Global Oral Cancer Forum – Working Group 3

Screening for oral cancer – Who, what, why and where?

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Introduction

Screening is defined as the application of a test to people who are apparently free of disease in order to identify those who may have the disease from those who may not (1). A screening test or examination is not diagnostic but is intended to identify tissue changes that may indicate the likelihood of having or developing the disease in question. Screening must be clearly distinguished from case-finding or early detection, which have the objective of identifying specific lesions either by examination or by application of a test. It must also be distinguished from "screening" studies, which survey cohorts of the population, often with the objective of determining the prevalence of a specific disease or lesion, or for the purpose of bringing patients to treatment. As properly defined, screening encompasses an ongoing process of examination and referral at periodic intervals, applied to a defined population and managed most often by a regional or national programme. Screening for cervical, breast and colo-rectal cancer are well known examples of screening programmes which have been implemented across many countries.

In the context of oral cancer, screening would involve the application of an oral examination or a test with the objective of identifying changes, which may precede or predict, with a high likelihood, the development of oral cancer. Patients identified as likely to have the disease, would then be referred to a specialist for a definitive diagnosis. The screening test would be applied to a defined population at regular intervals. Such a programme would be very similar to programmes for screening for cervical cancer. However before implementation, aspects of a screening programme must be properly evaluated and a number of criteria must be met. Wilson and Jungner, in 1968 (1) first defined screening and enumerated the ideal properties of a health screening programme. These are considered essential to ensure that the programme achieves maximum public health gains in a cost-effective manner. These criteria have been modified in subsequent decades to reflect the more rigorous standards of evidence required to prove effectiveness, and the increasing concerns about over-diagnosis (false positive tests, or lead time bias), whereby patients may be over-investigated or over-treated without receiving any

benefits and with possible additional risks or costs. The United Kingdom National Screening Committee now require that 19 criteria are met before a screening programme may be funded and implemented (2) (Table 1). In the USA, the National Cancer Institute (3) and the US Preventive Services Task Force (4), have similar criteria.

The condition:		
1.	Must be an important health problem	✔
2.	The epidemiology and natural history must be understood and there must be a detectable latent asymptomatic or early symptomatic phase	✗
3.	All cost-effective primary prevention interventions should have been implemented where possible	?
The Test		
4.	Should be simple, safe and validated	✔
5.	The distribution of test values should be known (eg. sensitivity and specificity) and the criteria for a positive test should be agreed	✗
6.	Should be acceptable to the population	✔
7.	There should be an agreed policy and process for the further referral and diagnostic investigation of individuals who test positive	?
The Treatment		
8.	Should be an effective treatment or intervention for patients found to have disease, and evidence that this early treatment leads to better outcomes	✔
9.	Should be evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered	✗
10.	Clinical management of the condition and patient outcomes should be optimised	✔
The Screening programme		
11.	There must be evidence from RCTs that the screening programme is effective in reducing mortality or morbidity	✗
12.	Should be clinically, socially & ethically acceptable	✔
13.	Benefit should outweigh any physical or psychological harm	?
14.	Cost effective	✔
15.	There must be a clear plan for managing the programme, and agreed quality assurance standards	✔
16.	There must be adequate staffing and facilities for the programme and for referrals, diagnosis and treatment	?
17.	All other options for managing the condition should have been considered	✔
18.	Evidence-based information explaining the positive and negative aspects of the programme must be available to participants	✔
19.	Screening intervals, eligibility for screening and the testing process should be scientifically justifiable to the public	?

Table 1. Criteria that must be met for the implementation of a screening programme.

Based on the UK National Screening Committee criteria (2)

It can be seen from the table that these criteria are rigorous and may be considered overly stringent. They are designed to try and address all issues regarding the disease, as well as concerns over public acceptability, costs and, when applied to a state-funded health system, evidence of value to the taxpayer and consumer. Whereas some of these criteria may have a political element and may be debatable, others clearly require hard scientific evidence or widely accepted guidelines or policies. All who work in the field of oral cancer research or clinical management, will see that many of these criteria have not yet been met, and for some it may not be possible to demonstrate compliance. In the table, we have indicated (✔) those criteria that we feel have been met, or should be easy to meet, were a programme implemented. This is only 9 of 19 criteria. We have also indicated four areas (✗) where the evidence is still not clear and where further research is needed. Other issues are yet to be considered or are uncertain (?). This paper will address some of these key issues.

