



## Review On Oral Squamous Cell Carcinoma: An Update

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### Abstract

Oral cancer is the sixth most common neoplasm occurring globally with an incidence rate of 6, 40,000 cases diagnosed annually. 90% of the oral cancers are squamous cell carcinomas. Although oral cancer has got multifaceted etiology alcohol consumption and tobacco chewing are the major risk factors. These pre-disposing factors are leading to the wide range of genetic events leading to cancer progression. Despite, the significant advances in the understanding of etiopathogenesis and molecular basis of the disease as well as continuing improvement in the management strategies, OSCC prognosis remains dismal. It is widely recognized that novel, more effective approaches to diagnosis, prevention and treatment are urgently needed. The major etiological factors for oral cancer development are potentially preventable through discontinuation of hazardous habits and vaccination in case of viral infections. Primary prevention of the disease appears as a challenging goal. However possibilities for secondary prevention appear achievable i.e early detection and treatment at an early stage during the process of carcinogenesis. The ongoing of genetic and epigenetic events that govern oral carcinogenesis at the molecular level holds great promise for identifying novel diagnostic and prognostic biomarkers as well as therapeutic bio targets. Intensive research efforts have analyzed a large number of potential molecular biomarkers for the better assessment of the risk of OSCC development and progression. Further biomarkers may play a prominent role in guiding individualized oral cancer treatment, according to which selection of the most appropriate therapeutic intervention will be based on the knowledge of a given tumor susceptibility to a specific anticancer treatment.

**Keywords:** Oral cancer, risk factors, prevention, diagnosis, Squamous cell carcinoma

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### Introduction

Oral cancer [OC] encompasses all malignancies originating in the oral cavity. Oral cancer ranks sixth in the overall incidence for the ten most common cancer sites worldwide and third in the developing countries [1]. Most of the oral cancers are squamous cell carcinomas and the majority is unequivocally associated with tobacco chewing and an early diagnosis greatly increases the probability of

cure, with minimum impairment and deformity [2]. They are of utmost concern as the mortality rate of the oral cancer for the past three and a half decades has remained high (over 50%) in spite of new treatment modalities. Despite numerous advances in treatment, the 5-year survival has remained approximately 50% for the last 50 years. Annually 75000 to 80000 new oral cancer cases develop in India [3]. Based on the increasing incidents of head and neck cancers, problems associated with late diagnosis and the public health dilemma they present, it seems prudent to enact screening protocols to check people at risk. Early diagnosis would allow for conservative therapeutic approaches with a brief recovery and a more favorable prognosis. Suspected patients should be more intensively examined and treated. The current trends in diagnosis focuses in the areas of molecular biology and advanced diagnostic aids will transform our traditional approaches to oral and dental disease management [4]. The approaches in the early detection of oral cancer include screening programs and employing specific diagnostic tools

that identify asymptomatic patients with suspicious lesions.

## Oral cancer epidemiology

OC is the most common cancer in the world, with the highest prevalence among men (5-year prevalence in men: 401,075) [5]. According to Ferlay *et al.* the worldwide cases of oral cancer in 2012 in both sexes were about 300,000 (2.1% of the total cancers) and approximately 145,000 cases were fatal [6]. According to the American Cancer society the incidence of OC is higher in developed countries when compared to developing countries, but the mortality rates remain higher in developing countries. In developing countries the incidence of OC is 107,700 in males and the estimated deaths are 61,200 [7].

In south-central Asia, OC is one of the most frequent types of cancer. In India the incidence rate is 12.6 per 100 000 population, and in other countries of Asia OC remains one of the most common cancers [8, 9]. Of interest, the incidence rate remains high in several developed countries such as Denmark, Poland, Germany, Scotland, and also in Australia, Japan, New Zealand and the USA [10, 11].

