

# Imperative role of early diagnosis in precancerous lesions: Old ideas, new findings, yet more questions

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## ABSTRACT

In India, cancers of the oral cavity and oropharynx are most common of all malignancies. Over 90% of these tumors are squamous cell carcinomas (SCCs), which arise from the oral mucosal lining. In spite of the ready accessibility of the oral cavity to direct examination, these malignancies still are often not detected until a late stage, and the survival rate for oral cancer has remained essentially unchanged over the past three decades. The purpose of this article is to review the clinical features of premalignant oral lesions, with an emphasis on early detection.

**Keywords:** Oral cancer, precancerous lesions, risk factors

## INTRODUCTION

Cancers of the oral cavity and oropharynx represent approximately two-third of all malignancies in India.<sup>[1]</sup> Squamous cell carcinoma, which arises from the oral mucosal lining, accounts for over 90% of these tumors.<sup>[2]</sup> Identifying and recognizing a premalignant lesion or a frank malignancy in the early stages will go a long way in averting the development of malignancy and will provide an excellent prognosis with minimal disfiguration and functional handicaps.<sup>[3-5]</sup> Mistakes committed in the process can prove costly for the patient who will end up with a disease that has progressed to the point where effective treatment is not possible. In the past decade, there has been a revolutionary advancement in molecular techniques that have unveiled the hidden aspects regarding pathogenesis

and diagnosis. Such assertive suppositions are always criticized by scientific as well as lay communities. Several recently identified risk factors have gained their attention and are contentious and controversial topics till date.

## RISK FACTORS

The strong association between cancers of the oral cavity and pharynx with tobacco use is well established.<sup>[5-8]</sup> Epidemiological studies show that the risk of developing oral cancer is 5-9 times greater for smokers than for nonsmokers, and this risk may increase to as much as 17 times greater for extremely heavy smokers who smoke 80 or more cigarettes per day.<sup>[9,10]</sup> The percentage of oral cancer patients (approximately 80%) is 2-3 times greater for smokers than that of the general population.<sup>[11]</sup> There is a common belief that waterpipe is less harmful than cigarette due to the water filter, which supposedly traps most of the smoke gases and nicotine. This fact may subconsciously increase the daily frequency of waterpipe smoking. Subsequently, smokers will be exposed to more toxic substances. Waterpipe smoking may affect different systems either directly by contact or the smoke itself (as in the respiratory system, lips, oral cavity, and hand skin) or indirectly by the metabolites of tobacco products. Yet, there is strong evidence that exposure to

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waterpipe smoking is as harmful as the exposure to cigarette smoking, if not more harmful.<sup>[12]</sup> Major researches exploring the risk factors associated with oral precancer/cancer are compiled in Table 1.

Snuff and chewing tobacco have also been associated with an increased risk for oral cancer.<sup>[30-33]</sup> Alcohol use has been identified as a major risk factor for cancers of the upper aerodigestive tract. In studies controlled for smoking, moderate-to-heavy drinkers have been shown to have 3-9 times greater risk of developing oral cancer.<sup>[34-36]</sup> In India and Southeast Asia, the chronic use of betel quid (paan) in the mouth has been strongly associated with an increased risk for oral cancer.<sup>[37-40]</sup> The quid typically consists of a betel leaf that is wrapped around a mixture of areca nut and slaked lime, usually with tobacco and sometimes with sweeteners and condiments. The slaked lime results in the release of an alkaloid from the areca nut, which produces a feeling of euphoria and well-being in the user. Betel quid chewing often results in a progressive, scarring precancerous condition of the mouth known as oral submucous fibrosis. In India, one study showed a malignant transformation rate of 7.6% for oral submucous fibrosis.<sup>[41,42]</sup>

The prototypic viruses implicated in oral cancer development are human herpes virus (mainly Epstein Barr virus, [EBV]), human papilloma virus (HPV), and herpes simplex virus. Recent evidence suggests that HPV may be associated with some oral and oropharyngeal cancers. HPV-16 has been detected in up to 22% of oral cancers.<sup>[43-46]</sup> E6 and E7 proteins of low-risk HPV types found in oral leukoplakia may stimulate suprabasal postmitotic infected keratinocytes to re-enter the S-phase of the cell cycle resulting in epithelial proliferation and disturbed maturation, without causing the genomic instability possibly associated with subsequent cell transformation. This mechanism may be a co-determinant of the development of the leukoplakia, but there is no concrete evidence to support this.<sup>[47]</sup> EBV has also been considered a potential risk factor in oral precancer and cancer but

the causal relationship of EBV with oral squamous cell carcinoma (OSCC) is still unclear. Prevalence studies have shown presence of EBV in OSCC patients but they do not prove a causal association.

