

Paying more than lip service to lip lesions

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ABSTRACT

OBJECTIVE To review the epidemiology, etiology, diagnosis, management, and prognosis of the most common, potentially lethal, lip lesions: leukoplakia, actinic cheilitis, and squamous cell carcinoma (SCC).

QUALITY OF EVIDENCE MEDLINE was searched from 1966 to 2002 for English-language articles on prevalence of lip lesions. No articles for a family physician audience were found. MEDLINE was searched again using the terms "leukoplakia," "actinic cheilitis," and "squamous cell carcinoma." Randomized, controlled trials were selected; non-blinded trials, population-based studies, and systematic reviews were also used.

MAIN MESSAGE Leukoplakia, actinic cheilitis, and SCC of the lips are relatively common presentations that can cause substantial morbidity and, more rarely, mortality. Any abnormality of the lips can be an embarrassment. Because of the seriousness and frequency of lip disease, it is important to look for, diagnose, and treat lip lesions to prevent morbidity and mortality and also to maintain social acceptance and self-esteem.

CONCLUSION Knowledge of leukoplakia, actinic cheilitis, and SCC of the lips will aid family physicians in diagnosing and managing these lesions and in preventing associated morbidity and mortality.

RÉSUMÉ

OBJECTIF Faire le point sur l'épidémiologie, l'étiologie, le diagnostic, le traitement et le pronostic des lésions labiales potentiellement létales les plus fréquentes: leucoplasie, chéilite actinique et épithélioma malpighien spino-cellulaire (ÉMSP).

QUALITÉ DES PREUVES Les articles de langue anglaise sur la prévalence des lésions labiales ont été répertoriés dans MEDLINE entre 1966 et 2002. Il n'y en avait aucun à l'intention des médecins de famille. Les termes «leucoplasia», «actinic cheilite» et «squamous cell epithelioma» ont été utilisés pour cette recherche. On a choisi les essais randomisés, mais on a également utilisé des essais ouverts, des études stratifiées et des revues systématiques.

PRINCIPAL MESSAGE La leucoplasie, la chéilite actinique et l'ÉMSP de la lèvre sont des lésions relativement fréquentes qui peuvent entraîner une morbidité appréciable et parfois même causer la mort. Toute anomalie des lèvres peut être une source d'embarras pour le patient. Parce que ces lésions sont fréquentes et potentiellement graves, elles doivent être recherchées, diagnostiquées et traitées si l'on veut prévenir la morbidité et la mortalité associées, et maintenir un bon niveau d'acceptation sociale et d'estime de soi.

CONCLUSION Le médecin qui connaît bien la leucoplasie, la chéilite actinique et l'ÉMSP des lèvres sera en mesure de faire un diagnostic et un traitement adéquats, tout en prévenant la morbidité et la mortalité associées à ces lésions.

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The anatomical placement of the lips results in maximal exposure to ultraviolet (UV) radiation, food, and tobacco, factors that can cause substantial morbidity and, more rarely, mortality. Because of the prominent position of the lips, abnormalities are obvious and can be a source of embarrassment. It is important to diagnose and treat lip lesions not only to prevent morbidity and mortality, but also to maintain patients' social acceptance and self-esteem.

Lip lesions are a common reason for patients to come to family physicians' offices. One large-scale screening study reported 29.6 people affected per 1000 patients screened in several communities in Minnesota.¹ This study revealed the most common lip anomaly to be a precancerous lesion in the form of leukoplakia. This article describes three serious lip lesions: leukoplakia, actinic cheilitis, and squamous cell carcinoma (SCC).

Quality of evidence

MEDLINE was searched from 1966 to 2002 for English-language articles. Initially, we used the MeSH terms "lips" and "prevalence" to establish which lesions were most common. References of articles selected were used to find additional relevant articles. After determining the most common lip lesions, we searched using the terms "leukoplakia," "actinic cheilitis," and "squamous cell carcinoma." Current controlled clinical trials were selected when available. We also used reviews; population-based studies, both prospective and retrospective; case-control studies; and case reports.

