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Oral cancer aetiopathogenesis; past, present and future aspects

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Abstract

Oral cancer appears to be increasing in incidence, and mortality has hardly improved over the past 25 years. Better understanding of the aetiopathogenesis should lead to more accurate and earlier diagnosis and more effective treatments with fewer adverse effects. Cancer is the result of DNA mutations arising spontaneously and from the action of various mutagens, especially in tobacco and alcohol. A sequence of genetic changes leads eventually to loss of growth control and autonomy.

Countering these changes are mechanisms to metabolise carcinogens, repair DNA damage, control growth, and defend against cancer. Cancer is a consequence of an interaction of these many factors. Diagnosis is increasingly aided by detection of cellular and now molecular changes. Treatment is increasingly looking towards chemotherapy and now gene therapy. However, there is no doubt that prevention is the most important aspect, particularly patient education and the reduction of lifestyle risk habits and environmental factors.

Key words: *Oral cancer; tobacco, alcohol, betel, prevention, diagnosis.*

Introduction

This paper is an overview, setting the stage for fuller in-depth papers in this issue on aetiopathogenesis of oral squamous cell carcinoma - the most common oral malignant neoplasm.

Oncogenesis (carcinogenesis) is the progression from a normal healthy cell to a pre-malignant or a potentially malignant cell - characterised by an ability to proliferate autonomously. Oncogenesis involves a series of genetic steps and also epigenetic -outside the gene - changes. These changes include the aberrant expression and function of molecules regulating cell signalling,

growth, survival, motility, angiogenesis (blood vessel proliferation), and cell cycle control.

The fundamental but grossly oversimplified concept of the genetic mechanism behind cancer is the over-expression of oncogenes and/or the silencing of tumour suppressor genes (TSGs). Cell cycle control is disturbed particularly by over-expression or over-activity (amplification) of oncogenes which drive cell proliferation. Working more towards cell protection are the TSGs. One of the most important of the TSGs is P16 which acts as a checkpoint in growth control. Another important TSG is P53, which will usually either repair a poten-

tially malignant cell or it will destroy it (by apoptosis). However, multiple oncogenes and TSGs are involved in carcinogenesis. Microarray technology has given researchers the ability to produce large amounts of data from nearly the entire known human genome, and has shown that many changes in genes can be involved in oncogenesis. Changes in over one hundred genes have now been implicated in some cancers.

-Oncogenes

The over-expression of oncogenes -such as the epidermal growth factor receptor (EGFR) gene – can promote growth, survival, and spread of cells - leading to the development of cancer. The range of oncogenes identified is quite broad, and the mechanisms by which they act are complex.

-Tumour Suppressor Genes

Tumour Suppressor Genes (TSGs) are genes that normally function in growth control - by regulating the cell cycle, programmed cell death (apoptosis), cell adhesion, and DNA repair. TSG function can be disturbed by aberrations such as deletions or mutations in TSG genes, or by TSG silencing from hypermethylation, and any of these changes can lead to cancer.

-Single nucleotide polymorphisms

Single nucleotide polymorphisms (SNPs) are gene areas that have altered DNA sequences which may not lead to an aminoacid alteration, or altered DNA sequences that do not seem to have any adverse effect in 'normal' individuals but may be markers for disease predisposition, or may be used to genetically identify patients, as they tend to cluster with ethnic background. SNPs in TSGs, xenometabolising enzymes, and DNA repair enzymes may also play a role in cancer development - at least in some individuals.

Cancer risk factors

DNA mutations occur spontaneously, especially via damage by oxidation and chemical free radicals. The rate of DNA mutations however, is vastly increased by various cancer risk factors - mainly exogenous factors: tobacco and alcohol appear particularly important. In some cases, chemicals, radiation (e.g. sunlight, ionising), infections, diet (some aspects can harm and some protect) or immuno-incompetence are relevant.

