Causes of oral cancer – an appraisal of controversies

S. Warnakulasuriya[1]

VERIFIABLE CPD PAPER

IN BRIEF

- Provides evidence-based information on important and relevant risk factors for oral cancer.
- Enables the dentist to advise their clients on harm reduction.
- Provides an opinion on debated controversies.

OPINION

Major risk factors for oral cancer are cigarette smoking and alcohol misuse. Among Asian populations, regular use of betel quid (with or without added tobacco) increases oral cancer risks. Dentists should be aware of some emerging risk factors for oral, and particularly oropharyngeal cancer such as the role of the human papillomavirus infection (HPV). Decreases in risk could be achieved by encouraging high fruit and vegetable consumption. Some controversies related to the aetiology of this disease also need clarification. The objective of this paper is to provide an opinion on these debated controversies.

INTRODUCTION

Oral cancer, defined as cancers of lip, tongue and mouth (ICD 10: C 01-06), is a serious and growing problem in many parts of the globe including Europe. Oral and oropharyngeal cancer (ICD 10: C01-06, C09-10, C14) grouped together is the sixth most common cancer in the world. The areas characterised by high incidence are in South Asia, Pacific regions, Latin America and in parts of central and eastern Europe. A recent review provides up to date information on the global epidemiology.[1]

In this context it is important for United Kingdom (UK) dental practitioners to be aware of some cancer statistics and figures for the UK. There were 5,325 new cases diagnosed in 2006. Since the 1980s, the numbers of incident oral cancers reported to the UK cancer registries have been rising every year and more recent data suggest a rise of 41.2% over a period of ten years. The Cancer Research (UK)[2] figures issued in August 2009 confirmed a further steep rise in the latest figures, while other tobacco-associated cancers, eg Lung cancer, have declined. In fact, based on these crude data (age unadjusted), no other cancer site has shown such a rapid rise in incidence in the past quarter of a century.

Oral cancer to a large extent is a self-induced disease.[3] In order to plan preventive measures it is important to understand the risk factors associated with the disease. The major risk factors are well known, have been reviewed recently[4] and will not be described in detail in this paper. However, there are some emerging risk factors for oral cancer that dentists should be aware of, and some controversies related to the aetiology of this disease that need clarification.

The objective of this paper is to provide an opinion on these debated controversies. Several factors that have been often cited as likely to be associated with oral cancer, namely heredity and familial risk, marijuana (cannabis) smoking, khat chewing, medicinal nicotine use, HIV infection and alcohol containing mouthwashes, have not been adequately validated as having sufficient evidence to be linked with oral cancer. It is important to clear some myths about the disease causation so that dentists can, with some confidence, discuss only the important and relevant risks with their patients.

MAJOR RISK FACTORS – TOBACCO, ALCOHOL AND BETEL QUID

Major risk factors for oral cancer in the UK population are cigarette smoking and alcohol misuse. There are several key epidemiological studies from many countries that confirm the associated risk with these two lifestyle habits. While all forms of smoking (cigarette or cigar) have equal excess risks, there is no clear evidence that specific alcoholic drinks (wine, beer, spirits) have different effects on oral cancer. The most prevalent alcoholic beverage in a given population would be the one with the highest risk in that population.

Smokeless tobacco (ST) use also significantly increases the risk of oral cancer.[5] The sale of ST is banned in the UK so the public have no access to this form of tobacco. However, chewing tobacco is available on sale mostly mixed with betel quid (areca nut). Betel quid is carcinogenic to humans (both with and without added tobacco)[6] and is an important risk factor among people with this habit in the Asian ethnic minorities residing the UK.[7] For this reason, being South Asian (ethnicity but not race) could be considered a risk factor.

The estimated elevated risks from these different agents and exposures (among smokers, regular users of alcohol and betel quid; adjusted for each other) compared to non-users are reported consistently from many populations. The elevated risks are confirmed by several meta-analyses or systematic reviews, providing proof of significant risks of these lifestyles for oral cavity cancers.[8–10] In the UK there is evidence that the increasing incidence of oral cancer, especially affecting younger people, is associated with increased intake of alcohol.[11] The synergistic effect on the

[1]Head, Department of Oral Medicine/WHO Collaborating Centre for Oral Cancer and Precancer, King's College London Dental Institute, Denmark Hill Campus, Bessemer Road, London, SE5 9RS
Correspondence to: Professor Saman Warnakulasuriya
Tel: +44 (0)20 3299 2430; Fax: +44 (0)20 3299 3426
Email: s.warne@kcl.ac.uk

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carcinogenic potency of tobacco in oral cancer by alcohol consumption is well documented.

