

Precipitants of oral cancer in India

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ABSTRACT

Oral cancers are malignant neoplasms that affect the mouth. Oral cancer remains a major personal tragedy and public health problem. There is a very high incidence of oral cancer in Southern Asia. In India, the oral cavity is the most common site for cancer. The majority of oral squamous cell carcinomas are related to tobacco, areca nut / betel quid chewing, alcoholism. Control of oral potentially malignant diseases will only be achieved by effective and comprehensive primary and secondary prevention by recognizing that the risk factors are common to most other diseases.

Key words: India, oral cancer, risk factors

INTRODUCTION

Oral cancers are malignant neoplasms that affect the mouth. They may be a primary lesion that originated in the mouth, metastasis from a distant site, or an extension from adjoining site. Globally, “oral cancer” is the eighth most common cause of cancer-related deaths.^[1] Of these oral cancers, more than 90% are squamous cell carcinomas arising in the mucous membranes of the mouth and oropharynx. There is a very high incidence of oral cancer in Southern Asia. In India, Bangladesh, Pakistan, and Sri Lanka, the oral cavity is the most common site for cancer and accounts for approximately one-third of all cancers.^[2]

The mean age of presentation of oral cancer is in the fifth and early sixth decades in Asian populations, compared with the seventh and eighth decades in the North American population.^[3] An alarming increase in incidence of oral cancers among younger people has been reported from many parts of the world, a trend that appears to be continuing. About 4–6% of oral cancers now occur at ages younger than 40 years.^[4] Asians are more likely to develop

malignancies in the buccal mucosa, reflecting their continued areca- and tobacco-chewing habits. A study in Mumbai, India,^[5] indicated a decreasing trend in oral cancer incidence among Indian men. However, there continues to be a high prevalence of smokeless tobacco use among young adult men and women, especially in the form of pan parag/gutka-type products, and cigarette smoking is increasing.

The term “oral potentially malignant disorders” (OPMD) was recommended by an International working group convened by the WHO Collaborating Centre for Oral Cancer and Pre-Cancer in London in 2005.^[6] It indicates that not all disorders will transform to invasive cancer – at least not within the lifespan of the affected individual. Leukoplakia, erythroplakia, oral sub-mucous fibrosis, lichen planus, palatal lesions in reverse smokers, actinic keratosis, discoid lupus erythematosus, dyskeratosis congenita, and epidermolysis bullosa fall into this broad definition of “OPMD.”^[6] Estimates of the global prevalence of oral potentially malignant disorders range from 1–5%.^[7] Wide geographical variations across countries and regions are mainly due to differences in socio-demographic characteristics, the type, and pattern of tobacco use and clinical definitions of disease.

The age and gender distribution of oral potentially malignant disorders varies considerably, mainly dependent on lifestyle and on geographical location and ethnicity. In the developed world, leukoplakia is usually found between the fourth and seventh decades of life, but in the developing world, it is found some 5–10 years earlier.^[7] Females are less

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commonly affected, largely reflecting greater use of relevant habits in men. A classic study of over 30,000 Indian villagers, performed in the 1970s with follow-up over 7 years, showed transformation rates between 10 and 24/100,000 per year.^[8]

ETIOLOGY OF ORAL CANCER AND OPMD

The majority of oral squamous cell carcinomas are related to tobacco, areca nut/betel quid chewing, alcoholism. In the developing world, use of tobacco and areca nut, either alone or in combination, accounts for the vast majority of oral cancers and oral potentially malignant disorders.^[9] Also, poor oral hygiene because of increased microbial load and chronic trauma from ill-fitting dentures or sharp restorations can contribute to OPMD.

A betel quid generally contains betel leaf, areca nut, and slaked lime and may contain tobacco. Betel quid with or without tobacco is considered carcinogenic to humans, with a risk of developing oral cancer and oral potentially malignant disorders. Slaked lime (calcium hydroxide) is added to betel quids in most of South Asia. When added to betel quids, it causes erosion of oral mucous membranes, facilitating penetration of betel quid carcinogens through the mucosa. Meta-analysis of 10 previous studies indicates that betel quid chewing without tobacco, adjusted for smoking, has an odds ratio of 3.5.^[10] Betel leaf contains betel oil, contains several phenols. These compounds to some extent have antioxidant properties. However, the presence of such phenols does not justify use (mastication) of these substances. Apart from leaf, other parts of the vine such as the stem, inflorescence (flowers or pods) are consumed with areca nut in some cultures. Betel inflorescences contain a high concentration of phenolic compounds, including eugenol, isoeugenol, and safrole. Safrole, classified as a weak carcinogen in rats, is banned as a food and cosmetic additive by the Food and Drug Administration in the USA. However, there is no direct evidence for its carcinogenicity in man.

