Screening for and diagnosis of oral premalignant lesions and oropharyngeal squamous cell carcinoma

Role of primary care physicians

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ABSTRACT

OBJECTIVE To describe the role that primary care physicians can play in early recognition of oral and oropharyngeal squamous cell carcinomas (OOSCCs) and to review the risk factors for OOSCCs, the nature of oral premalignant lesions, and the technique and aids for clinical examination.

QUALITY OF EVIDENCE MEDLINE and CANCERLIT literature searches were conducted using the following terms: *oral cancer and risk factors, pre-malignant oral lesions, clinical evaluation of abnormal oral lesions,* and *cancer screening.* Additional articles were identified from key references within articles. The articles contained level I, II, and III evidence and included controlled trials and systematic reviews.

MAIN MESSAGE Most OOSCCs are in advanced stages at diagnosis, and treatment does not improve survival rates. Early recognition and diagnosis of OOSCCs might improve patient survival and reduce treatment-related morbidity. Comprehensive head and neck examinations should be part of all medical and dental examinations. The head and neck should be inspected and palpated to evaluate for OOSCCs, particularly in high-risk patients and when symptoms are identified. A neck mass or mouth lesion combined with regional pain might suggest a malignant or premalignant process.

CONCLUSION Primary care physicians are well suited to providing head and neck examinations, and to screening for the presence of suspicious oral lesions. Referral for biopsy might be indicated, depending on the experience of examining physicians.

RÉSUMÉ

OBJECTIF Décrire le rôle éventuel du médecin de première ligne dans la détection des épithéliomas malpighiens spinocellulaires oraux et oro-pharyngés (ÉMSOO) et revoir les facteurs de risque associés, la nature des lésions orales précancéreuses, et les techniques et outils facilitant l'examen clinique.

QUALITÉ DES PREUVES On a répertorié MEDLINE et CANCERLIT à l'aide des rubriques suivantes: *oral cancer and risk factors*, *pre-malignant oral lesions*, *clinical evaluation of abnormal oral lesions*, et *oral cancer screening*. Des articles additionnels ont été identifiés à partir des références-clés des articles. Les articles présentaient des preuves de niveaux I, II et III, et incluaient des essais randomisés et des revues systématiques.

PRINCIPAL MESSAGE La plupart des ÉMSOO sont à un stade avancé au moment du diagnostic, et le traitement n'améliore pas le taux de survie. Une détection et un diagnostic précoces pourraient améliorer la survie et réduire la morbidité associée au traitement. Un examen minutieux de la tête et du cou devrait faire partie de tout examen médical ou dentaire. La tête et le cou devraient être inspectés et palpés à la recherche d'ÉMSOO, notamment chez les patients à risque élevé et en présence de symptômes suspects. Une tuméfaction cervicale ou une lésion orale accompagnée d'une douleur dans la région pourrait suggérer une lésion cancéreuse ou précancéreuse.

CONCLUSION Le médecin de première ligne est bien placé pour faire l'examen de la tête et du cou, et pour détecter des lésions orales suspectes. Une biopsie pourra être demandée, selon l'expérience du médecin examinateur.

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Oral cancer most often refers to squamous cell carcinoma of the oral cavity (the anatomic region that extends from the lip to the junction of the hard and soft palate superiorly and the vallate papillae of the tongue inferiorly). Oropharyngeal cancers include cancers of the base of the tongue, tonsil, soft palate, and posterior pharyngeal wall. Many oropharyngeal cancers are difficult to see, even when using a tongue blade and light source.

Approximately three-quarters of oral and oropharyngeal squamous cell carcinomas (OOSCCs) occur among those living in developing countries. In Southeast Asia, OOSCCs account for 40% of all cancers compared with approximately 4% in developed countries.[1-3] The American Cancer Society estimates that approximately 30 000 new cases of OOSCCs are diagnosed and more than 8000 people die of these cancers in the United States each year.[4] In England, the incidence of OOSCCs is 4/100 000 per year across all age groups, but more than 30 cases per 100 000 are diagnosed among those older than 65 years of age.[5] More than 90% of OOSCCs occur among patients older than 40 years of age.[6]

