Aetiology of oral cancer

SADJ November 2012, Vol 67 no 10 p554- p556

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SUMMARY

Oral cancer (OC) and oral squamous cell carcinoma (OSCC) are used interchangeably, as more than 95% of all OCs are OSCCs. Worldwide up to 275 000 new cases of OC are seen every year. Most of these cases are seen in developing countries such as South Africa. Up to 50% of all patients living with OC will die within five years, and this survival rate has not improved over the last few decades. Tobacco and alcohol usage account for up to 75% of all OC cases. As these causative factors can be avoided, all oral health workers should be aware of the aetiology of OC so that sound preventive advice may be given to their patients.

Infections and nutrition play a lesser but still important role in the aetiology of OC. This article reviews the importance of the aetiology of OC, with the emphasis on tobacco and alcohol.

INTRODUCTION

Oral cancer affects up to 275 000 new patients per year.[1] Oral squamous cell carcinoma (OSCC) and oral cancer (OC) are used synonymously, as most OC's are in fact OSCCs.[2] The survival rate of oral cancer has not changed significantly over the last 50 years and up to 50 % of patients will succumb to this disease within five years.[1]

The first step in the process of carcinogenesis will often be a DNA mutation. These are increased by certain exogenous risk factors, such as tobacco and alcohol.[3] Although these two remain the most commonly seen risk factors, causing up to 75% of oral cancers, infections and nutrition can also play a role.[3,4] Betel quid chewing (with or without the addition of tobacco) is also an important aetiological factor in oral cancer.[3,5,6] The prevalence of smoking (1.25 billion people), alcohol drinking (2 billion people) and betel quid chewing (up to 1.2 billion people) worldwide, places numerous individuals at the most serious risk of oral cancer.[3,6-8] The usage of betel quid is fairly common amongst the Indian community.

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ACRONYMS

ADH:	Alcohol Dehydrogenase
ALDH:	Aldehyde Dehydrogenase
HPV:	Human Papilloma Virus
OC:	Oral Cancer
OSCC:	Oral Squamous Cell Carcinoma
OSF:	Oral Sub-mucous Fibrosis

In South Africa we have one of the largest Indian populations outside of India and in KwaZulu Natal province; Indian female betel quid chewers outnumber male chewers in the ratio 13:1.[6,9]

TOBACCO

The use of tobacco, whether being smoked or chewed, is on the increase in the developing world, which includes South Africa. All tobacco products are carcinogenic and can be considered aetiological factors in the development of oral cancer.[8,10] There are thousands of constituents within tobacco, too numerous to list,[8] but the most important are the N-Nitrosamines.[8] Blot *et al.* found that drinking alcohol and smoking in combination will increase the risk of oral cancer, but each independently is also a separate causative factor.[7] There appeared to be a strong dose-response effect in their study, with the adjusted odds ratios for moderate smokers at 2.8, and for heavy smokers at 4.4.[7]

Smokeless tobacco is also a major risk factor for oral cancer.[6-8,10] It may be taken orally or nasally, and the more well-known products include snuff (nasal intake) and betel quid (oral intake).[6,8] Tobacco chewing dates back to the 15th century, when it was used by the native people of South America to quench thirst and whiten teeth.[8] Exposure to tobacco products over a prolonged period of time will lead to DNA mutations within epithelial cells, which may cause genetic instability and ultimately lead to oral squamous cell carcinoma.[11]

The prevention of smoking remains the most important strategy in lowering OC rates.

BETEL QUID

Betel quid usually refers to the areca nut (normally shavings of the nut), which is mixed with slaked lime and rolled in the betel leaf. It may contain tobacco.[6] The important chemical constituents of the areca nut are the polyphenols and the alkaloids.[6]

A workshop held in Kuala Lumpur in 1996 and published as a consensus report, defined the term "quid" as "*a substance, or mixture of substances, placed in the mouth or chewed and remaining in contact with the mucosa, usually containing one or both of the two basic ingredients, tobacco or areca nut, in raw or any manufactured or processed form*".[11] One should thus reserve the term "Betel quid" to describe a quid which contains the betel leaf. The betel quid is often referred to as betel-nut, which is incorrect. What is clear from the consensus report is that many categories of quid exist, and one should always describe the exact nature of the quid.

