Introduction
In the United States, cancers of the oral cavity and oropharynx represent approximately 3% of all malignancies.\textsuperscript{1,2,3} An estimated 30,000 people will be diagnosed with oral cancer this year, and about half of them will eventually die of the disease.\textsuperscript{3} Over 90% of these tumors are squamous cell carcinomas which arise from the oral mucosal lining.\textsuperscript{2} Ironically, while most oral cancers are mucosal lesions, and theoretically readily detectable upon exam, they are often not detected until a late stage. Subsequently, the survival rate for oral cancer has remained relatively unchanged over the past three decades.

Epidemiology
Age is the epidemiologic factor that confers the strongest associated link to oral cancer. Oral cancer most commonly occurs in middle-aged and older individuals, although in recent years a disturbing number of malignancies have been documented in a much younger age population. Intraoral and oropharyngeal tumors are more common among men than women, with a male to female ratio of over 2:1.\textsuperscript{1,2,4} This disparity in the male:female ratio has become less pronounced over the past half century. This change may reflect the increased incidence of smoking among women and the greater proportion of females in the over 65 age category. The annual incidence of oral and pharyngeal cancer in Black males in the United States has increased dramatically, while non-Black males have shown a gradual decrease since 1980.\textsuperscript{1} In contrast to intraoral and oropharyngeal carcinomas, cancers of the lip vermillion demonstrate a pathophysiology more akin to squamous cell carcinoma of sun-exposed skin. Carcinoma of the lip vermillion is primarily found in white males with a history of chronic sun exposure.\textsuperscript{1,2,4}

Risk factors
A strong association between tobacco use and cancers of the oral cavity proper and oropharynx has been well established. Epidemiologic studies have shown that the percentage of oral cancer patients who smoke (approximately 80%) is 2 to 3 times greater than that of the general population.\textsuperscript{2} In addition, oral cancer patients who continue to smoke following treatment have a 2.6 times greater risk for developing a second primary carcinoma of the upper aerodigestive tract.\textsuperscript{2,3}

The use of snuff, smokeless tobacco, and chewing tobacco may have an increased risk for oral cancer, however, the data supporting this evidence is conflicting in the literature. Snuff is a moist, nonfermented tobacco product originating from the species *Nicotinum tabacum*.\textsuperscript{5} Recent studies from Scandinavia have suggested that the use of Swedish snuff, which differs from what is commonly referred to as snuff in the United States, is not associated with an increased risk for oral cancer.\textsuperscript{2} Approximately 15% of all adult males in Sweden use, or have used, an oral snuff produced predominately in Sweden. Regardless, the use of any type of smokeless tobacco appears to be associated with a much lower cancer risk than that associated with smoked tobacco.\textsuperscript{1,2,4,5,6} However, many patients who use smokeless tobacco also consume cigarettes and alcohol and thereby increase their risk of oral cancer. Moreover, the use of smokeless tobacco also carries with it other health risks such as elevated blood pressure, physiologic dependence, and worsening periodontal disease. According to the World Health Organization, any tobacco product is an etiologic agent for the formation of oral leukoplakia, which has been defined as a white patch or plaque that does not wipe off and cannot be characterized clinically or pathologically as any other disease.\textsuperscript{2} Oral leukoplakia is by far the most common oral premalignancy representing 85% of white nonremoveable lesions of the oral mucosa.\textsuperscript{1,4} This is of particular concern to our military population. A study by Grasser and Childers demonstrated that the prevalence of smokeless tobacco use in the U.S. Army was greater than 32%.\textsuperscript{7} This was 8 times higher than the goal set by the U.S Department of Health and Human Services.\textsuperscript{1} Various studies have shown the rate of malignant transformation of oral leukoplakia to be from 0.13 to 20%.\textsuperscript{1,2,4,7}

Alcohol consumption and abuse has been identified as a major risk factor for cancers of the upper aerodigestive tract.\textsuperscript{1,2,4,8} Interestingly, experimental studies have not implicated alcohol itself as a carcinogen.\textsuperscript{8} However, alcohol may promote carcinogenesis by a variety of mechanisms. Such mechanisms include nutritional deficiencies, contaminants within alcohol itself, induction of microsomal enzymes, and the capacity of alcohol to solubilize carcinogens or enhance their penetration into oropharyngeal tissues.\textsuperscript{2,9}

