EDITORIAL

The benefit and risk of screening for oral potentially malignant epithelial lesions and squamous cell carcinoma

The perspective of an individual regarding his or her personal well-being often conflicts with that of the public health view. For the individual, a disease is either present or absent, whereas from the public health perspective, a disease is measured in terms of probability and risk. Screening for the early detection of a variety of diseases, including oral potentially malignant disorders (OPMD), oral squamous cell carcinoma (OSCC), and oropharyngeal carcinoma (OPC), has been promoted and is an expectation of the public and health care professionals. Ideal screening protocols successfully balance risk versus benefit—in the other words, to do more good than harm. This is a challenge in low-prevalence diseases, such as cancer. Recently numerous cancer screening protocols have been modified, focusing on high-risk groups and often with recommendations for less frequent screening, in an effort to improve the risk/benefit ratio. Not surprisingly, these changes have resulted in increased anxiety from the perspective of the individual. Significant changes have occurred in the etiology of OSCC and OPC, with decrease in the burden of tobacco- or alcohol-associated disease and an increase in human papilloma virus (HPV)−associated disease burden.[1-6] This shift is most apparent in OPC, where an estimated 85% of cases are attributed to HPV. Most cases of OSCC and OPC continue to be diagnosed at an advanced stage, resulting in the need for more complex and more costly therapy and ultimately compromising favorable outcomes.[7,8] Premalignant, potentially detectable lesions are expected in the majority of OSCC, but it is not known if OPC arises from potentially clinically detectable precursor lesions. It is anticipated that increasing early detection and management of OPMD and early-stage SCC will lead to improved outcomes.

PUBLIC HEALTH SCREENING

The prevalence of disease in a community of patients plays an important role in assessing the utility of screening. In the detection of OPMD and OSCC, it is critical to differentiate these low-prevalence conditions from much more commonly occurring benign conditions, which have been estimated to be present in 10% of the U.S. population.[9] For rare conditions, such as OPMD, OSCC, and OPC, proving the efficacy of screening is challenging. To better appreciate this challenge, a brief review of other screening protocols that have been more thoroughly studied may be helpful.

Hypertension is a common condition affecting 29.1% of the U.S. adult (>18 years of age) population,[10] and the procedure to determine its presence is easily accomplished, inexpensive, and noninvasive. As a result, universal screening for hypertension is recommended for all adult patients as part of routine care. Breast cancer is a relatively common cancer, with an incidence of 124.8 cases per 100,000 per year and a prevalence of 2,975,314 in 2012,[11] and mammography-based screening protocols have been in place for several decades to detect early disease. These screening guidelines were recently modified in terms of both age of initiation and frequency of screening in an effort to reduce overdiagnosis and treatment.[12] In contrast, cervical carcinoma in women is a rare condition, with an incidence of 7.7 cases per 100,000 and a prevalence of 249,512 in 2012.[13] The Papanicolaou smear screening test has been in place for several decades and is a proven screening protocol to detect early or precursor cervical disease. The Papanicolaou smear protocol was recently modified to incorporate new outcome-based evidence to improve the risk/benefit profile of the screening procedure.[14] Finally, as another example, the prevalence of lung cancer in 2012 was 408,808. Computed tomography scans for lung cancer has shown[15] utility in screening of high-risk patients (e.g., heavy tobacco users) aged 55 to 74 years but is not recommended for others because of the cost of testing, radiation exposure, and the need for follow-up testing if positive (e.g., lung biopsy).

SCREENING FOR ORAL POTENTIALLY MALIGNANT EPITHELIAL LESIONS AND SQUAMOUS CELL CARCINOMA

There is insufficient evidence to either support or refute general population screening for OPMD and OSCC[15-17]; however, opportunistic screening during dental visits has been suggested.[18,19]

One study supports screening in a high-risk population in India, where risk factors include tobacco use, betel nut use, and nutritional risks, which differ from those in populations in Western nations, and therefore, generalization may not be appropriate.[20] In this study, clinical examination was conducted annually for 3 years in 96,517 patients, among whom 205 cases of

OSCC were diagnosed, compared with cancers diagnosed in 87,655 patients who were not examined. This study identified earlier-stage cancers in the screened population and found a 21% reduction in oral cancer–related mortality compared with the control population. There are no studies available in the literature supporting screening of the population in Western countries for OSCC.

