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Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas

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The American Cancer Society (ACS) estimated that there would be 35,720 new cases of cancer of the oral and pharyngeal region in the United States in 2009, with 7,600 deaths from the disease.[1] When focusing specifically on the oral cavity, ACS estimated that in 2009, there would be 23,110 new cases of cancer of the oral cavity (hereafter referred to as "oral cancer") and 5,370 deaths.[1] Nearly 90 percent of these malignancies are squamous cell carcinomas.[2] More than 97 percent of U.S. cases of these cancers occur among adults 35 years and older.[3] Although the incidence rate (IR) of oral and pharyngeal cancers is decreasing overall, the IR of cancers of the tongue, oropharynx and tonsil is increasing.[3] The 2002–2006 age-adjusted (to the 2000 U.S. population) IR of oral and pharyngeal cancers in the United States was 10.3 per 100,000 per year. The age-adjusted IR was more than twice as high among men (15.9) as among women (6.0), as was the mortality rate (men, 4.0; women, 1.5).[3]

ABSTRACT

JADA CE CONTINUING EDUCATION ARTICLE 1

Background. This article presents evidence-based clinical recommendations developed by a panel convened by the American Dental Association Council on Scientific Affairs. This report addresses the potential benefits and potential risks of screening for oral squamous cell carcinomas and the use of adjunctive screening aids to visualize and detect potentially malignant and malignant oral lesions.

Types of Studies Reviewed. The panel members conducted a systematic search of MEDLINE, identifying 332 systematic reviews and 1,499 recent clinical studies. They selected five systematic reviews and four clinical studies to use as a basis for developing recommendations.

Results. The panel concluded that screening by means of visual and tactile examination to detect potentially malignant and malignant lesions may result in detection of oral cancers at early stages of development, but that there is insufficient evidence to determine if screening alters disease-specific mortality in asymptomatic people seeking dental care.

Clinical Implications. The panel suggested that clinicians remain alert for signs of potentially malignant lesions or early-stage cancers while performing routine visual and tactile examinations in all patients, but particularly in those who use tobacco or who consume alcohol heavily. Additional research regarding oral cancer screening and the use of adjuncts is needed.

Key Words. American Dental Association (ADA); biopsy; brush; cancer; carcinoma; squamous cell; evidence-based dentistry; mouth neoplasms; oral cancer; practice guidelines.

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Among the groups described in data from the National Cancer Institute's Surveillance Epidemiology and End Results program,[3] African-American men are at the highest risk of developing oral and pharyngeal cancers of any group in the United States (IR 16.7 per 100,000 per year).[3] The five-year relative survival rate varies widely by stage at the time of diagnosis, from 81.8 percent for patients diagnosed in localized stages and 52.1 percent for patients with regional lymph node involvement to 26.5 percent for patients with distant metastasis.[3] Yet, oral and pharyngeal cancer is diagnosed at a localized stage in only one-third of patients in the United States.[3] The overall five-year relative survival rate for the 1999-2005 period was 61.0 percent and varied significantly by race (62.4 percent for white men and 38.2 percent for black men).[3] Much of the racial disparity in survival rates was due to the greater proportion of tumors diagnosed at late stages among black men than among white men.[3]

SCOPE AND PURPOSE OF THE RECOMMENDATIONS

This report was developed by a panel convened by the American Dental Association (ADA) Council on Scientific Affairs to address the benefits and limitations of oral cancer screening and the use of adjunctive screening aids to visualize and detect potentially malignant and malignant oral lesions. The panel's work was supported in part by the Centers for Disease Control and Prevention (CDC), Atlanta.

We have excluded squamous cell carcinomas of the lips from this article, because the risk factors, stage-at-diagnosis patterns, morbidity and mortality of those carcinomas differ from those of cancer in sites in the oral cavity. We also excluded from this report cancers of the oropharynx (including the posterior one-third [base] of the tongue and the tonsils). Although the oral cavity and the oropharynx overlap in the region of the hard and soft palate and tonsils, recent systematic reviews suggest that human papillomavirus (HPV) is a risk factor for cancers of the base of the tongue and the tonsils.[4-6] In contrast, HPV does not appear to be a significant risk factor for cancer of the anterior two-thirds of the tongue or the remaining oral cavity. The importance of this distinction is highlighted by evidence that HPV-related carcinomas have a better prognosis overall than do non-HPV–related carcinomas.[7,8]

The clinical recommendations in this article, which presents a critical evaluation and summary of the relevant scientific evidence, do not represent a standard of care. Instead, this report is intended to assist the clinician in the decision-making process. Its clinical recommendations should be integrated with the practitioner's professional judgment and the individual patient's needs and informed preferences.