## Major risk factors

### Tobacco and Alcohol

The major risk factors associated with OC are tobacco use, in any available forms, and heavy alcohol consumption (people who drink five to eight drinks per day with one drink containing 1.5 oz or 10-15 g of alcohol) [12, 13]. The combined effects of alcohol and tobacco smoking have been shown to be synergistic. Of interest, a recent study showed that drinking is inversely associated with OC in non-smoking betel quid non-chewing individuals [14].

The risk for developing OC is five to nine times greater for smokers than non-smokers [15, 16]. The mechanism of oral carcinogenesis is induced by the tobacco smoking constituents [17]. In particular the polymorphic variability in the enzymes involved in biotransformation of tobacco-related pro-carcinogens plays an important role in modulating oral cancer susceptibility [18]. Alcohol consumption is correlated to oral cancer because many chemical carcinogens derived from alcohol degradation are metabolized into active forms that have deleterious effects on organisms. Ethanol is oxidized to acetaldehyde, a suspected carcinogen.

### Areca-nut and betel-quid

Another common risk factor is betel-quid and areca-nut chewing. Betel-quid and areca-nut chewing are common social and cultural habits in many parts of Asia. Betel-quid consists of betel leaf, areca nut and slaked lime to which tobacco is often added. Frequent areca nut chewing is carcinogenic to humans [19] are coline, an alkaloid present in areca nut, causes cell death, apoptosis, and cell cycle arrest of epithelial cells contributing to the pathogenesis of oral carcinogenesis [20, 21].

## Age and family history of cancer

Age indicates a temporal component in the biochemical and biophysical processes of cells that allow malignant transformation or the reduction of the immune system competence. Specifically, the long-term exposure to risk factors may affect the gene products that control epithelial cell proliferation and death resulting in an uncontrolled malignant proliferation of cells. Also, family history of oral cancer plays an important role and is considered a risk factor. However, more studies are necessary to elucidate which molecules and genes are responsible for oral cancer susceptibility in families. Family history of OC is mostly associated with an onset of the disease at an early age (about 45 years old) [22]. OC is also seen in family members without habits such as tobacco chewing, smoking or alcohol consumption [23].

## HPV infection

Although the association between HPV infection and oropharyngeal cancer is now well established, it is still unclear whether HPV infection may lead to OC as well. Several studies suggest an association between human papillomavirus (HPV) infection and oropharyngeal cancers [24], particularly HPV 16 (90-95% of HPV-positive tumors). In the US there has been a recent increasing incidence of cancer of the oropharynx due to persistent HPV infection, especially among young white men [25]. HPV oncoproteins E6 and E7 inactivate the retinoblastoma RB pathway, cause TP53 degradation and P16 upregulation leading to HPV-associated squamous cell carcinoma of the oropharynx. Of interest, the 3-year survival of these cancers is significantly better than for conventional squamous cell carcinoma (82.4% vs. 57.1%); the prognosis may also be improved if the tumor is p16 positive regardless of HPV status.

The role of the protective effect of HPV vaccines against oropharyngeal cancer remains unclear [26]. However, a recent randomized

controlled trial has shown that the prevalence of oral HPV four years after vaccination is lower when compared to women who did not receive the vaccine. This suggests that the vaccine may have potentially important implications for prevention of increasingly common HPV-associated oropharyngeal cancers [27].

### **Immunosuppression**

Immunosuppressed subjects individuals are at increased risk for malignant tumor of the oral cavity and elsewhere in the body [28]. In particular HIV-infected individuals may develop OC, non-Hodgkin lymphoma and Kaposi sarcoma. Also transplant patients are at risk for multiple malignancies including OC [29].

### **The malignant progression**

Normal cells transform into preneoplastic cells and then to cancer after a series of clinical and histopathological stages involving genetic and molecular changes. These stages are clinically represented by manifestations on oral mucosa, such as leukoplakia, erythroplakia or leukoerythroplakia, and they all represent a predictive factor of malignant transformation [30].

