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Screening for Oral Potentially Malignant Epithelial Lesions and Squamous Cell Carcinoma: A Discussion of Benefit and Risk

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From an individual's point of view, early diagnosis is a must; however, from the public health view, it is a measure of probability. These perspectives are often at odds. Although screening for early detection of disease has been promoted for many years, recently the practice has been under increasing scrutiny for many conditions. This paper reviews the issues surrounding screening for oral potentially malignant disorders (OPMD), oral squamous cell carcinoma (OSCC) and oropharyngeal carcinoma (OPC).

A significant change in OSCC and OPC incidence is occurring because of a decrease in the number of cases associated with tobacco, while human papilloma virus (HPV) is increasing the number of new cancers. Up to 20% of new cases of OSCC and up to 85% of new cases of OPC are associated with HPV.[1,2]

The etiopathogenesis of squamous cell carcinoma is important as HPV-associated OSCC and OPC have higher cures rates than OSCC and OPC associated with tobacco and alcohol risk factors.[3] Unfortunately, approximately 2/3 of lesions are identified at an advanced stage, thus affecting treatment options, requiring more complex therapy and increasing the morbidity of treatment and cost of care. The expectation that management of OPMD and early-stage squamous cell carcinoma will lead to improved outcomes has led to the goal of increasing efforts toward early detection. Although most OSCC cases are expected to be preceded by OPMD, it is not known whether OPC arises from potentially detectable precursor lesions.

Public Health Screening

The prevalence of disease in a population plays an important role in assessing the utility of screening. In uncommon conditions, such as OPMD and OSCC, proving utility presents a challenge. Indeed false positive results may add a burden to the patient and the health care system. In oral screening, distinguishing common inflammatory lesions from OPMD and OSCC has been a key concern with current adjunctive modalities. Other key considerations include the methods available for screening, the potential risk of testing, the cost of the test, the utility of the results and the consequences of false positive and false negative outcomes (**Table 1**).

Table 1 Key questions and test characteristics that determine the utility of oral cancer screening

Key questions:
▪ Is there a detectable early stage of disease? ▪ Is there benefit from early detection? ▪ Is the prevalence of the disease high? ▪ If prevalence is low, is it useful to assess high-risk groups?*

Characteristics of tests that affect utility:

- Technical nature of test
- Amount of experience or training required
- Invasive versus noninvasive
- Validation in the setting or population in which the test is to be used
- Risk of false positive or false negative results
- Frequency of use
- Steps taken if results are positive or negative
- Cost of test or equipment

*See risk factors listed in Table 3.

To understand oral cancer screening better, it is instructive to review screening for other diseases, such as breast, cervical, prostate, colon, skin and lung cancer. Other common conditions, such as hypertension, also provide guidance. Hypertension is a common condition, with known high-risk populations; screening is non-invasive, rapid and low cost and, thus, recommended. In oncology, however, dysplastic and even cancer cells may resolve and, because of this, cervical Papanicolaou tests are now not recommended for women younger than 21 years. We do not have data on remission of OPMD, OSCC and OPC. Computed tomography scans for lung cancer have been shown[4] to be of value in screening high-risk patients (e.g., heavy tobacco users) aged 55–74 years, but are not recommended for others because of the high cost of testing, radiation exposure and the need for follow-up testing (e.g., lung biopsy), which incurs additional costs and risk. Controversy regarding prostate-specific antigen testing and mammography continues, and, hence, guidelines are reviewed on an ongoing basis as new information becomes available. These examples illustrate some of the issues surrounding screening for disease that must be considered in the case of OPMD, OSCC and OPC.

Screening for Oral Potentially Malignant Epithelial Lesions and Squamous Cell Carcinoma

Current guidelines do not support population screening for OPMD and OSCC.[4–6] However, opportunistic screening has been suggested in conjunction with oral examination during dental visits.[7,8]

A single study supports screening in a high-risk population in India.[9]In this study, clinical examination to detect early-stage OSCC was conducted annually for 3 years for 96 517 patients among whom 205 cases of OSCC were diagnosed. Of these cases, 41% were stage I or II cancers and 5-year survival rate was 50%. Among 87 655 people not evaluated annually, 158 cases were diagnosed, 23% of which were stage I or II cancers and the 5-year survival rate was 34%. Thus, identification of earlier stage cancers in the screened population translated into a 21% reduction in oral cancer mortality.[9]

Screening and diagnostic tests must be evaluated in terms of test characteristics and outcomes (**Table 2**). Risk of over-diagnosis (false positive results) of OSCC and OPC may lead to additional and sometimes invasive testing (typically a minor biopsy with short-lived discomfort and cost) and the potential for overtreatment.[9] The results of biopsy is also subject to variable accuracy.[10] It is important to be aware that most studies do not address the value of correct diagnosis of benign conditions that, of themselves, require management, but in screening studies are frequently referred to as "false positive" results. False negative results are potentially of greatest concern, as they may be reassuring and allow undetected cancer to progress before diagnosis. In general, more sensitive tests are at risk of producing a higher rate of false positive outcomes and lead to increased evaluation and testing with inherent risks and costs.

