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# Recognition of oral potentially malignant disorders and transformation to oral cancer

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## ABSTRACT

Oral potentially malignant disorders refer to oral mucosal disorders with increased risk for malignant transformation, primarily to oral squamous cell carcinoma (SCC). Leukoplakia and erythroplakia are the most common of these disorders, but others have been identified. Transformation rates to oral cancer vary based on multiple factors. Healthcare providers should be aware of risk factors and clinical manifestations of these disorders and should intervene early to monitor and/or treat them to reduce the potential for malignant transformation.

**Keywords:** oral potentially malignant disorders, cancer, leukoplakia, erythroplakia, oral squamous cell carcinoma, malignant transformation

## Learning objectives

- Discuss factors associated with the development of oral cancer and describe their relative prevalence based on geography and/or patient ethnicity.
- Compare and contrast the clinical features of the OPMDs discussed in the article.
- Describe the rates of transformation to oral cancer of the selected OPMDs.

More than 53,000 new cases of oral cancer are expected in the United States in 2020, representing 2.9% of all new cancer cases.<sup>1</sup> The number of new cases of oral and pharyngeal cancers per 100,000 persons has been rising almost 1% per year for the last 10 years.<sup>1</sup> The tongue is the primary site of cancer except in South and Southeast Asia, where the buccal mucosa is a more common location.<sup>2</sup> About 90% of oral cancers are squamous cell carcinomas (SCC), which arise from the mucosal lining and typically are advanced at the time of detection.<sup>3</sup> If detected and treated early, local oropharyngeal cancers have a 5-year survival rate of 84.4%.<sup>1</sup> Once regional or distant spread has occurred, the 5-year survival rate drops to 66% and 39%, respectively.<sup>1</sup> Although rates of 5-year survival have improved from 54.8% in 1986 to

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DOI:10.1097/01.JAA.0000718268.52634.59

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**Key points**

- OPMDs are oral mucosal disorders with increased risk of transformation into oral cancer.
- Most cases of oral cancer are preceded by asymptomatic OPMDs.
- Leukoplakia is the most common OPMD.
- Most oral cancers are squamous cell carcinoma.

69.8% in 2011, nearly one-third of patients die within 5 years of diagnosis.<sup>1</sup>

*Oral potentially malignant disorders* (OPMDs) refer to oral mucosal disorders with increased risk for malignancy.<sup>4</sup> This replaces the terms *precancerous* or *pre-malignant*, and more appropriately reflects the fact that not all of these lesions or conditions will ultimately transform into oral cancer.<sup>5</sup> OPMDs are a diverse spectrum of oral lesions and conditions ranging from the more well-known (leukoplakia and erythroplakia) to the lesser-known (reverse smoker's palate) and rare hereditary conditions (dyskeratosis congenita).<sup>6</sup> Most cases of oral cancer are preceded by asymptomatic OPMDs; however, the rate of malignant transformation for OPMDs varies.<sup>6,7</sup> Factors that affect malignant transformation include patient demographics and modifiable risk factors, OPMD appearance and size, anatomic location, and presence of oral epithelial dysplasia on histopathology, which represents cytological atypia and/or epithelial architectural alterations.<sup>4</sup>

The World Health Organization (WHO) uses a three-tier system to grade dysplasia as mild, moderate, or severe.<sup>7</sup> The grade of oral epithelial dysplasia is considered the most significant predictor for malignant transformation and the best guide for treatment and management.<sup>4,7</sup> This article reviews major risk factors for oral cancer and highlights the more common OPMDs in Western populations and their potential for malignant transformation.

**ORAL CANCER RISK FACTORS**

Tobacco and alcohol cause about 75% of all oral cancers and are the two major risk factors for patients in the United States.<sup>8</sup> Combined cigarette smoking and alcohol consumption have a synergistic effect on the development of oral and oropharyngeal cancers.<sup>2</sup>

The association between tobacco and oral cancer is well established, with rates of oral cancer in tobacco users as high as 20 times that of nonusers depending on the type of tobacco, amount, and duration of use.<sup>9,10</sup> Tobacco products contain more than 70 known carcinogens, each associated with an increase in cancer occurrence in tobacco users.<sup>11</sup> N-nitrosornicotine, a carcinogen commonly found in tobacco products, is specifically associated with the development of head and neck tumors.<sup>11</sup> The International Agency for Research on Cancer has classified tobacco (smoked and smokeless) as a group 1 carcinogen for oral

cancer, which means sufficient evidence exists to conclude that these products are carcinogenic to humans.<sup>2</sup>

