REVIEW ARTICLE

Risk Factors For Oral Cancer: Revisited

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ABSTRACT

Oral cancer has always been the subject of interest because of its varied presentation and association with a wide array of etiological factors. Oral cancer when spoken in context to Oral Squamous cell carcinoma (OSCC) is a big medical issue in countries like India, many parts of Asia, United States of America and Europe. The differences in the cultural, habitual, lifestyle factors in various parts of the world make oral cancer a difficult disease to be understood and cured owing to its multifactorial etiology. Oral Squamous Cell Carcinoma is the sixth most common malignancy worldwide and encompasses at least 90% of all oral Cancers. OSCC is associated with severe disease and treatment- related morbidity and is often reported as having high rates of recurrence and poor disease-free survival despite advances in cancer treatment. Though oral cancer has multifaceted etiology, the use of tobacco is considered to be widely accepted as the major risk factor. Other Risk factors include alcohol abuse, age, sunlight, dental factors, viral etiology, genetic factors, dietary factors, use of mouthwashes and lifestyle modifications.

Keywords: Oral cancer, Oral squamous cell carcinoma, Tobacco, Alcohol, HPV, Genetics

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INTRODUCTION

Oral cancer is a debilitating disease owing to various factors like change in behavioural practices, adaptation of habits like consumption of tobacco both in smoking and smokeless forms especially in the economically developing countries. Oral and pharyngeal cancer is the sixth most common cancer in the world. Squamous cell carcinoma accounts for about 90% of the oral malignancies as reported in literature.[1] The cancer statistics in accordance with WHO also suggest that oral cancer is the third most common cancer in India. Recent decades have shown a lot of advancements in the field of diagnosis and treatment planning of oral cancer. Attributable to its multifactorial etiology and varied presentation no single treatment has been defined as successful till date. Since the incidence and prevalence of oral cancer are on the rise, it is the need of the hour to identify the etiological risk factors which could cause oral cancer and if appropriate knowledge of these risk factors can help in developing a custom-built treatment for patients affected with the disease. This article aims at the revisiting the various risk factors associated with the development of oral cancer categorizing them as established risk, moderate risk and possible risk factors based on literature review.

METHODS

A web-based English literature search was conducted to search for the key words "Risk factors for Oral cancer". Indexed articles from PubMed/Medline were considered for the review. Journals pertaining to Oral and maxillofacial Pathology, Surgery and oncology were also researched for relevant literature.

In order to achieve a concise and informative text the authors were engaged in the selection of the information to be used, first on an individual basis and the final choice accomplished by group

consensus. We have subsequently devised a category from the wide-ranging selection of factors with potential influence on the outcome of this disease on the basis of established risk, moderate risk and possible risk factors (Table 1). No additional statistical analysis has been conducted.

Established Risk Factors	Moderate Risk Factors	Possible Risk factors
Tobacco	Age / Gender	Nutrition
HPV	Alcohol	Miscellaneous Factors
Genetics	UV radiation	
	Immunity	

Table-1: Categorization of Risk factor

REVIEW OF LITERATURE

Age

According to cancer statistics squamous cell carcinoma (SCC) of the oral cavity and oropharynx is rare in patients of age 45 and younger and is usually seen in patients above 60 years of age.[2,3] Literature suggests that approximately 6% of oral cancers occur in young people below the age of 45 years.[1,2]

In high incidence countries of the world, many cases are reported before the age of 40.With the change in habits of chewing tobacco and smoking which is now considered an epidemic amongst the younger generation predisposes them to cancer at an earlier age.[5,6]

Gender

Most published data on oral cancer are related to men as compared to women. With an era of change in lifestyle and habits like smoking and alcohol consumption which are becoming popular in the female gender, the risk of oral cancer increased in subsequent levels of smoking with alcohol intake and was also related to smoking across each level of alcohol consumption.[1,7]

An increased incidence of oral cancer has been reported in men across the globe reasoned to a greater indulgence in tobacco and alcohol consumption. Also the incidence of lip cancer was found to be higher in men who had outdoor occupations causing an increased exposure to sunlight.[7,8]

Tobacco

There is absolutely no doubt that on a global scale, the use and abuse of tobacco and its products is the major cause of cancer. Tobacco is defined as any preparation of the leaves of plants of the genus Nicotiana, of the nightshade family. Nicotine is only a minor component of tobacco leaves and constitutes about 5% of the total weight of dry plant leaves. When tobacco smoke is inhaled, nicotine is primarily absorbed through the absorbent surface of the lungs and also by the oral and nasal mucosa, when tobacco is chewed or snorted. The use of tobacco for ritualistic practices was only marginal in the beginning, as it had several medical and therapeutic applications in general bodily ills, such as toothache, headache, catarrh, colds, and fevers, as an aid to digestion and in prevention of hunger and thirst, as a purgative and narcotic. Tobacco consumption has now reached the proportions of a global epidemic. Tobacco companies are producing cigarettes at the rate of five and a half trillion a year, nearly 1000 cigarettes for every man, woman, and child on the planet. Asia, Australia and the Far East are by far the largest consumers.[9]

