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## Review Article

### Oral Cancer and Precancerous Lesions: A Review

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#### ABSTRACT:

Oral cancers form a significant portion of the cancer burden accounting for approximately 3% of all malignancies and is a significant worldwide health problem. A significant number of these cases would present initially with precursor lesions that are further classified as precancerous lesions and precancerous conditions. This article will review the epidemiology and clinical features of oral squamous cell carcinoma, with a special emphasis on the recognition of early cancer and premalignant oral lesions.

**Key words:** Leukoplakia, oral cancer, precancer.

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#### INTRODUCTION:

Oral cavity cancer accounts for approximately 3% of all malignancies and is a significant worldwide health problem. These are one of the leading cancers in India today, with an age standardized incidence rate of 12.6 per 100 000 population. A significant number of these cases would present initially with precursor lesions that are further classified as precancerous lesions and precancerous conditions.

A precancerous lesion is a morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart, for example, Leukoplakia, Erythroplakia etc. A precancerous condition is a generalized state associated with a significantly increased risk of cancer, for example, submucous fibrosis, Lichen planus etc. However, in a World Health Organization (WHO) Workshop, held in 2005, the terminology, definitions and classifications of oral lesions with a predisposition to malignant transformation have been discussed and recommended to use the term "potentially malignant disorders" (PMD's) to eliminate terminological confusion.<sup>1</sup>

The most common oral precancerous lesions are oral leukoplakia, oral submucous fibrosis (OSMF), and oral erythroplakia. Actinic cheilitis, some miscellaneous inherited diseases such as xeroderma pigmentosum and Fanconi's anemia, and immunodeficiency are another potentially malignant disorders for oral carcinoma as well as these three diseases.<sup>3</sup> Some risk factors such as tobacco chewing, tobacco smoking, and alcohol play an important

role in development of potentially malignant oral conditions. While tobacco chewing is a major risk factor for oral leukoplakia, OSMF, and erythroplakia, tobacco smoking may be a risk factor for oral leukoplakia. Alcohol drinking may increase the risk by 1.5-fold for oral leukoplakia, by 2-fold for OSMF, and 3-fold for erythroplakia. According to Thomas et al, while alcohol drinking and tobacco chewing may possibly be risk factors for multiple oral premalignant lesions, smoking was not associated with the risk of multiple oral premalignant lesions.<sup>3</sup>

Early oral cancers and precancerous lesions are often subtle and asymptomatic. Therefore, it is important for the clinician to maintain a high index of suspicion, especially if risk factors such as tobacco use or alcohol abuse are present. Invasive oral squamous cell carcinoma is often preceded by the presence of clinically identifiable premalignant changes of the oral mucosa. We think that the following criteria should be taken into consideration in terms of the importance of early diagnosis: (1) symptomatic and/or non-symptomatic non-healing lesions of oral mucosa; (2) history of smoking, chewing tobacco, alcohol consumption, oral HPV infection, drug use, long-term exposure to sunlight; (3) advanced age; (4) the presence of immunodeficiency; (5) the presence of genetic disease; and (6) poor oral hygiene.

This article will review the epidemiology and clinical features of oral squamous cell carcinoma, with a special emphasis on the recognition of early cancer and premalignant oral lesions.

### **ORAL LEUKOPLAKIA:**

The term "leukoplakia" was coined by Schwimmer of Budapest in 1877, for white changes on the tongue, seen prior to lingual cancer development in tertiary syphilis. It is the most common premalignant lesion and the most studied PMD. The WHO working group defines leukoplakia as "a keratotic white patch or plaque that cannot be scraped off and cannot be characterized clinically or pathologically as any other disease."

The prevalence of oral leukoplakia varies between 1.1% and 11.7%, with a mean value of 2.9%.<sup>4</sup> Although leukoplakia can occur at any age, it often occurs in individuals under the age of 40.<sup>5</sup> Leukoplakia is seen six times more among smokers than among non-smokers.