Category 1 may be further sub-divided into quid containing only areca nut, or quid containing areca nut rolled in betel leaf but no tobacco. Category 2 may be further sub-divided into quid containing only tobacco, tobacco mixed with lime, burned tobacco applied to gingiva and teeth (mishri), a type of tobacco snuff (niswar) and others. Category 3 may be further sub-divided into betel quid with tobacco and into areca-lime-tobacco mixture.[11]

The workshop came up with a description of five different lesions associated with quid usage, namely; chewer's mucosa, areca nut related lesion, quid induced lesion, oral sub-mucous fibrosis (OSF) and betel-quid lichenoid lesion.[11] OSF is regarded as a potentially malignant disorder which may develop into oral cancer. OSF usually presents with palpable fibrous bands in the sub-mucosa, a blanched appearance of the mucosa and a leathery feel to the mucosa when palpated.[9,11] Dental practitioners should be familiar with this clinical picture and be vigilant when examining patients of Indian or Asian descent. This is of major relevance in South Africa with its large Indian population.

ALCOHOL

The main substance of all alcoholic beverages is ethanol. Although there is a lack of clear experimental evidence for pure ethanol to be considered a carcinogen, alcoholic beverages are important in the aetiology of oral cancer with a dose-responsive relationship found by most researchers.[2,7,12-15] Consumption of alcohol (ethanol), including so-called "binge drinking", is widespread in most communities worldwide.[2,16] Alcohol is also one of the most common forms of drug abuse and has been causally related to more than sixty different medical conditions.[2,3] Alcohol consumption may increase the risk of OC with odds ratios of 3.0-14.8.[2] There also appears to be a cumulative effect of alcohol intake on OC and long-term drinkers are at much higher risk.[15]

The approximate global daily consumption is in the region of 14 grams ethanol (between one and two drinks per day) per adult (e.g. one drink can be: 330ml bottle of beer, 150ml of wine, or 36ml of spirits).[2,12,16] Ethanol and water are the main components of most alcoholic beverages, which also contain volatile and non-volatile flavour compounds.[16] Specific alcohol beverages have also been shown to contain impurities or contaminants that can also be carcinogenic. N-nitrosodimethylamine is present in some beer and whiskies and is associated with an increased risk of oral cancer.[16,17] Polycyclic aromatic hydrocarbons, some of which considered to be carcinogenic, are found in many brands of whisky.[16]

The major alcohol-metabolising enzymes in the body are alcohol dehydrogenase (ADH), which oxidises ethanol to acetaldehyde (a known carcinogen) and aldehyde dehydrogenase (ALDH), which detoxifies acetaldehyde to acetate.[2,16] Acetaldehyde is responsible for the carcinogenic effect of ethanol due to its multiple mutagenic effects on DNA.[16] Genetic variations in the activities of the enzymes (ADH and ALDH) may influence the outcome of exposure to alcohol and its carcinogenicity.[3] The role of micro-organisms in the conversion of alcohol to acetaldehyde within the oral cavity is addressed later in this article.

It has also been suggested that ethanol may increase the penetration of carcinogens across the oral mucosa. This may be through intercellular passage of carcinogens entering the oral mucosa or alternatively by increasing the permeability of the epithelial cell membranes. Different levels of concentration of ethanol apparently carry similar levels of risk for oral cancer.[12]

A not-insignificant number of oral cancers arise in people who do not smoke or drink and that has prompted consideration of other sources of alcohol (e.g., mouthwashes). Friederich and Kristen (2003) found that many mouthwashes were cytotoxic.[12] In a more recent study it was shown that the regular use of mouthwashes containing alcohol could raise the levels of acetaldehyde in the oral cavity to levels similar to those seen after the consumption of alcohol-containing beverages.[18] One could speculate that people who use mouthwashes do so because they have higher bacterial loads and thus are at higher risk for acetaldehyde formation in the mouth (see role of infectious agents below).