Leukoplakia

Leukoplakia can occur at any site in the oral cavity, including the lip. It was the most common lip lesion (overall prevalence 9.3/1000) diagnosed among 23616 white Americans in a study by Bouquot and Gundlach.¹ This is a serious concern due to the relatively high rate (5% in 5 years) of malignant transformation associated with these lesions.² The lip vermilion border was the site most frequently involved, with a predilection for the lower lip.¹ Another study of oral mucosal leukoplakia found age- and sex-specific factors related to the prevalence of leukoplakia: men

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have a much higher risk of developing this precancerous lesion as they age.³ Experts attribute this to exposure to the sun and the higher proportion of actinic changes in older male farmers.¹

Dermatologic presentation of leukoplakia varies. Leukoplakia can develop as single or multiple white patches or plaques with either sharply defined or indistinct borders and sometimes adjacent ulceration (Figure 1).⁴ Leukoplakia can also present as slightly thickened and smooth, wrinkled and indurated, or even raised corrugated verrucous plaques.⁴ A more subtle presentation is shown in Figure 2, where the lip vermilion border has become blurred and indistinct.

Figure 1. Leukoplakia affecting the lower lip of a 70-year-old male farmer with a history of smoking



Figure 2. Leukoplakia affecting the lower lip of a 72-year-old man and blurring the lip vermilion border



Epithelial changes that give rise to leukoplastic lesions are associated with many factors including tobacco⁵⁻⁸; alcohol^{6,8}; candidal and human

papillomavirus (HPV) infection⁹; low body mass index⁸; diabetes mellitus⁵; and irritants, such as ill-fitting dentures.¹⁰ Tobacco and alcohol use have the strongest correlation and are associated with malignant transformation. Leukoplastic changes related to chronic irritation from ill-fitting dentures, for example, do not result in overt malignancy.⁴

Tobacco has a well documented dose-response relationship with development of oral cancer. Studies show a similar relationship for development of oral leukoplakia. Both smokeless and smoked forms of tobacco have been implicated, although the association with smokeless tobacco is stronger.⁵⁻⁸ Alcohol is an independent risk factor for development of oral leukoplakia.⁸ Interestingly, one large-scale, case-control study found this association stronger in women than men.⁸

Pathogenesis of leukoplakia is related to inflammatory and immunologic changes, as well as DNA changes caused by the aforementioned factors.⁴ Early management of leukoplakia includes taking a careful history and recommending removal of any risk factors, most importantly use of alcohol and tobacco. If lesions have no apparent cause or are still present 4 weeks after removal of "causative" irritants, a biopsy should be performed.¹¹ If the biopsy indicates benign epithelial changes, no further treatment is necessary, but monitoring is important. Histologic changes consistent with atypia require treatment.

Treatments include excision, electrodesiccation and curettage (EDC), cryotherapy, and laser ablation.¹¹ One study of 142 patients with oral leukoplakia showed that the malignant transformation rate at follow up more than 6 months later was much lower in those treated with surgical excision (1.3%) than in those who received non-surgical treatment (7.8%).¹²

Prognosis of oral leukoplakia is very good if lesions are histologically benign or if atypia is discovered and treated early. A high index of suspicion, close monitoring, and educating patients about risk factors can improve long-term outcome. All patients with a long history of alcohol or tobacco use should have their oral cavities carefully inspected as part of periodic health examinations.

