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Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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TABLE OF CONTENTS

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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i

[Diagnostic Test Accuracy Review]

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults

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ABSTRACT

Background

The early detection of oral cavity squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD), followed by appropriate treatment, may improve survival and reduce the risk for malignant transformation respectively. This is an update of a Cochrane Review first published in 2013.

Objectives

To estimate the diagnostic test accuracy of conventional oral examination, vital rinsing, light-based detection, mouth self-examination, remote screening, and biomarkers, used singly or in combination, for the early detection of OPMD or OSCC in apparently healthy adults.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 20 October 2020), MEDLINE Ovid (1946 to 20 October 2020), and Embase Ovid (1980 to 20 October 2020). The US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. No restrictions were placed on the language or date of publication when searching the electronic databases. We conducted citation searches, and screened reference lists of included studies for additional references.

Selection criteria

We selected studies that reported the test accuracy of any of the aforementioned tests in detecting OPMD or OSCC during a screening procedure. Diagnosis of OPMD or OSCC was provided by specialist clinicians or pathologists, or alternatively through follow-up.

Data collection and analysis

Two review authors independently screened titles and abstracts for relevance. Eligibility, data extraction, and quality assessment were carried out by at least two authors independently and in duplicate. Studies were assessed for methodological quality using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2). We reported the sensitivity and specificity of the included studies. We provided judgement of the certainty of the evidence using a GRADE assessment.

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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1

Main results

We included 18 studies, recruiting 72,202 participants, published between 1986 and 2019. These studies evaluated the diagnostic test accuracy of conventional oral examination (10 studies, none new to this update), mouth self-examination (four studies, two new to this update), and remote screening (three studies, all new to this update). One randomised controlled trial of test accuracy directly evaluated conventional oral examination plus vital rinsing versus conventional oral examination alone. There were no eligible studies evaluating light-based detection or blood or salivary sample analysis (which tests for the presence of biomarkers for OPMD and OSCC). Only one study of conventional oral examination was judged as at overall low risk of bias and overall low concern regarding applicability.

Given the clinical heterogeneity of the included studies in terms of the participants recruited, setting, prevalence of the target condition, the application of the index test and reference standard, and the flow and timing of the process, the data could not be pooled within the broader categories of index test. For conventional oral examination (10 studies, 25,568 participants), prevalence in the test accuracy sample ranged from 1% to 51%. For the seven studies with prevalence of 10% or lower, a prevalence more comparable to the general population, the sensitivity estimates were variable, and ranged from 0.50 (95% confidence interval (CI) 0.07 to 0.93) to 0.99 (95% CI 0.97 to 1.00); the specificity estimates were more consistent and ranged from 0.94 (95% CI 0.88 to 0.97) to 0.99 (95% CI 0.98 to 1.00). We judged the overall certainty of the evidence to be low, and downgraded for inconsistency and indirectness.

Evidence for mouth self-examination and remote screening was more limited. We judged the overall certainty of the evidence for these index tests to be very low, and downgraded for imprecision, inconsistency, and indirectness. We judged the evidence for vital rinsing (toluidine blue) as an adjunct to conventional oral examination compared to conventional oral examination to be moderate, and downgraded for indirectness as the trial was undertaken in a high-risk population.

Authors' conclusions

There is a lack of high-certainty evidence to support the use of screening programmes for oral cavity cancer and OPMD in the general population. Frontline screeners such as general dentists, dental hygienists, other allied professionals, and community healthcare workers should remain vigilant for signs of OPMD and OSCC.

PLAIN LANGUAGE SUMMARY

What are the most accurate tests for screening for cancer of the mouth (oral cancer) and conditions that may lead to oral cancer?

Key messages

- There is a lack of high-certainty evidence to support the use of screening tests for cancer of the mouth and conditions that may lead to mouth cancer in the general population.
- General dental practitioners and healthcare professionals should be watchful for signs of oral potentially malignant disorders (OPMD) and malignancies whilst performing routine oral examinations in practice for other common oral lesions/conditions.

Detection of oral cancer

Cancer of the mouth (oral cancer) is a serious condition, and only half of those that develop the disease will survive after 5 years. This is because it is often detected late. Early detection when the oral cancer is small or as a 'preceding' condition or lesion (which can become cancer) can result in simpler treatment and much better outcomes. As a result, there is a need to understand how good different types of tests are at the early detection of oral cancer and the lesions that precede it.