### **Molecular changes**

The multi-step progression of cancer involves a combination of acquired and inherited alterations in the DNA sequence. Genetic changes in keratinocytes cause a progressive acquisition of a malignant phenotype from premalignant to cancer, characterized by invasion across the epithelial basement membrane and eventual metastasis. The over expression of oncogenes causes a disruption in the cell cycle driving to abnormal cell proliferation, while the expression of the tumor suppressor genes, especially the proteins p53 and p16 in the dysplastic epithelium are significant markers to detect preneoplastic lesions in the oral cavity [31].

Risk factors can lead to genetic and epigenetic alterations; the most observed cases of mutation of these genes are present in people from Asia due to the tobacco chewing and betel quid [32, 33]. Furthermore, epigenetic may cause an alteration of gene expression through aberrant DNA methylation, histone modifications and expression of microRNAs [34].

### **Potentially malignant disorders**

Potentially malignant disorders comprise leukoplakia, erythroplakia, oral lichen planus and oral submucous fibrosis. These lesions are characterized by sequential accumulation of molecular changes that can lead to dysplasia (mild,

moderate or severe) and then to frank invasive carcinoma [35].

Oral Lichen Planus (OLP) is an immunomediated inflammatory condition of the oral mucosa [36]. It occurs in 1 to 2 % of adults and may be idiopathic or associated with a variety of systemic and local conditions. OLP usually affects the buccal mucosa and tongue bilaterally, and can present with three distinct forms: reticular/keratotic (classic), erosive/erythematous, and ulcerative forms. Less than 1% of OLP evolve in OC [37, 38].

Leukoplakia is a white lesion that can affect any site of the oral cavity, and its diagnosis it is made by the exclusion of any known diseases. The malignant transformation rate of all leukoplakias is 9-37%. There are three clinical different types of leukoplakia (the homogeneous, non-homogeneous and verrucous type); the most aggressive form is the proliferative verrucous type (60-100% of proliferative leukoplakias develop carcinoma) [39].

According to the WHO definition oral erythroplakia is defined as “any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterized clinically or pathologically as any other recognizable condition”. The risk of malignant transformation of erythroplakia is the highest between the others premalignant forms (90%). This lesion presents as red areas mainly affecting the floor of the mouth, the soft palate and the ventral tongue.

Oral submucous fibrosis is a condition characterized by a fibrous aspect, a significant morbidity with pain and reduced oral opening which may affect any site of the oral cavity [40]. It is associated with areca nut chewing especially in Southeast Asia and the reported risk of malignant transformation varies from 2.3-7.6% [41].

### **Scope for Primary Prevention**

As described previously, tobacco use has a deleterious effect of on oral cavity. Approximately 630,000 deaths occur every year in India and risk of mortality is invariably higher in tobacco users than among non-users. These observations through numerous studies conducted in this regard show that there is a strong need for all the dental health professionals to join hands in connection to prevent oral cancer and also other diseases caused by tobacco[42].

### **Effects of Primary Prevention**

Primary prevention aims at avoiding or reducing risk factors. The rural population of India has been resource for various studies conducted in

this regard. Motivation by various communications imparts such as personal communications, films newspaper articles, radio programs, folk-art, and posters, a great amount of population approximating to 15% of the tobacco users have quit the use and substantial amount of people showed reduction appreciably. As most of oral cancers arise from precancerous lesion, the relative reductions in these lesions have an indirect effect on reduction of oral cancer.

### **Secondary prevention**

Secondary prevention aims at early detection of cancer of easily accessible sites and oral cavity in one such site, prompt treatment is most essential for a successful secondary prevention, secondary prevention is also called cancer control. This collaborative effort is most required because the elders, may need dental visits than those of physician visits. Which is most common in regions of low literacy and limited access [43]. The ideal time to detect cancer is when it is small and has not spread. In general the greatest chances of cure and prolonged survival exists when such small cancers are detected and treated. In this context dentists have prime responsibility in detecting cancer by screening oral cavity which should be performed on every new patient and at all recalls.[44]

### **Tertiary prevention**

Tertiary prevention aims at the terminal stages. Over 70% of cancers have severe pain and other distressing symptoms in the advanced stages. Pain control and palliative care are major strategies of tertiary prevention.