The second largest risk factor for oral cancer development is alcohol consumption.<sup>2,3</sup> Alcohol has been identified as an independent risk for oral SCC in a dose-response relationship.<sup>2</sup> Alcohol is thought to act as a solvent that either increases the solubility of carcinogens or increases the permeability of the oral mucosa to carcinogens.<sup>12</sup> The way alcohol is metabolized also may contribute to the development of oral cancer. Although most alcohol is metabolized in the liver, extrahepatic metabolism of alcohol to acetaldehyde occurs in the oral mucosa.<sup>13</sup> Acetaldehyde, a carcinogen, may then accumulate in the oral tissues.<sup>13</sup> Alcohol use also may induce epithelial cell damage, inhibit DNA repair, and cause systemic effects, such as malnutrition or immunosuppression, which alter the liver's ability to metabolize or eliminate potentially carcinogenic agents.<sup>12</sup> Regardless of the underlying mechanism, studies have demonstrated that the risk of developing oral cancer rises with increasing alcohol consumption.<sup>14</sup> Other studies have shown that the total amount and duration of alcohol use is more relevant to the development of oral cancer than the type of alcohol consumed.<sup>13,14</sup>

Globally, up to 1.2 billion people chew betel quid, with the highest rates of use in Asian populations.<sup>2</sup> Chewing this substance produces psychostimulatory effects of euphoria.<sup>2,13</sup> Although contents vary based on region of use, betel quid generally consists of a mixture of slaked lime, areca nut, and betel leaf with or without tobacco.<sup>2</sup> Although the areca nut itself is carcinogenic, traditionally the carcinogenicity of betel quid has been attributed to its tobacco content.<sup>2</sup> The overall risk of developing oral precancerous lesions and oral cancer in users of these smokeless tobacco products ranges from twice the rate of nonusers to a 15-fold increased risk.<sup>15</sup>

Although the relationship between high-risk human papillomavirus (HPV) and oropharyngeal SCC has been established, the link between HPV and OPMDs is less clear.<sup>4</sup> The prevalence of high-risk HPV in the oral cavity is between 1% and 3%, with HPV-16 being most common.<sup>16</sup> One recent study demonstrated malignant transformation of HPV-positive oral epithelial dysplasia lesions to invasive SCC in 15% of the patients studied.<sup>16</sup>

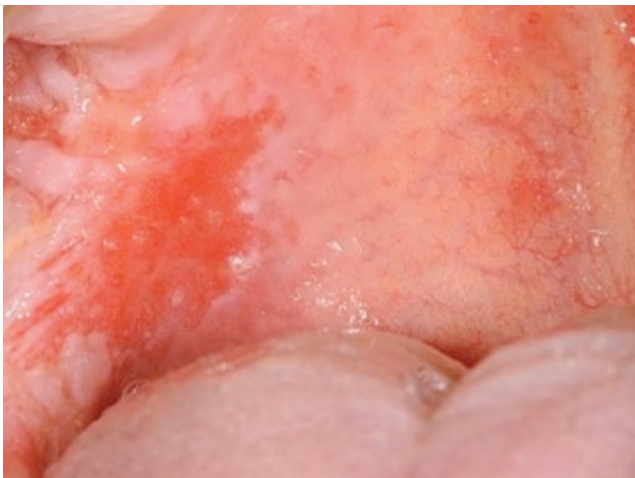
**LEUKOPLAKIA**

The WHO defines leukoplakia as "a white plaque of questionable risk having excluded (other) known-diseases or disorders that carry no increased risk for cancer."<sup>5</sup> Leukoplakia is the most common OPMD with an estimated worldwide prevalence of 1.5% to 2.6%.<sup>7</sup> It is more common in men and usually diagnosed after age 40 years.<sup>6</sup>

Most cases of leukoplakia are associated with tobacco, alcohol, or betel quid use.<sup>6</sup> Leukoplakia is six times more common in smokers than nonsmokers.<sup>6</sup> Alcohol use is considered an independent risk factor for leukoplakia.<sup>6</sup> Any portion of the oropharyngeal cavity may be affected,



**FIGURE 1.** Leukoplakia



**FIGURE 2.** Erythroplakia

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but the most common locations for leukoplakia in Western populations are the lateral margins of the tongue and the floor of the mouth (Figure 1).<sup>6</sup> The buccal mucosa and the buccal grooves are more commonly affected in Asian populations due to the placement of betel quid.<sup>7</sup>