The synergistic effect of heavy alcohol consumption and tobacco smoking can be staggering. Together, these agents function in a multiplicative fashion rather than additive. Studies have shown more than a 35 fold increase risk among those who consume two or more packs of cigarettes and more than four alcoholic drinks in a day.\textsuperscript{9}

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.\textsuperscript{9} This quid typically consists of a betel leaf that is wrapped around a mixture of areca palm nuts, slaked lime, and usually includes tobacco or sweeteners. This compound of natural substances is chewed for its psychostimulatory effects. Betel quid chewing often results in a progressive, scarring precancerous condition of the mouth known as oral submucous fibrosis. Among the betel quid users in Asia, the lifetime risk of developing oral cancer is 8%.\textsuperscript{1,2,9}

Recent evidence has suggested that human papillomavirus (HPV) may be associated with some oral and oropharyngeal cancers. HPV subtypes 16, 18, 31, and 33 are the strains that have been most commonly reported to be associated with some oral and oropharyngeal cancers. HPV subtypes 16, 18, 31, and 33 are the strains that have been most commonly reported to be associated with dysplasia and squamous cell carcinoma.\textsuperscript{1,2} Other risk factors may include iron deficiency anemia (Plummer-Vinson Syndrome), immunosuppression (AIDS), syphilis, ionizing radiation therapy, phenols, and vitamin A deficiency.\textsuperscript{1,2,4}

Pathogenesis
Oral cancer, like most other malignancies, arises from the accumulation of a number of discrete genetic events that lead to invasive cancer.\textsuperscript{9} These changes occur in genes that code for proteins that control the cell cycle, cell survival, cell motility, and angiogenesis.\textsuperscript{10} Genetic mutations confer a selective growth advantage, permitting clonal expansion of mutant cells with an increased malignant potential.\textsuperscript{2,4,10} Essentially, oral cancers progress through two important biological steps. The first is loss of cell cycle control through increased proliferation via reduced cellular apoptotic mechanisms. The second key step is increased tumor cell motility, thus leading to epithelial cells penetrating the basement membrane and eventual metastasis. Both stages are the direct result of the
activation, or up-regulation, of oncogenes and the inactivation, or down-regulation, of tumor suppressor genes. Oncogenes, or protooncogenes under normal circumstances, are altered genes which overexpress encoded proteins, thus allowing for clonal expansion. Tumor suppressor genes, on the other hand, are genes which normally encode for proteins that negatively regulate or suppress the cell cycle. Alteration of these genes will essentially “release the brake” on cellular proliferation. Tumor suppressor genes appear to play a more important role in the development of oral cancer than oncogenes.\textsuperscript{2,4,10}

**Histopathologic evolution of oral cancer**

Oral cancer classically evolves through stages of epithelial dysplasia: mild, moderate, severe dysplasia, and full thickness epithelial dysplasia or carcinoma in-situ. Finally, obliteration of the epithelial basement membrane and invasion into the underlying connective tissue results in invasive squamous cell carcinoma.\textsuperscript{1,2,4} However, it should be noted that an orderly progression of dysplastic change is not a prerequisite prior to the development of squamous cell carcinoma. If lesions demonstrate epithelial dysplasia histologically, follow-up studies have shown that approximately 15\% of cases will transform into invasive squamous cell carcinoma.\textsuperscript{2,4} The histopathologic diagnosis of carcinomatous transformation rests upon the identification of invasion into the underlying connective tissue.\textsuperscript{1,2,4}

**Identification of precancerous lesions**

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 and alcohol abuse are identified. Invasive oral squamous cell carcinoma is often preceded by the presence of clinically identifiable premalignant changes of the oral mucosa. Most oral cancers present as painless mucosal ulcerations or exophytic masses.\textsuperscript{1,2,4} However, any non-healing ulceration, unexplained white lesion (leukoplakia) or red lesion (erythroplakia), induration, fixed enlargement, or lymphadenopathy requires biopsy and/or appropriate referral. The concept of precancerous mucosal change is paramount for early detection. Precancerous lesions have been primarily categorized according to color.