Actinic cheilitis

Actinic cheilitis is a term used to describe degenerative, premalignant skin changes that occur on the lips. It is caused by exposure to UV radiation. "Actinic" refers to the chemically active rays of the electromagnetic spectrum; "cheilitis" refers to inflammation of the lips. Ultraviolet B radiation is primarily responsible for actinic damage.¹³ As much as 70% of

UVB rays are absorbed by the skin; only 5% to 10% are reflected.¹⁴ Actinic cheilitis is most commonly seen on the lower lip of middle-aged and older (40 to 80 years), fair-skinned men, who have had excessive exposure to sun during their lives.¹⁵

Actinic cheilitis can be the initial lesion in a progression to SCC.¹⁶ The rate of malignant transformation of all forms of actinic keratoses to SCC is controversial, but rates lower than 1/1000 per year are often cited.¹⁷ Unfortunately, SCC of the lips has a higher metastatic potential than other cutaneous SCCs.¹⁸ Clinical presentation of actinic cheilitis cannot always be distinguished from early SCC, making accurate diagnosis and monitoring these lesions even more important for primary care physicians.¹⁶

Actinic cheilitis presents as rough, scaly lips with fissures and ulcerations.¹⁶ Usually there is a single lesion, but multiple lesions also occur. The initial sun-induced lesion is whitish-gray or brown, and the lip vermilion border becomes indistinguishable and shows generalized atrophy. Plasticity is lost. Marked folds appear along the vermilion perpendicular to the long axis of the lips. Patients often complain that their lips are constantly dry as well. The lower lip is more commonly affected due to the angle of the UV rays striking the vermilion surface. For the same reason, the labial surface is more commonly affected than the angle of the lips. Palpation is important in diagnosis because actinic cheilitis has a fine, "sandpapery" feel to it.¹³ An example of actinic cheilitis is shown in **Figure 3**.

Figure 3. An 84-year-old man with features characteristic of actinic cheilitis affecting the lower lip



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Risk factors for developing actinic cheilitis include immunosuppression; genetic conditions, such as xeroderma pigmentosum; fair skin; and exposure to sunlight.^{13,15,16} Many studies suggest an association with tobacco use.^{13,18} Exposure to damaging UV rays causes dysplastic changes at the cellular level that result in a buildup of keratin.⁴ Reasons for lips' susceptibility to actinic changes are numerous and include lack of keratin covering, thinner epithelium, smaller amounts of melanin, and decreased secretions from sebaceous and sweat glands, all of which normally protect skin from radiation.¹³

The degree of histologic damage and subsequent malignant potential cannot be predicted clinically. Each case of actinic cheilitis must be thoroughly investigated and managed aggressively.¹³ Any suspect lesions should be biopsied and examined under a microscope or referred for specialist care. Once diagnosis is confirmed, many treatments are available. Topical 5-fluorouracil or chemical peels with trichloroacetic acid can be effective, but both these therapies are painful and have been associated with recurrence (50% to 70%) of clinically suspect lesions within 4 years.¹⁹ Lip shaves, or "vermilionectomies," involve excision of all or part of the vermilion.¹⁹ The benefit of this treatment is that the specimen can be examined histologically afterward. Carbon dioxide laser treatment has also proven effective, and electrodesiccation has been shown to be a practical, inexpensive alternative.²⁰ As with most diseases, however, identification of those at risk and recommending preventive measures are key to treating actinic cheilitis.

Prognosis is good with early diagnosis and treatment of actinic cheilitis. A prospective study of 40 patients with actinic cheilitis showed no recurrence after treatment with vermilionectomy or carbon dioxide laser 4 years later.¹⁹

Squamous cell carcinoma

The most common type of oral cancer is SCC.²¹ Although easily detectable, oral cavity cancers are often discovered too late, and 60% are ultimately fatal.⁴ Incidence of skin and oral cancer increases with age: most oral cancers are found in patients aged 50 to 70.²² Incidence of SCC is increasing as the population ages and as life expectancy increases.