Other factors that require investigation include the influence of type, quantity and years of exposure to alcohol, as well as whether nutritional or haematologic deficiencies influence such results.[12] Greater education of the public and professionals (both medical and dental) is necessary to create a greater awareness of the potential association between OC and alcohol.[12]

TOBACCO AND ALCOHOL

It is an accepted fact that alcohol consumption and smoking can separately increase the risk for OC.[7] There is a greater than joint multiplicative risk for OSCC in people who are both alcohol drinkers and heavy tobacco smokers.[7,14,19] The combination of heavy smoking (more than 40 cigarettes per day) and heavy drinking (more than four alcoholic drinks per day) may increase the risk for oral cancer by more than 35-fold.[7]

Ethanol damages the phospholipids of cell membranes and increases permeability, enhancing the penetration of tobacco-specific carcinogens across the oral mucosa.[15,16] Ethanol also impairs DNA repair mechanisms and acts as a solvent, allowing the carcinogens from tobacco to penetrate into tissue, possibly catalysing their activation.[15,16] Smoking increases the acetaldehyde burden following alcohol consumption. Alcohol- drinking also enhances the activation of pro-carcinogens present in tobacco due to increased metabolic activation by the cytochrome P450-dependent microsomal biotransformation system in the mucosa and liver.[19]

DIETARY FACTORS

Eating fruits and vegetables is believed to reduce the risk of cancer, including oral cancers.[3] Yellow/orange vegetables

and diets varied in vegetables and fruit are of benefit in protection against OC.[19] A study from Italy showed that during an eight-year period, the daily consumption of six or more plant foods, fruits, cereal, olive oil, wine and low intake of meat and dairy products gave protection against oral and pharyngeal cancer when compared with those whose daily intake of these Mediterranean-type dietary items was less.[3]

Alcohol is highly calorific. It lessens the protective effect of beneficial foods such as fruits and vegetables, by depressing hunger.16 There also seems to be an inverse relationship between high coffee intake and OC, with coffee providing a protective effect against OC.[20]

INFECTIOUS AGENTS

Several oral microorganisms can produce carcinogenic acetaldehyde from alcohol.[3] Poly-microbial supra-gingival plaque, which includes both oral streptococci and Neisseria, has mutagenic interaction with saliva and may synthesise acetaldehyde from alcohol.[19] This may explain why poor oral hygiene is often associated with oral cancer in heavy drinkers and smokers. Their salivary acetaldehyde concentrations are significantly increased along with their poor oral hygiene.[3] In a recent study, periodontitis was found to be an additional risk factor for leukoplakia, independent of smoking and with a dose-dependent relationship. Leukoplakia is a potentially malignant disorder and this link with periodontitis needs further investigation.[21]

Candidal leukoplakias may sometimes develop into carcinomas because nitrosamines produced by candida may activate specific pro-oncogenes.[3] Added to that, candida may also convert ethanol into carcinogenic acetaldehyde.[3]

Human Papilloma Virus (HPV) has been linked to oropharyngeal cancer as well as OC.[22,23] In a recent meta-analysis it was found that HPV[16] was strongly related to OC.[22] In contrast, Boy *et al*. (2006), in their study on the detection of HPV in OC, found that laboratory techniques could be blamed for certain positive results and that HPV was probably not important in the pathogenesis of OC.[24]

CONCLUSIONS

It is worth noting that certain types of alcoholic beverages have been found to be more carcinogenic than others. This may well be attributable to the dominant beverage consumed within a specific study population and not actually reflect the true carcinogenic potential of that specific beverage. It is common knowledge that certain communities will prefer beer over wine or spirits and vice versa. South Africa has more beer drinkers than wine and spirits combined.[2] Thus it would not be possible to claim that beer is more carcinogenic than wine, if the study group consisted of beer drinkers. Cognisance has to be taken of the fact that in South Africa there is a substantial amount of home brewed alcohol consumed. The carcinogenic potential of this is as yet undetermined. The same applies to self-rolled cigarettes, using non-commercial products, i.e. newspaper rolled cigarettes and home-made pipes with no filters.

The dentist and oral hygienist remain the only healthcare workers who routinely examine the oral cavity and are trained to diagnose OC. The history of a patient regarding exposure to aetiological factors should serve as an initial pointer to high risk groups.

Declaration: No conflict of interest declared

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