Many physical agents have been proposed, including tobacco, alcohol, chronic friction, electro galvanic reaction between unlike restorative metals, and ultraviolet radiation. Tobacco smoking is by far the most accepted factor and smokers are six times more prone to leukoplakia than nonsmokers. There are conflicting results of studies related to the possible role of human papilloma virus infection.<sup>4,6,7</sup>

Clinically it can be divided into two subtypes including homogeneous and non-homogeneous types. Homogenous lesions are characterized by uniformly flat, thin, uniformly white in colour and shows shallow cracks of the surface keratin<sup>5</sup>. Non-homogenous lesions have been defined as a white and red lesion (known as *erythroleukoplakia*) that may be either irregularly flat (speckled) or nodular. Verrucous leukoplakia is yet another type of non-homogeneous leukoplakia. Although verrucous leukoplakia usually has a uniform white appearance, its verrucous texture is the distinguishing feature from homogeneous (flat) leukoplakia. Proliferative verrucous leukoplakia (PVL) is a subtype of verrucous leukoplakia, being characterized by multifocal presentation, resistance to treatment and a high rate of malignant transformation.<sup>8</sup>

The diseases considered in the differential diagnosis includes aspirin burn, chemical injury, oral pseudomembranous and hyperplastic candidiasis, frictional lesions, oral hairy leukoplakia, leukoedema, linea alba, lupus erythematosus, morsicatio buccarum, papilloma and allied lesions, mucous patches in secondary syphilis, tobacco-induced lesions, smoker's palate (nicotinic stomatitis), stuff-induced lesion, white sponge nevus, oral lichen planus (OLP), and lichenoid reaction.<sup>9</sup> Oral leukoplakia should be confirmed by mucosal biopsy.

The frequency of dysplastic or malignant alterations in oral leukoplakia has ranged from 15.6 to 39.2% in several studies. In Indian studies, the rate of malignant transformation ranges from 0.13% to 2.2% per year. In systematic review, Petti has calculated a global transformation rate for oral leukoplakia of 1.36% per year.<sup>12</sup> The lesions that are present in the floor of mouth, lateral tongue and lower lip are more likely to show dysplastic or malignant changes.

### **ORAL ERYTHROPLAKIA:**

Erythroplakia is defined as "a fiery red patch or bright red velvety plaques that cannot be characterized clinically or pathologically as any other definable disease." There are various clinical variations such as:Homogeneous erythroplakia, erythroleukoplakia and Granular or speckled erythroplakia (embracing the lesion described as speckled leukoplakia). It is not as common as leukoplakia and has an incidence reported between 0.02% and 0.83%.<sup>13</sup>

Mostly, a solitary lesion occurs over the surface of any part of the oral cavity. But the most commonly affected areas were reported as the soft palate, the floor of the mouth, and the buccal mucosa. Etiopathogenesis is not known exactly. Chewing tobacco and alcohol use are the possible etiologic factors for the development erythroplakia. Histopathologically, moderate or severe dysplasia was usually seen in lesion with erythroplakia. Malignant transformation rates is very high (vary from 14% to 50%), so it needs to be treated expeditiously.<sup>13</sup> Its differential diagnosis includes: Oral candidiasis, oral histoplasmosis, oral tuberculosis, atrophic OLP, lupus erythematosus, pemphigus, pemphigoids, amelanotic melanoma, haemangioma, telangiectasia, lingual varies, Kaposi's sarcoma, early squamous cell carcinoma, local irritation, mucositis, drug reaction, median rhomboid glossitis, and oral purpura may be confused with oral erythroplakia.<sup>14</sup>

### **ORAL LICHEN PLANUS:**

Lichen planus is an autoimmune disorder of the skin and/or mouth membranes which usually affects middle-aged persons but may occur at any age with a strong female predilection (M:F = 1:2). It is a T-cell-mediated autoimmune disease in which autoreactive CD8<sup>+</sup> T cells trigger apoptosis of oral epithelial cells.<sup>15,16</sup>

Even though OLP may affect any part of the oral mucosa, most commonly affected areas are dorsum of the tongue, buccal mucosa, and gingiva[. Clinically, OLP may be seen as six types including papular, reticular, plaque-like, atrophic, erosive, and bullous type.<sup>16</sup> The most common type is the reticular pattern which present as fine white striae known as "Wickham's striae". Typically, lesions present symmetrically and bilaterally, and usually asymptomatic.