Table 2 Impact of screening test results

True positive	False positive*
Early detection, early diagnosis	Anxiety
Less complex treatment	Additional medical/dental

	visits
Increased likelihood of cure with reduced morbidity	Increased cost
Reduced cost of care	Morbidity related to the test
True negative	**False negative**
Reassurance, no further testing	Delay in true diagnosis
	Potential progression of disease

*Often increased in tests with high sensitivity.

Discussion

Although early detection of OPMD, OSCC and OPC is a desirable goal, evidence supporting screening is limited. A focus on high-risk populations (**Table 3**) where prevalence is greater may increase the potential value of screening. The issues surrounding screening for low-prevalence diseases lead to challenges in detection and an increased risk of false positive and false negative outcomes and higher costs. These will continue to challenge oral cancer detection. Current best evidence is limited to high-risk populations, such as those with prior upper aerodigestive tract cancer, exposure to heavy tobacco and alcohol use, exposure to HPV and immunosuppression. These populations may be best evaluated in high-risk clinics, such as mucosal disease clinics, cancer centres and clinics for sexually transmitted diseases. The guidance provided by the American Dental Association for better available adjunctive tests (**Table 4**) focuses on use in high-risk clinics and practice settings.[7]

Table 3 Recognized risk factors and symptoms of oral cancer

Risk factors	Symptoms*
▪ Tobacco: smoking, chewing	▪ White/red lesions, mouth sores, mass (> 2 weeks)
▪ Betel nut: chewing	▪ Bleeding: mouth, throat
▪ Alcohol abuse	▪ Pain/numbness: unilateral
▪ Sexual activity: past or current HPV-16, 18	▪ Limited movement of involved tissue
▪ Immunosuppression: medical therapy, genetic (e.g., Fanconi anemia), infectious (HIV)	▪ Loose teeth

▪ Prior head and neck radiation, chemotherapy	▪ Neck mass
▪ Premalignant epithelial lesions: e.g., dysplasia, lichen planus	▪ Sore throat, dysphagia, dysphonia
	▪ Weight loss

*Although there is no evidence that oral self-examination provides useful benefits or leads to diagnosis, health professionals have emphasized the importance of patient-reported symptoms.
Note: HPV = human papillomavirus.

Table 4 Approaches to screening for head, neck and oral cancer

Currently available methods	Developing technologies

▪ Patient self-examination
▪ History: risk factors, symptoms
▪ Clinical examination
▪ Imaging:
  ▪ Light (low-energy light, fluorescence)
  ▪ Diagnostic radiology, MRI, other imaging
▪ Tissue staining: toluidine blue
▪ Exfoliative cytology
▪ Biopsy: histology, molecular testing
	▪ Imaging:
	  ▪ Optical coherent tomography
	  ▪ Raman spectroscopy
	▪ Exfoliative cytology + molecular testing
	▪ 3D cytology

Note: MRI = magnetic resonance imaging.

Opportunistic screening in conjunction with routine dental and medical examination has been suggested, especially for the high-risk populations described above. Unfortunately, some members of these high-risk populations are unlikely to present for routine dental and medical evaluation. Barriers include cost of care and limited community knowledge.

Diagnosis of benign conditions has value for the patient and can lead to appropriate treatment and follow up, thus rendering false positive results indicating a benign condition a useful outcome for reassurance and treatment. False negative results may lead to delayed diagnosis. In diagnosis of oral lesions, the challenge is to distinguish common inflammatory changes from dysplastic and malignant change. OPMD and even OSCC are complex processes with unpredictable progression, although the likelihood of progression of OPMD to cancer is higher with more advanced molecular change and dysplasia.[11]

Of the currently available diagnostic methods, the Council on Scientific Affairs of the American Dental Association recommends[7]

the use of toluidine blue staining by experts for high-risk patients (level I evidence) and exfoliative cytology (level II evidence) in these circumstances, but, because of limited data, it does not recommend these tests by non-expert providers or in non-high-risk settings. Fluorescence imaging has been suggested for use in known cases of OPMD and SCC to assist in margin delineation.[7] Visual detection of oral mucosal lesions and histologic diagnosis are variable, and it appears that clinical experience, appropriate use of methods and development of new tools and devices are needed to enhance diagnosis.[12,13] Because of limited study of all adjunctive methods in general practice settings where false positive and false negative rates are unknown, no recommendations can be made and all methods are considered elective.

