds) and there is also the opportunity for the flushing effect of saliva to disperse any residual mouthwash.<sup>54</sup>

In another investigation of exposure risk, German authorities in 2010 reviewed all available evidence related to acetaldehyde toxicological risk, the results of which were cited by Boyle et al.<sup>71</sup> in their literature review. The German researchers concluded that the expected acetaldehyde exposure from twice-daily use of mouthwash (0.25  $\mu\text{g}/\text{kg}$  bodyweight) is small in comparison to the exposure from food and beverages containing alcohol, and that alcohol in mouthwash should not be considered as a health risk with regard to the formation of acetaldehyde.

Some years earlier, another national authority, the US FDA, concluded that there was no causal relationship between alcohol-containing mouthwash and oral cancer based on a review of the available mechanistic (including exposure risk) and epidemiological data in 2003.<sup>86</sup>

Finally, based on their measurements of acetaldehyde exposure in saliva, Lachenmeier et al. estimated the lifetime risk of cancer associated with twice-daily use of alcohol-containing mouthwash to be 3-4 cases per 1,000,000 people.<sup>87,88</sup> This level of risk appears small compared with the general lifetime risk of oral cancer being 1 in 75 for males and 1 in 147 for females according to Cancer Research UK.<sup>89</sup> Lachenmeier suggested that, as evidence that the risk of alcohol-based mouthwash at a public health level appears low relative to other routes of exposure to alcohol and acetaldehyde, the priority for risk management strategies should continue to be reduction of alcohol consumption and smoking.<sup>87</sup>

## Mouthwash options

Alcohol-free mouthwashes are available for use by people who have concerns about the safety of mouthwash, people at high-risk (e.g. oral cancer patients) and those for whom alcohol-containing mouthwash is contraindicated (e.g. infants, those who

are immunocompromised, have mucositis, a history of alcohol abuse, and/or are receiving radiation therapy for head and neck cancer).<sup>90</sup>

It is also worth noting that the American Dental Association's Seal Product Category, the Australian Dental Association's Seal of Approval Listing and the New Zealand Dental Association's Approved Products continue to include a vetted selection of both alcohol-containing and alcohol-free mouthwashes.

### Role of alcohol in mouthwash

Pharmaceutical grade ethanol plays an important role in the formulation of mouthwash because it:

1. Acts as a solubilizer to dissolve non-water soluble ingredients, such as essential oils or flavor oils, into the aqueous base.
2. Acts as a stabilizer to prevent precipitation.
3. Acts as a preservative to maximize shelf-life.
4. Provides a sensory cue and makes the solution palatable.
5. Enhances antiplaque efficacy, i.e. it provides an adjuvant effect.

## EXPERT COMMENTARY – PROFESSOR LAKSHMAN SAMARANAYAKE

We are currently witnessing an unprecedented era of knowledge explosion. Two main reasons for this are the incessant advances in new technology as well as the social media revolution, which has engulfed, subsumed, and virtually saturated the scientific as well as the clinical community. The foregoing review therefore provides the busy practitioner a comprehensive, timely, and a succinct overview of two major contemporary issues in dentistry, the role, if any, of the oral microbiome in oral cancer, and the control of periodontal disease and managing the plaque biofilm through prophylactic mouthwashes.

New generation technology (such as next generation sequencing, NGS) is now providing us with a tantalizing glimpse of the hitherto unknown, complex world of microbial passengers – we continue to harbor in our oral habitat from birth to death. Although the vast majority of these are our friends, lurking amongst them are 'terrorist' microbes, which may inflict damage, destruction, and chaos within the microbiome leading to host pathology.

The first section of the review provides a roundup of the putative role of the microbiome in oral cancer. Data on the association between the oral virome, including papilloma viruses, previously thought to be harmless commensals, and cancer are relatively strong whilst the role of periodontopathogens, and oral cancer appear to be less so, but emerging. The latter association is predicated upon the ability of these organisms to convert ethanol in saliva to acetaldehyde, a recognized human carcinogen. In particular, *P. gingivalis* and *F. nucleatum*

possess attributes that are consistent with a role in cancer development and progression. The role of oral yeast populations (*Candida albicans* mainly) in oral carcinoma has also been raised in this context, as they have similar biochemical properties. Interestingly, there is perhaps the future possibility that the presence of specific combinations of bacteria in the plaque microbiome may be used as a biomarker or harbinger organisms for predicting systemic cancers such as pancreatic cancers.<sup>92</sup>

On the contrary, there is incontrovertible evidence that dysbiosis of the oral plaque biofilm leads to periodontal disease due to the emergence of key dysbiotics, 'the terrorist bacteria' (so-called red complex bacteria) destroying the communal harmony of a healthy biofilm. What is also clear is that, a routine use of a mouthwash together with other oral hygiene measures, such as flossing and brushing, is likely to favor, rejuvenate, and sustain a healthy plaque microbiome and its communal lifestyle.

In my view, the vexed question of alcohol in mouthwashes and the possibility of its carcinogenic potential should be laid to rest as there is an ample body of accumulating evidence to indicate that it is not the case. Moreover, those who are still uncomfortable with alcohol supplements due to scientific, cultural, or religious beliefs, now have the option of using alcohol-free mouthwashes that are likely to be equally effective. All in all, a comprehensive, state of the art review that is truly read-worthy.

### TAKE-HOME MESSAGES:

- Increasing evidence implicates periodontal disease and the oral biofilm in the etiology of oral cancers.
- The oral microbiome species, *P. gingivalis* and *F. nucleatum* possess attributes that are consistent with a role in cancer development and progression.
- Improved oral hygiene, regular dental check-ups, and professional treatment of periodontitis may be helpful in reducing the incidence of oral cancer.
- Oral healthcare professionals should be proactive in treating periodontal disease, managing the biofilm, and screening their patients for oral cancer.
- Oral healthcare professionals should also emphasize to their patients the need for regular oral health check-ups and the importance of oral hygiene home care, i.e. brushing, flossing, and use of mouthwash.
- Mouthwash is a valuable adjunct to the mechanical control of the oral biofilm.
- Current epidemiological and biological mechanistic evidence does not support a causal relationship between oral cancer and use of alcohol-containing mouthwash.
- Alcohol-free mouthwashes are available for people at high-risk and those for whom alcohol-containing mouthwash is contra-indicated.

# RESEARCH REVIEW EDUCATIONAL SERIES

## Oral Healthcare in the Prevention of Oral Cancer

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