

COMMENTARY

Dilemmas of Oral Cancer Screening: An Update

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Abstract

Oral cancer is a global health burden with high mortality and morbidity. Advances in treatment have failed to improve the relatively poor survival rate due to late-stage diagnosis. Early detection and screening have been shown to be effective in reducing mortality and morbidity of most common cancers. Several studies have evaluated the effectiveness of oral cancer screening programs but clear results were not obtained. This narrative commentary aimed to give a critical insight into the dilemma of oral cancer screening and to suggest recommendations for future trends. Conventional oral examination still constitutes the gold standard screening tool for potentially malignant oral lesions and cancer. Interestingly, the findings of the most lasting (15-year) randomized controlled trial on oral cancer screening using visual examination (Kerala) supported the introduction of a screening program in high-risk individuals. Several screening adjuncts exist but are still not at the introduction stage. Further research to find an appropriate adjunct reliable tool for oral cancer screening is needed. In conclusion, oral cancer fulfills most of the essential principles of cancer screening but still many points need to be clarified. Therefore, there is a striking need to establish a global consortium on oral cancer screening that will oversee research and provide recommendations for health authorities at regular intervals.

Keywords: Oral - cancer - screening - diagnostic aids

Asian Pacific J Cancer Prev, **14** (5), 3369-3373

Introduction

Head and neck cancer is a global health burden with high mortality and morbidity. It has been ranked as the sixth most common cancer worldwide with over 650,000 new cases with 50% associated deaths each year (Warnakulasuriya, 2009; Ferlay et al., 2010). Five-year survival rates exceed 50% in only the best treatment centres. Causes are predominantly lifestyle-related: tobacco, areca nut, alcohol, poor diet, viral infections, and pollution are all important etiological factors (Johnson et al., 2011). Late-stage diagnosis, field of cancerisation and second primary tumors were considered to play a major role in the poor prognosis of oral cancer (Seoane-Romero et al., 2012). The fight to reduce oral cancer mortality can be accomplished on three different levels: (i) primary prevention; (ii) secondary prevention, screening and early detection; (iii) improved treatment.

Early detection and screening has shown to be effective in reducing mortality and morbidity of most common cancers. Screening has been defined as a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition (Epstein et al., 2008). Another

interesting definition is early detection and diagnosis, achieved by surveillance and secondary prevention (Tyagi et al., 2012). Screening for oral cancer implies searching for oral potentially malignant and cancerous lesions, typically before symptoms occur. A number of established cancer screening programs for a variety of malignancies have been shown to significantly reduce patient morbidity and mortality - including the Pap test for cervical cancer and mammography for breast cancer. Unlike other major cancers, screening program of oral cancer, either as a targeted, opportunistic or population based measure, is still has not been inaugurated to the routine health services as its effectiveness remains a pivotal question that needs a definitive answer. We aimed in this perspective to give critical insight into the dilemma of oral cancer screening and to suggest recommendations for future trends.

The latest update of the ongoing Cochrane systematic review on the effectiveness of oral cancer concluded that "although there is evidence that a visual examination as part of a population based screening programme reduced the mortality rate of oral cancer in high-risk individuals, whilst producing a stage shift and improvement in survival rates across the population as a whole, the evidence is limited to one study and is associated with a high risk of bias. This was compounded by the fact that the effect of cluster randomisation was not accounted for in the analysis.

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Furthermore, no robust evidence was identified to support the use of other adjunctive technologies like toluidine blue, brush biopsy or fluorescence imaging within a primary care environment. Further randomised controlled trials are recommended to assess the efficacy, effectiveness and cost-effectiveness of a visual examination as part of a population based screening programme” (Brocklehurst et al., 2010).

In addition, the American Dental Association council on scientific affairs expert panel on screening for oral squamous cell carcinomas has stated “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” (Rethman et al., 2010).

The randomised controlled trial, more than other any other methodology, provides high-level, evidence-based practice for patient care (Begg et al., 1996). Therefore, the best-chosen methodology to assess the effectiveness of any test or program should be a randomized controlled trial. Most of the published evidence on oral cancer screening is based on observational, case cohort studies. There is only single ongoing randomised controlled trail that is aimed to assess the effectiveness of screening population based programme in Kerala, India using visual inspection (Sankaranarayanan et al., 2000; 2005; 2013; Ramadas et al., 2003; Subramanian et al., 2009). Their most recent results have interestingly showed “sustained reduction in oral cancer mortality during the 15-year follow-up, with larger reductions in those adhering to repeated screening rounds support the introduction of population-based screening programs targeting users of smoking or chewing tobacco or alcohol or both in high-incidence countries” (Sankaranarayanan et al., 2013). Kujan et al. (2006) highlighted that the RCT Kerala study was found to have number of methodological weaknesses which include lack of allocation concealment, the small number of clusters randomised, and variations in risk factors at baseline. In addition, no clear explanation of drop outs in each treatment group and the relatively low compliance rate of the positive screened subjects. More importantly, there was no hard information on the harms of screening (Kujan et al., 2006a). Sankaranarayanan et al. (2013) responded to the critics of the Kerala RCT study by highlighting that the important issues to consider when implementing screening programs are not necessarily the same as those needed for scientific assessment of the effectiveness of a procedure and whether a technique should be part of a cancer prevention strategy depends on health priorities and health service resources in a given setting after issues such as the technique’s effectiveness and public health importance of the disease have been assessed (Ramadas et al., 2006)