As in other parts of the body, progression of oral lesions to cancer cannot be predicted; dysplasia or even early cancer may resolve without treatment, thus complicating diagnosis and treatment decisions. While more predictable tools for diagnosis and measures of lesion behaviour are sought, current clinical decisions are based on available evidence and experience. Distinguishing between inflammatory lesions and dysplasia and consistent clinical follow up, with histopathology when indicated, is the current standard. Management of OPMD is based on limited data, with medical management and close follow up indicated, as is the case for dysplastic lesions at other sites, while the search for more effective therapy continues.[14,15] Surgery may be considered more often with severe dysplasia, but risk of progression to cancer continues and follow up is needed.

Screening of populations for malignant oral lesions, OSCC and OPC is not advocated by public health authorities. However, research is ongoing. Meanwhile, opportunistic evaluation during standard dental examinations is suggested, as there is no additional economic cost, unless expensive testing methods are employed.

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References

1. Isayeva T, Li Y, Maswahu D, Brandwein-Gensler M. Human papillomavirus in non-oropharyngeal head and neck cancers: a systematic literature review. *Head Neck Pathol.* 2012;Suppl 1:S104-20.
2. Centers for Disease Control and Prevention. Human papillomavirus-associated cancers — United States, 2004–2008. *MMWR Morb Mortal Wkly Rep.* 2012;61:258-61.
3. Cleveland JL, Junger ML, Saraiya M, Markowitz LE, Dunne EF, Epstein JB. The connection between human papillomavirus and oropharyngeal squamous cell carcinomas in the United States: implications for dentistry. *J Am Dent Assoc. 2011;142(8):915-24*.
4. U.S. Preventive Services Task Force issues draft recommendation statement: screening for oral cancer. *USPSTF Bulletin*, 2013;Apr 9 [accessed 2013 Feb 14]. Available: www.uspreventiveservicestaskforce.org/bulletins/oralcanbulletin.pdf.
5. Oral cancer. Ottawa: Health Canada; 2009. [Accessed 2013 Feb 13]. Available: www.hc-sc.gc.ca/hl-vs/oral-bucco/disease-maladie/cancer-eng.php.
6. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for early detection of cancer, 2005. *CA Cancer J Clin.* 2005;55(1):31-44.
7. Rethman MP, Carpenter W, Cohen EE, Epstein J, Evans CA, Flaitz CM, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. *J Am Dent Assoc.* 2010;141(5):509-20.
8. Cancer screening protocols. Newport Beach, Cal.: The Oral Cancer Foundation; n.d. [Accessed 2013 Feb 14]. Available: www.oralcancerfoundation.org/dental/screening.htm.
9. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Thomas G, Anju G, et al. Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. *Oral Oncol.* 2013;49(4):314-21.

10. Fischer DJ, Epstein JB, Morton TH, Schwartz SM. Interobserver reliability in the histopathologic diagnosis of oral pre-malignant and malignant lesions. *J Oral Pathol Med. 2004;33(2):65-70*.

11. Zhang L, Poh CF, Williams M, Laronde DM, Berean IK, Gardner PJ, et al. Loss of hetrozygosity (LOH) profiles — validated risk predictors for progression to oral cancer. *Cancer Prev Res (Phila). 2012;5(9):1081-9*.

12. Epstein JB, Güneri P, Boyacioglu H, Abt E. The limitation of the clinical oral examination in detecting dysplastic oral lesions and oral squamous cell carcinoma.*J Am Dent Assoc.* 2012;143(12):1332-42.

13. Le A, Messadi D, Epstein J, Wilder-Smith P. Toward multimodality oral cancer diagnosis in the XXI century: blending cutting edge imaging and genomic/proteomic definition of suspicious lesions. *Bioinformation.* 2011;5(7):304-6.

14. Brennan M, Migliorati CA, Lockhart PB, Wray D, Al-Hashimi I, Axéll T, et al. Management of epithelial dysplasia: a review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103(Suppl S19):e1-12.

15. Al-Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M, Migliorati CA, et al. Oral lichen planus and lichenoid lesions: diagnosis and therapeutic considerations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(Suppl S25):e1-12.

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