What did we want to find out?

The aim of this review was to find out the accuracy of different screening tests for cancer of the mouth and conditions that may lead to mouth cancer.

What did we do?

We searched for studies that reported the test accuracy of different screening tests in detecting cancer of the mouth or OPMDs during a screening procedure. Diagnosis of cancer of the mouth or OPMDs was provided by specialist clinicians or pathologists, or alternatively through follow-up. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We included 18 studies recruiting 72,202 participants, published between 1986 and 2019. These studies evaluated a conventional oral examination (COE) or visual inspection (10 studies), mouth self-examination (four studies), and remote screening (three studies). One randomised controlled trial of test accuracy directly compared conventional oral examination plus vital rinsing with conventional oral examination alone.

No eligible studies evaluated the accuracy of tests of blood or saliva.

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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2

There was substantial variation in the participants that were recruited, the setting, the prevalence of mouth cancer or OPMDs, and how the different tests were carried out, and so we were unable to pool the data.

- Most studies evaluated the accuracy of the different COEs (10 studies, 25,568 participants). The prevalence of mouth cancer or OPMDs in these studies ranged from 1% to 51%. For the seven COE studies with a prevalence of 10% or lower, a prevalence more comparable to the general population, the sensitivity estimates (proportion of true positives) ranged from 0.50 to 0.99 with specificity estimates (proportion of true negatives) from 0.94 to 0.99.

- Evidence for mouth self-examination (4 studies, 35,059 participants) and remote screening (3 studies, 3600 participants) was more limited.

What are the limitations of the evidence?

We judged the overall certainty of the evidence for COE to be low and downgraded for the variation across studies and applicability of the study samples. We judged the overall certainty of the evidence for mouth self-examination and remote screening to be very low, and downgraded for variation across studies, applicability of the study samples, and imprecise accuracy estimates.

How up to date is this evidence?

The evidence is up to date to October 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: conventional oral examination/visual inspection for the detection of oral cavity cancer and oral potentially malignant disorders in apparently healthy adults

Question	What is the performance of conventional oral examination/visual inspection for the detection of oral cavity cancer and oral potentially malignant disorders in apparently healthy adults?
Population	OSCC or OPMD symptom-free individuals screened opportunistically, or through an organised screening programme
Index test	Oral examination (conventional oral examination by a dentist or visual inspection by trained healthcare workers)
Target condition	OSCC or OPMD
Referencestandard	Examination and clinical evaluation by a physician with specialist knowledge or training. Long-term follow-up was accepted as a suitable reference standard for those participants who screened negative
Study type	Individuals attending for opportunistic screening, organised screening programme, validation as part of an organised screening programme, or randomised controlled trial, or screening as part of a routine surveillance appointment
Quantity of evidence	10 studies including 25,568 participants. The prevalence varied widely across the studies from 1.4% to 50.9%
Findings	

Due to differences in region, setting, nature of the index test, and reference standard we elected not to pool the studies

For the 7 studies with low prevalence (10% or less) the sensitivity estimates were highly variable, and ranged from 0.50 (95% CI 0.07 to 0.93) to 0.99 (95% CI 0.97 to 1.00), but the specificity estimates were more consistent and ranged from 0.94 (95% CI 0.88 to 0.97) to 0.99 (95% CI 0.98 to 1.00). For the 3 studies with higher prevalence sensitivity estimates ranged from 0.94 (95% CI 0.90 to 0.97) to 0.97 (95% CI 0.96 to 0.98), and specificities ranged from 0.75 (95% CI 0.73 to 0.77) to 0.98 (95% CI 0.98 to 0.99). For many of the studies the sensitivity estimates were imprecise, often reflective of the low disease prevalence in the samples

Limitations		Test accuracy certainty of the evidence
Risk of bias	3 studies were judged to be at low risk of bias overall. 5 studies were judged to be at unclear risk of bias primarily due to insufficient information regarding blinding of the results of the index test. 2 studies were judged to be at high risk of bias arising from the flow and timing domain (high levels of attrition following a positive screen and time from positive screen to receipt of the reference standard)	⊕⊕○○ LOW
Applicability of evidence to question	We judged concern regarding the applicability of the studies to the review question to be high for the patient selection domain for 1 study that recruited males only in a hospital setting, 1 study that recruited male smokers, and 1 study that recruited participants that had previously received treatment for head and neck cancer	
Overall certainty of the evidence	We judged the overall certainty of the evidence to be low, and downgraded for inconsistency and indirectness	

CI = confidence interval; OPMD = oral potentially malignant disorders; OSCC = oral squamous cell carcinoma.