Table 1 presents definitions of the terms used in this report.

ORAL CANCER SCREENING: DEFINITION AND CONTEXT

This report defines "screening" as the process by which a practitioner evaluates an asymptomatic patient to determine if he or she is "likely" or "unlikely" to have a potentially malignant or malignant lesion. In "mass screening" programs, also known as "community-based" or "population-based" screening, the target group is invited to participate specifically for the purpose of detecting potentially malignant lesions. These screenings may have a specific goal of detecting potentially malignant oral lesions, or they may be broader in scope and involve assessment of a person's general oral health status. In a dental setting, the act of "screening" for oral cancer occurs when a patient reports for care. This often is referred to as an "opportunistic screening."

The practitioner obtains a health history to assess the patient's general health and risk of developing disease. A thorough health history review should yield information about the patient's tobacco and alcohol use, hospitalization history, surgery experience, dietary patterns, medication regimen and other illnesses.[9] Investigators have observed an increased risk of developing oral cancer with increasing age,[3] in people who use tobacco,[10] in people who consume alcohol heavily (for men an average of more than two drinks daily and for women an average of more than one drink daily),[10,11] in people who have a history of upper aerodigestive tract cancer[12-14] and in people who have certain inherited diseases, such as Fanconi anemia.[15-17] The practitioner also conducts a visual and tactile examination (referred to as "examination" throughout this

ABBREVIATION KEY. ACS: American Cancer Society. **ADA:** American Dental Association. **CDC:** Centers for Disease Control and Prevention. **HPV:** Human papillomavirus. **IR:** Incidence rate. **LED:** Light-emitting diode. **RCT:** Randomized controlled trial.

report) to detect the presence of any oral abnormality. Some of the mucosal abnormalities noted on examination could be a potentially malignant or malignant lesion. This examination should not be viewed as a series of distinct subsegments intended to detect individual diseases. Screening for oral cancer is but one component of the comprehensive patient evaluation provided by dentists to detect all forms of oral pathoses, including those of neoplastic, infectious, reactive/inflammatory or developmental origin.

Clinical signs of cancer. ***Invasive cancer.*** Clinical signs of invasive cancer can include induration; persistent ulceration; tissue proliferation or destruction; red and white color variegation; lack of mucosal mobility; progressive growth or enlargement of the affected site; pain or dysesthesia, paresthesia or loss of function; and cervical lymphadenopathy. Most oral squamous cell carcinomas exhibit one or more of these clinical signs, which often are identifiable on routine examination.

Early-stage cancer. Clinical features of oral lesions identified during a routine visual and tactile examination that might raise suspicion of potential malignancy include sharp or distinct margins, a red component (color variation), a nonhomogenous white component (surface irregularity), persistent ulceration and size larger than 1 centimeter. The clinician also should view with suspicion any persistent or progressive lesion of the ventrolateral tongue or the floor of the mouth (both of which are high-risk sites for oral squamous cell carcinoma).

TABLE 1

Definitions of terms used in this report.

PATHOLOGY	
Oral Squamous Cell Carcinoma	A malignant condition of the tissues lining the oral cavity (oral mucosal epithelium) that can arise at any location within the anatomical confines of the oral cavity, which is capable of local, regional and distant spread; tissues that may be involved as the site of origin include the labial and buccal mucosa, the anterior two-thirds of the tongue, the retromolar pad, the floor of the mouth, the gingiva and the palate
Oropharyngeal Cancer	A malignant condition of the tissues lining the oropharynx; structures within the oropharynx include the palatine and lingual tonsils, the posterior one-third (base) of the tongue, the soft palate and the posterior pharyngeal wall
Potentially Malignant Lesion	Morphologically altered tissue noted on clinical examination in which cancer is more likely to occur than in normal tissue; such lesions could be precancerous or premalignant and may exhibit dysplasia on histopathologic examination
OUTCOMES	
Morbidity	State of sickness due to the disease or secondary to a diagnostic or therapeutic procedure
Mortality	Death due to the disease or secondary to a diagnostic or therapeutic procedure
EPIDEMIOLOGY	
Incidence Rate	The number of new cases of the disease occurring in a defined population during a specified interval, usually expressed as the number of cases per 100,000 people at risk per year
Disease-Specific Mortality Rate	The number of deaths with disease given as the underlying cause of death occurring in a defined population during a specific time, usually expressed as the number of deaths due to disease per 100,000 people per year
Disease Prevalence	The proportion of people alive on a certain date in a population who previously had a diagnosis of the disease; this includes new (incident) and preexisting cases and is a function of past incidence rates, past survival rates and the size and age structure of the population
Five-Year Relative Survival Rate	The net survival rate that is calculated by comparing observed five-year survival rates in diseased patients with expected five-year survival rates in a comparable set of people who do not have the disease
TEST MEASURES	
Sensitivity	The proportion of people who test positive for a specific disease among a group of people who have the disease
Specificity	The proportion of people who test negative for a specific disease among a group of people who do not have the disease
False Positive	An erroneously positive test or screening result
False Negative	An erroneously negative test or screening result
Positive Predictive Value	The proportion of people in a specified population with positive test results who have the disease
Negative Predictive Value	The proportion of people in a specified population with negative test results who are disease-free