There is also good evidence to suggest that cessation of these habits leads to reduced risk, though it may take up to ten years to reach the low risk status of never users. The main role of oral health professionals is to stimulate quit attempts among their patients using brief interventions[12] and when appropriate, to refer to cessation clinics for further treatment of tobacco dependence.[13]

EMERGING RISK FACTORS

Human papillomavirus infection (HPV)

There is sufficient evidence based on recent studies (mostly conducted in the USA)[14,15] that infection with HPV (subtypes 6 and 16) is a risk factor particularly for the oropharynx (posterior tongue, tonsil and the [visible] part of pharynx in continuity with the oral cavity). The aetiological role of HPV in cervical cancer has been well established and new data confirm that a proportion of oral and oropharyngeal cancers can be attributed to HPV infection and seropositive status (particularly among young subjects with no tobacco or alcohol history). How this virus may inoculate the oral cavity (and integrate with the oral mucosa) remains controversial and some authors have speculated sexual practices as contributory.[16]

HPV vaccines (Cervarix and Gardasil) are now available. These are not therapeutic but are expected to offer protection against cervical cancer when given to young adolescent women. Results are awaited to confirm their efficacy to reduce cancer incidence in young adult women with prior exposure to HPV, or for infections in organs other than the cervix, such as the oral cavity or oropharynx.

Immunosuppression

Lip cancer is reported to be increased following kidney transplantation[17] and is significantly associated with current use of immunosuppressive agents (azathioprine and cyclosporin).[18] Extended use of immunosuppressive agents (azathioprine) during the management of inflammatory bowel disorders (Crohn's disease) may also increase the risk of tongue cancer.[19]

Diet and nutrition

There is accumulating evidence that indicates a positive correlation between low intake of fresh vegetables and fruits and an increased risk of oral cancer. This information is relevant to our European populations as some of this evidence has been accrued in continental Europe,[20,21] including southern England.[22,23] Higher risks are also associated with high intake of meat and processed meat products.[24] An estimated 50% reduction in risk for oral cancer is noted among people who consume an adequate daily amount of fresh fruits and vegetables.[25]

Mate drinking

Mate is an infusion of the herb *Iler paraguariensis*, cultivated throughout South America. In Argentina, Uruguay, Paraguay and southern Brazil, it is normally drunk very hot through a metal straw. The role of mate drinking in increasing the risk of cancer of the oral cavity is supported by several epidemiological studies conducted in South America that adjusted for other risks. A recent meta-analysis estimated an increased risk (OR of 2.11; 95% CI: 1.39, 3.19) confirming this association.[26] The role of mate when drunk very hot is not proven but the high temperature of this beverage could act as a co-factor by causing chronic irritation to the exposed oral mucosa.

Socio-economic status

Oral cancer is seen more often in people from lower socio-economic groups and those living in deprived areas. A higher prevalence of smoking, alcohol use and poor diet in these groups was thought to account for this unequal distribution. However, new research suggests that lower socio-economic status (measured in various ways: occupation, income or education) is a significant risk factor for oral cancer independent of lifestyle behaviours.[27]

CONTROVERSIAL FACTORS WITH LIMITED EVIDENCE

Ethnicity and race

It has been speculated that susceptibility to oral cancer from tobacco and alcohol use may differ by race and ethnicity. Oral cancer incidence rates vary considerably across racial/ethnic groups in the world[1] and by ethnicity in some parts of the UK.[28] South Asians have higher rates of oral cancer than people from most other countries and black males (in the USA) have higher rates than whites for oropharyngeal cancer. Nutritional differences, smoking patterns (eg bedi smoking in Asians), difference in amounts smoked or alcohol drunk and the two-way and three-way interaction of betel quid chewing with smoking and alcohol, rather than genetic factors, may play a role in these observed variations in populations and high incidence in some ethnic and racial groups.