Leukoplakia is a clinical term that does not connote any specific histologic tissue alteration.\textsuperscript{1,2,4,10} Although leukoplakia has been overemphasized in its relationship to cancer, the etiology of any white lesion should be determined or monitored. The causes of leukoplakia are varied and include both intrinsic and extrinsic factors. Extrinsic factors include: tobacco, alcohol, and actinic radiation. Intrinsic factors include: vitamin deficiencies, immunodeficiencies, and genetic predisposition. A classic study by Waldron et al. revealed that 80\% of these lesions showed benign changes such as hyperkeratosis, thickening of the epithelium (acanthosis) without any evidence of epithelial dysplasia (a pre-cancerous condition), a male predilection, and occurred mainly in patients in 50-70 years of age.\textsuperscript{11}

Two specific tobacco-related lesions of the oral mucosa, nicotinic stomatitis and tobacco pouch keratosis, have often been included under the broad umbrella of leukoplakia. However, since these lesions have a specific known cause and prognosis, most authorities prefer to classify them separately from leukoplakia.\textsuperscript{1,2}

Early or thin leukoplakia appears clinically 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 (homogenous or thick leukoplakia).\textsuperscript{1,2} Some leukoplakias develop surface irregularities and are referred to as granular leukoplakias. Other lesions develop a papillary surface and are known as verruciform leukoplakias. One uncommon variant, known as proliferative verrucous leukoplakia (PVL), is characterized by wide spread multifocal sites of involvement, often in patients without any known risk factors.\textsuperscript{1,2} The condition begins with conventional flat white patches that, over time, tend to become much thicker. This papillary proliferation may progress to the point where the lesion can be categorized microscopically as a verrucous carcinoma. However, in spite of treatment, these lesions have a high recurrence rate and often eventually transform into a more aggressive squamous cell carcinoma.

In recent years, a number of oral white patches have been identified that appear to be related to the use of toothpaste or mouth rinses containing the herbal extract, sanguinaria.\textsuperscript{1,2} Such lesions most frequently have been identified on the maxillary alveolar mucosa and buccal vestibule. 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. Because sanguinaria-associated keratoses can be extensive or multifocal, sometimes they are misinterpreted as early proliferative verrucous leukoplakia.\textsuperscript{1,2}

The clinical appearance of leukoplakia tends to correlate with the underlying histology and likelihood of dysplasia or malignant features.\textsuperscript{1,2} Some leukoplakias occur in combination with adjacent red patches or erythroplakia. When these areas are intermixed, they are often referred to as speckled leukoplakia and have a much higher risk of oral cancer.\textsuperscript{1,2,4}

Erythroplakia is classically described as an erythematous macule or plaque with a velvety or granular appearing surface. The boundaries of these lesions may be poorly defined, irregular, and may demonstrate a blending of inflamed and normal mucosa. Like leukoplakia, erythroplakia is reserved as a clinical term. Although erythroplakia is less common than leukoplakia, it has a much greater propensity to be severely dysplastic at the time of biopsy.\textsuperscript{7} Approximately 90\% of all biopsies of erythroplakia will show epithelial dysplasia, carcinoma in-situ, or invasive squamous cell carcinoma.\textsuperscript{1,2,4} Most suspicious erythroplakias are found in patients considered to be heavy drinkers and smokers 40 years and older.\textsuperscript{2,4,8} In high risk patients, the red, velvety lesions appear long before any ulceration, bleeding, induration, dysfunction, pain, or lymphadenopathy.

Clinical Update Part II will examine a more in depth view of squamous cell carcinoma, variants of squamous cell carcinoma, histologic grading and AJCC staging overview, as well as common treatment modalities.

**References**


Dr. Steven Marc Stokes is a resident in the Oral and Maxillofacial Pathology Department, and Dr. Castle is Chairman of the Oral and Maxillofacial Pathology Department.

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