- Lifestyle factors

The aetiology of oral cancer is multifactorial the most important risk factors being tobacco, excess consumption of alcohol and betel quid usage, factors which act separately and synergistically. Often it is these lifestyle factors that are the most important in predisposing to cancer but in some instances of cancer, environmental and genetic factors may also play a role to varying degrees.

Most people have their cancer risks greatly increased by exposure to tobacco and/or alcohol or betel. These

adverse lifestyle behaviours are widespread: worldwide 2 billion people consume alcohol; 1 billion men and 250 million women smoke cigarettes; and 600 -1,200 millions people chew betel quid. Much oral and other cancer therefore is potentially preventable by lifestyle change.

The risk of developing oral cancer increases with advancing age, most cases occurring in people aged 50 years or over (1). However, about 6% of oral cancers occur in young people under the age of 45 years (2) and, in high incidence countries of the world, many cases are reported before the age of 40. A rising incidence in oral and oropharyngeal cancer in young adults was first reported in Scotland and Denmark and subsequently in many countries in the European Union and in United States of America (3-6)

Among young people (defined as under the age of 45 years) there is a sub-group of patients (about 25%) not exposed to the known major risk factors, in whom other factors such as human papillomavirus (HPV) infection may be involved - particularly for tonsil and oropharynx carcinoma (7, 8)

• Tobacco

Tobacco use is widespread worldwide and increasing in the developing world. All forms of tobacco are carcinogenic and capable of causing oral and pharyngeal cancer (9-12).

Tobacco generates carcinogens (cancer-causing chemicals), such as the TSNAs - tobacco-specific nitrosamines (e.g. NNN, NNK, NAT and NAB), and free radicals that can impede antioxidant enzymes (glutathione-S-transferase (GST), glutathione reductase, superoxide dismutase, catalase, and glutathione peroxidase). In people who smoke tobacco, and thereby expose their upper aerodigestive tract to tobacco carcinogens, genetic changes affect the whole of the aero-digestive mucosae (mouth, nose, pharynx, trachea, bronchi, lungs) and persist for many years, even if the patient stops smoking. Potentially malignant disorders (PMDs), and second primary tumours (SPTs) are found in the upper aerodigestive tract in over 20 per cent of patients (13). There is also an increase in tumours elsewhere, presumably because carcinogens are absorbed and circulate in the blood to other organs, and there are many other possible adverse health consequences. Cigarette smoking is particularly linked also for example, to chronic obstructive pulmonary disease, atherosclerotic heart disease, and cancers of the lung, oesophagus, and bladder (12).

• Betel

Areca nut (betel) chewing is a habit of something like 20 per cent of the world's population, especially Asian communities. Similar chewing habits such as khat use may also be implicated in some communities. In people who use betel there can be changes in the mouth and also pancreas and many other organs (14-16).

The carcinogenicity of other psychotropic products such as marijuana is more controversial.

- Alcohol

Alcohol (ethanol) use is widespread in most communities worldwide, save Islamic and other communities such as seventh day Adventists. In people who drink alcohol, the upper gastrointestinal tract is exposed to alcohol, as is the liver (which can be damaged and may also result in cancer there), and there are often other medical and social sequelae. Alcohol is the most common drug of abuse, has been shown to be causally related to more than sixty different medical conditions. Some of these conditions, such as suicide, homicide, different forms of accidents (e.g., falls, poisoning, accidents) are acute consequences of alcohol use. Other conditions, such as liver cirrhosis, chronic pancreatitis, haemorrhagic stroke and various cancers are consequences of chronic alcohol use (17).

Alcohol may be carcinogenic via various mechanisms but an important route is by its oxidation to acetaldehyde (a carcinogen) by enzymes (alcohol dehydrogenases; ADHs). Acetaldehyde is then degraded to acetate by aldehyde dehydrogenases (ALDH). Genetic variations in the activities of these enzymes (ADH and ALDH) may influence the outcome of exposure to alcohol, and its carcinogenicity.