Is screening for oral cancer feasible and why should we consider implementing screening programmes?

Oral cancer is a serious health problem and despite slight improvements in survival rates about 50% of patients still die of disease. In addition, there is clear evidence that oral and oropharyngeal cancer are increasing in incidence, and although there is a shift in the site of lesions with a greater increase in the oropharynx, intra-oral or mouth lesions are still the most common and the greatest cause of morbidity and mortality (5).

For these reasons, oral cancer meets criterion 1 in Table 1 and for many oral health care workers it is inconceivable that we should not easily be able to implement an oral cancer screening programme. The oral cavity is easy to examine, oral lesions are relatively easy to detect and oral cancer is, in most cases, preceded by an oral potentially malignant disorder (OPMD). The term *OPMD is* a state of precancer in the oral cavity that carries an increased risk of progression to squamous cell carcinoma (6,7). The most common disorders recognised as potentially malignant are *leukoplakia* and *erythroplakia* (6,8) and these have characteristic clinical features. However, although these disorders have a statistically increased risk of progression to cancer (7,9), they may remain stable or regress and, for the present time, the prognostic significance of an individual lesion is difficult to determine, and none of the currently available histological or molecular markers have proved to be prognostically significant and few have yet been evaluated in large prospective studies (10,11).

The existence of OPMD suggest that oral cancer screening is feasible since this is evidence for an early detectable preclinical ("latent/ asymptomatic") phase of the disease. Although this partly meets criterion 2 in Table 1, there is uncertainty regarding the natural history of OPMD since we do not know which actual lesions will progress and have been unable to define clear criteria for a positive screening test. This is discussed further in the next section.

Evaluation of oral cancer screening tests

The validity of a screening test is measured by the frequency with which the result of that test is confirmed by an acceptable diagnostic procedure. The ability of a test to classify as positive

those persons with the disease is termed "sensitivity" and the ability to class as negative those without the disease "specificity"; that is, sensitivity is a measure of the false-negative rate and specificity of the false-positive rate (1). For population-based (organized) screening, the most sensitive test may not be chosen for a nationwide programme, since it risks a higher rate of false-positives. However, high specificity is important in reducing avoidable costs due to unnecessary work-up of false-positive results and associated adverse effects (12). At a population level, higher test specificity and less frequent screening help to minimize both physical and psychological harms by reducing unnecessary diagnostic evaluations and potential overtreatment (12).

While many studies have evaluated a conventional oral examination (COE) as a screening test for oral cancer screening, only ten have tested negative cases against a gold standard diagnosis by an expert clinical examination, which enables effectiveness to be determined in terms of sensitivity and specificity (13-22). These are summarised in Table 2.

	n	% positive	Sensitivity	Specificity	PPV	NPV
Chang et al. (13)	13606	2.1	0.99	0.99		
Downer et al. (14)	309	5.5	0.71	0.99	0.86	0.98
Ikeda et al. (15)	154	9.7	0.60	0.94	0.67	0.96
Jullien et al. (16)	2027	2.7	0.74	0.99	0.67	0.99
Mathew et al. (17)	2069	10.3	0.94	0.98	0.87	0.99
Mehta et al. (18)	1921	1.4	0.59	0.98	0.31	0.99
Warnakulasuriya et al. (19)	1872	21.6	0.95	0.81	0.58	0.98
Monteiro et al. (20)	727	3.4	0.96	0.98	0.96	0.98
Nagao et al (21)	137	68*	0.92	0.64	0.78	0.86
Sweeney et al. (22)	88	4.5	0.50	0.98		

Table 2. Reports of evaluations of conventional oral examinations, in which sensitivity and specificity of the test have been calculated

Walsh et al (23) included a number of these studies (13-19,22) in a Cochrane systematic review undertaken to estimate the diagnostic accuracy of COE, vital rinsing, light-based detection, biomarkers and mouth self examination (MSE), used singly or in combination, for the early detection of oral cancer and potentially malignant disorders (PMDs) in apparently healthy adults. The review found that COE has a variable degree of sensitivity (greater than 0.70) and a consistently high value for specificity (greater than 0.90). Additionally, one RCT study found a higher detection rate for oral cavity cancer in the COE plus vital rinsing adjunct trial arm. Furthermore, there was insufficient evidence to satisfactorily determine the diagnostic test accuracy of MSE as part of an organised screening programme.