## EARLY DIAGNOSIS

Early diagnosis depends on an astute clinician or patient who may identify a suspicious lesion or symptom while it is still at an early stage.<sup>[43,45,47]</sup> However, it is apparent that many clinicians, including dentists and physicians, may not be knowledgeable about the risk factors, diagnosis, and early detection of these cancers and/or are not performing routine oral cancer examinations. The Centers for Disease Control and Prevention's 1998 National Health Interview Survey (NHIS) Adult Prevention Supplement included questions regarding examinations for oral cancer.<sup>[48,49]</sup> Participants were asked "Have you ever had a test for oral cancer in which the doctor or dentist pulls on your tongue, sometimes with gauze wrapped around it, and feels under the tongue and inside the cheeks?" 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.<sup>[49]</sup> Invasive OSCC is often preceded by the presence of clinically identifiable premalignant changes of the oral mucosa.<sup>[49]</sup> These lesions often present as either white or red patches, known as leukoplakia and erythroplakia. As the cancer develops, the patient may notice the presence of a nonhealing ulcer. Later stage symptoms include bleeding, loosening of teeth, difficulty wearing dentures, dysphagia, dysarthria, odynophagia, and development of a neck mass.<sup>[50]</sup> Clinicians may wish to include an examination for cancerous and precancerous lesions of the oral cavity in the periodic health examination of persons who chew or smoke tobacco (or did so previously), older persons who drink regularly, and anyone with suspicious symptoms or lesions detected through self-examination. Appropriate counseling should be offered to those persons who smoke cigarettes, pipes, or cigars, those who chew tobacco or snuff, and those who demonstrate evidence of alcohol abuse. Unfortunately, there has been little improvement in the early detection of oral cancer because many patients do not present for diagnosis and treatment until they have Stage III or Stage IV disease. Therefore, in order to improve oral cancer survival, public education efforts are also necessary to encourage patients to avoid high-risk behaviors and to ask their health care providers about regular oral cancer screening examinations.<sup>[50,51]</sup>

## LEUKOPLAKIA

The term leukoplakia was first used by Schwimmer in 1877 to describe a white lesion of the tongue, which

**Table 1: Major risk factors associated with oral pre cancer and cancer**

Risk factors	Pioneer workers
Smoking tobacco	Mehta <i>et al.</i> (1972), <sup>[13]</sup> Johnson <i>et al.</i> (2001) <sup>[14]</sup>
Smokeless tobacco	Muir <i>et al.</i> (1986), <sup>[15]</sup> Johnson <i>et al.</i> (1993) <sup>[16]</sup>
Alcohol	Hashibe <i>et al.</i> (2000), <sup>[17]</sup> Hindle <i>et al.</i> (2000) <sup>[18]</sup>
HPV	Herrero <i>et al.</i> (2003), <sup>[19]</sup> Bertolus <i>et al.</i> (2012) <sup>[20]</sup>
EBV	Sand <i>et al.</i> (2002), <sup>[21]</sup> Cruz <i>et al.</i> (2000) <sup>[22]</sup>
Candida	Rindum (1994), <sup>[23]</sup> McCullough (2002) <sup>[24]</sup>
Dietary deficiencies (iron, vitamins A, C, E)	De Stefani <i>et al.</i> (1999), <sup>[25]</sup> Soler (2001) <sup>[26]</sup>
Imbalance in sex hormones	Singh <i>et al.</i> (2012) <sup>[27]</sup>
Genetic predisposition	Park(2000), <sup>[28]</sup> Copper (1995) <sup>[29]</sup>