Eighty-one percent of patients with OOSCCs will survive for at least 1 year following diagnosis, while the 5-year relative survival rate for all stages of OOSCCs is approximately 50%.[4] Unfortunately, the 5-year survival rate has not changed substantially in the past few decades, despite advances in surgery, radiation therapy, and chemotherapy.[7,8] For early stage OOSCCs (stage I and II), the 5-year relative survival rate is approximately 80%; whereas for advanced disease (stage III and IV), the 5-year survival rate is less than 25%.[4-7] In addition, advanced disease requires more aggressive therapy, employing combined treatments that might result in increased morbidity and cost of care and reduced quality of life. The most logical approach to decreasing morbidity and mortality associated with OOSCCs is to increase detection of suspicious oral premalignant lesions (OPLs) and early detection of OOSCCs. Educating medical and dental professionals and the public about the benefits of preventive screening might help achieve this goal.

The purpose of this article is to review and update the risk factors for OOSCCs, the nature of OPLs, and the technique and aids for clinical examination for reliable clinical screening, and to describe the role that primary care physicians can play in early recognition of OOSCCs.

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Quality of evidence

MEDLINE and CANCERLIT literature searches were conducted using the following terms: *oral cancer and risk factors, pre-malignant oral lesions, clinical evaluation of abnormal oral lesions,* and *cancer screening*. Additional articles were identified from key references within articles. The articles contained level I, II, and III evidence and included controlled trials and systematic reviews.

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

Risk factors

Oral and oropharyngeal squamous cell carcinomas are associated with several well-recognized etiologic risk factors (**Table 1**). Patients with higher relative risks of developing OOSCCs include those with history of tobacco and alcohol use. More than 70% of patients with OOSCCs report history of tobacco use,[9] and about 80% of cases are associated with alcohol or tobacco abuse.[10] The risk of OOSCCs increases approximately ninefold among those individuals who have had prior upper aerodigestive tract cancer, compared with the general population.[11] Similarly, 20% to 30% of patients with prior history of upper aerodigestive tract cancer

Table 1. Risk factors for oral premalignant lesions and oropharyngeal squamous cell carcinoma

RISK FACTORS
Age older than 45 y
Combined tobacco and alcohol use or abuse
Betel nut use
Immunosuppression (disease or therapy related)
Prior upper aerodigestive tract cancer
Sun exposure (lips)
Oral human papillomavirus infection
HIV infection*

*HIV infection might be associated with increased risk of oral premalignant lesions and oropharyngeal squamous cell carcinoma.

develop recurrent disease or second primary cancers.[12] The risk of second primary cancers is greater than that attributable to continued tobacco or alcohol use, suggesting that host risk factors further increase the risk of OOSCCs.[13]

Other reported risk factors for OOSCCs include the following: betel nut chewing; oral human papillomavirus (HPV) infection; and chronic immunosuppression following solid organ transplant, hematopoietic cell transplant, and, possibly, HIV infection and AIDS. For example, squamous cell carcinoma of the tonsil has the highest prevalence of HPV-16 DNA among the OOSCCs, suggesting increased risk associated with HPV in this location.[14] In addition to tobacco and alcohol use, HPV infection, immunodeficiency, and, possibly, genetic changes represent risk factors for OOSCCs among patients with HIV infection.[14-18] Individuals older than 45 years of age and African Americans also have higher risks of OOSCCs.[3,19]

Oral premalignant lesions

Oral premalignant lesions include leukoplakia, erythroplakia, dysplastic leukoplakia, dysplastic lichenoid lesion, oral submucous fibrosis, and lichen planus (**Figures 1-3**). The clinical presentations of oral mucosal lesions are presented in **Table 2**. Oral premalignant lesions have shown a rate of progression of up to 17% within a mean period of 7 years after diagnosis. The highest transformation rate is seen in those lesions with clinically irregular or heterogeneous erythroplakia and dysplastic changes.[20,21] Features of OPLs associated with risk of progression to cancer include colour (red, red-white), irregularity (lack of homogeneity), surface texture (granular, verrucous), and location (floor of mouth, ventral or posterolateral border of the tongue).[6,22] Ultrastructural changes, including phenotypic change (the presence and severity of dysplasia), DNA instability, and allelic loss (particularly involving chromosome arms 3p, 9p, and 17p, and other molecular markers), affect the risk of developing OOSCCs.[22,23]

Table 2. Clinical presentations of oral mucosal lesions: *Risk sites include the posterolateral border of the tongue, the floor of the mouth, and the oropharynx (tonsil, base of tongue).*