Downer et al. (24) undertook a meta-analysis of some of these studies (14-19) and reported pooled values of sensitivity and specificity of 0.85 (95%CI; 0.73-0.92) and 0.97 (95%CI; 0.93-0.98) respectively.

In a more recent systematic review on the effectiveness of oral cancer screening tests in Europe, Warnakulasuriya et al. (25) further demonstrated the feasibility of screening for OPMD

and oral cancer using COE. They reviewed sixteen studies that used COE to detect relevant lesions, but none were RCTs and none were screening programmes as properly defined (see above). Nine of the studies were descriptive only and the validity of the data could not be judged. The review postulated that opportunistic screening in dental practices or screening of selected high-risk population groups may be considered, but that further studies were needed to determine the effectiveness of these interventions in these settings.

Overall these studies and reviews indicate that a COE results in a satisfactory test performance with sensitivities and specificities similar to those reported for breast and cervical cancer screening programmes. Furthermore, a number of these studies utilised non-medical or non-dental, healthcare workers as screeners (17-19), and showed similar results. This indicates that trained health care workers or dental care professionals (dental auxiliaries) are equally able to examine the mouth and detect relevant lesions. This has been confirmed by a number of studies that have evaluated directly lesion identification by trained health workers, including primary care physicians, or have compared the accuracy of different members of the dental team to identify lesions (26-30).

Although these studies have identified both the advantages and shortcomings of a COE (summarised in Table 3), the data do suggest that screening is feasible, in that dentists and allied health workers can accurately detect oral lesions.

Advantages	Shortcomings	Future approaches
Minimally invasive	May depend on the quality of the examiner	Establish a clear definition of a positive screen and continuous training programme
High validity (sensitivity and specificity, in case of experienced examiners)	Training and calibration of the screeners is needed	
Applicable in primary care setting	Cannot distinguish between benign lesions, cancer and OPMDs	Need scientifically evaluated adjunctive tests or biomarkers
Minimum examination time once trained	Low compliance and screen positives may not attend for secondary examinations	Basic strategies for health promotion, "advocacy, enabling and mediating" (16). Need well developed referral and monitoring
Can be repeated, no morbidity	Cost-effectiveness is uncertain	Studies must be carefully costed
No special facilities needed	Difficult to maintain a simple record of COE	Lesions can be photographed, standardisation can be desirable
Can be undertaken together with any other general and dental examinations		

Table 3. Advantages and shortcomings of conventional oral examination (COE) and possible future approaches

However care must be taken not to interpret these studies to mean that a good screening test is available. Most of these studies have used a lesion consistent with an oral potentially malignant disorder or oral cancer as the criteria for a positive screen. In most cases this has been a white patch, red patch or persistent ulcer. Leukoplakia is the most common OPMD and while these lesions have been detected with a prevalence of between 1.4 and 22% (31,32) (Table 2), it is important to remember that clinical appearance does not correlate well to histology and that

only about 5% overall will progress to cancer (7). This means that about 95% of detected lesions will not progress and are therefore not relevant to a test designed to detect lesions with a high likelihood of progressing to oral cancer. Although some molecular markers, especially analysis of loss of heterozygosity (LOH) (33), and some salivary markers (34), have potential as screening tests, at the present time no biomarkers have been shown to have utility in screening trials (10,11). A variety of new and emerging diagnostic aids and adjunctive techniques have been described to assist clinical diagnosis, but mostly these have been used to aid in categorisation of clinical lesions and will be discussed by Group 4. Evaluation of these adjuncts has taken place in secondary care facilities, often with patients at increased risk of mucosal change and not in primary care settings and therefore there is still no evidence that they may assist in the screening of healthy asymptomatic subjects for the detection of OPMD or otherwise occult oral cancerous lesions (35-38). Patton et al (36) reviewed 23 articles describing use of adjunctive techniques. Although they found evidence of utility, as diagnostic aids, in high risk individuals in a secondary care setting they identified a lack of studies in primary care or community settings and found no evidence of utility as tests for screening. A Cochrane systematic review concluded that none of the tests evaluated that were additional to a visual examination can be recommended as a replacement for the currently used diagnostic standard of a scalpel biopsy and histological assessment (38).

