

Oral Cancer: Etiology and Its Diagnostic Aids

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ABSTRACT

Oral cancer is of major concern as it is southeast Asia primarily because of the prevalent oral habits of betel quid chewing, smoking, and alcohol consumption. Recent advances in diagnosis and therapeutic techniques of these lesions have yielded novel molecular targets, uncovered signal pathway dominance and advanced early cancer detection. This paper is an overview of the various etiological agents and risk factors implicated in the development of oral cancer and also diagnostic aids in oral cancer.

Keywords: Etiology, Tobacco, Oral Cancer, Diagnostic Aids

Introduction

Oral cancer, ranked as the sixth most common cancer across the globe [1], is increasing remarkably [2] in southern countries of Asia including India.[3]In India, oral cancer is more common among males when compared to females[4]. Recent studies confirm that oral cancer forms a large part of the cancer load in parts of India. [5] Tobacco and alcohol are the two most important known risk factors for the development of oral cancer. [6] Cofactors in OSCC include dietary factors, immunodeficiency and viral infections like HPV 16/18.

Tobacco

Oral neoplasia has been associated with chewing of tobacco with betel quid (BQ) in India and other Asian countries, whereas in western countries, cigarette smoking and heavy alcohol consumption are the main risk factors. In 2007 the IARC concluded that "there is quite an evidence to establish that snuff smoke is carcinogenic, and for example, it causes cancer of the oral cavity and pancreas" [7]. The risk of developing oral cancer is 3 times higher in smokers compared with nonsmokers. Chewing of tobacco with BQ increases

exposure to carcinogenic tobacco-specific nitrosamines (TSNA) and to nitrosamines derived from areca nut alkaloids.[8.] Tobacco use in any form is greatest in young adulthood and middle age (15-65 years) and is lower in older people. This trend is less obvious in Asian countries, where higher proportions of people aged 65 and above use tobacco. [ref]. Sanctions on the use and advertising of tobacco have had a substantial impact on consumption. Nearly 10% of countries have completely prohibited all forms of promotion. In India, tobacco products are labelled as hazardous, and advertisements are used to create awareness about tobacco-related oral cancer. Higher taxation on tobacco products can potentially decrease consumption, particularly in low and middle-income countries [9, 10].

Betel quid and areca nut

Betel quid chewing with different ingredients is the most common habit in Southeast Asia, especially in the Indian subcontinent. In India, areca nut is used either alone as a nut or as a raw or processed form mainly along with tobacco. The intake usually begins with munching a packet or two a day. Children are getting addicted to it as they find it more attractive than candy and toffees The youth is also fascinated by celebrities and famous public figures endorsing such areca products and brands. These products are easily available in shiny, glittery attractive looking packets in local shops at cheap rates [11].

Alcohol

Alcohol, acting both independently as well a synergistically with smoking, has been implicated in oral carcinogenesis. The systemic effects of alcohol are mainly due to hepatic damage. Alcohol addiction leading to cirrhosis and other diseases (e.g., cardiomyopathy, stroke, and dementia) inhibits the detoxification of carcinogenic compounds such as N-nitrosodiethylamine [12]

Diet

Diet plays an important role in preventing oral diseases including dental caries, dental erosion, developmental defects, oral mucosal diseases and, to a lesser extent, periodontal disease. Following global recommendations that encourage a diet high in starchy staple foods, fruit and vegetables and low in free sugars and fat will protect both oral and general health. 13]. Although the individual micronutrients responsible have not been formally identified, vegetables and fruits that protect against oral cancer and precancer, are rich in b-carotene, vitamin C and vitamin E, with anti-oxidant properties

Viruses

Another risk factor is human papillomavirus (HPV), which is also closely associated with benign and malignant oral lesions. Among those, only a small fraction of HPV-infected lesions rarely proceed to malignant transformation, especially those with HPV subtypes 16,18 [14-16]. HPV infections have been postulated as a possible risk factor for at least some varieties of oral cancer. Quite a few studies have detected the DNA of HPV in a considerable proportion of malignant tumors of the head and neck cancers, with rates of detection ranging from 0% to 100% There were merely few studies which focused on evaluating the reliable diagnostic method in the detection of HPV-related oral and oropharyngeal cancers. [17]

Immune Deficiency

Immunosuppressed individuals are more prone to develop oral cancers. Human immunodeficiency virus (HIV)-infected patients are predisposed to developing Kaposi's sarcoma HPV infections have been postulated as a possible risk factor for at least some varieties of oral cancer. Quite a few studies have

detected the DNA of HPV in a considerable proportion of malignant tumors of the head and neck cancers, with rates of detection ranging from 0% to 100% and lymphomas, although not to OSCC. However, the direct role of immunosuppression with lip cancer development was not proven in the studies. [18]