Oral hygiene and dentition

Although poor oral hygiene and poor dentition (faulty restorations, sharp teeth and ill-fitting dentures) have been implicated in a few epidemiological studies,[29–31] it is not clear whether confounding by tobacco and alcohol have been addressed in these studies. It is likely that chronic irritation from dental factors may facilitate exposure to carcinogens, so this may act as a co-factor in high-risk individuals only. Oral microbes (together with biofilms) may also be a factor in chronic alcohol users as some microbes facilitate the metabolism of ethanol to acetaldehyde (a potent carcinogen) in the oral cavity. This may contribute to acetaldehyde formation in the oral environment and acetaldehyde adducted to oral cancer cells among chronic alcoholics was recently demonstrated in a joint UK/Japan study.[32]

Indoor air pollution

Studies from Germany and Brazil have reported increased risks for head and neck and upper digestive tract cancers (including oral) from indoor air pollution due to daily exposure to fossil fuels from stove heating (with oil, coal or wood)[33,34] and from use of a wood stove for cooking.[35] Volatile carcinogenic compounds formed during cooking processes have been attributed to excess mortality from oral cancer among cooks in Switzerland.[36]

CITED CONTROVERSIAL FACTORS WITH INCONSISTENT EVIDENCE

Heredity and familial risk

There is no evidence to suggest that oral cancer is more common among families that have an increased risk for other

cancers. Oral cancers have not been reported in hereditary cancer syndromes such as Li-Fraumeni syndrome (breast cancer), familial adenomatous polyposis (colon cancer), familial retinoblastoma (retinoblastoma and sarcomas), Peutz-Jeghers syndrome (colorectal, breast and ovarian cancers), Gorlin syndrome (basal cell skin cancer), multiple endocrine neoplasia (MEN2) (medullary thyroid cancer), ataxia telangiectasia (AT) (lymphoma), Bloom syndrome (solid tumours), xeroderma pigmentosum (XP) (skin cancer), or in Fanconi anaemia (acute myeloid leukaemia). The only exceptions are Cowden syndrome (with a few reported cases of head and neck cancer) and dyskeratosis congenita, a rare genetic disorder that may present with oral white lesions in young people, which have a risk of transformation to cancer.[37]

So far, inherited polymorphisms that may contribute to a genetic predilection specifically to oral cancer have not been demonstrated. Despite this lack of a clear hereditary trait for oral cancer, cancer cells (from oral cavity cancers) contain genetic damage (eg gene mutations and chromosomal deletions) due to environmental exposure to carcinogens and should be considered a genetic disease.[38]

Marijuana (cannabis) smoking

Marijuana is the most commonly abused illicit drug in most countries, usually smoked as a 'joint' or in a pipe. It is also smoked in blunts, which are cigars that have been (partially) emptied of tobacco and refilled with marijuana and possibly combined with tobacco ingredients. An increased risk for head and neck cancer was reported in the US by Zhang *et al.*[39] but there is no consistent evidence to implicate cannabis as causing oral cancer. Any causal inference shown could be due to interaction with heavy tobacco use. Data from a group of young people diagnosed with oral cancer in southern England showed no association.[22,23]

Khat (qat) chewing

Khat (*Catha edulis* Forsk) is a plant cultivated in territories of Somalia, Ethiopia, Djibouti, South and North Yemen, Madagascar, Tanzania and down to south eastern Africa. Khat leaves are extensively consumed by these populations. Its use is increasingly reported among ethnic migrants from Somalia to the UK.[40] There are a few case reports (or case series) of oral leukoplakia and cancer suggesting an association with khat use.[41,42] So far, no epidemiological studies on oral cancer and khat use have been reported and there is no evidence to link khat chewing with oral cancer. Evidence from experimental studies is also limited and there are no *in vivo* data to show any carcinogenicity of khat in animal models.