Experimental studies suggest that there are more than 60 carcinogens in cigarette smoke and at least 16 in unburned tobacco or smokeless form of tobacco. The most important ones are tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons and aromatic amines which have been associated with the molecular pathogenesis of oral cancer as chemical carcinogens.[9]

Much of tobacco in the world is consumed without combustion, by being placed into contact with the mucous membranes. In developing countries like India tobacco is mostly consumed mixed with other ingredients as betel quid/Paan, gutkha, khaini, mishri, zarda, gadakhu, mawa, toombak and naswar. Carcinogenicity of tobacco chewing and smoking tobacco also is evident and dose-dependent, with sufficient evidence in animal models and some evidence in human studies.[1,9-17]

It is important to highlight that in 2004, the International Agency for Research on Cancer (IARC) declared chewing of betel quid and chewing of arecanut by themselves as Group I carcinogens.[15,16] The consumption of betel quid

and arecanut is reported to be higher in developing countries like India, Taiwan and other Asian countries which is associated with a rise in the prevalence of oral potentially malignant disorders as well as oral cancer.[15,16]

Several studies have been conducted in India to assess the risk of oral cancer in smokeless tobacco users. In a population based case control study in Bhopal in 2000, the population attributable risk percentage (PARP) was found to be 66.1% for tobacco chewers for development of oral cancer. The risk for oral cancer increased about 5 times with increase in duration from 20 years to > 30 years of chewing tobacco.[11]

Alcohol

Alcohol is not a proven independent factor for oral cancer but alcohol use synergises with tobacco as a risk factor. The addition of alcoholic drink intake to tobacco chewing/smoking further increases the risk for oral cancer. A case–control study from India reported the risk being 11-fold greater with joint tobacco/betel quid chewing, bidi/cigarette smoking and heavy alcoholic drinking.[17]

There are several ways in which alcohol is thought to contribute to oral cancer by both local and systemic manifestations as discussed in the IARC monograph comprehensively describing the mechanisms associated with alcohol consumption and increased risk of oral cancer. The major alcohol metabolising enzymes are alcohol dehydrogenase, that oxidises ethanol to acetaldehyde and aldehyde dehydrogenase that detoxifies acetaldehyde to acetate. Acetaldehyde is responsible for the oral carcinogenic effect of ethanol owing to its multiple mutagenic effects on DNA.[9,18-20]

The combination between alcoholic drink and tobacco use transforms moderate drinking (8–25 drinks weekly) and smoking (20– 45 cigarette packs yearly) individuals, generally at low or no head and neck cancer risk, into high-risk subjects. In addition, ethanol is not the only carcinogen present in alcoholic drinks, other minor components, such as nitrosamines, acrylamide, oxidized polyphenols are classified as probable carcinogenic to humans, with animal experiments showing mutagenic activity on oral epithelial cells.[19] Nevertheless, with similar levels of exposure to tobacco carcinogens only some individuals develop oral cancer, thus suggesting the important role of alcohol in cancer development and progression exerted by genetic factors.[9,20]

Human Papilloma Viruses

The specific role of human papillomaviruses (HPV) in the development of potentially malignant disorders and oral squamous cell carcinoma (OSCC) continues to be debated topic. Understanding the role of viruses in human carcinogenesis has expanded enormously in the past two to three decades. Viruses contribute to the multistep process of carcinogenesis in many human cancers. The papilloma viruses are species and tissue specific. More than 75 types of papilloma viruses are described in literature and the ones associated with much benign lesions are termed as “low-risk types”, conversely “high-risk types” are associated with squamous cell carcinomas. IARC has classified HPV 16 and 18 as Group I carcinogens in humans. The E6 and E7 Open reading frames (ORFs) are particularly important because they encode transforming proteins and can be regarded as viral oncogenes. They act by binding to and inactivating the cell cycle regulatory tumor suppressor gene proteins p53 an pRb respectively. Nevertheless even the high risk HPVs do not appear to be directly carcinogenic but seem to require an additional modification of host cell genes brought about by physical or chemical carcinogens. This is consistent with the multifactorial and multi-step nature of human carcinogenesis in the light of which detection of HPV infection may be a useful risk marker for subsequent malignancy.[20,22]

Diet and Nutrition

The role of dietary factors has been the centre of many recent studies. Evidence of such role is from many in-vivo, in-vitro, population based, and hospital based case control/ cross sectional studies looking on the dietary intake and serum micronutrients. Finding from such studies led to accumulating evidence that some micronutrients like Vitamin A, C and E, Carotene (mainly beta-carotene), iron and selenium may decrease the incidence of epithelial dysplasia. The protective roles of these micronutrients have been attributed

to their antioxidant properties. Antioxidants act by reducing the free radical reactions that can cause DNA mutations and changes in lipid peroxidation of the cellular membranes and changes in the enzymic activities. Other functions of these include modulation of carcinogen metaboli- sm, affects cell transformation and differentiation, inhibition of cell proliferation, oncogene expression, immune function and inhibition of endogenous formation of carcinogen.[23]