Unfortunately, SCC lesions found on oral mucosa, including labial mucosa, are more aggressive and more likely to metastasize than lesions in other locations.²² Metastatic rates of 14% are reported for SCC of the lip, higher than for other cutaneous SCCs.¹⁸ Some have suggested that the higher rate of

metastasis is due to the lack of subcutaneous fat and the rich supply of lymphatic vessels to the lips.²³

One third of patients with SCC can expect to develop another SCC within 5 years of therapy for the primary lesion.²⁴ This is due to the concept of "condemned mucosa" that applies to all mucosal cancers of the head and neck. In condemned mucosa, prolonged exposure of the aerodigestive mucosa to carcinogens causes changes at the molecular level that involve the entire mucosa.²⁵ With time, these changes can develop into premalignant and malignant lesions, causing high rates of second primary cancers.

Squamous cell carcinoma begins on the surface and initially spreads superficially. Then it spreads deeper into the submucosa. It is not until the late stages that SCC reaches the deeper vessels and thick fascia underlying the tissue. Presentation varies: some early lesions present as elevated, firm plaques, while others present as verrucous areas of mucosal thickening (which can be mistaken for leukoplakia). Erythroplakia refers to mucosal SCC in situ and is another early presentation. It appears as a solitary, pink, scaly plaque with irregular edges. Usually, SCC lesions enlarge, begin to protrude and necrose centrally, and produce an irregular ulcer. Lip SCC tends to metastasize to the submental and submaxillary lymph nodes.¹⁸ Examples of SCC of the lips are shown in **Figures 4 and 5**.

The lips are considered a high-risk site for development of SCC due to their chronic exposure to sunlight. The lower lip receives maximal exposure.²² Tobacco and alcohol use are implicated in SCC, but actinic radiation and pipe smoking are more specifically related to SCC of the lip.⁴ All risk factors for leukoplakia also predispose to SCC of the lip since leukoplakia sets the stage for malignant changes.¹⁰ These predisposing

Figure 4. A 62-year-old man with a 4-month history of a keratotic lower lip lesion: Biopsy showed a well differentiated squamous cell carcinoma.



Figure 5. A 75-year-old woman with a 6-month history of a lower lip lesion: Biopsy showed a well differentiated squamous cell carcinoma.



factors deregulate cell growth and death, giving the squamous epithelial cells a selective growth advantage that ultimately results in carcinoma at the expense of the remaining healthy cells.

Management of presumed SCC begins with a full-thickness skin biopsy to identify the neoplasm. Histologic features help to predict clinical behaviour and the chance of recurrence or metastasis of the lesion. Various biopsy techniques, such as punch, shave, incisional, or excisional, can be used, and all can be done in outpatient settings.

Once diagnosis of malignancy is made, the tumour must be eradicated. Various treatments, including standard excision, Mohs micrographic surgery, radiation therapy, cryosurgery, and EDC, can be used. Mohs micrographic surgery is most efficacious in preventing local recurrence of SCC of the lips and gives the best cosmetic result, but it is readily available only at tertiary care centres.²⁶ All remaining treatments have roughly the same cure rates.²⁶ Patients with biopsy-proven SCC of the lips should be referred to dermatologic, oral, plastic, or general surgeons as dictated by geographical circumstances.