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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4

Summary of findings 2.   Summary of findings: mouth self-examination for the detection of oral cavity cancer and oral potentially malignant disorders in apparently healthy adults

Question	What is the performance of mouth self-examination for the detection of oral cavity cancer and oral potentially malignant disorders in apparently healthy adults?
Population	OSCC or OPMD symptom-free individuals screened through an organised screening programme
Indextest	Mouth self-examination
Targetcondition	OSCC or OPMD
Referencestandard	Examination and clinical evaluation by a physician with specialist knowledge or training or trained health worker
Study type	Organised screening programmes
Quantity of evidence	4 studies including 35,059 participants. The prevalence varied widely across the studies from 0.6% for the largest study to 63.6% for the smallest study

Findings	

Due to the small number of eligible studies and heterogeneity in the region, setting, conduct of index test, and reference standard we elected not to pool the studies

In 2 studies the sensitivity was much lower than the specificity (sensitivity 0.18 (95% CI 0.13 to 0.24), specificity 1.00 (95% CI 1.00 to 1.00) and sensitivity 0.09 (95% CI 0.04 to 0.15), specificity 0.95 (95% CI 0.88 to 0.99), respectively). Sensitivity and specificity values were similar for 2 other studies (sensitivity 0.43 (95% CI 0.24 to 0.63), specificity 0.44 (95% CI 0.20 to 0.70) and sensitivity 0.33 (95% CI 0.10 to 0.65), specificity 0.54 (95% CI 0.37 to 0.69), respectively)

Limitations		Test accuracy certainty of the evidence
Risk of bias	The overall risk of bias for the studies that evaluated mouth self-evaluation was judged to be unclear for 3 studies and high for 1 study	⊕◯◯◯ VERY LOW
Applicability of evidence to question	We judged concern regarding the applicability of the studies to the review question to be high for the patient selection domain for 1 study that recruited and evaluated participants with Fanconi anaemia in a hospital setting, and participants that were identified and invited to participate based on their physician assessed risk of oral cancer	
Overall certainty of the evidence	We judged the overall certainty of the evidence to be very low, and downgraded for imprecision, inconsistency, and indirectness	

CI = confidence interval; OPMD = oral potentially malignant disorders; OSCC = oral squamous cell carcinoma.

Summary of findings 3.   Summary of findings: vital rinsing (toluidine blue) as an adjunct to conventional oral examination compared to conventional oral examination alone for the detection of oral cavity cancer and oral potentially malignant disorders in apparently healthy adults

Question	What is the performance of vital rinsing (toluidine blue) as an adjunct to conventional oral examination compared to conventional oral examination alone **for the detection of oral cavity cancer and oral potentially malignant disorders in apparently healthy adults**?
Population	OSCC or OPMD symptom-free individuals with tobacco habits

Indextest	Conventional oral examination plus vital rinsing (toluidine blue)
Comparator test	Conventional oral examination alone
Targetcondition	Oral cancer as indicated by the National Cancer Registry
Referencestandard	Biopsy and histopathologic diagnosis, long-term follow-up through the National Cancer Registry
Study type	Randomised controlled trial of screening strategies
Quantity of evidence	1 study including 7975 participants. 4.6% prevalence in conventional oral examination plus vital rinsing trial arm, 4.4% in conventional oral examination alone trial arm[a]
Findings	

Conventional oral examination plus vital rinsing: sensitivity 0.40 (95% CI 0.05 to 0.85) and specificity 0.91 (95% CI 0.90 to 0.91) with a prevalence of 0.12%

Conventional oral examination alone: sensitivity 0.50 (95% CI 0.12 to 0.88) and specificity 0.92 (95% CI 0.91 to 0.93) with a prevalence of 0.15%

Limitations		Test accuracy of certainty of the evidence
Risk of bias	Low risk of bias for patient selection, index test, and flow and timing domains, unclear risk of bias for reference standard as whether this was interpreted without knowledge of the results of the index tests is unclear	⊕⊕⊕⊝ MODERATE
Applicability of evidence to question	We judged the trial to be of high concern regarding applicability for the patient selection domain as individuals who "lacked oral habits" such as smoking or betel quid chewing were ineligible for the trial	
Overall certainty of the evidence	We judged the certainty of the evidence as moderate, and downgraded 1 level due to indirectness	

CI = confidence interval; OPMD = oral potentially malignant disorders; OSCC = oral squamous cell carcinoma.