- Tobacco and alcohol

Smoking increases the acetaldehyde burden following alcohol consumption and alcohol-drinking enhances the activation of pro-carcinogens present in tobacco. Tobacco and alcohol use have an additive carcinogenic effect, and these lifestyle habits often co-exist. Attributable risk of oral cancer due to tobacco and alcohol combined is estimated to be more than 80%. Heavy drinkers and smokers have 38 times the risk of abstainers from both products.

-Infectious agents

- Bacterial infections

Poor oral hygiene may be an independent risk factor for oral cancer. Patients with oral cancer often present with poor oral health i.e. carious teeth and periodontitis. The number of teeth lost has been associated with cancer but oral health related variables also link with use of tobacco and alcohol. This confounding factor is difficult to control for in epidemiological studies (18). Nevertheless, periodontal disease has been shown to increase the statistical risk for head and neck cancer and the association persisted in subjects who never used alcohol or tobacco. Periodontitis patients were also more likely to have poorly differentiated oral squamous cell carcinomas than did periodontally healthy patients (19). Interestingly, practicing no regular oral hygiene also conferred a risk for oesophageal cancer (20).

Several oral micro-organisms can produce carcinogenic acetaldehyde from alcohol (21). This may explain why

poor oral hygiene is often associated with oral cancer in heavy drinkers and smokers; namely their salivary acetaldehyde concentrations are significantly increased along with their poor oral hygiene (22). It remains to be shown if controlling these bacteria could affect the incidence of oral cancer.

- Candidiasis

Candida albicans is the yeast most commonly isolated from the oral cavity but increasing numbers of non-*albicans* *Candida albicans* (NACA) are seen - particularly in medically compromised patients. *Candida* in general is more prevalent on carcinoma lesions than on healthy mouth mucosa: NACA strains have emerged increasingly in oral cancer patients. Yeasts may invade oral epithelium and may be causally involved in dysplastic changes. Candidal leukoplakias may sometimes develop into carcinomas. Nitrosamines produced by *Candida* may activate specific proto-oncogenes. Malignant transformation however, is often also associated with other risk factors such as smoking and alcohol. Hence a synergistic effect with candidosis and life-style factors may exist in oral carcinogenesis. *Candida* also efficiently converts ethanol into carcinogenic acetaldehyde (23-25). However, there are no studies showing that control of *Candida* would affect the incidence of oral cancer.

-Virus infections

- Human papillomavirus infections

Currently more than 100 types of human papilloma viruses (HPV) are known. HPV-6, -11, -16, -18, -31, -33, and -42 have been isolated from the oral cavity. HPV-16 and HPV-18 and others are regarded as carcinogenic. HPV-16 and -18 have been the most common virus types identified in oral carcinoma (26-30)

HPV-associated oropharyngeal cancers appear to be less associated with tobacco or alcohol use, but more associated with marijuana and oral sex, and to have a better prognosis (8, 31-38).

- Herpes viruses

Herpes simplex viruses (HSV) have also been associated with carcinogenesis. HSV nucleic acids have been found in lip cancer (39), antibody levels to HSV-1 and -2 are higher in oral cancer patients when compared with controls, and HSV seropositivity together with smoking has been associated with increased cancer risk (27).

Epstein-Barr virus has also been implicated in oral cancer but the evidence thus far is controversial (40-45).

-Dietary factors

Eating fruits and vegetables is believed to reduce the risk of cancers, including oral cancers. One US study showed an inverse association between total fruit and vegetable intake and 5-year incidence of head and neck cancer (46). The so-called Mediterranean diet has been shown to be particularly associated with a reduced cancer risk. One study from Italy showed, for example, that during an 8-year period the daily consumption of six

or more plant foods, fruits, cereals, 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 (47). This suggests a diet deficient in antioxidants is a further factor that predisposes towards the development of oral cancer and for precancer (48-50).

Randomised Clinical Trials (RCTs) are needed to explore the effectiveness of dietary supplementation to reduce the risk of oral cancer by chemoprevention as well as to reverse oral PMDs (leukoplakia and erythroplakia) among high risk groups.