## **Methods of Oral Cancer Prevention**

### **Chemoprevention**

Chemoprevention refers to the administration of an agent to prevent a cancer from occurring. The agent can be a drug or a natural product. Candidate agents for chemoprevention should have certain characteristics. The agent must be easy to administer, cause little or no toxicity, cause no long term adverse sequelae, be affordable, and ideally, need to be administered only for a short time.

### **Retinoids**

Mechanism of action of these compounds for chemoprevention is not well understood. Studies have documented lower carotene (a precursor of vitamin A) serum concentrations in patients who develop cancer of the head and neck, than in patients who do not develop these cancerous tumours.

Retinoids can act through induction of differentiation and can inhibit proliferation, as well as cause programmed cell death.

### **Carotene**

Carotene is one of several carotenoids in the body and is a precursor of vitamin A. It is found in leafy green vegetables and yellow and orange fruits and vegetables, and it is also available in tablet form. To some extent it is converted to vitamin A in the body and is not associated with hypervitaminosis A syndrome. Several studies have noted lower blood levels of carotene in patients who develop aero digestive tract cancers compared to patients who do not develop cancer. These findings led to a hypothesis that a carotene deficiency may predispose cancer formation. The mechanism of action of carotene as a chemopreventive agent may involve antioxidant mechanisms as well as inhibition of free radical reactions.

### **N-Acetylcysteine**

N-Acetylcysteine is an antioxidant and free-radical scavenger that has shown chemo preventive activity in lung and tracheal tumors in animals.

### **Non-Steroidal Anti-inflammatory Agents**

In animal studies, nonsteroidal anti-inflammatory agents (NSAIDs) have chemopreventive activity in several tissues and have shown activity in tumour inhibition in preclinical head and neck cancer models. Because these compounds may be inhibitors of proliferation, they may be useful as chemopreventive agents.

### **Vitamin E**

Epidemiologic studies have noted an inverse relationship between serum vitamin E levels and oral cancer. Its mechanism of action postulated to be as an antioxidant agent.

### **Interferons**

Interferons have shown additive or synergistic antitumor effects in combination with retinoids.

### **Curcumin**

Curcumin is the major component of turmeric, which is widely used in curry. Curcumin has inhibited carcinogen-induced tumorigenesis in an oral cancer model and is nontoxic. This agent is under consideration as cancer preventive.

## **Recent advances in diagnosis of oral cancer**

### **Genomics and proteomics**

Regular histopathological evaluation gives very limited information in terms of rate of proliferation, capacity for invasion and metastases, and development of resistance mechanisms to certain treatment agents. Biomarkers help in early detection of cancer by providing valuable information about the status of a cell at any given point in time. As the cell transforms from non-diseased to neoplastic, distinct changes occur that could be potentially detected through the identification of the appropriate biomarkers. Proteomics is the study of expressed proteins, including identification and elucidation of the structure–function relationship under normal or disease conditions, such as in cancer. It also provides an avenue to understand the interaction between the functional pathways of a cell and its micro environment.

Cancer proteomics encompasses the identification and quantitative analysis of differentially expressed proteins relative to healthy tissue counterparts at different stages of disease, from preneoplasia to neoplasia. Proteomic technologies can also be used to identify markers for cancer diagnosis, to monitor disease progression, and to identify therapeutic targets. It is valuable in the discovery of biomarkers because the proteome reflects both the intrinsic genetic program of the cell and the impact on its immediate environment of protein. At the protein level, distinct changes occur during the transformation of a healthy cell into a neoplastic cell, ranging from altered expression, differential protein modification, and changes in specific activity, to aberrant localization, all of which may affect cellular function. Identifying and understanding these changes are the underlying themes in cancer proteomics.