probably represented a syphilitic glossitis. The definition of leukoplakia has often been confusing and controversial—so much so that some clinicians now avoid using this term in their lexicon. As defined by the World Health Organization, leukoplakia<sup>[51,52]</sup> is “a white patch or plaque that cannot be characterized clinically or pathologically as any other disease. As such, leukoplakia should be used only as a clinical term; it has no specific histopathological connotation and should never be used as a microscopic diagnosis. In the evaluation of the patient, leukoplakia is a clinical diagnosis of exclusion. If an oral white patch can be diagnosed as some other condition (e.g., candidiasis, lichen planus, leukoedema, etc.), then the lesion should not be considered to be an example of leukoplakia. Sometimes, a white patch is initially believed to represent leukoplakia, but the biopsy reveals another specific diagnosis. In such cases, the lesion should no longer be categorized as a leukoplakia.<sup>[41,48]</sup> The usage of the term leukoplakia continues to undergo refinement. Frequently, oral white patches are seen secondary to identifiable local irritation. For example, thickened hyperkeratotic changes are frequently found on the edentulous areas of the alveolar ridges, especially in patients who do not wear an overlying dental prosthesis.<sup>[51]</sup> Because these exposed edentulous sites receive more irritation during mastication, there is a natural tendency for the epithelium to become more hyperkeratotic as a protective phenomenon, similar to a callus developing on one’s hand. Two specific tobacco-related lesions of the oral mucosa, nicotine stomatitis and tobacco pouch keratosis, have often been included under the broad umbrella of leukoplakia.<sup>[36,37]</sup> As these lesions have a specific known cause and prognosis, we prefer to classify them separately from leukoplakia. The most common sites are the buccal mucosa, alveolar mucosa, and lower lip; however, lesions in the floor of mouth, lateral tongue, and lower lip are most likely to show dysplastic or malignant changes.<sup>[50]</sup> Early or thin leukoplakia appears as a slightly elevated grayish-white plaque that may be either well defined or may gradually blend into the surrounding normal mucosa. As the lesion progresses, it becomes thicker and whiter, sometimes developing a leathery appearance with surface fissures (homogeneous or thick leukoplakia). Some leukoplakias develop surface irregularities and are referred to as granular or nodular leukoplakias.

Other lesions develop a papillary surface and are known as verrucous or verruciform leukoplakia. One uncommon variant, known as proliferative verrucous leukoplakia (PVL),<sup>[53]</sup> is characterized by wide spread, multifocal sites of involvement, often in patients without known risk factors. The condition begins with conventional flat white patches that, over time, tend to become much thicker and papillary in nature and has high risk of malignant transformation. In recent years, a number of oral white

patches have been identified that appear to be related to the use of toothpastes or mouth rinses containing the herbal extract, sanguinaria.<sup>[52,53]</sup> Microscopically, these lesions usually show hyperkeratosis and epithelial atrophy, sometimes in association with true dysplasia, although the potential for the development of cancer is uncertain. Some leukoplakias occur in combination with adjacent red patches or erythroplakia called as speckled leukoplakia or speckled erythroplakia.

## ERYTHROPLAKIA

The term erythroplakia was originally used by Queyrat to describe a red, precancerous lesion of the penis.<sup>[36,41]</sup> The term erythroplakia is used for a clinically and histopathologically similar process that occurs on the oral mucosa. Similar to the definition for leukoplakia, erythroplakia is a clinical term that refers to a red patch that cannot be defined clinically or pathologically as any other condition.<sup>[41]</sup> This definition excludes inflammatory conditions that may result in a red clinical appearance. Oral erythroplakia occurs most frequently in older men and appears as a red macule or plaque with a soft, velvety texture. The floor of mouth, lateral tongue, retromolar pad, and soft palate are the most common sites of involvement.<sup>[41]</sup> Often the lesion is well demarcated, but some examples may gradually blend into the surrounding mucosa. Some lesions may be intermixed with white areas (erythroleukoplakia). Erythroplakia is often asymptomatic, although some patients may complain of a sore, burning sensation. Although erythroplakia is not nearly as common as leukoplakia, it is much more likely to show dysplasia or carcinoma.<sup>[31]</sup> True clinical erythroplakia is a much more worrisome lesion than leukoplakia. Likewise, in a mixed erythroleukoplakia, the red component is more likely to demonstrate dysplastic changes than is the white component; when selecting an appropriate biopsy site in a mixed lesion, the clinician should make sure that the specimen includes the red component.<sup>[52]</sup>

## NICOTINE STOMATITIS

Nicotine stomatitis is a thickened, hyperkeratotic alteration of the palatal mucosa that is most frequently related to pipe smoking, but milder examples can also develop secondary to cigar smoking or, rarely, from cigarette smoking.<sup>[51]</sup> The palatal mucosa becomes thickened and hyperkeratotic, sometimes developing a fissured surface. The surface often develops popular elevations with red centers, which represent the inflamed openings of the minor salivary gland ducts. The term nicotine stomatitis is actually a misnomer because it is not the nicotine that causes the changes; the changes are caused by the intense heat generated from smoking.<sup>[36]</sup> Although nicotine stomatitis is a tobacco-related pathosis, it is not considered to be premalignant and it is

readily reversible with discontinuation of the tobacco habit. However, in some Southeast Asian and South American countries, individuals practice a habit known as reverse smoking<sup>[34]</sup> in which the lit end of the cigarette or cigar is placed in the mouth. This habit creates a more severe heat-related alteration of the palatal mucosa known as reverse smoker's palate, which has been associated with a significant risk of malignant transformation.<sup>[34]</sup>