[a]Comparative effectiveness for health outcomes. Detection rate of OSCC and OPMDs after referral was 4.6% in conventional oral examination plus vital rinsing arm; 4.4% in conventional oral examination alone (rate ratio 1.05 (95% CI 0.74 to 1.41)). Incidence rate of OSCC (x 10^{-5}) of 28 compared to 35.4. Relative incidence rate of 0.79 (95% CI 0.24 to 1.23).

Summary of findings 4.   Summary of findings: remote screening for the detection of oral cavity cancer and oral potentially malignant disorders in apparently healthy adults

Question	What is the performance of remote screening for the detection of oral cavity cancer and oral potentially malignant disorders in apparently healthy adults?
Population	OSCC or OPMD symptom-free individuals screened through an organised screening programme
Indextest	Remote screening of the oral cavity
Targetcondition	OSCC or OPMD
Referencestandard	Examination and clinical evaluation by a physician with specialist knowledge or training or trained health worker

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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6

Study type	Organised screening programme, pilot, and feasibility studies
Quantity of evidence	3 studies including 3600 participants. The prevalence varied across the studies from 12.2% to 30.9%

Findings

Due to the small number of eligible studies and heterogeneity in the region, setting, and case definition for the target condition we elected not to pool the studies

Findings for sensitivity and specificity for each of the studies were as follows: sensitivity 0.85 (95% CI 0.81 to 0.88), specificity 0.99 (95% CI 0.99 to 1.00); sensitivity 0.82 (95% CI 0.57 to 0.96), specificity 1.00 (95% CI 0.91 to 1.00); and sensitivity 0.94 (95% CI 0.70 to 1.00), specificity 0.72 (95% CI 0.63 to 0.80)

Limitations		Test accuracy certainty of the evidence
Risk of bias	The overall risk of bias was judged to be low in the organised screening programme and unclear in the pilot and feasibility studies due to a lack of information regarding the patient selection and index tests	⊕◯◯◯ VERY LOW
Applicability of evidence to question	Concern regarding the overall applicability of the studies to the review question was high for 2 studies arising from the patient selection domain where the samples were primarily composed of older, male smokers	
Overall certainty of the evidence	We judged the certainty of the evidence as very low, and downgraded 2 levels due to indirectness (applicability of the study sample) and for inconsistency	

CI = confidence interval; OPMD = oral potentially malignant disorders; OSCC = oral squamous cell carcinoma.

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

7

BACKGROUND

Target condition being diagnosed

The target conditions of interest are oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD) of the oral cavity. OSCC is the most common form of oral cavity cancer (Bagan 2020; Chi 2015) and a proportion of carcinomas are preceded by OPMD. OPMD represent a heterogeneous group of conditions including leukoplakia, erythroplakia, proliferative verrucous leukoplakia, oral lichen planus/oral lichenoid lesions, oral submucous fibrosis, and actinic keratosis (Warnakulasuriya 2007; Warnakulasuriya 2020).

The natural history of OSCC is not fully understood; not all OPMD undergo malignant transformation, some remain stable, and some affected sites can revert back to health (Speight 2017). Equally, some OSCC can develop from lesions in which epithelial dysplasia was not previously diagnosed (Dost 2014), or from apparently normal mucosa that may contain significant molecular aberrations that increase the likelihood of cancer (Farah 2019; Nikitakis 2018; Thomson 2017). Proliferative verrucous leukoplakia has the highest malignant transformation rate (MTR) followed by erythroplakia (Locca 2020). Oral leukoplakia is the most common OPMD but has a varied MTR (Arduino 2013; Chaturvedi 2020; Warnakulasuriya 2016). In a systematic review of the literature, Warnakulasuriya 2016 reported the MTR of oral leukoplakia to be between 0.1% and 34%, and more recently a review from 2015 to 2020 reported that the MTR varied between 1.1% and 40.8%, with a pooled proportion of 9.8% (95% confidence interval (CI) 7.9% to 11.7%) (Aguirre-Urizar 2021). Petti 2003 calculated a global MTR of oral leukoplakia of 1.4% per year (95% CI 0.7% to 2%), but when this is applied to the prevalence of the condition, it far exceeds the numbers of actual cases of OSCC reported. However, the MTR in hospital-based studies is consistently higher than in community-based studies.