Early-stage lesions often are asymptomatic and may mimic other conditions, whereas others may not be readily evident in routine examination. Also, because malignant and benign lesions may not be clinically distinguishable,[18] the clinician cannot predict the biological relevance of lesions on the basis of their physical features alone.

ADJUNCTIVE SCREENING AIDS

Adjunctive screening aids are marketed to assist clinicians with the detection of early cancerous

changes or for the assessment of the biological relevance of mucosal lesions.

Devices intended to assist in lesion detection. These devices feature special light sources designed according to principles of tissue reflectance and tissue autofluorescence to enhance the oral examination process. Manufacturers of these devices claim that they may help the practitioner to visualize oral mucosal abnormalities that are not readily detectable with conventional operatory lighting, or that they can enhance the practitioner's ability to specifically identify potentially malignant lesions.

Devices based on tissue reflectance. These devices are claimed to help practitioners detect oral mucosal abnormalities that otherwise would be difficult to discern on routine visual examination. The following commercial tissue-reflectance–based devices are available in the United States: Microlux/DL (AdDent, Danbury, Conn.), Orascoptic DK (Orascoptic, a Kerr Company, Middleton, Wis.) and ViziLite Plus (Zila Pharmaceuticals, a division of Tolmar, Phoenix).

ViziLite Plus uses a disposable chemiluminescent light packet, and the MicroLux/DL and Orascoptic DK units use a reusable, battery-powered light-emitting diode (LED) light source that provides a similar blue-white (440-nanometer range) illumination.[19] Each system employs a 1 percent acetic acid wash before use of its respective light source. Under blue-white illumination, abnormal squamous epithelium is reported to be distinctly white (acetowhite).[20] ViziLite Plus also provides a toluidine blue solution (TBlue, Zila Pharmaceuticals), which is intended to mark an acetowhite lesion for subsequent biopsy.

The MicroLux/DL and Orascoptic devices use a similar reusable insert or probe to transmit light from the LED source in the handpiece to the oral tissues.[21,22] Both units are marketed as multiuse devices because their handpieces are designed to accept a separate transillumination tip for detection of tooth fractures or caries, as well as another insert that provides the dentist with a lighted mirror.[21,22]

Device based on autofluorescence. VELscope (LED Dental, Burnaby, British Columbia, Canada) is marketed as an adjunct to visual examination in the identification of oral mucosal abnormalities that otherwise may not be apparent with conventional operatory lighting. Under the blue-light excitation (400-460 nm) provided by the unit, normal oral mucosa emits a pale green autofluorescence when viewed through the filter set incorporated within the handpiece. In contrast, the manufacturer states that abnormal tissue exhibits decreased levels of autofluorescence and appears dark compared with the surrounding tissue.[23] The manufacturer cautions, however, that loss of autofluorescence is not limited strictly to epithelial abnormalities and can be seen with prominent surface vascularity, including areas of inflammation, and melanin pigmentation.[23]

Device based on autofluorescence and tissue reflectance. Identafi 3000 (Trimira, Houston) combines the technologies of tissue reflectance and autofluorescence with a conventional white light source.[24] It is claimed to help the practitioner identify oral mucosal abnormalities that otherwise may not be apparent.[24] It also is claimed to help the practitioner discern the superficial vascularity of the tissue.[24]

Device intended to assist in lesion assessment. This type of device is designed to help practitioners assess the biological relevance of mucosal lesions and determine the need for surgical biopsy and tissue diagnosis. By providing a transepithelial (full-thickness) collection of disaggregated cells from the lesional tissue, the device allows subsequent identification of atypical cells that may indicate malignancy.