-*Social and economic status (SES)*

A recent meta-analysis has shown that low social and economic status (SES) and deprivation, are significantly associated with an increased risk of oral cancer. Compared to those with high SES strata pooled ORs for those with low educational attainment were 1.85 (95%CI 1.60-,2.15), for those with low occupational social class 1.84 (95%CI 1.47-2.31) and for those with low income 2.41 (95%CI 1.59-,3.65) with the highest rates occurring in the most disadvantaged sections of the population. These associations were particularly strong for men (51).

An exception is the young group in whom 25% are from professional classes (52, 53).

- *Environment*

Environmental factors, for example, ionizing radiation from natural or therapeutic sources or nuclear accidents (e.g. the Chernobyl accident) may contribute to cancer risk but data are scarce for oral cancer.

- *Genetics*

Genetic variation in mechanisms protective against cancer may also be implicated in oral carcinogenesis. Such protective mechanisms that may fail and predispose to cancer include the genes for the liver enzymes (xenobiotic metabolizing enzymes; XME) that degrade chemical carcinogens; genes with the ability to repair DNA mutations (DNA repair genes); genes that result in the repair of damaged growth control or the controlled death of cancerous cells (TSGs); and genes related to immune protection.

For example, patients suffering from Li Fraumeni syndrome have a genetic predisposition to develop multiple tumours due to an inherited mutation in one allele of the p53 locus which results in susceptibility to develop sarcomas and other tumours in successive generations. Patients suffering from Fanconi anaemia, a recessively inherited disease characterized by congenital anomalies and bone marrow failure, have a predisposition to develop cancer, particularly squamous cell carcinomas in the head and neck and anogenital regions (54).

These and other genetic factors such as oncogenes may well help explain differing susceptibilities of individual

people to cancer - causing the varying effects of known risk factors such as tobacco and alcohol. Thus there are at one extreme end of the spectrum, patients who with their families can be at high risk of cancer whatever their exposure to known risk factors, while at the other end of the spectrum are some people apparently unharmed by exposure to large amounts of known risk factors.

Early diagnosis

There is abundant evidence that early diagnosis would reduce the morbidity and mortality from oral cancer. Increased clinical suspicion and the introduction of diagnostic aids may help achieve earlier diagnosis.

The drawbacks of conventional histopathology are becoming evident, along with the human limitations in diagnosis in this as in many other fields of medicine. This is especially the case in tissue biopsies from close to previous suspicious lesions in the upper aerodigestive tract (55).

Hopefully, molecular examination of tissue might prove useful in, for example, examining biopsies from PMDs; from tumour surgical margins that appear histologically clear, and to detect clinically undetected lymph node metastases (56-63).

The most predictive of the tissue molecular markers thus far available and assessed in oral cancer development (64) include the TSG p53 protein expression, and changes in chromosomes 3p or 9p (probably due to changes in the TSG p16).

The use of these markers as an adjunct to routine histopathological examination may eventually help in prognostication and effective management of these lesions but routine use is hampered thus far by the cost and complexity of the tests, the lack of facilities in some laboratories, and limited outcome studies (65).

Prevention

At least three-quarters of oral cancers could be prevented by the elimination of risky lifestyles such as tobacco smoking and alcohol consumption. Smoking cessation contributes to reducing the risk of oral cancers, with a 35% reduction in risk within 1-4 years and 80% reduction of risk by 20 years, reaching the level of never smokers (66).

Treatment of tobacco dependence is an important step to reduce oral cancer in high risk groups. Tobacco cessation among high-risk patients ie those with potentially malignant disorders need to be addressed through the primary care practitioners (including dentists) and where possible with assistance from specialist smoking cessation clinics (67).

Protection against solar irradiation could further reduce the incidence of lip cancers. Vaccination against HPV among young adults might affect oropharyngeal cancers (68) as might use of condoms.

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