Several recent systematic reviews have reported an MTR for oral lichen planus close to 1%. For example, in a meta-analysis of 78 studies with 25,848 patients, Gonzalez-Moles 2019 reported a malignant transformation rate of 1.1% (95% CI 0.8% to 1.5%), results similar to Fitzpatrick 2014 (1.1%), Giuliani 2019 (1.4%), and Locca 2020 (1.4% (95% CI 0.9% to 1.9%)). In a meta-analysis of 33 studies with 12,838 oral lichen planus patients, Idrees 2021 reported that 151 cases were initially considered to have progressed to carcinoma (1.2%). Following the application of strict criteria (the presence of a properly verified oral lichen planus histological diagnosis with absence of epithelial dysplasia, a clear description of the cancerous lesion developing at the same site as the verified oral lichen planus lesion, and a follow-up period of a minimum of 6 months prior to carcinoma development), this figure was reduced to 0.4%, with an overall pooled proportion MTR of 0.2% (95% CI 0.1% to 0.3%) (Idrees 2021). Ramos-García 2021 summarised the systematic reviews in this area.

The early detection and excision of high-risk oral leukoplakias (OL) may reduce the risk of malignant transformation (Mehanna 2009a). Leukoplakias can be treated by a number of different methods however, there is relatively little empirical evidence from randomised controlled trials and there remains some debate in the literature as to their effectiveness (Holmstrup 2006; Lodi 2016). Systematic reviews have evaluated the evidence for surgical interventions (including laser therapy). Surgical laser excision of OL may decrease recurrence rates but have no effect on malignant transformation when compared with conventional treatments (de Pauli 2020). There is scant experimental evidence for non-surgical interventions, though clinical resolution was observed, relapses were common (Lodi 2016).

In the United Kingdom, patients presenting with any new growth, an ulcer, or a white and red or red lesion persisting for more than 2 to 3 weeks, are urgently referred to Oral Medicine Units or Oral and Maxillofacial Surgery Units for further investigation (NICE 2016). Technologies to manage OSCC have progressed substantially (Bulsara 2018; Furness 2011; Glenny 2010; Shaw 2020), but surgery, radiotherapy, chemotherapy, and now immunotherapy are associated with significant morbidity. Despite this, mortality and survival rates have, however, remained high (approximately 50%) and typically have remained unchanged over several decades (Warnakulasuriya 2009; Warnakulasuriya 2020), and this appears to point to the late presentations or aggressive biological behaviour of some OSCCs. There is a need for centralization of expertise while remaining accessible to the patient (Ogden 2020). If the lesion is diagnosed as OSCC the traditional treatment is surgery and radiotherapy, but the associated morbidity is high. This is in marked contrast to the improved mortality and survival rates in many other cancers, such as those of the breast and the colon (Cancer Research UK 2020). Reasons for this include that late presentation of OSCC may be related to delayed diagnosis (a combination of patient factors such as infrequent visits to the dentist or physician, and clinician factors, such as failure to screen the entire mouth, failure to raise the index of suspicion regarding any lesion they may see or delays in onward referral) (Seoane 2016). Yet early OSCC can often be asymptomatic and is more amenable to a cure if detected as localised stage I or II disease (Ganly 2012).

Index test(s)

Reviews of primary studies for the detection of OPMD and OSCC have identified a number of index tests which have been developed with respect to accurate and timely detection (Fedele 2009; Kerr 2020; Lestón 2010; Lingen 2017; Liu 2016; Madhura 2020; Omar 2015; Patton 2008; Rashid 2015; Rethman 2010). These tests include:

- conventional oral examination/visual inspection by a dentist, physician, or other healthcare worker;
- vital staining or rinsing (e.g. toluidine blue, tolonium chloride); oral cytology (e.g. OralCDx brush biopsy, Cyte ID);
- light-based detection (e.g. VELscope, Orascoptic DK, Identafi 3000, ViziLite Plus, Microlux/DL);
- mouth self-examination;
- remote clinical examination (including telemedicine); and
- blood and saliva analyses.