For these reasons oral cancer screening fails to meet criteria 2, 5 and 9 in Table 1.

Evaluation of oral cancer screening programmes

Although there have been many studies evaluating potential screening tests (eg. Table 2) there are few which have evaluated actual screening programmes. There is only one properly conducted randomised controlled trial that has used mortality as the primary outcome. This oral cancer screening trial was a community-based cluster-randomized control trial carried out in North Trivandrum, Kerala, India from 1996-2004 (39-43). The study was undertaken in 13 municipalities or clusters, which were dichotomized into two arms: an intervention (screened) arm (7 clusters; n=96,517) and control (not screened) arm (6 clusters; n=95,356). Screening included healthy residents ≥ 35 years of age. Non-medical university graduates performed the screening. They were trained, for three months, in recording socio-demographic features and visual examination to identify potentially malignant diseases, including white/red lesions, oral submucous fibrosis, lichen planus, and ulcers suspicious of malignancy. Over a 15 year period there were four rounds of screening, completed in 1998, 2002, 2004 and 2009.

A detailed analysis of the outcomes was reported in 2005 after three rounds of screening (41). In the intervention arm, oral findings were recorded as normal, non-referable lesions or referable lesions (screen positive). Referable lesions (screen positive) were referred to a dentist/oncologist for final diagnosis by examination/biopsy and a number of parameters were recorded (Table 4). In the control arm, the participants were not screened and only received awareness education and normal access to routine health care facilities. The primary outcome was the difference in mortality due to oral cancer in the intervention and control groups.

Ninety-one percent in the intervention and 84% in the control arm were interviewed. 87,655 individuals (91%) were screened at least once and 5,145 (6.55%) screened positive. Of these, only 3,218 (62%) complied with referral. The detection rate of OPMD or oral cancer per 1000

screened people was 28.0, 11.6, and 11.3 in the first, second and third rounds respectively. 205 (131 screen-detected, 59 interval cancers and 15 non-participants) cases of oral cancer were diagnosed in the intervention clusters, and 158 in the control group. Seventy-seven (37.6%) persons died of oral cancer in the intervention arm and 87 (55%) in the control arm, but this difference was not significant. There was a significant difference in 5 year survival (intervention arm, 50%: Control arm 34%) and in the number of cases diagnosed in stages I and II (42% and 23% respectively). However in the population as a whole there was no significant reduction in mortality (16.4% and 20.7%).

Participation
Screen positivity
* Prevalence of oral cancer and precancer
Compliance with referral
Sensitivity and specificity of the oral examination
Positive predictive value for detection of oral precancerous lesions.
Program sensitivity and specificity for detection of oral cancer
* Incidence rate of oral cancer in the study groups per 100,000 person-years
* Characteristics of oral cancer (TNM Staging)*
* Mortality for oral cancer cases*

Table 4: The Kerala screening study. Parameters recorded in the screen positive groups
(* These parameters were also recorded in the control arms)

The data were further analysed to determine if the effects were greater in high risk groups (defined as users of tobacco and/or alcohol). In males who used tobacco and/or alcohol there was a significant (43%) reduction in mortality from 42.9% in the control group to 24.6% in the intervention group. There was no significant reduction in females.

A subsequent (fourth) round of screening was reported in 2013 (42). After four rounds there was an overall significant improvement in 5 and 10 year survival rates and in early detection (stage shift), but there was no significant improvement in death rates or overall mortality. However for those individuals who participated in all four cycles of screening there was an overall reduction in mortality of 79% in the intervention arm (17.1 per 100,000 reduced to 3.0) and of 81% in the high risk group (39 Vs 7.1). This reduction in mortality was significant. However, it is important to note that only 19,288 persons completed four rounds of screening – 20% of the eligible population.