There is still no consensus in the literature whether patients with oral lichen planus (OLP) carry an increased risk of developing squamous cell carcinomas, with majority favoring it. The reported annual malignant transformation rate is usually well below 1%. and some studies attribute a higher rate in specially the atrophic and erosive-ulcerative types.<sup>17</sup>

### **ORAL SUBMUCOUS FIBROSIS:**

Oral submucous fibrosis, was first described by Schwartz in 1952, is chronic and potentially malignant disorder characterized by juxtaepithelial fibrosis of the oral cavity. Fibroelastic change of the lamina propria and epithelial atrophy occur in consequence of juxta epithelial

inflammatory reaction, and eventually, stiffness of oral mucosa, trismus and an inability to eat develops.<sup>18</sup> OSMF is usually seen in Asians population (particularly Indians) from the southern states and Taiwanese. Predominantly, it occurs in the second and third decade, and both sexes may be affected. Its etiology is not well-known and thought to be multifactorial. The strongest risk factor for OSMF is the chewing of betel quid containing areca nut. Other factors like genetic and immunologic predisposition also play a role in OSMF because of reported in families whose members are not in the habit of chewing betel quid or areca nut.<sup>18,19</sup>

Symptoms such as burning sensation and/or intolerance to spicy food are the most common symptoms in the initial phase of the disease. Over time, it gradually progresses and fibrosis develops that can affect mouth opening.<sup>18</sup> In India, it affects between 0-2% and 1.2% of an urban population attending dental clinics. There is a positive association between the incidence of leukoplakia and oral cancer with OSMF. Paymaster firstly described its premalignant nature in 1956. This malignant transformation rate was reported 7%-30%.<sup>20</sup>

#### SCREENING OF ORAL POTENTIALLY MALIGNANT DISORDERS:

The National Screening Committee defines screening as "a process of identifying apparently healthy people who may be at increased risk of a disease or condition." Screening programs can be undertaken for a population at large, or targeting high risk groups, for example, tobacco and alcohol users for oral cancer.

An ideal screening test must be easily applicable and acceptable to the population, cost effective, detect disease early in its natural history and have a high positive predictive value and low false negatives (high sensitivity).<sup>21,22</sup>

Various screening tools includes:

1. Conventional oral examination.
2. Mouth self examination
3. Brush cytology
4. Toluidine blue
5. Light based detection system
6. Chemiluminisence
7. Tissue fluorescence imaging

#### ORAL CANCER:

Cancers of the oral cavity and oropharynx represent approximately three percent of all malignancies in men and two percent of all malignancies in women in the United States. It is estimated that these tumors will account for 28,900 new cases and 7,400 deaths in 2002 in the United States. Squamous cell carcinoma, which arises from the oral mucosal lining, accounts for over 90 percent of these tumors.<sup>23</sup>

Oral cancer most commonly occurs in middle aged and older individuals, although a disturbing number of these malignancies is also being documented in younger adults in recent years. The strong association between cancers of the oral cavity and pharynx with tobacco use is well established. Epidemiological studies show that the risk of developing oral cancer is five to nine times greater for

smokers than for nonsmokers, and this risk may increase to as much as 17 times greater for extremely heavy smokers of 80 or more cigarettes per day.<sup>24,25</sup> Also, Alcohol, betel quid, Iron deficiency anemia and immunosuppression has been identified as a risk factor for oral cancers. Recent evidence suggests that human papillomavirus (HPV) may be associated with some oral and oropharyngeal cancers.<sup>26</sup>

Development of oral cancer in is a multistep process. Complex series of cellular and molecular changes participating in cancer development are mediated by a diversity of endogenous and exogenous stimuli and important amongst this is generation of reactive oxygen species (ROS). Elevated levels of ROS and Reactive Nitrogen Species (RNS) and lowered antioxidants are found in pathogenesis of both oral precancer and cancer. Clinically, Early squamous cell carcinoma often presents as a white patch (leukoplakia), red patch (erythroplakia), or a mixed red and white lesion (erythroleukoplakia). With time, superficial ulceration of the mucosal surface may develop. As the lesion grows, it may become an exophytic mass with a fungating or papillary surface. Pain is not a reliable indicator as to whether a particular lesion may be malignant; larger, advanced carcinomas will often be painful, but many early oral cancers will be totally asymptomatic or may be associated with only minor discomfort.

The most common site for intraoral carcinoma is the tongue, which accounts for around 40 percent of all cases in the oral cavity proper. These tumors most frequently occur on the posterior lateral border and ventral surfaces of the tongue. The floor of the mouth is the second most common intraoral location. Less-common sites include the gingiva, buccal mucosa, labial mucosa, and hard palate.<sup>27</sup>

#### CONCLUSION:

Potentially malignant disorders are an important spectrum of diseases that need to be identified and followed up closely. Correct diagnosis and timely treatment of potentially malignant lesions with high risk of malignant transformation may help to prevent malignant transformation. Clinical examination and histopathology remain the "gold standard" for the detection of oral cancer. However, other than visual examination, no single method for screening seems to be applicable and cost effective in the general population.

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