CLINICAL PRESENTATIONS
Leukoplakia (white)
Erythroplakia (red)
Erythroleukoplakia (red and white)
Nonhealing ulcers
Possible associated pain

Screening

Population-based screening programs for OPLs and OOSCCs are costly given the low number of lesions in

Figure 1. Irregular leukoplakia (verrucous leukoplakia) with squamous cell carcinoma in the upper right vestibule where a mass can be seen, and dysplasia in the remaining leukoplakia

Figure 2. Asymptomatic red (erythroplakic) lesion involving the soft palate and tonsillar fossa, diagnosed as squamous cell carcinoma

Figure 3. Mixed red and white lesion on the floor of the mouth, a high-risk site for cancer

the general population in developed countries. Screening performed by professionals, although more accurate, is more expensive than screening performed by health care auxiliaries.[24] Patient participation and settings vary, and economic constraints make it necessary to direct screening efforts toward high-risk individuals.[25-29] A simulation model of population screening for OPLs and OOSCCs indicated that approximately 18 000 patients would need to be screened in order to save 1 life.[30] 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 OPLs and OOSCCs in target individuals.

Definitive guidelines for screening of oral cancer are not well established. The most recent US Preventive Services Task Force report (2004) found insufficient evidence to recommend for or against screening for oral cancer among smokers older than 50 and those at low risk.[31] The task force found little data on sensitivity and specificity of oral examination for cancer (level II and III evidence). Opportunistic oral cancer screening is recommended by the Canadian Dental Association and the American Dental Association; these organizations emphasize that early detection allows treatment at earlier stages of disease (level III evidence).[32,33] The Canadian Task Force on Preventive Health Care reported that there was insufficient evidence to recommend for or against opportunistic screening and fair evidence to exclude population screening for oral cancer; they did, however, recommend annual examinations for high-risk patients (level II evidence).[34] Other authors have argued that targeted clinical examination of high-risk individuals might be more effective than mass screening in facilitating early detection of oral cancers.[35] 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 not given oral screening examinations (level I evidence).[36] 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. A study that examined the feasibility of self-examination of the oral cavity[37] reported that of 247 subjects presenting to the participating clinics, 6 (2.4%) had stage I OOSCCs, and only 1 individual was diagnosed with an advanced stage of disease. The detection rate of oral cancer following self-examination compared favourably with examination by trained health care workers.[37]

Examination

The examination (**Figure 4**) must include a comprehensive inspection of the head and neck, with assessment

Figure 4. Oral, head, and neck examination

STEPS

Take the patient's history:
- oral and neck lesions
- pain or bleeding
- change in function

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Inspect and palpate for masses or enlargement of the following:
- cervical lymph nodes
- thyroid
- salivary glands

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Perform a cranial nerve examination

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Perform an intraoral inspection and palpation:
- assess lips, cheeks, and floor of mouth
- retract tongue and assess lateral tongue borders, tonsillar pillars and fossae, hard palate, soft palate, and gingival tissue
- examine for white, red, and mixed red and white lesions; masses; ulcerations; pigmentations; bruising; bleeding; and altered function

EQUIPMENT

White light source (halogen)
Gauze
Tongue blade
Gloves
Adjuncts:
- toluidine blue
- chemiluminescence
- exfoliative cytology

of cervical lymph nodes and cranial nerve function. A neck mass or mouth lesion combined with regional pain might suggest a malignant or premalignant process. A gloved hand and tongue blade or dental mirror can be used to retract the lips and extend the cheeks for visual examination and palpation. Use gauze wrapped around the tongue to assist with retraction and examination of the lateral borders of the tongue. A white light source (halogen) provides the best illumination with colour balance. The highest risk oral sites, including the lateral borders of the tongue, the floor of the mouth, the posterior aspect of the cheek, and the oropharynx, must be evaluated. The first site of spread of OOSCCs beyond the aerodigestive tract is usually to the cervical lymph nodes. Palpation of these nodes must be included as part of every comprehensive head and neck examination. Any lymph node larger than 1 cm should be noted, and the patient should be referred for further evaluation and diagnosis. Some patients with OOSCCs initially present with enlarged lymph nodes without any other signs or symptoms.