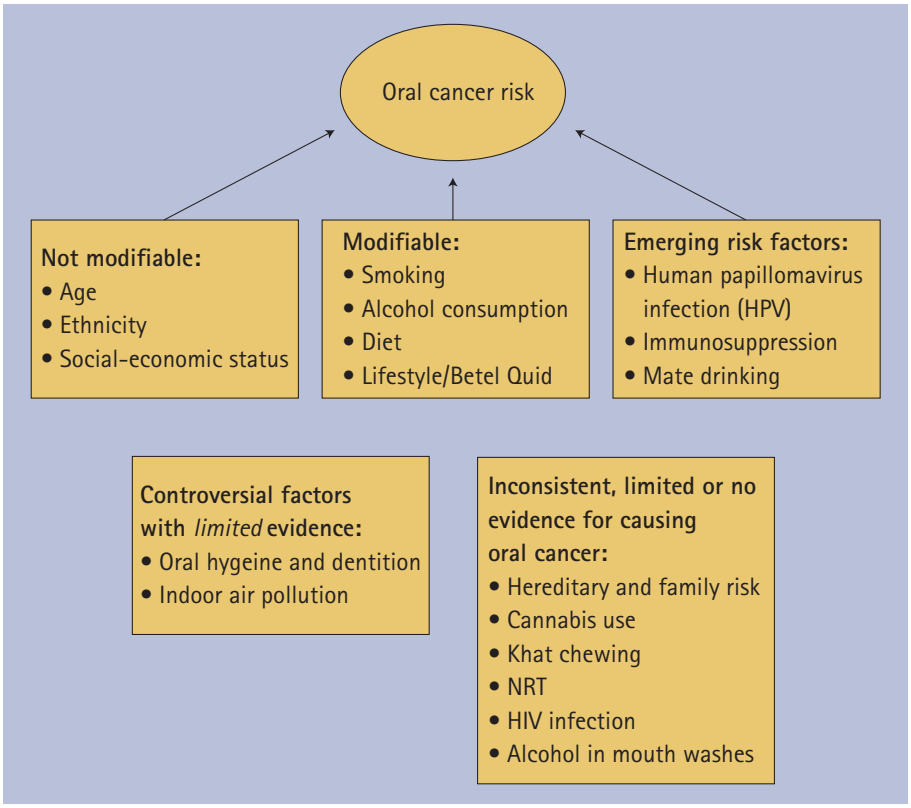

Fig. 1 Factors influencing risk of oral cancer and those with no scientific evidence

Nicotine replacement therapy (NRT)

There is some confusion in the minds of professionals and patients as to whether nicotine replacement therapy could have the potential to cause cancer as these agents contain pure nicotine. There is no clear evidence that medicinal nicotine causes cancer. A recent study based on surveillance data among patients with chronic obstructive pulmonary disease in the US found no independent increased risk for any cancer among NRT users.[43] The authors, however, noted that the surveillance time in this study was short (five years).

HIV infection

Though it was conceived before the era of highly potent antiretroviral therapy that moderate immunosuppression in HIV disease could increase the risk for oral cancer, there is no strong epidemiological evidence based on cohort studies to confirm an association of HIV infection or AIDS with oral squamous cell carcinoma.[44] Oropharyngeal cancers with a known infective cause (HPV) may be moderately increased in people with HIV disease but the excess risk could also be attributable to tobacco use. However, it is important to note that two different neoplasms are associated with HIV disease, Kaposi sarcoma and lymphomas, but these are normally not listed under the term oral cancer.

Alcohol in mouthwashes

There has been some controversy about the risks of alcohol containing mouthwashes (MW) for the causation of oral cancer. While an earlier study from the USA distinguished non-alcohol MW from alcohol containing MWs in their study[45] and reported an increased risk for subjects in the latter group, other studies have not considered this distinction in MW use. In addition to the Winn *et al.*[45] study referred to above, of the eight epidemiological studies available to examine any associated risks, two showed significant increases,[46,47] two showed non-significant

elevated risks[14,48] and four studies indicated non-significant, lower or similar oral cancer risks among mouthwash users (compared to non-users).[49–52] In addition to a lack of a consistent association, a dose-response has not been established.

McCullough and Farah[53] in a non-systematic, narrative review of selected studies found sufficient evidence linking mouth cancer with alcohol-based mouthwash use. However, the most recent meta-analysis conducted by a reputable group of epidemiologists in Europe[54] confirmed that there is no excess risk for oral cancer from mouthwash use (with or without ethanol). Unpublished pooled data from seven studies illustrates the lack of any significant association (OR 1.13; 95% CI 0.89, 1.44) for mouthwash use and oral cancer. Their conclusion supports a previous evaluation by Lewis and Murray[55] who found no association of mouthwash use and oral cancer. These recent analyses taken together with a report from the US Food and Drug Administration (FDA) subcommittee findings[56] appear to conclude that the available data do not support a causal association between the use of mouthwashes and oral cancer.

It has been speculated that mouthwash use in people who developed oral cancer was a measure to mask their tobacco smell or was initiated after the development of symptoms in an attempt to control the disease.

CONCLUSION

To prevent cancers of the oral cavity it is important for dentists to recognise the major risk factors that are appropriate for the population. This article provides evidence on established and modifiable risk factors (Fig. 1). As interventions should be based on good scientific evidence it is important to take into consideration reported controversies. This paper provides scientific information based on current evidence to allow dentists to disregard factors for which available epidemiological evidence is either weak or not suggestive. Clearing some myths on factors considered non-relevant to this cancer is important so that information provided to the patients and the public is not misleading and paves the way to plan strategies for prevention.

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