Vital rinsing/staining has been an available adjunct to a conventional oral examination (COE) for several years (Lestón 2010; Lingen 2008), whilst light-based detection systems have become commercially available more recently. Blood analysis and saliva analysis are at a relatively early stage of evaluation (Additional Table 1). Index tests evaluated up to this point of specific interest to opportunistic screening or mass screening programmes outside of a clinical setting include conventional oral examination by clinicians or trained healthcare workers, mouth self-examination, blood and saliva analyses, or remote assessment.

Where access to clinicians, such as dentists/dental hygienists or physicians/allied medical workers is limited, population screening using oral examination, vital staining or rinsing, light-based detection, blood and saliva analyses, and remote examination could, in principle, be undertaken by trained community healthcare workers.

Mouth self-examination is a simple technique with universal application. This is usually undertaken in the home setting in accordance with instructional material, and the target condition is typically the presence of a visible lesion in the oral cavity. It is simple to carry out and has a limited cost, but the significant disadvantage is that it is being performed by a trained or untrained novice who can only determine, at best, the presence or absence of oral lesions. Mouth self-examination cannot definitively differentiate between OSCC, OPMDs, and benign lesions. Studies examining the ability of individuals to perform mouth self-examination have reported the quality of examinations of adolescents and adults to be unsatisfactory in terms of retraction and visualisation of the oral mucosa, and care and attention whilst carrying out the examination (Furquim 2014; Pivovar 2017a). The participants in these studies received no supporting literature or instruction prior to carrying out the self-examination.

A companion Cochrane Review evaluates the diagnostic accuracy of index tests in individuals presenting with clinically evident lesions (Walsh 2021).

Clinical pathway

Typically, individuals receive a COE as part of a routine dental appointment. The COE involves a standard visual and tactile examination of the oral mucosa under normal (incandescent) light. Alternatively, patients may occasionally present to the dental clinic with symptoms. Upon discovering a lesion, the clinician i.e. the dentist or dental hygienist, makes a subjective judgement based upon clinical presentation. If an OPMD or OSCC is suspected, the frontline clinician refers onward to an oral specialist for a scalpel biopsy to render the definitive diagnosis. In some healthcare systems, for example in Spain, the biopsy is often carried out by the dentist.

Not all individuals regularly attend for a routine dental appointment, particularly in countries where access to healthcare resources are limited. Given the clear benefits of early detection, the screening of asymptomatic individuals would seem sensible. Screening can be carried out opportunistically, when an individual presents for a dental appointment, as part of a routine surveillance appointment for patients with a history of OPMDs or OSCC who need close monitoring, or as part of an organised screening programme carried out by a dentist or other healthcare worker. If the outcome of the screening activity detects a lesion that elicits concern, the individual is usually referred for further investigation by a specialist; it could be an examination/biopsy by an oral medicine specialist, oral pathologist, oral surgeon, or otolaryngologist at a secondary or tertiary clinic.

The policies for promoting screening programmes for OPMD and OSCC remain controversial, with the US Preventive Services Task Force concluding that there is insufficient evidence regarding the benefits and harms of screening for OPMD and OSCC by primary care providers in asymptomatic adults (Moyer 2014). In asymptomatic high-risk individuals, however, the picture may

be different. A population-based national screening programme in Taiwan targeting betel-quid-chewing or cigarette-smoking individuals deemed to be at high risk of oral cancer compared health outcomes between screened and non-screened individuals. With an overall screening rate of 55.1%, the study reported a risk ratio (RR) of death from oral cancer of 0.53 (95% CI 0.51 to 0.56) compared with the expected risk of oral cancer deaths in the absence of screening (RR 0.74 (95% CI 0.72 to 0.77) after adjusting for self-selection bias), and a RR of 0.62 (95% CI 0.59 to 0.64) for advanced oral cancer (RR 0.79 (95% CI 0.76 to 0.82) after adjustment for self-selection bias) (Chuang 2017). A re-analysis of the Kerala Oral Cancer Screening Trial where healthcare workers performed visual oral examinations reported that mortality was reduced by 27% in the screening arm compared to the control arm (hazard ratio (HR) 0.73; 95% CI 0.54 to 0.98), including a 29% reduction in ever-tobacco or ever-alcohol users or both (HR 0.71; 95% CI 0.51 to 0.99) (Cheung 2021). Galvão-Moreira 2017 suggested that screening strategies for OSCC should target populations at greater risk of disease in areas with high incidence of disease through visual examination by trained health workers or specialists in order to decrease the burden of disease. Similarly Mandal et al suggested that screening of habitual tobacco or alcohol users with oral examination may be prudent in countries with a high burden of oral cancer where healthcare resources are sparse or where competing healthcare priorities exist (Mandal 2018). There is limited evidence available, but the addition of adjunct tools to the COE by dentists may not prove fruitful in terms of reducing oral cancer incidence in a screening programme. For example, in a randomised controlled trial of screening with COE plus toluidine blue versus COE alone carried out in Taiwan amongst 28,167 high-risk individuals, a non-significant reduction of 21% in oral cancer incidence was reported in the individuals screened with COE plus toluidine blue (28.0 x 10(-5) versus 35.4 x 10(-5)) (Su 2010).