The head and neck examination should include inspection and palpation of the cheeks, parotid glands, and submandibular glands. Asymmetry should be noted and any cutaneous lesions assessed. Intraoral examination is best accomplished with an external light source that enables both hands to be free to retract the cheeks, buccal mucosa, tongue, and lips, allowing full view of all mucosal surfaces. Most hospital rooms do not have appropriate external light sources and require physicians to hold light sources, such as penlights, otoscopes, or ophthalmoscopes, to illuminate the oral cavity. Unfortunately, this prevents a bimanual examination. Examination of the oropharynx, nasopharynx, and larynx is important in any patient with OOSCCs in order to search for second primary tumours and for risk factors and symptoms, including odynophagia, dysphagia, sore throat, or dysphonia. This type of examination requires a mirror and a fiberoptic nasopharyngoscope or laryngoscope. If these are not available, referral to an otolaryngologist might be indicated.

Various aids have been advocated to assist in early detection of OPLs and OOSCCs, but these have not yet been incorporated into guidelines.[38] Examination adjuncts have been compared with standard examinations among high-risk or referred populations in several trials providing level II evidence. One randomized controlled trial of toluidine blue provided level I evidence.[39] Use of toluidine blue, as a mouth rinse or applied with cotton-tipped applicators to sites of tissue change, has been advocated for identifying lesions, accelerating decision to biopsy, and guiding biopsy site selection.[39] Chemiluminescence might make OPLs easier to see; it is used as an adjunct to the Papanicolaou smear to increase detection of dysplastic and neoplastic changes in the cervix.[40,41] One study of chemiluminescence for detection of oral lesions found that although white lesions and lesions that were both red and white showed enhanced brightness and sharpness, chemiluminescence did not make red lesions more visible.[42] A recent multicentre trial that assessed patients following visual examination with chemiluminescence and toluidine blue applied with swabs found that stain retention reduced the false-positive rate by 55% while maintaining a 100% negative predictive value (level I evidence).[43] Additional trials (level II evidence) have assessed tissue autofluorescence in patients known to have cancer and found it to have high sensitivity and specificity,[44,45] although this technology has not been applied in noncancer patient evaluations and the role in screening is unknown. Additionally, an exfoliative cytology (brush-type "biopsy") technique has been developed for accumulating cellular samples of deeper epithelial layers for computerized morphologic and cytologic examination followed by pathologist review.[46] Definitive diagnosis, however, requires an open biopsy.

EDITOR'S KEY POINTS

- Oral and oropharyngeal cancers account for 4% of cancers in developed countries and up to 40% in developing countries. Risk factors include tobacco and alcohol use.
- The Canadian Task Force on Preventive Health Care does not recommend population screening but suggests annual examinations for those at high risk.
- Careful clinical examination is essential for the early detection of oral and oropharyngeal cancers. Examination adjuncts, such as toluidine blue, can be helpful in identifying suspicious lesions.
- Definitive diagnosis requires a biopsy.

POINTS DE REPÈRE DU RÉDACTEUR

- Les cancers oraux et oro-pharyngés représentent 4% des cancers dans les pays développés et jusqu'à 40% dans les pays en voie de développement. Les facteurs de risque incluent le tabagisme et la consommation d'alcool.
- Le Groupe d'Étude Canadien sur les Soins de Santé Préventifs ne préconise pas de dépistage universel mais suggère plutôt des examens annuels pour les sujets à risque élevé.
- La détection précoce des cancers oraux et oro-pharyngés exige un examen clinique minutieux. Des examens accessoires comme le bleu de toluidine peuvent être utiles pour identifier les lésions.
- Le diagnostic définitif requiert une biopsie.

Conclusion

The oral cavity and oropharynx are important areas that should be carefully inspected and palpated, particularly

in tobacco and alcohol users, to evaluate for oral and oropharyngeal cancer. A red or white patch or a change in colour, texture, size, contour, mobility, or function of intraoral, perioral, or extraoral tissue should arouse suspicion of the presence of malignant or premalignant lesions in these regions. Comprehensive head and neck examinations should be part of all medical and dental examinations. Primary care physicians are well suited to providing head and neck examinations and to screening for the presence of suspicious lesions. Referral for biopsy and further diagnosis might be indicated, depending on the experience of examining physicians. In the future, examination and screening for oral and oropharyngeal cancers will likely include novel technologies aimed at detecting molecular markers of premalignant and malignant changes.

Competing interests

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