Areca consumption is common in India. The major constituents of the nut are carbohydrates, fat, proteins, fiber, polyphenols (flavonols and tannins), alkaloids, and minerals. The nuts contain at least 6 related alkaloids, of which 4 (arecoline, arecaidine, guvacine, and guacoline) have been well characterized.^[11] Nitrosamines are produced by nitrosation of the alkaloids in dried-stored nuts, when in the mouth, in the presence of nitric oxide generated by bacteria. Endogenous nitrosation is significantly higher in subjects with poor oral hygiene as determined by volumes of dental plaque.^[12] On the basis of the availability of substrates from both areca nut and tobacco, there is more extensive formation of nitrosamine in subjects with poor oral hygiene if they also chew tobacco. Generation of reactive oxygen

species, such as the hydroxyl radical (HO), in the oral cavity by auto-oxidation of polyphenols contained in areca nut has been reported.^[13] A variety of packaged areca products are now available. These are mostly manufactured in India and Pakistan, and are exported worldwide. The most common are gutka and pan masala.

Tobacco is often added to the betel quid mixture. Edible tobacco in the Indian sub-continent is prepared from sun-dried, partly fermented, coarsely cut leaves of *Nicotiana rustica* and *Nicotiana tabacum* without further processing. Chewing tobacco results in local exposure of oral mucosa to at least 16 carcinogens, including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons.^[14] Unusually, high levels of carcinogenic tobacco-specific nitrosamines [e.g. N-nitrosornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)] were reported in the saliva of tobacco chewers in India.^[15] Further, they have significant cardiovascular effects^[16] and produce oral mucosal lesions and local damage to the periodontium.^[17]

Tobacco smoke contains more than 60 carcinogenic combustion products. In particular, NNK, NNN, and polycyclic aromatic hydrocarbons have been causally linked to upper aero-digestive tract cancer. The activity of carcinogens is generally exerted through DNA adducts.^[18] Tobacco smoking and quid chewing both cause oxidative stress to tissues, i.e. the sustained presence of reactive oxygen species, which initiate free radical reactions. Reactive oxygen species can damage proteins, lipids, carbohydrates, and DNA. Minor DNA damage may result in mutations that may be part of the causal chain for malignant transformation, while sustained DNA damage may result in further perturbations of cell-cycle control.^[19] A well-controlled meta-analysis has determined the relative risk for oral cancer in current smokers to be 3.43 and this risk is strongly dose-dependent.^[20]

Consumption of alcohol is a major public health problem. Ethanol and water are the main components of most alcoholic beverages, which also contain volatile and non-volatile flavor compounds. Ethanol is oxidized to acetaldehyde, which is responsible for the oral carcinogenic effect of ethanol, due to its multiple mutagenic effects on DNA. Ethanol damages the phospholipids of cell membranes and increases permeability. It also impairs DNA repair mechanisms and acts as a solvent, allowing the carcinogens from tobacco to penetrate into tissue, possibly catalyzing their activation.

Prolonged exposure to sunlight represents an important risk for the development of squamous cell carcinoma of the lip in people with fair complexions and those with outdoor occupations. Such evidence comes from many countries,

closer to the equator with regular long hours of sunshine such as rural Greece, where lip cancer accounts for 60% of oral cancers,^[21] and in India, for example in fishermen,^[2] although some protection may exist in darker-skinned races or individuals. Trends in occupation have been changing in the last few decades in India where most resort to “white collar” jobs. Decreases in the incidence of lip cancer can be interpreted as being due to reduced occupational exposure to sunlight.

Although tobacco and alcohol are the main etiologic factors for nearly three-fourth of these cancers, no definite etiologic factor can be identified in one-fourth of the cases. One of the most important developments in head and neck oncology is the demonstration of human papillomavirus (HPV)-mediated oropharyngeal cancers. In a systematically review by Isayeva *et al.*,^[22] on data regarding the role HPV in carcinomas of the oral cavity, high-risk HPV-16 is the predominant type; it commonly affects the younger age-groups, with males appearing to have a predisposition for infection with this strain. The overall prevalence of HPV in oral squamous cell carcinoma (OSCC) ranges between 20-50% according to an Indian study.^[23] OSCCs associated with HPV have been found to have better outcomes, being more responsive to radiotherapy and showing higher survival rates. In view of the association of HPV with OSCC, it should be worthwhile to conduct further experimental studies to elucidate its role in oral carcinogenesis.

To conclude, oral cancer remains a major personal tragedy and public health problem in India. Most of the evidence base described has been understood for decades, and it is past time when this evidence should be applied more effectively.

Oral cancer displays substantial differences in trends among developing countries including ours. Whilst better access to care is required, control will only be achieved by effective and comprehensive primary and secondary prevention by recognizing that several of the risk factors are common to many/most other diseases. Multidisciplinary and interdisciplinary working with other health and social support networks is essential to achieve this, via a “common risk factor approach.”^[24]

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