Device based on transepithelial cytology. The OralCDx BrushTest (OralCDx Laboratories, Suffern, N.Y.) is intended for the evaluation of lesions that do not immediately raise suspicion of cancer.[25] The Oral CDx BrushTest consists of a disposable, circular plastic brush that the clinician rubs or rotates against the lesion until he or she observes pinpoint bleeding. The clinician uses this clinical endpoint to confirm penetration of the basement membrane and acquisition of a transepithelial (full-thickness) sample. After the clinician transfers the sample to a glass slide, he or she applies a fixative solution, then returns the fixed sample to the company for computer-assisted analysis and interpretation by a pathologist.

The specimen analysis will yield one of four results[26]:

- incomplete specimen—too few cells from all cell layers;
- negative—no evidence of abnormal cells;
- atypical—abnormal epithelial cells of uncertain significance;
- positive—definitive evidence of dysplastic or cancer cells.

In the case of atypical or positive results, the

company recommends surgical biopsy of the lesion. This is because the test result is limited to reporting the presence or absence of cellular abnormalities and does not provide a final diagnosis.

METHODS

The ADA Council on Scientific Affairs convened a panel to evaluate the available evidence regarding oral cancer screening and the use of adjuncts. The Council selected panelists on the basis of their expertise in the relevant subject matter. At a workshop held at ADA Headquarters April 13-15, 2009, the panel evaluated the published evidence and developed evidence-based clinical recommendations for oral cancer screening and the use of adjuncts.

Conflict-of-interest disclosures. The panel comprised 20 people who represented a broad range of expertise. Each panelist completed a standard conflict-of-interest questionnaire.

Literature search. Staff members of the ADA Center for Evidence-Based Dentistry searched MEDLINE through PubMed to identify systematic reviews that addressed the four clinical questions. (For information about the clinical questions and detailed methods, see Appendix 1 in the supplemental data to the online version of this article at "http:jada.ada.org".) On the basis of the inclusion and exclusion criteria, they identified five systematic reviews.[27-31] They conducted a second search to identify clinical studies published after the last search date within the systematic reviews. They identified four additional clinical studies.[32-35] Appendix 1 in the supplemental data online (found at "http://jada.ada.org") provides a detailed description of the search methodology and the inclusion and exclusion criteria, as well as a list of excluded publications.

Data synthesis and critical appraisal. The panel performed a qualitative synthesis of data from the included studies in a narrative format. For the included studies, they performed quality assessment of the individual articles by using standard U.S. Preventive Services Task Force methodology for determining internal and external validity.[36] (For information about the quality assessment, see Appendix 2 of the supplemental data to the online version of this article at "http:jada.ada.org".) The panel asked Drs. Patton and Epstein, authors of a systematic review of adjunctive screening devices, to update the results of their systematic review with data from the three included clinical studies of screening devices.[32,33,35] (For information about the update, see Appendix 3 of the supplemental data to the online version of this article at "http:jada.ada.org".)

TABLE 2

Grading evidence statements and clinical recommendations.*

GRADE	CATEGORY OF EVIDENCE
Ia	Evidence from systematic reviews of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one other type of quasiexperimental study, such as time series analysis or studies in which the unit of analysis is not the individual
III	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, cohort studies and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities
CLASSIFICATION	**STRENGTH OF RECOMMENDATIONS**
A	Directly based on grade I evidence
B	Directly based on grade II evidence or extrapolated recommendation from grade I evidence
C	Directly based on grade III evidence or extrapolated from grade I or II evidence
D	Directly based on grade IV evidence or extrapolated from grade I, II or III evidence

* Amended with permission of BMJ Publishing Group from Shekelle and colleagues.[37]

Grading evidence statements and clinical recommendations. On the basis of the included studies, the panel developed evidence statements and graded them according to a system developed by Shekelle and colleagues[37] (Table 2). The panel developed clinical recommendations based on its interpretation of this evidence. They classified clinical recommendations according to the strength of the evidence that formed the basis for the recommendation, again by using a system modified from that of Shekelle and colleagues.[37] The classification of the recommendation directly reflects the level of scientific evidence that supports the recommendation.

Process for developing clinical recommendations. When the panel was unable to reach a consensus when translating evidence into clinically relevant recommendations, it used a

majority vote to make final determinations.

Review process. The panel submitted its clinical recommendations for comment to both internal and external scientific experts and organizations. After reviewing all submitted remarks, the panel revised its recommendations where appropriate. (For information about the external reviewers, see Appendix 4 of the supplemental data to the online version of this article at "http:jada.ada.org".) The ADA Council on Scientific Affairs approved the final clinical recommendations.

Role of the funding source. The work of this panel was commissioned by the Council on Scientific Affairs and was funded jointly by the ADA and CDC.

DISCUSSION

The panel came to the following conclusions on the basis of the evidence. The corresponding grade of evidence appears in parentheses.