DISCUSSION

Early detection and diagnosis of OPMD, OSCC, and OPC is desirable; however, evidence supporting universal screening is limited. Screening protocols must be evaluated in terms positive (malignant) and negative (benign) results. True positive and negative outcomes are obvious, but the risk of overdiagnosis (false-positive results) underdiagnosis (false-negative results) must be understood. False-negative results are of greatest concern, as negative results may allow undetected cancer to progress before diagnosis. However, overdiagnosis may lead to unnecessary investigation and treatment. In general, the more sensitive tests are at risk of producing a higher rate of false-positive results. False-positive results for OPMD, OSCC, and OPC may result in increased patient anxiety, additional unnecessary testing (typically a minor biopsy with short-lived discomfort and cost), and the potential for overtreatment. Furthermore, it is important to be aware that the pathologic interpretation of tissue biopsy is variable.[21] To illustrate this point, let us assume a screening process with an overly optimistic sensitivity of 98% and specificity of 98% in identifying an oral mucosal malignancy. Based on the 2008–2012 cases and deaths, the age-adjusted rate for oropharyngeal cancer is 10.8 per 100,000 men and women per year.[22] Assuming an adult (>18 years of age) population of 250,000,000,[23] screening 1,000,000 patients would identify 108 true positives, 19,998 false positives, 979,892 true negatives, and 2 false negatives. The resultant 185:1 burden of false positives to true positives clearly shows the challenge of universally screening for oropharyngeal cancer, a rare, low-prevalence disease.

It must be noted that patients do not simply present with either cancer or no cancer but are more likely to have one or more of a multitude of benign lesions that commonly occur in the oral cavity. In assessing screening protocols, such benign lesions are often classified as "false positives," which confounds the utility of screening for oropharyngeal cancer. However, confirming the presence of a benign or inflammatory lesion is of value in patient care, and a comprehensive head and neck and oral cavity examination remains a crucial part of the evaluation of any condition affecting the oral mucosa.

A focus on high-risk populations in which OSCC incidence is greater may increase the potential utility of screening. This would target those who abuse tobacco, betel nut, and alcohol; have a history of sexual activity (e.g., HPV exposure risk), immunosuppression (medical therapy, genetic, infections [e.g., HIV]); prior history of upper aerodigestive tract cancer and OPMD (e.g., dysplasia, lichen planus). OPMD conditions, such as dysplastic lesions and lichen planus, may also increase the potential, but clear distinction between inflammatory and reactive disorders versus neoplastic disorders is needed. Thus, if we refine our model above to only consider smokers who have a minimal fourfold increase in the risk of developing oropharyngeal cancer, we can estimate there are 44 cases of oropharyngeal cancer per 100,000 adult tobacco smokers. In screening 100,000 of these higher-risk patients, we would identify 43 true positives, 1999 false positives, 97,957 true negatives, and 9 false negatives. The burden of false positives to true positives would drop to 47:1.

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. Further, in OPMD and SCC, differentiation from common inflammatory changes remains a key challenge in the detection and diagnosis of neoplastic change. Current best evidence for screening is limited to high-risk populations, such as those with prior upper aerodigestive tract cancer, exposure to heavy tobacco and alcohol use, and betel nut use, and immunosuppressed people. These populations may be best evaluated in clinics treating high-risk cases, such as clinics treating mucosal disease, cancer, and sexually transmitted diseases, as supported by the guidance provided by the American Dental Association.[18]

Opportunistic screening at the time of dental and medical examinations has been suggested, especially for the high-risk populations described above. We support this justification for all of our patients, as dentists do not perform oral cancer screenings as an isolated event but, rather, as part of their routine conventional oral examination.[24] Such examinations represent an opportunity to assess the patient for any number of abnormalities—benign, inflammatory, infectious, and dysplastic—not simply oral cancer.[18] These guidelines also discuss examination by experienced providers and the use of appropriate adjunctive devices in high-risk populations in high-risk settings.

In order for any screening protocol to be effective, the patient must participate. The fact that over 35% of patients do not see a dentist on a routine basis represents another significant challenge to overcome.[25] Programs to improve patient awareness and access to

care, along with measures to reduce anxiety, are warranted. Indeed, it is thought that many higher-risk patients may not be seeking routine dental care on a regular basis.

In the diagnosis of oral lesions, the challenge is to distinguish common inflammatory changes from dysplastic and malignant changes. In addition, OPMD and even OSCC are complex processes with unpredictable progression. Although the likelihood of progression or regression of OPMD to cancer is higher with more advanced molecular change,[26,27] molecular testing for these conditions is currently clinically unavailable.[26] In the case of OPC, it is not known if premalignant manifestations are common or identifiable and therefore amenable to early detection, as in most cases, disease is not diagnosed until it is advanced and often accompanied by lymphadenopathy. While more predictable tools for diagnosis and measures of lesion behavior are being sought, current clinical decisions are based on available evidence and experience. Furthermore, management of OPMD is based on limited data, with medical management and close follow-up indicated, as is the case for dysplastic lesions affecting other body sites, while study of more effective therapy continues.[28,29] Surgery may be considered more often with severe dysplasia, but the risk of progression to cancer remains, so strict follow-up is required.

Ultimately, while the evidence to support general population screening for malignant oral lesions remains equivocal and not advocated by public health authorities, the opportunistic evaluation for any abnormality to include OPMD, OSCC, and OPC during conventional oral examination remains the current clinical standard.

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