Table 1. Important points about lip lesions

QUESTIONS	LEUKOPLAKIA	ACTINIC CHEILITIS	SQUAMOUS CELL CARCINOMA
Who is at risk?	Men more than women ³ Old more than young ³	White men ¹⁵ aged 40–80 years ¹⁵ exposed to the sun	Same as for leukoplakia and actinic cheilitis
Other associations?	Tobacco use ^{5,8} Alcohol use ^{6,8} Candidal and HPV infection ⁹ Low BMI ⁶ Diabetes mellitus ⁵ Irritants (eg, ill-fitting dentures ¹⁰)	Immunosuppression ^{13,15,16} Genetic conditions (eg, xeroderma pigmentosum ^{13,15,16}) Possibly tobacco use ^{13,20}	Same as for leukoplakia and actinic cheilitis Especially pipe smoking and ultraviolet exposure ⁴
What to look for?	Single or multiple white patches or plaques Possibly adjacent ulceration	Lower lip involvement Rough, scaly lips Single or multiple lesions Initially whitish-gray or brown lesions Marked folds along vermilion border	Variable presentation Elevated, firm plaques Verrucous areas of mucosal thickening Protruding and ulcerate lesions Submental and submaxillary lymphadenopathy
Why the concern?	Associated with malignancy	Associated with many newly diagnosed SCCs	Higher metastatic potential than other SCCs ¹⁸
What to do about it?	Reduce risk factors Biopsy if no apparent cause or lesions persist >4 weeks after risk-factor reduction ¹¹ Remove lesion if it has atypical histology ¹¹ Treatment • Best: excision ¹² • Other: EDC, cryotherapy, laser ablation ¹¹	Biopsy any suspect lesion Consider referral to specialist Treatment • Best: excision ¹⁹ • Other: carbon dioxide laser, EDC ²⁰	Full-thickness skin biopsy Consider referral to specialist Treatment • Best: Mohs micrographic surgery ²⁶ • Other: non-Mohs excision, radiation therapy, EDC ²⁶
What is the prognosis?	Malignant transformation in 5/1000 per year	Malignant transformation in <1/1000 per year (controversial)	If no lymph node metastases, 90% 5-year survival ⁴ With metastases, 34.4% 5-year survival ²⁶

BMI—body mass index, EDC—electrodessication and curettage, HPV—human papillomavirus, SCC—squamous cell carcinoma.

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Squamous cell carcinoma of the lips has the best prognosis of all oral forms of this malignancy. Lip lesions detected early and excised are reported to have 90% 5-year recurrence-free rates.⁴ A review of all studies since 1940 on prognosis of SCC of the lips reported a 2.3% recurrence rate and a 7.6% metastatic rate at follow up more than 5 years after Mohs surgery.²⁶ In comparison, other treatments yielded a 10.5% recurrence rate and a 13.7% metastatic rate.²⁶ Combining data from all treatments of metastatic SCC of the lip, Rowe et al found a 34.4% 5-year survival rate.²⁶ It takes months to years for SCC of the oral cavity to progress from carcinoma in situ to invasive malignancy. Early diagnosis and cure are possible in most cases. **Table 1**^{3-13,15,16,19,20,26} shows important points discussed for each lesion.

Conclusion

Lip lesions are a common presentation in family physicians' offices. These lesions are often benign and might require treatment only for cosmetic reasons. A small number of lip lesions, however, are potentially lethal and thus require appropriate intervention to prevent further morbidity and mortality. Comprehensive medical care includes looking for, diagnosing, and treating the various lip lesions. ❖

Competing interests

None declared

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Editor's key points

- Although relatively uncommon, lip lesions are seen in family practice. Diagnosing serious lesions early is important.
- The three most common, serious lesions are leukoplakia, actinic cheilitis, and squamous cell carcinoma. They might be associated with environmental exposure to tobacco and sunlight.
- Early diagnosis and treatment can usually lead to complete cure.
- Excision is usually the most effective treatment, but other methods, including electrodesiccation, cryotherapy, laser treatment, and Mohs micrographic surgery, can be used.

Points de repère du rédacteur

- Même si les lésions labiales sont relativement rares, le médecin de famille en rencontre dans sa clientèle. Les lésions graves nécessitent un diagnostic précoce.
- La leucoplasie, la chéilite actinique et l'épithélioma malpighien spino-cellulaire sont les trois lésions sérieuses les plus fréquentes. Elles pourraient être associées à une exposition au tabac et aux rayons solaires.
- Un diagnostic et un traitement précoces permettent généralement une guérison complète.
- En général, l'excision est le traitement le plus efficace, mais d'autres méthodes, comme l'électrodesiccation, la cryothérapie, le traitement au laser et la chirurgie micrographique de Mohs, peuvent aussi être utilisées.

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