The data from these studies show that oral cancer screening using COE, even in high prevalence settings, does not reduce mortality in the population. The data do suggest however that screening of high risk groups may be effective in reducing mortality. The authors concluded that opportunistic screening of high risk groups is likely to be an effective intervention (42).

The results from the Kerala studies suggest that oral cancer screening only partly meets criteria 11 in Table 2.

Evidence Based Recommendations for Oral Cancer Screening

The rationale for a systematic review is to establish whether findings are consistent and can be generalised across populations, settings, and treatment variations, and to limit bias and provide recommendations and guidance for practice (44).

A Cochrane systematic review was undertaken to assess the effectiveness of oral cancer screening programmes (45). The primary outcome was evidence of reduced mortality from oral cancer, with secondary outcomes including early stage detection (stage shift), incidence and costs. The review identified 30 potentially eligible studies but only one RCT met the inclusion criteria. This was the Kerala study described above (39-42). Although this systematic review acknowledged the significant findings of the Kerala study, the reviewers identified a number of methodological weaknesses that might impact the validity of the study findings. The reviewers found insufficient evidence to recommend population-based screening programmes. However, visual screening may reduce the mortality rate in users of tobacco, alcohol or both and can produce a stage shift. The review concluded that targeted screening programmes could be effective in reducing oral cancer mortality. Nevertheless, further RCTs are warranted to provide the highest level of evidence for practice.

This Cochrane review concludes that there is insufficient evidence from RCTs to satisfy criteria 11 in Table 2.

Is Screening for oral cancer cost effective?

The Kerala group undertook costing analyses of their screening programmes and interventions (43). The overall benefit obtained from screening was 270 life-years saved per 100,000 population, but this rose to 1,438 life years per 100,000 in the high risk groups. The cost per life-year saved was $835 (USD) for the whole population and $156 for the high risk groups. The cost per screening examination was only $6 per person. The results of this study show that oral visual examination screening may be cost-effective, especially when applied to high risk groups where there is a larger yield and the potential to increase the number of life-years-saved. These financial calculations may be very different in western settings impacting any discussion of cost-effectiveness.

RCTs are very difficult or impossible to conduct in populations where the prevalence of the disease under study is low. For this reason it is extremely unlikely that a funding agency will fund an oral cancer screening RCT in any low prevalence country, and cost-effectiveness analyses will be a challenge to achieve. An alternative to RCTs for the evaluation of interventions is computer simulation modelling (46). An interesting study used a decision-analytic simulation model to determine the incremental costs and outcomes of alternative oral cancer screening programmes conducted in a primary care environment (47). The study found that opportunistic high-risk screening, particularly in general dental practice, may be cost-effective. The cost per life year saved was £22,850 (GBP), and was only marginally greater if screening was performed in medical practice (£23,728). Screening may more effectively be targeted to younger age groups, particularly those aged between 40–60 years. Although these costs are considerably more than those found in the Kerala Study, they are still within the acceptable cost per life saved which is considered value for money by the UK NHS (48).

These data suggest that oral cancer screening may meet criteria 14 in Table 2.

Summary and future directions

The cumulative evidence suggests that it is feasible to screen for oral cancer, but that there is considerable uncertainty regarding a number of key issues (Table 1). Clinicians recognise OPMD and there is evidence that these can be detected with a sensitivity and specificity sufficient to justify COE as a screening test. However the criteria for detected lesions (for a positive test) is not specific to lesions that have a high likelihood of progression, since overall only about 5% of screen detected lesions are likely to progress to cancer (7). Even for those that will progress, the rates of progression and the significance of individual markers are still uncertain. In their decision model, Speight et al. (47) undertook a Value of Information (VOI) analysis which showed that the greatest source of uncertainty in determining the outcomes of screening lay in our lack of understanding of malignant transformation of OPMD and disease progression. More accurate tests are needed and further research on the natural history of the disease and the use of adjunctive aids is needed.