- While stage of cancer at diagnosis has an impact on treatment decisions and resultant health outcomes, community-based screening by means of visual and tactile examination in the general adult population intended to detect early and advanced oral cancers may not alter disease-specific mortality[30] (Ib).
- Community-based screening by means of visual and tactile examination may decrease oral cancer–specific mortality among people who use tobacco, alcohol or both[30] (Ib).
- Screening by means of visual and tactile examination may result in detection of oral cancers at early stages of development (stages I and II)[30,34] (Ib).
- In asymptomatic patients seeking dental care, there is insufficient evidence to determine whether screening by means of visual and tactile examination to detect potentially malignant and malignant lesions alters disease-specific mortality[28] (III).
- There is insufficient evidence that commercial devices based on autofluorescence enhance visual detection of potentially malignant lesions beyond that achieved through a conventional visual and tactile examination[27] (III).
- There is insufficient evidence that commercial devices based on tissue reflectance enhance visual detection of potentially malignant lesions beyond that achieved through a conventional visual and tactile examination[27] (III).
- There is insufficient evidence to assess the validity of transepithelial cytology of seemingly innocuous mucosal lesions[27] (III).
- In suspicious mucosal lesions with high potential for malignancy, transepithelial cytology has validity in identifying disaggregated dysplastic cells[27] (III).

A conclusion of "insufficient evidence" does not necessarily mean that the intervention is or is not effective, but instead means that the panel did not find sufficient evidence to support a recommendation.

Table 3 is a summary of the expert panel's conclusions. The box (page 516) presents the panel's recommendations for research.

Rationale for recommendations: oral cancer screening. Screening by means of examination can detect potentially malignant and malignant lesions at an early stage.[30,34] Yet just as clinical features alone cannot reliably distinguish between benign and malignant lesions,[38,39] neither can the clinician accurately predict the likelihood or rate of progression to cancer (malignant transformation) for a given potentially malignant lesion on the basis of routine biopsy, histopathological examination and diagnosis.[40] Further complicating matters is the relatively low prevalence of potentially malignant and malignant oral mucosal lesions in the general U.S. population. In relatively rare diseases, only a small proportion of lesions that yield positive screening results will be true positives, even when the clinician uses a screening test with high sensitivity and specificity.

Researchers who conducted a randomized controlled trial (RCT) in India suggested that screening by means of visual and tactile examination to detect potentially malignant lesions may not lower the disease-specific mortality rate in the general adult population, even in a country such as India, which has a higher prevalence rate of oral cancer than does the United States.[41] The evidence also suggested that a community-based screening program (that is, examination of a target group of people whose participation is solicited via invitation) that identified people with early and advanced stages of the disease in the general adult population may not lower mortality rates. However, members of the panel questioned the applicability of this evidence to asymptomatic patients seeking dental care in the United States.

Successful translation of oral cancer screening regimes into reduced mortality requires that patients receive confirmatory diagnosis, have continual access to a health care delivery system and complete a curative treatment regimen. In the

TABLE 3

Recommendations of the American Dental Association Council on Scientific Affairs Expert Panel on Screening for Oral Squamous Cell Carcinomas,* based on evidence.

Screening for oral cancer is one component of a thorough hard-tissue and soft-tissue examination that follows patient history and risk assessment

TOPIC	RECOMMENDATION	CLASSIFICATION
Screening During Routine Examinations†	The panel suggests that clinicians remain alert for signs of potentially malignant lesions or early-stage cancers in all patients while performing routine visual and tactile examinations, particularly for patients who use tobacco or who are heavy‡ consumers of alcohol	D
Follow-up for Seemingly Innocuous Lesions	For seemingly innocuous lesions, the panel suggests that clinicians follow up in seven to 14 days to confirm persistence after removing any possible cause to reduce the potential for false-positive screening results	D
Follow-up for Lesions That Raise Suspicion of Cancer and Those That Are Persistent	For lesions that raise suspicion of cancer or for lesions that persist after removal of a possible cause, the panel suggests that clinicians communicate the potential benefits and risks of early diagnosis Considerations include the following: ▬ that even suspicious lesions identified during the course of a routine visual and tactile examination may represent false positives; ▬ that clinical confirmation (a second opinion) can be sought from a dental or medical care provider with advanced training and experience in diagnosis of oral mucosal disease so as to reduce the potential for a false-positive or false-negative oral cancer screening result; ▬ that a malignancy or nonmalignancy can be confirmed only via microscopic examination that requires a surgical biopsy; ▬ that a decision to pursue a biopsy to confirm the presence or absence of malignancy should be made in the context of informed consent	D
Use of Lesion Assessment Devices	Although transepithelial cytology has validity in identifying disaggregated dysplastic cells, the panel suggests surgical biopsy for definitive diagnosis	D