Diagnostic Aids in Oral Cancer

1. Vital Staining: Lugol's iodine and toluidine blue have been used together in the detection of early carcinoma and the diagnosis of oral lesions

(A) Toluidine Blue

Toluidine blue (tolonium chloride) is an acidophilic metachromatic dye of the thiazine group which selectively stains acidic tissue components (sulfates, carboxylates, and phosphate radicals), thus staining DNA and RNA. It stains mitochondrial DNA, cells with greater than normal DNA content or altered DNA seen in dysplastic and malignant cells.[19] The test is sensitive, simple, non-invasive, and highly cost-effective. It assists in identifying the preferred area of biopsy and marking the borders of the lesion. This may lead to early detection, diagnosis, and in directing surgical management. [20,21]

(B) Lugol's Iodine

Lugol's iodine solution produces a brown-black stain by a reaction of the iodine with glycogen. The use of toluidine blue and Lugol's iodine as an adjunct to sound clinical judgement is of value in the diagnosis of at-risk patients, selecting the site for biopsy, delineating the extent of Erythroleukoplakic lesion; wide field cancers before treatment and follow-up of patients after treatment for cancer. These tissue stains should be used as additional aids in assessing high-risk patients and suspicious oral lesions. [21]

2. Vizilite

The Velscope uses a blue light with peak intensity at approximately 436 nm; this wavelength especially stimulates a green fluorescence. The principle of tissue autofluorescence was used in the screening and diagnosis of precancerous lesions in the lung, uterine and skin in the past. This concept of diagnosing dysplastic lesions in the oral cavity is based on the structural and metabolic changes of the epithelium as well as the connective tissue when interacting with the light. [22]

1. Photodiagnosis: It is a non-invasive procedure that provides tissue diagnosis in real-time through optical spectroscopy. There are intensive researches on the use of optic methods for early diagnosis, based on fluorescence measurements. These techniques called medical optoelectronic, come from cancer photochemotherapy and have applications in optical biopsies. In photodynamic therapy (PDT) a non-cytotoxic photosensitizer localizes preferentially in neoplastic tissue and gets toxic by light excitation. For the photodiagnosis, one can study either the natural autofluorescence of background of the concerned tissue, or the distribution of fluorescence for an oxygen fluorescence like those used in photochemotherapy, or the combination of both [23]

2. Histopathological Methods

(A) Biopsy: A biopsy is the controlled and planned removal of tissue from a living organism for the purpose of microscopic examination. [24] It is considered to be confirmative for evaluating the cancerous or precancerous nature of a lesion. The techniques used to perform a biopsy of the oral mucosal lesion are Incision biopsy, Punch biopsy and Excision biopsy[25]. Brush biopsy a little planning and thought can

greatly improve the diagnostic value obtained. Careful handling of the tissue and prompt appropriate fixation will enable a confident histological diagnosis to be reached. Inadequate care at any stage could result in a non-diagnostic biopsy and may necessitate the patient having a repeat procedure with its ensuing physical and psychological morbidity [26]

3. Molecular Techniques

1. Gene alterations: Nowadays malignancy is considered a process caused by the accumulation of multiple genetic alterations, which affect the cell cycle as well as normal cell differentiation. Most of the oral cavity carcinogens are chemical (tobacco), physical (radiation) and infectious (Human papillomavirus, Candida) mutagenic agents that may cause changes in gene and chromosome structure by point mutations, deletions, insertions, and rearrangements. These genetic alterations, which occur during carcinogenesis, can be used as targets for detecting tumour cells in clinical samples [27-29]. Spafford et al. identified genetic alterations (LOH or MI) in all of the malignant lesions of the oral cavity included in their sample [28]

2. Proliferation index and AgNOR analysis: Ki 67 has been studied in oral cytological smears using Immunocytochemistry to evaluate the nature of lesion and response to treatment. PAP staining in combination with the AgNOR technique act as a reliable indicator to measure the effects of smoking on the oral mucosa. Other proliferative indices such as Ki-67 may be used for comparison with the AgNOR method as well. It was also concluded that bidi smokers show higher cellular proliferation as compared to nonsmokers, which is similar to results obtained for cigarette smokers. [30]

Conclusion

It is clear from the above review that several risk factors are implicated in the development of oral cancer, of which the most common and established are tobacco smoking and alcohol. The global increase in frequency and mortality, as well as the poor prognosis of head and neck squamous cell carcinoma, has intensified current research efforts in the field of prevention and early detection of this disease. The detection, diagnosis, and management of oral diseases are complex. Refinements and continued research will undoubtedly improve our ability to detect any disease at the earliest possible stage. New technologies may emerge which will prove much more valuable in early diagnosis with a probability of cure. Hence, it is important for the public and the clinicians to be completely aware of the risk factors for oral cancer and it is prudent for dentists to look carefully for early signs of oral cancer.

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