Although there has been considerable research on potential screening tests, there has been only one evaluation of a screening programme – the Kerala study. However a systematic review (45) suggested that there is considerable uncertainty in this study and the findings have not been accepted by national governments as sufficient evidence to justify the implementation of screening programmes (2-4). An expert panel for the American Dental Association also reviewed the literature (37) and found insufficient evidence to show that community based screening may alter disease specific mortality, although they did suggest that screening by COE may reduce mortality in high risk groups. They also found no evidence for the effectiveness of adjunctive tests except in high risk patients by expert providers. They could not advocate population based screening but recommended that clinicians should opportunistically "screen" all patients for signs of OPMD or early oral cancer (37). At the present time it is now generally agreed that patients, especially those in high risk groups, should be opportunistically examined for any signs of oral cancer or precancer as part of their routine dental care (49). The use of adjunctive tests does however show promise but further studies are needed in primary care settings and on populations relevant to a screening test (35,36).

Natural history of the disease:
Malignant transformation rates
Rates of progression through stages of disease from precancer to cancer
Clinical and molecular biomarkers of the high-risk lesion
Screening tests
Evaluation of adjunctive tests
Criteria for positive and negative tests
Evaluations in appropriate populations with sensitivity and specificity as endpoints
Evaluations of diagnostic accuracy among different groups of health care workers
Screening Programmes
Further evaluations of programmes: RCTs, but also simulation and demonstration studies
Evaluation of opportunistic programmes in different healthcare settings
Identification of relevant high-risk groups and methods of targeting
Evaluation of risk reduction advice at time of screening

Table 5. Suggested priority areas for further research

Ideally further large scale RCTs are needed, but these would be extremely costly to undertake, especially if population mortality is used as the endpoint in low prevalence populations. It is unlikely that any funding agency will underwrite an RCT of the required scale. Consideration needs to be given to further simulation studies or to trials using surrogate endpoints, such as yield, stage shift or rates of disease progression. Demonstration studies could also be undertaken, using demographically similar populations as controls.

The accumulated evidence does support the view that opportunistic screening of high risk groups may be cost effective (43,45,47). However, it has been suggested that relevant high-risk groups do not attend a dentist on a sufficiently regular basis to make opportunistic screening in dental practice feasible (50). Further research is needed to determine how opportunistic screening may be implemented, and in which health care environments. Screening by non-medical or non-dental healthcare workers has been shown to be effective and utilising this group may be the best and most cost-effective way of improving early detection. Table 5 summarises key areas that should be considered for further research

References

1 Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva: WHO; 1968. Available from: http://apps.who.int/iris/bitstream/10665/37650/1/WHO_PHP_34.pdf

2 UK National Screening Committee. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme. London, UK: National Screening Committee, 2003. Updated 2015: http://legacy.screening.nhs.uk/oralcancer

3 Oral cancer Screening. National Cancer Institute: U.S. National Institutes of Health. Available at: http://www.cancer.gov/cancertopics/pdq/screening/oral/healthprofessional

4 U.S. Preventive Services Task Force: Screening for Oral Cancer: Recommendation Statement. Rockville, Md: U.S. Preventive Services Task Force, 2004. Available online: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/oral-cancer-screening1

5 Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45(4–5):309–16

6 Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007; **10**: 575-80

7 Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. Journal of Oral Pathology and Medicine 2008;37 (1):1–10.

8 Gale N, Pilch BZ, Sidransky D et al. Tumours of the Oral Cavity and Oropharynx. Epithelial Precursor Lesions. In: Barnes L, Eveson JW, Reichart P, Sidransky D (eds). World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours 2005. IARC Press, Lyon, 2005: Ch4; 177-179

9 Bouquot J, Speight PM, Farthing PM. Epithelial Dysplasia of the Oral Mucosa – diagnostic problems and prognostic features. Current Diagnostic Pathology 2006; **12**: 11-22

10 Warnakulasuriya S, Reibel J, Bouquot J, Dabelsteen E. Oral epithelial dysplasia classification systems: predictive value, utility, weaknesses and scope for improvement. J Oral Pathol Med. 2008; **3**:127-33.

11 Warnakulasuriya S. Lack of molecular markers to predict malignant potential of oral precancer. J Pathol. 2000 Mar;190(4):407-9.

12 Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer. 2004 Sep 1;101(5 Suppl):1201-13.