* The expert panel was convened in April 2009 to address the benefits and limitations of oral cancer screening and the use of adjunctive screening aids to visualize and detect potentially malignant and malignant oral lesions.
† There is insufficient evidence that use of commercial devices for lesion detection that are based on autofluorescence or tissue reflectance enhance visual detection of potentially malignant lesions beyond a conventional visual and tactile examination. Source: Patton and colleagues.[27]
‡ Heavy alcohol consumption is defined as follows: for men, consumption of an average of more than two drinks per day; for women, consumption of an average of more than one drink per day. Sources: Pelucchi and colleagues[10] and Centers for Disease Control and Prevention.[11]

India-based RCT, only 63 percent of the patients whose screenings (by trained health care workers) yielded positive results for leukoplakias, erythroplakias, submucous fibrosis or oral cancer complied with referral to a physician for confirmation and, if warranted, surgical biopsy.[41] Furthermore, in that study, a greater percentage of the cases were diagnosed in stages III and IV of the disease as compared with those diagnosed in stages I and II.[42] Of the 122 patients whose cancer was diagnosed in early stages (stages I and II), only five were "low-risk" patients (nonusers of tobacco and alcohol).[42] Although these articles did not provide treatment details, the panel contacted the authors to obtain additional information. The authors reported that one-third of patients who complied with referral did not receive care with intent to treat (Dr. R. Sankaranarayanan and Dr. R. Muwonge, electronic communication, Sept. 10, 2009). The lower IR of oral cancer in the United States makes it difficult to perform a similar RCT in this country, which may explain in part the paucity of U.S. data supporting a positive health outcome resulting from oral cancer screening.

The extent (stage) of cancer at diagnosis guides treatment. But members of the panel found insufficient evidence to determine whether screening favorably altered disease-specific outcomes—including treatment-related morbidity (such as esthetics, speech and swallowing)—or affected patients' quality of life, either positively or negatively. Furthermore, in the routine setting of asymptomatic patients' seeking dental care, there is insufficient evidence to determine whether screening by means of visual and tactile examination to detect potentially malignant and malignant lesions alters disease-specific mortality.

A disease-screening regimen should include a comparison of the risks of intervention and nonintervention, and the benefits of intervention and nonintervention. For example, a screening program may fail to detect a disease that otherwise

BOX

Recommendations for research.

- Determine the prevalence of potentially malignant oral mucosal lesions in the United States
- Determine whether periodic patient examination reduces oral cancer–specific morbidity and mortality, in both the general adult population and high-risk populations
- Determine stage-specific treatment outcomes
- Determine whether detection of cancers at early stages results in improved patient outcomes, including survival, function and other quality-of-life measures
- Determine whether periodic patient examination reduces oral cancer–specific morbidity and mortality in younger and older age groups and in people who are immunocompromised
- Determine the value of salivary diagnostics in identifying biologic markers, including serum and cellular markers, as a means of reducing morbidity and mortality resulting from oral cancer
- Identify factors that would increase clinicians' confidence and competence in identification and management of potentially malignant lesions or early-stage malignancies, including the provision of surgical biopsies
- Determine whether, in addition to the oropharynx, there is an association between human papillomavirus and cancer specific to the oral cavity
- Determine whether there are additional risk factors (for example, nonsmokers' exposure to secondhand smoke) associated with the development of oral cancer
- Determine the outcomes of treatment of potentially malignant lesions, including the incidence of and time frame for progression to subsequent squamous cell carcinoma
- Determine reasons for delays in patient treatment after reaching a diagnosis of oral cancer
- Determine the spectrum and best management of oral health and disease in the patient with oral cancer from diagnosis through survivorship (disease-specific survival time subsequent to diagnosis)
- Determine the comparative effectiveness, including cost effectiveness, of visual and tactile examination and adjunctive devices for detection and visualization of potentially malignant and early malignant lesions
- Determine whether the use of adjunctive devices for margin delineation in surgical settings improves disease-specific morbidity and mortality
- Determine whether the use of adjunctive devices improves patient education and adherence to follow-up care

might be successfully treated. Screening also may reveal highly aggressive life-threatening cancers whose outcome may not have been changed by early detection—that is, for which treatment would be futile. In addition, screenings may falsely identify nondiseased sites as diseased and may detect disease that, if undetected, might not ever interfere with a patient's life. The latter two scenarios can result in needless worry, unnecessary interventions and wasted resources.