## TOBACCO POUCH KERATOSIS

Another specific tobacco-related oral mucosal alteration occurs in association with smokeless tobacco use, either from snuff or chewing tobacco.<sup>[35]</sup> Such lesions typically occur in the buccal or labial vestibule where the tobacco is held, but they can also extend onto the adjacent gingiva and buccal mucosa. Early lesions may show slight wrinkling that disappears when the tissues are stretched. Other lesions may appear as hyperkeratotic, granular patches.<sup>[35]</sup> Advanced lesions exhibit greatly thickened zones of grayish-white mucosa with well-developed folds and fissures.<sup>[35]</sup> Microscopically, smokeless tobacco keratoses show hyperkeratosis and acanthosis of the mucosal epithelium. True epithelial dysplasia is uncommon; when dysplasia is found, it is usually mild in degree. However, significant dysplasia or squamous cell carcinoma occasionally may be discovered.<sup>[49]</sup>

## SCREENING

Population-based screening programs for oral precancerous lesions are costly given the low number of lesions in the general population in developed countries. Screening performed by professionals, although more accurate, is more expensive than screening performed by health care auxiliaries. Patient participation and settings vary, and economic constraints make it necessary to direct screening efforts toward high-risk individuals. A simulation model of population screening for oral premalignant lesions (OPLs) and oral and oropharyngeal squamous cell carcinomas (OOSCCs) indicated that approximately 18,000 patients would need to be screened in order to save one life. This rate is comparable to that for cervical cancer. Therefore, incidental screening has been suggested when patients are seen for other examinations by health care providers. Primary care physicians can provide this type of screening for these lesions in target individuals. Definitive guidelines for screening of oral cancer are not well established. Clinical examination appears to provide valid screening, especially when performed by highly trained health care personnel. A recent study in India enrolled nearly 100,000 patients who received oral examinations and compared their outcomes with those of a similarly sized control group who did not receive oral screening examinations (level evidence). Among those screened, 205 oral cancers were diagnosed and

77 patients died of oral cancer; in the control population, 158 oral cancers were diagnosed and 87 patients died of oral cancer. Screening examinations were, therefore, associated with reduced mortality among high-risk patients. Self-examination might be a cost-effective option for OPL and OOSCC screening.<sup>[36,38,40]</sup> A study that examined the feasibility of self-examination of the oral cavity reported that of 247 subjects presenting to the participating clinics, 6 (2.4%) had stage I *oral squamous cell carcinoma* (OSCC), and only one individual was diagnosed with an advanced stage of disease. The detection rate of oral cancer following self-examination compared favorably with examination by trained health care workers.<sup>[41,52-55]</sup>

## MOLECULAR MARKERS IN CANCER/PRE-CANCER

Cancer cells result from disruptions in circuits that regulate proliferation and homeostasis of normal cells. Numerous studies had been conducted in past decade to find a reliable marker which can early predict the behavior of precancer. The most predictive molecular markers, thus far available and assessed in OSCC development, include the tumor suppressor genes (TSG) p53 protein expression, chromosomal polysomy (deoxyribonucleic acid [DNA] ploidy), and changes (termed loss of heterozygosity [LOH]) in chromosomes 3p or 9p (probably due to changes in the TSG p16).<sup>[56]</sup> The use of such biomarkers as adjuncts to routine histopathological examination may help prognostication and effective management of potentially malignant lesions (PMLs) but their routine use is still hampered by the cost and complexity of the tests, the lack of facilities in some laboratories, and limited outcome studies to date. More readily available markers, such as those of cell proliferation (Ki-67 antigen) and apoptosis (Bax, Bcl-2), may also play a diagnostic role: apoptotic Bcl-2 expression decreases significantly in dysplastic and early invasive lesions and then increases almost to normal tissue level in consequent stages, whereas Ki-67 expression increases sharply in initial stages of OSCC, but significantly decreases in later stages.<sup>[57]</sup> Oral cavity showed an important change in the cytokeratin expression pattern for Ck8/18 and 19 in the initiation and progression of SCCs and its precursor lesions.<sup>[58]</sup>

## CONCLUSION

The ability to control oral and oropharyngeal cancer will depend on two cornerstones: prevention and early diagnosis. Continuing educational campaigns are needed on the local, state, and national levels in order to educate the public about the risk factors and early signs/symptoms associated with this disease. Individuals also need to be encouraged to seek regular professional oral examinations by a dentist and/or physician. Finally, health care workers

must be encouraged to perform oral cancer examinations as part of their patient care regime, and to be knowledgeable about early signs of oral carcinoma.

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