13 Chang IH, Jiang RS, Wong YK, Wu SH, Chen FJ, Liu SA. Visual screening of oral cavity cancer in a male population: experience from a medical center. Journal of the Chinese Medical Association

2011;74(12):561–6.
14 Downer MC, Evans AW, Hughes Hallett CM, Jullien JA, Speight PM, Zakrzewska JM. Evaluation of screening for oral cancer and precancer in a company headquarters. Community Dentistry and Oral Epidemiology 1995;23(2): 84–8.
15 Ikeda N, Downer MC, Ishii T, Fukano H, Nagao T, Inoue K. Annual screening for oral cancer and precancer by invitation to 60 year-old residents of a city in Japan. Community Dental Health 1995;12(3):133–7.
16 Jullien JA, Downer MC, Zakrzewska JM, Speight PM. Evaluation of a screening test for the early detection of oral cancer and precancer. Community Dental Health 1995;12: 3–7.
17 Mathew B, Sankaranarayanan R, Sunilkumar KB, Kuruvila B, Pisani P, Nair MK. Reproducibility and validity of oral visual inspection by trained health workers in the detection of oral precancer and cancer. British Journal of Cancer 1997;76(3):390–4.
18 Mehta FS, Gupta PC, Bhonsle RB et al. Detection of oral cancer using basic health workers in an area of high oral cancer incidence in India. Cancer Detect Prev 1986; 9: 219–225
19 Warnakulasuriya S, Pindborg JJ. Reliability of oral precancer screening by primary health care workers in Sri Lanka. Community Dental Health 1990;7(1):73–9.
20 Monteiro LS, Salazar F, Pacheco JJ, Martins M, Warnakulasuriya S. Outcomes of invitational and opportunistic oral cancer screening initiatives in Oporto,Portugal. J Oral Pathol Med. 2015 Feb;44(2):145-52
21 Nagao T, Ikeda N, Fukano H, Miyazaki H, Yano M, Warnakulasuriya S. Outcome following a population screening programme for oral cancer and precancer in Japan. Oral Oncol. 2000 Jul;36(4):340-6. PubMed PMID: 10899672
22 Sweeny L, Dean NR, Magnuson JS, Carroll WR, Clemons L, Rosenthal EL. Assessment of tissue autofluorescence and reflectance for oral cavity cancer screening. Journal of Otolaryntology Head and Neck Surgery 2011;145(6): 956–60
23 Walsh T, Liu JL, Brocklehurst P, Glenny AM, Lingen M, Kerr AR et al. Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. Cochrane Database Syst Rev. 2013 Nov 21;11:CD010173.
24 Downer MC, Moles DR, Palmer S, Speight PM. A systematic review of test performance in screening for oral cancer and precancer. Oral Oncol. 2004 Mar;40(3): 264-73.
25 Warnakulasuriya S, Fennell N, Diz P, Seoane J, Rapidis A; LDV Lifelong Learning Programme. An appraisal of oral cancer and pre-cancer screening programmes in Europe: a systematic review. J Oral Pathol Med. 2015 Sep;44(8):559-70
26 Warnakulasuriya KA, Nanayakkara BG. Reproducibility of an oral cancer and precancer detection program using a primary health care model in Sri Lanka. Cancer Detect Prev 1991; 15: 331–334
27 Warnakulasuriya KA, Ekanayake AN, Sivayoham S et al. Utilization of primary health care workers for early detection of oral cancer and precancer cases in Sri Lanka. Bull World Health Organ 1984; 62: 243–250.
28 Mathew B, Sankaranarayanan R, Sunilkumar KB, Kuruvila B, Pisani P, Nair MK. Reproducibility and validity of oral visual inspection by trained health workers in the detection of oral precancer and cancer. Br J Cancer. 1997;76(3):390-4.
29 Brocklehurst P, Pemberton MN, Macey R, Cotton C, Walsh T, Lewis M. Comparative accuracy of different members of the dental team in detecting malignant and non-malignant oral lesions. Br Dent J. 2015 May 8;218(9):525-9.
30 Epstein JB, Gorsky M, Cabay RJ, Day T, Gonsalves W. Screening for and diagnosis of oral premalignant lesions and oropharyngeal squamous cell carcinoma: role of primary care physicians. Can Fam Physician. 2008;54(6):870-5.
31 Petti S. Pooled estimate of world leukoplakia prevalence: a systematic review. Oral Oncology 2003;39(8):770–80.
32 Lim K, Moles DR, Downer MC, Speight PM. Opportunistic screening for oral cancer and precancer in general dental practice: results of a demonstration study. Br Dent J 2003; 194: 487–502.
33 Zhang L, Poh CF, Williams M, Laronde DM, Berean K, Gardner PJ, Jiang H, Wu L, Lee JJ, Rosin MP. Loss of heterozygosity (LOH) profiles validated risk predictors for progression to oral cancer. Cancer Prev Res (Phila). 2012 Sep;5(9):1081-9.
34 Elashoff D, Zhou H, Reiss J, Wang J, Xiao H, Henson B, Hu S, Arellano M, Sinha U, Le A, Messadi D, Wang M, Nabili V, Lingen M, Morris D, Randolph T, Feng Z, Akin D, Kastratovic DA, Chia D, Abemayor E, Wong DT. Prevalidation of salivary biomarkers for oral cancer detection. Cancer Epidemiol Biomarkers Prev. 2012 Apr;21(4):664-72