In the context of the limited evidence available, the panel members agreed that for oral squamous cell carcinomas, the evidence suggests that routine oral screenings (consisting of visual and tactile examinations) of asymptomatic patients can detect some potentially dangerous lesions at earlier stages. This suggests the potential for less invasive treatments with less attendant morbidity and improved mortality—if one makes the plausible assumption that a number of these early lesions would have progressed had there been no intervention. As noted previously, however, there is insufficient evidence in this context to determine whether early detection and treatment alter disease-specific outcomes, such as morbidity or mortality, or whether screening affects patients' quality of life, either positively or negatively. Yet, despite the likelihood of biases inherent in this comparison, the five-year survival rate of patients with early-stage oral squamous cell carcinomas (stages I and II) is higher than that of patients with cancers detected at later, more advanced stages.

In light of the lack of evidence regarding the effects of routine screening of asymptomatic dental patients on morbidity or mortality in the United States, the panel weighed the potential benefits and the potential risks of such screening in making its recommendations. The panel agreed that routine screening might extend the lives of some patients but also might have associated risks for many others. Applying their clinical experiences and professional judgment to the available evidence, the majority of the panel members concurred that the potential life-saving benefits for the smaller percentage of patients with treatable malignant lesions was more important than the potential physical and psychological harms incurred by the higher percentage of patients with benign or nonprogressive lesions. Because of these considerations, the majority of the panel members stressed the need for clinicians to remain alert for signs of potential malignancy when performing a routine visual and tactile examination in dental patients, especially those with a history of tobacco and heavy alcohol use.

Recognizing the need to minimize false-positive screening results, the panel suggested that clinicians follow up with patients within seven to 14 days after first removing or treating any potential cause(s) of lesions to confirm persistence or progression of lesions, especially in lesions that initially appeared innocuous. Because many oral soft-tissue lesions are transient and will resolve if the suspected etiologic factor is removed or treated (for example, eliminating a local irritant

or dental trauma), limiting biopsies to only those lesions that persist may improve screening accuracy. When a clinician observes a persistent or progressive lesion, he or she may consider prompt referral to a dental or medical provider with advanced training and experience in diagnosis of oral mucosal disease before performing tissue biopsy. This will further limit possible morbidity associated with false-positive results. However, should a clinician suspect potential malignancy in a mucosal abnormality on initial examination, he or she may want to perform a biopsy immediately or ensure that the patient receives prompt evaluation (and possible biopsy) by a dental or medical care provider who has advanced training and experience in diagnosis of oral mucosal disease.

When a definitive diagnosis is needed, a clinician should perform a surgical biopsy with subsequent specimen processing and histopathological examination.[43] The panel also suggested that clinicians understand and clearly communicate to the patient the benefits of early diagnosis and the potential risks to assist the patient in health care decision making.[44]

Clinicians should be aware that understanding the etiology of cancer along with the differences in clinical presentation of other similar abnormalities remains of primary importance.

Visualization devices. In studies published thus far, researchers have evaluated ViziLite, ViziLite Plus and VELscope. There is no published evidence regarding the utility of MicroLux/DL, Orascoptic DK or Identafi 3000. Overall, there is insufficient evidence that the commercially available devices based on tissue reflectance (ViziLite and ViziLite Plus) and autofluorescence (VELscope) improve the detection of potentially malignant lesions beyond that of a conventional visual and tactile examination.

Two studies of ViziLite showed the device to have high sensitivity but low specificity when researchers confirmed its findings through histopathological examination.[45,46] There is some evidence that VELscope may improve the determination of surgical margins and selection of the optimal biopsy site in large or multifocal lesions or during surgery.[47,48] The manufacturer has extrapolated this evidence to suggest that this device could help identify potentially malignant lesions that may not be readily apparent or visible to the naked eye.[24] However, to our knowledge, no peer-reviewed publications support this claim. Overall, visualization aids may affect a lesion's appearance in terms of brightness, texture and delineation of margins and in patients with previously detected lesions,[20,49,50] but they have not been shown to enhance the practitioner's ability to identify potentially malignant lesions specifically or to identify lesions not visible under normal operatory lighting. Furthermore, there is insufficient evidence that these devices improve patient compliance or aid in patient education.

As mentioned earlier, a visual examination cannot identify specifically the small proportion of lesions that exhibit early cancerous changes. Using currently available visualization aids does not allow a clinician to overcome this limitation. Clinicians should be aware that understanding the etiology of cancer along with the differences in clinical presentation of other similar abnormalities remains of primary importance. Use of these devices can be associated with an increased risk of false-positive findings.[22] The panel found insufficient evidence to make a recommendation for or against general dentists' use of these devices in their patients.