As dietary intake is concerned recent decades has shown reports on association of low intake of fresh fruits and vegetables with increased in cancer prevalence and incidence. The protective effects of antioxidant micronutrients against oral cancers and precancers have also been accumulating worldwide via micronutrient studies and chemoprevention trials using vitamin A, C and E and carotenoids (particularly beta-carotene supplements). Several epidemiologic studies in the Indian subcontinent, Malaysia, Japan and other western countries support the association of lack of micronutrients to increased prevalence of oral precancer and cancer.[23]

Ultraviolet radiation

It is well established that outdoor workers are at a greater risk of developing lip cancer due to prolonged exposure to ultraviolet (UV) radiation. Those with occupations such as farming, fishing, forestry or postal delivery are at a higher risk. The evidence is collected from many countries like Finland, Sweden, California and India which are closer to the equator with regular hours of long sunshine. The lesions that develop are usually well differentiated squamous cell carcinomas and arise out of long standing lesions like solar keratosis.[24,25]

It is suggested by various experimental studies that ultraviolet radiation is carcinogenic. The ultraviolet B (UVB) is a whole carcinogen whereas ultraviolet A (UVA) is considered an indirect carcinogen. UVB radiation has the potential to cause direct DNA damage either by formation of chemical primers or formation of singlet oxygen species which are highly reactive and can cause DNA damage indirectly. UVA radiation on the other hand induces DNA damage indirectly with formation of reactive oxygen species such as singlet oxygen and hydrogen peroxide.[24,25] Molecular studies suggest that UVA and UVB radiation lead to differential expression of p53 and bcl-2 proteins which could play a significant role in regulation UV induced apoptosis.[25]

Though the available literature supports the increased incidence of melanoma with radiation exposure as compared to squamous cell carcinomas, there is clear evidence that PUVA [psoralen (P) and ultraviolet A (UVA)] increases the risk for SCC with a relatively short latency period, although it is again difficult to distinguish the contribution of PUVA from other factors, given that treated patients have usually received multiple carcinogenic treatments. [24,25]

Genetics

There is not substantial evidence of a strong familial and genetic predisposition to oral cancer. Studies from India, Netherlands, Israel and USA support the genetic predisposition of oral cancer. There is rapidly expanding literature describing the susceptibility related to inherited capacity to metabolise carcinogens or pro-carcinogens or inability to repair the subsequent DNA damage involving the CYP genes, polymorphisms in the GST genes and the cytochrome P-450 system. Studies also suggest an association of oral cancer with hereditary disorders like Xeroderma pigmentosum, Dyskeratosis congenital and Fanconi's anemia.[1,20]

Hence it could be said that genetic predisposition to oral cancer if any is at best small, and is swamped by other environmental factors. Determination of these genetic factors would have a larger benefit, not only to atrisk family members or first degree relatives, but in unravelling the molecular basis of oral carcinogenesis thereby opening a better way for prevention and treatment planning for oral cancer.[20]

Immunity

With the wide literature available on various risk factors on oral cancer the exact role of immunity and immunodeficiency still remains a controversial issue. Individuals with Human immuno deficiency virus/ Acquired immuno deficiency syndrome (HIV/AIDS) are at an increased risk of neoplasms like Kaposi's sarcoma and

Lymphomas which commonly present in the oral cavity, but the incidence of squamous cell carcinomas is not particularly associated with these infections. Moreover the Oral hairy Leukoplakia (OHL) which is commonly associated with HIV disease does not undergo malignant transformation. Immunosuppressed organ transplant patients are at an increased risk of developing lip cancer.[10,20]

Miscellaneous factors

Dental practitioners have identified several other miscellaneous factors that could increase the chances of developing oral cancer. To enumerate a few poor oral hygiene, poor dental status, ill-fitting dentures, sharp tooth, fungal infections, use of mouthwashes appear as a correlate in several studies. Though these factors are not independently proven as sole factors for oral cancer but they can act as a source of chronic irritation on the oral mucosa predisposing it to carcinogenesis.[10,20,26]

CONCLUSION

Oral cancer remains a fatal disease for increased incidence of cases diagnosed annually. Studies have reported an alarming lack of awareness about oral cancer, its symptoms and causes and these gaps in knowledge need to be addressed by further public education, possibly targeted at high-risk groups.

There are very few studies which have highlighted an individual risk factor by eliminating the other confounding factors, hence it becomes cumbersome to suggest that oral cancer could be attributed to a single predisposing etiology. To conclude, adequate knowledge about the various risk factors and diagnosis of the potentially malignant disorders at an earlier stage would aid in the improvement of mortality and morbidity associated with oral cancer. Moreover, with the attentiveness about the underlying molecular mechanisms, more specific tumor markers can be developed for prevention and early detection of oral cancer.

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