35 Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol. 2008 Jan;44(1):10-22.
36 Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. J Am Dent Assoc. 2008 Jul;139(7):896-905
37 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. Journal of the American Dental Association 2010;141(5):509–20.
38 Macey R, Walsh T, Brocklehurst P, Kerr AR, Liu JL, Lingen MW et al. Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. Cochrane Database Syst Rev. 2015 May 29;5:CD010276
39 Sankaranarayanan R, Mathew B, Jacob BJ, Thomas G, Somanathan T, Pisani P, Pandey M, Ramadas K, Najeeb K, Abraham E. Early findings from a community-based, cluster-randomized, controlled oral cancer screening trial in Kerala, India. The Trivandrum Oral Cancer Screening Study Group. Cancer. 2000 Feb 1;88(3):664-73.
40 Ramadas K, Sankaranarayanan R, Jacob BJ, Thomas G, Somanathan T, Mahe C, Pandey M, Abraham E, Najeeb S, Mathew B, Parkin DM, Nair MK. Interim results from a cluster randomized controlled oral cancer screening trial in Kerala, India. Oral Oncol. 2003 Sep;39(6):580-8.
41 Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, RajanB. Trivandrum Oral Cancer Screening Study Group. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. Lancet. 2005 Jun 4-10;365(9475):1927-33.
42 Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Thomas G, Anju G, Mathew B. Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. Oral Oncol. 2013 Apr;49(4):314-21.
43 Subramanian S, Sankaranarayanan R, Bapat B, Somanathan T, Thomas G, Mathew B, Vinoda J, Ramadas K. Cost-effectiveness of oral cancer screening: results from a cluster randomized controlled trial in India. Bull World Health Organ. 2009 Mar;87(3):200-6.
44 Mulrow CD. Rationale for systematic reviews. British Medical Jour 1994; 309: 597-9.
45 Brocklehurst P, Kujan O, O'Malley LA, Ogden G, ShepherdcS, Glenny AM. Screening programmes for the early detection and prevention of oral cancer. Cochrane Database of Systematic Reviews 2013, Issue 11. [DOI:10.1002/14651858.CD004150.pub3]
46 Fone D, Hollinghurst S, Temple M, Round A, Lester N, Weightman A, Roberts K, Coyle E, Bevan G, Palmer S. Systematic review of the use and value of computer simulation modelling in population health and health care delivery. J Public Health Med. 2003 Dec;25(4):325-35.
47 Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, Augustovski F. The cost-effectiveness of screening for oral cancer in primary care. Health Technol Assess. 2006 Apr;10(14):1-144
48 National Institute for Healthcare Excellence (NICE). Judging whether public health interventions offer value for money. September 2013: https://www.nice.org.uk/advice/lgb10/chapter/judging-the-cost-effectiveness-of-public-health-activities
49 Epstein JB, Huber MA. The benefit and risk of screening for oral potentially malignant epithelial lesions and squamous cell carcinoma. Oral Surg Oral Med oral Pathol Oral Radiol 2015;120(5):537-40
50 Netuveli G, Sheiham A, Watt RG. Does the 'inverse screening law' apply to oral cancer screening and regular dental check-ups? J Med Screen 2006;13(1):47-50