Transepithelial cytology of disaggregated cells (Oral CDx BrushTest). While results of the Oral CDx BrushTest may help the practitioner identify the presence of atypical cells in seemingly innocuous mucosal lesions, clinicians must note that atypical findings frequently are obtained when this test is performed on inflammatory or reactive lesions. Receiving an "atypical" test result is more common when the BrushTest is used on an inappropriate type of lesion, such as a pigmented mucosal lesion. Application of the BrushTest to common mucosal abnormalities that may mimic precancerous changes clinically, such as reactive frictional keratosis, without observation during a follow-up examination seven to 14 days after initial detection also raises the probability of receiving an "atypical" result. These results (essentially false positives) may lead, in turn, to unwarranted referral of the patient for further evaluation by a dental or medical care provider with advanced training and experience in diagnosis of oral mucosal disease; they may even trigger tissue biopsies that otherwise might have been deemed unnecessary by practitioners who have advanced training and experience in diag-

nosis of oral mucosal disease. Thus, there is insufficient evidence to support a recommendation for or against the use of Oral CDx BrushTest in seemingly innocuous mucosal lesions.[22]

In clinically suspicious lesions, the Oral CDx BrushTest has validity in identifying disaggregated dysplastic cells.[22] Despite this, the panel members believe that clinically suspicious lesions should be biopsied immediately for a diagnosis. On the other hand, the panel members believe that the Oral CDx BrushTest may prove useful for patients in specific clinical situations. These might include patients who have multiple lesions throughout the oral cavity and no history of oral cancer (as an alternative to multiple scalpel biopsies); noncompliant patients who are unlikely to return for follow-up care or comply with an immediate referral for further evaluation by a dental or medical care provider who has advanced training and experience in diagnosis of oral mucosal disease[51]; adults who have physical and intellectual disabilities or a complex medical status who cannot safely tolerate a surgical procedure or who have severe access-to-care restraints; and those who have a history of previously treated upper aerodigestive tract cancer.

Stand-alone use of toluidine blue. Toluidine blue (also known as tolonium chloride) is a vital dye that differentially stains abnormal tissues, including those that are premalignant and malignant in nature. While not approved by the U.S. Food and Drug Administration for use as a stand-alone adjunct for oral cancer detection in the United States, toluidine blue is used widely in other parts of the world as a means of assessing mucosal abnormalities for evidence of possible malignant or premalignant changes.

In people with a history of oral cancer or people older than 50 years who smoke and drink, toluidine blue may assist dental or medical care providers who have advanced training and experience in diagnosis of oral mucosal disease in the clinical assessment of potentially malignant lesions. However, there is insufficient evidence to recommend for or against the stand-alone use of toluidine blue to enhance the identification of potentially malignant lesions in the general population.

FUTURE TECHNOLOGIES

A number of promising new technologies have been proposed to improve the effectiveness of early oral cancer detection, including the use of saliva as an oral cancer screening platform; the use of cytology plus ploidy analysis; loss-of-heterozygosity analysis; identification of bacterial markers in biofilms; identification of individual or multiple protein biomarkers revealed via tissue biopsies; the use of in vivo molecular probes and paints; and the use of other imaging modalities. We have not reviewed these technologies in this article.

CONCLUSION

These recommendations are intended to help practitioners with issues related to assessment and detection of oral cancer. They should not be viewed as rigid guidelines or standards of care, but as evidence-based recommendations to be used together with each practitioner's professional judgment and experience in the context of the needs or informed preferences of the individual patient. Although the panel formulated these recommendations on the basis of careful review of published scientific evidence, the panel acknowledges that the current literature related to oral cancer screening is not robust. Additional well-designed epidemiologic studies and prospective controlled clinical trials are needed. Regarding screening adjuncts, the panel found insufficient evidence to support recommendations for or against the use of light-based technologies compared with conventional operatory lighting alone. While the OralCDx BrushTest has demonstrated validity as an adjunct to lesion assessment in specific clinical situations, practitioners must remember that the diagnostic gold standard for oral cancers and potentially malignant lesions continues to be histopathological examination of surgical biopsy specimens.

Screening for oral cancer is only one component of a thorough oral examination and evaluation that includes obtaining a patient history and an oral cancer risk assessment. When a mucosal lesion is noted, re-evaluation in seven to 14 days to confirm lesion persistence can reduce the potential for errors in clinical diagnosis. Similarly, the clinician can reduce the risk of performing unnecessary biopsies by obtaining an opinion by a dental or medical care provider who has advanced training and experience in diagnosis of oral cancer and its precursor lesions. ■

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