Clinically, the two main types of leukoplakia are homogenous and nonhomogenous.<sup>5,6</sup> Homogenous leukoplakia lesions are uniformly flat, thin lesions with shallow surface keratin cracks or fissures.<sup>5,6</sup> Nonhomogenous leukoplakia include nodular, verrucous (warty) lesions, and speckled

white and red lesions (erythroleukoplakia) with the red component representing possible *Candida* species colonization.<sup>5,6</sup> Proliferative verrucous leukoplakia (PVL) is a rare exophytic variant of leukoplakia involving multiple sites and often appearing in patients without known risk factors.<sup>2,6</sup>

Although leukoplakia is the most common OPMD, in most patients it will not progress to cancer.<sup>2,4</sup> The exact rate of malignant transformation of leukoplakia to oral SCC is unknown. In a systematic review of 24 observational studies, Warnakulasuriya and Ariyawardana estimated a 3.5% mean malignant transformation rate for the study population.<sup>17</sup> The authors reported a higher malignant transformation rate for homogenous leukoplakia than for nonhomogeneous leukoplakia and identified tongue lesions as having the highest rate of malignant transformation (more than 22%).<sup>17</sup> Other factors associated with an increased risk of malignant transformation of oral leukoplakia to SCC include female sex, advanced age, longer duration of leukoplakia, higher degree of dysplasia, leukoplakia lesions greater than 200 mm<sup>2</sup> in size, presence of *C. albicans*, and leukoplakia in nonsmokers.<sup>2,7,17</sup>

### ERYTHROPLAKIA

Erythroplakia is the red counterpart to leukoplakia and is defined by the WHO as “a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease.”<sup>5</sup> Oral erythroplakia is less common than leukoplakia, with a prevalence of less than 1%.<sup>4</sup> Erythroplakia most commonly occurs in older adults and is associated with tobacco and alcohol use.<sup>18</sup>

Erythroplakia lesions may be flat or depressed with a velvety or granular texture and are most common on the soft palate (Figure 2).<sup>6</sup> Lesions may be irregular in outline, but they typically have well-defined borders and present in a solitary fashion.<sup>6,18</sup> Most erythroplakia lesions are asymptomatic, but some patients may complain of an associated burning sensation.<sup>2</sup> Erythroplakia should be distinguished from erythematous candidiasis, a benign lesion that occurs more commonly and is easily treatable.<sup>6</sup> Erythematous candidiasis also may present with a burning sensation in the mouth but lesions usually occur in a bilaterally symmetrical pattern.<sup>18</sup>

Although erythroplakia is less common than leukoplakia, in most patients it will undergo malignant transformation and demonstrate some degree of high-grade dysplasia, carcinoma in situ, or invasive SCC.<sup>2</sup> The true rate of malignant transformation is unknown.<sup>18</sup>

### ORAL LICHEN PLANUS

Lichen planus is a mucocutaneous inflammatory disorder affecting less than 2% of the population.<sup>19</sup> Oral lichen planus may occur in conjunction with cutaneous lesions or as the sole manifestation of the disorder (Figure 3).<sup>19</sup> This condition is more common in women and older adults.<sup>19</sup>

Subtypes of oral lichen planus include reticular, linear, annular, papular, plaque, bullous, ulcerative, and atro-





**FIGURE 3.** Oral lichen planus

phic.<sup>6,19</sup> The reticular subtype occurs most frequently and presents as bilaterally symmetric lace-like white striae (Wickham striae), most commonly located on the buccal mucosa and lateral margins of the tongue.<sup>6</sup> Most lesions, regardless of type, are asymptomatic; however, ulcerative oral lichen planus typically presents with either a burning sensation or soreness in the oral cavity.<sup>6</sup>

Oral lichen planus may be chronic with intermittent flares and remissions.<sup>6</sup> It can be diagnosed clinically based on patient history and appearance, but biopsy and histopathology confirms definitive diagnosis.<sup>6</sup> A recent meta-analysis identified an annual malignant transformation rate of 0.2%.<sup>19</sup> Erosive lesions and lesions located on the tongue are associated with higher rates of malignant transformation.<sup>4</sup> Other factors associated with higher rates of malignant transformation include female sex, smoking, alcohol use, and hepatitis C infection.<sup>4</sup>