In fact, the rate of visual detection of potentially malignant oral lesions at an early stage has remained problematic because early lesions of oral cancer and potentially malignant lesions are often subtle and rarely demonstrates the clinical characteristics observed in

advanced cases: ulceration, induration, pain or associated cervical lymphadenopathy. Besides their clinical subtlety, potentially malignant oral lesions are highly heterogenous in their presentation and may mimic a variety of common benign or reactive conditions. Oral visual examination may detect lesions such as a red patch, white patch but recent data suggests that some precancerous lesions may be lurking within mucosa that appears clinically normal by clinical examination alone. Visual inspection is subjective and has associated with false-positive and false-negative results that have undermined the use of this test. While visual examination has shown to be useful in the discovery of some oral lesions, it has failed to identify all potentially oral malignant lesions, nor does it accurately detect the small proportion of biologically relevant lesions that are likely to progress to cancer (Epstein et al., 2008; Lingen et al., 2008).

Remarkably, The American Cancer Society has recommended incorporating visual inspection of the oral cavity as part of a periodic health examination in dentist’s or physician’s office (Smith et al., 2011). Similarly, The British Dental association (2000) has also advocated screening high-risk group of patients opportunistically for oral cancer, when they attend for routine examination (Speight and Warnakulasuriya, 2010).

A variety of diagnostic aids and adjunctive techniques are available to potentially assist in the screening of healthy patients for evidence of otherwise occult cancerous change and to assess the biologic potential of clinically abnormal mucosal lesions (Lingen et al. 2008; Fedele 2009). Recent clinical diagnostic tools include toluidine chloride or toluidine blue dye, Oral CDX[®] brush biopsy kits, salivary diagnostics and lastly optical imaging systems. More importantly, the efficacy of all adjunct methods to visual inspection, with an exception to toluidine blue, has been studied as diagnostic tool not as screening test.

Toluidine blue, is a metachromatic dye that binds to DNA, has been used as a vital stain to highlight potentially malignant oral lesions since the early 80s. Interestingly, a randomised controlled trail on community-based oral cancer screening in Taiwan has revealed that the use of toluidine blue as an adjunctive tool for visual screening can detect significantly more submucous fibrosis and slightly more leukoplakia among individuals with habits of cigarette smoking or betel quid chewing as compared to visual screening alone (Su et al., 2010). The results of this RCT are limited due to some methodological weaknesses such as unequal sample size, short period of follow-up (5 years) and conduction in a community with high-risk oral habit (betel quid chewing) that is uncommon outside of Asia (Macek et al., 2011).

Oral CDX[®] brush biopsy is a computer-assisted method of analysis of the oral brush biopsy for the detection of precancerous and cancerous lesions of the oral mucosa first described in 1999. A debate on the efficacy of this technique exists and further research was recommended (Lingen et al., 2008; Fedele, 2009). Adjunctive techniques like DNA image cytometry (DNA-ICM) have been attributed to enhance the diagnostic performance of oral brush biopsies. A latest study has concluded that

DNA-ICM has the potential to substantially improve the sensitivity of a pure morphological interpretation of oral brush biopsies (Kämmerer et al., 2013).

Chemiluminescence is a clinical inspection of oral mucosa with the aid of chemiluminescent blue/white light (Vizilite®). Several studies have shown improvement in the identification of mucosal abnormalities with respect to the use of normal incandescent light (Kerr et al., 2006). A combination with toluidine blue was proposed to improve the very low positive predictive value of Vizilite® and is called ViziLite Plus® (Seoane-Leston and Diz Dos 2010). Another new chemiluminescence device (MicroLux DL™) has been introduced as an adjunct tool for oral lesion identification but few studies have been published to assess its effectiveness in detecting potentially malignant oral lesions (McIntosh et al., 2009)

Similarly, the VELscope™ system was approved by the Federation Dentaire Association for direct visualization of autofluorescence in the oral cavity. Although this technique has reported high sensitivity and specificity values (SeoaneLeston and Diz, 2010), recent studies showed that the device was unable to discriminate high-risk from low-risk lesions (Awan et al., 2011; McNamara et al., 2012).