## PCR

The polymerase chain reaction (PCR) is a technology in molecular biology used to amplify a single copy or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence. These include DNA cloning for sequencing, DNA-based phylogeny, or functional analysis of genes; the diagnosis of hereditary diseases; the identification of genetic fingerprints (used in forensic sciences and DNA paternity testing) and the detection and diagnosis of infectious diseases.

The method relies on thermal cycling, consisting of cycles of repeated heating and cooling of the reaction for DNA melting and enzymatic replication of the DNA. Primers (short DNA

fragments) containing sequences complementary to the target region along with a DNA polymerase, which the method is named after, are key components to enable selective and repeated amplification. As PCR progresses, the DNA generated is itself used as a template for replication, setting in motion a chain reaction in which the DNA template is exponentially amplified. PCR can be extensively modified to perform a wide array of genetic manipulations [45].

## Microarrays

New technologies are developed, such as, DNA microarray and DNA chips, that give hundreds to thousands more genetic information in a shorter period of time than the original PCR techniques. Microarrays are needed to appropriately classify tumor subtypes, molecular information can be extracted and integrated to find common patterns within a group of samples. They can be used in combination with other diagnostic methods to add more information about the tumor specimen by looking at thousands of genes concurrently. This new method is revolutionizing cancer diagnostics because it not only classifies tumor samples into known and new taxonomic categories, and discovers new diagnostic and therapeutic markers, but it also identifies new subtypes that correlate with treatment outcome [46, 47].

## Nanodiagnosics

Use of nanodiagnosics is cost effective and has increased sensitivity. The tools include quantum dots (QDs), gold nano particles and cantilevers. QDs are semiconductor nano crystals characterized by high photo stability, single wavelength excitation, and size tunable emission. Bar coding of specific analytics can be done by QDs and magnetic nano particles. Hence they are bio bar code assay which has been proposed as a future alternative to PCR. The applications of QDs being used for tumor detection, tissue imaging, intracellular imaging immunohistochemistry, infectious agent detection, multiplexed diagnostics and fluoroimmuno assays [48].

## Next-generation sequencing (NGS)

It is arguably one of the most significant technological advances in the biological sciences. They have advanced rapidly to the point that several genomes can now be sequenced simultaneously in a single instrument run in under two weeks. Targeted DNA enrichment methods allow even higher genome throughput. The sensitivity, speed and reduced cost

per sample make it a highly attractive platform compared to other sequencing modalities [49].

## Conclusion

Despite advances in cancer treatment, the survival rates of patients suffering from head and neck cancer has not improved substantially. Sources emphasize the necessity of early detection of the disease as survival is influenced by the extent of the disease at the time of diagnosis. More emphasis should be placed on education programmes to the public so that they don't adopt the habit of smoking. Tobacco and heavy alcohol consumption are the most common risk factors for OC, with betel-quid and areca-nut chewing in some Asian countries. The role of HPV in the oral cavity is still controversial. Of interest, new trends are emerging in younger patients with no known risk factors. New diagnostic techniques are available for early detection although their reliability and validity is still unclear. Incisional biopsy remains the gold standard along with visual and tactile examination.

Oral cancer requires a multimodality approach together with the oral medicine specialist, the dentist, the surgeon, the radiotherapist and oncologist. Treatment planning depends on the TNM staging system. Physicians have multiple diagnostic options and multidisciplinary approaches for the treatment of oral cancer, however further research is needed to better understand the natural history of Oral Cancer. Clinicians should screen their patients to detect early lesions and educate them about the risk factors that can lead to cancer.

There are several obstacles to be addressed before genomics and proteomics reach an optimal yield and be beneficial for the patients. In the future, methods used in genomics and proteomics will be useful for the discovery of tumor specific marker genes and 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 probability of cure, with minimum impairment and deformity. These findings suggest that the key to prevent oral cancer is to educate the mass in the primary level to quit the etiological factors. Mortality and morbidity of oral cancer can be significantly reduced if detected in early stages.

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