### ORAL DISCOID LUPUS

Lupus erythematosus is an autoimmune condition characterized by vascular changes in various parts of the body.<sup>6</sup> The disease has several forms, but oral lesions can occur in patients with the systemic form and are more common in those with the discoid form.<sup>6,20</sup> Oral lesions in a patient with discoid lupus are irregular keratotic white plaques with central erythema or ulcerations bordered by white striations and, in some cases, telangiectasias (Figure 4).<sup>6,20</sup> These lesions tend to form on the labial mucosa, buccal mucosa, palate, and at the vermillion border of the lower lip.<sup>6,20</sup> Up to 20% of patients with skin manifestations of lupus also will have these oral lesions; and, though rare, some patients will present with only oral lesions and no



**FIGURE 4.** Discoid lupus

evidence of skin disease.<sup>20</sup> The clinical features of oral discoid lupus are strikingly similar to oral lichen planus, but the two can be distinguished by biopsy.<sup>20</sup>

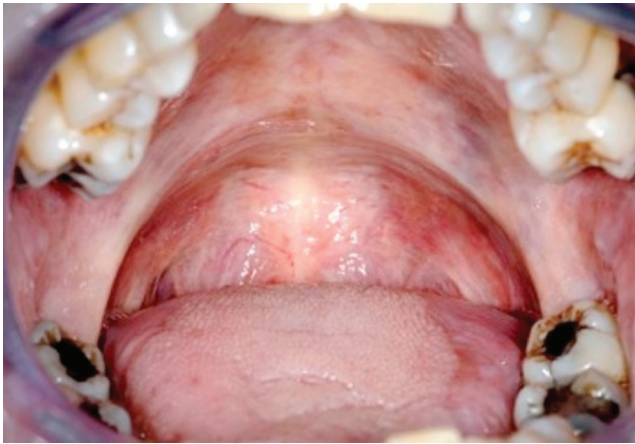
The WHO considers discoid lupus a potentially malignant disorder, though transformation is very rare.<sup>6</sup> Reported rates of transformation of discoid lupus lesions to SCC on sun-exposed areas of the face are about 3%; rates of transformation for oral discoid lupus lesions to any form of cancer have not been reported but are presumed to be lower than that of sun-exposed areas.<sup>21</sup>

### ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis is a chronic disorder with resultant loss of fibroelasticity of the oral cavity, oropharynx, and upper third of the esophagus (Figure 5).<sup>5</sup> This disorder is most common in South and Southeast Asian populations because of the use of betel quid and areca nut chewing, which are the predominant risk factors.<sup>4,6</sup>

Early features include a characteristic burning sensation of the oral mucosa in response to spicy foods as well as atrophy and whitening of oral cavity structures.<sup>6</sup> Advanced findings include palpable fibrous bands and a leathery mucosal texture.<sup>6</sup> These changes result in tongue rigidity and decreased mobility and progressive limitation of mouth opening, a characteristic feature of oral submucous fibrosis.<sup>6</sup>

Studies of oral submucous fibrosis have demonstrated a varying rate of malignant progression, from 1.9% to 9.1%.<sup>4</sup> Data suggest that malignant transformation occurs more



**FIGURE 5.** Oral submucous fibrosis

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frequently when patients also have oral epithelial dysplasia and concomitant leukoplakia lesions.<sup>4</sup>

## CONCLUSION

Historically, oral cancers have been associated with advanced presentations and lower survival rates. Oral cancer often is preceded by an OPMD; however, no single criterion exists to predict malignant transformation.<sup>4,7</sup> Biopsy is required to confirm the diagnosis of an OPMD and to grade oral epithelial dysplasia, if present.<sup>7</sup> Because of its high risk of malignant transformation, erythroplakia usually requires surgical excision.<sup>18</sup> Other OPMDs, (including leukoplakia, oral lichen planus, oral discoid lupus, and oral submucous fibrosis) may remain unchanged, show complete regression, or take years to transform to oral SCC.<sup>18</sup> Risk factors (tobacco, alcohol, and betel quid) should be eliminated whenever possible.<sup>22</sup> Treatment is based on a variety of considerations including patient profile, lesion type, and associated characteristics.<sup>4,18</sup> Management options, which are beyond the scope of this article, may include surgical excision or nonsurgical options such as chemoprevention or observation.<sup>22</sup> Periodic lifelong evaluations have been recommended at 3- to 6-month intervals to examine for new or changing clinical manifestations that may indicate malignant transformation.<sup>18</sup>

Clinicians should educate and screen patients on risk factors of OPMDs and oral cancer, perform thorough head, neck, and oral cavity examinations, and recognize features of various OPMDs and oral cancer. Early intervention by performing a thorough history and conducting regular examinations of the oral cavity continues to be the most effective means of diagnosing oral cancer early and reducing patient morbidity and mortality. **JAAPA**

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