Furthermore, the autofluorescence spectroscopy system was recently tested (McGee et al., 2008; Schwarz et al., 2010). Identafi™ 3000 technology consists of a small optical fiber that produces various excitation wavelengths and a spectrograph that receives and records on a computer and analyzes, via a dedicated software, the spectra of reflected fluorescence from the tissue. The findings of a more recent study support the ability of noninvasive multimodal optical imaging to accurately identify neoplastic tissue and premalignant lesions (Pierce et al., 2012). This promising technology has an impact on detection and treatment of patients with oral cancer and other epithelial malignancies but further clinical studies are needed.

In addition, many studies have suggested that molecular markers could be useful as screening tool. They are based on the fact that tumour markers may be present in saliva, body cavity fluids, blood circulation, cell membranes and cell cytoplasm when released by cancer cells or produced by the host in response to cancerous substances. However, the vast majority of these studies concentrated on the test diagnostic characteristics rather than the use of these tests for screening (Lavelle and Scully, 2005).

In fact, saliva from patients is noninvasive, patient-friendly tool. Several tests that are based on saliva such as DNA promoter hypermethylation analysis has been found to be an efficient tool for the early diagnosis of oral cancer (Ovchinnikov et al., 2012). Additionally, a promising recent study showed detection of aberrant expression of long non coding RNAs (lncRNAs) in cases of oral cancer and metastasis. lncRNAs has been functionally associated with certain types of cancer, including lung, breast and prostate carcinomas. The current findings suggest that the detection of lncRNAs in saliva may be used as a noninvasive and rapid diagnostic tool for the diagnosis of oral cancer (Tang et al., 2013). However, the accuracy of

this test in the screening setting is still unstudied. Lingen (2010) has highlighted, in a recent review on biomarkers of oral cancer and precancer screening, the need to develop an assay or adjunct tool to help in screening for HPV-related oropharyngeal lesions.

We agree with Sankaranarayanan et al. (2011) that screening research projects created considerable awareness among the public, health-care providers and policy makers on the need not only for early detection programs of cancer and catalysed the development of widespread opportunistic screening services (Lingen, 2010). Oral cancer is not an exception and will definitely benefit from these future trials. It will also help to provide a better understanding for the natural history of oral cancer. In cervical cancer screening programmes, adjunctive methods to visual examination have proved pivotal for detection of early lesions using risk markers. This will lead us into a striking question is “which are which?” (Sankaranarayanan et al., 2011) Therefore, more research is needed both to understand the natural history of oral cancer at the molecular level and to develop objective clinical methods for identification of early oral lesions. Lessons from existing screening programmes should be taken into account when planning future trials.

In conclusion, the question “to screen or not to screen” has still not clearly answered. If a yes is the answer, then we should have answers on how, when, where and to whom. We tried in the following points to highlight the pitfalls of the current research on oral cancer screening and to give suggestions to achieve the optimum goal of oral cancer screening: i) Foundation of a global consortium on oral cancer screening that is supported by the international health societies that will oversee the research, education and practice on oral cancer screening. It will be responsible to make final decision based on the balance between the benefits and harms of screening. This balance is related to the ability of a screening test to distinguish between individuals who have oral cancer and those who do not. ii) Urging the funding bodies, particularly the health authorities in the Western countries, to fund a multi-centre perfectly designed CONSORT randomised controlled trial on the efficacy of oral cancer screening in reducing mortality and morbidity. Special attention should be paid to the associated harms of screening; particularly psychological and physical effects of false-positive and incurable cases; costs, screening tools, end-point outcomes and staffing, in addition to settings, referrals and interventions to screened and control groups of patients (Kujan et al., 2005; Speight and Warnakulasuriya, 2010). iii) There is still a need to better understanding of the natural history of oral cancer and potentially malignant lesions. Further research is needed (Speight and Warnakulasuriya, 2010). iv) Improving awareness among general public on oral cancer morbidity and mortality to enhance prevention measures and to keep compliance with referral as a result to positive screening test. Compliance is a threat to any screening program. Lack of compliance may lead to the whole screening program being a complete failure (Kujan et al., 2006a). v) Interventions for the positive screened patients should be reassessed and identified (Speight and Warnakulasuriya,

2010). vi) Identifying the appropriate adjuncts aids to visual examination in oral cancer screening. In fact, there are promising adjunctive tools that merit the fund to be evaluated. In addition, the identification of the genes transcripts and proteins involved in oral cancer is an essential prerequisite to the development of molecular markers for screening (Lingen et al., 2008; Seoane-Lestón and Diz, 2010; Sankaranarayanan et al., 2011). vii) Incorporate the education on oral cancer screening into the dental graduate curriculum (Kujan 2006b; Lingen, 2011).

Reducing oral cancer mortality and morbidity and improving the quality of life remain the primary goal and in the time to find an appropriate adjunct reliable tool for oral cancer screening, conventional oral examination constitutes the gold standard screening tool for potentially malignant oral lesions and cancer.

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