Rationale

Cochrane Oral Health undertook an extensive prioritisation exercise in 2020 to identify a core portfolio of titles that were the most clinically important ones to maintain in the Cochrane Library. Consequently, this review was identified as a priority title (COH priority reviews).

Oral cancer is a significant global health problem with an estimated 354,864 new cases and 177,384 deaths in 2018 (Bray 2018), and reported increases in incidence and mortality rates in many countries in the globe (Jin 2016; Shield 2017; Warnakulasuriya 2009). More recently, the trends of oral cancer incidence indicated two contrasting patterns between the sexes; in males, most cancer registry populations exhibited decreasing trends while in females, rising rates were seen in most populations (Miranda-Filho 2020). There is wide geographic variation in disease incidence and mortality, with almost double the incidence in lower- and middle-income countries compared to high-income countries, and a three-fold increase in mortality. Tobacco use, alcohol consumption, betel-quid-chewing and low socioeconomic status are the most important risk factors for oral cancer (Conway 2008; IARC 2012). Human papillomavirus is not considered a significant risk for oral cavity cancers but is a major risk factor for oropharyngeal cancer (Kreimer 2020). Men have a higher incidence of oral cancer than women, but the gender difference has narrowed in recent decades from a ratio of five males to one female diagnosed with OSCC in the 1960s to less than two to one in 2008 (Ferlay 2010). Although

traditionally the risk of oral cancer increases with age, since the 1980s the incidence amongst younger adults has increased in the European Union and the United States (Warnakulasuriya 2009).

Oral cancer mortality can be reduced by: (i) primary prevention, (ii) secondary prevention (screening and early detection), and (iii) improved treatment (ERO-FDI 2019). Accurate case detection and early treatment of oral cancers can substantially improve an individual's outlook with respect to morbidity, mortality, and quality of life (Speight 2017). However, no national population-based screening programmes for oral cancer has yet been implemented in high-income countries, although opportunistic screening has been advocated (Speight 2017). Oral cancer screening models feasible for high-risk countries have recently been reviewed (Nagao 2020).

There is some debate in the literature on anticipated differences in diagnostic accuracy of prospective population-based invitational screening programmes and a more opportunistic approach (when patients attend their dental practitioner or to a lesser extent their physician, for routine examination or for treatment). In Downer et al's systematic review of test performance in screening for OSCC and OPMDs, only prospective investigations of population screening with specified reference standards were included. The pooled sensitivities and specificities were 0.85 (95% CI 0.730 to 0.919) and 0.97 (95% CI 0.930 to 0.982) respectively (Downer 2004). An opportunistic approach that focuses on high-risk groups is also possible (McGurk 2010; Sankaranarayanan 1997). A simulation study which used neural network and machine learning techniques suggested opportunistic screening aimed at high-risk groups may be both effective and cost-effective (Speight 2006). However, many individuals with risk factors may not attend the dentist (or the physician) and are therefore not amenable to an opportunistic approach (Netuveli 2006; Yusof 2006). A review of the literature on screening models for OPMDs and OSCC has identified a huge potential for new research directions in this area (Warnakulasuriya 2021).

In this systematic review we have identified screening tests for OPMD and OSCC to evaluate the diagnostic accuracy of the COE and other index tests, used alone or in combination, in asymptomatic adults. The index tests proposed for evaluation in this review are suitable for use in a general dental practitioner's office as part of a dental examination, or in an organized community screening event. The proposed index tests cannot confirm whether a 'positive' finding is indeed an OSCC or dysplastic OPMD before deciding on referral to secondary care; biopsy with histopathology is currently the only confirmatory method of diagnosing OSCC or dysplasia.

This diagnostic test accuracy review complements a number of intervention reviews undertaken by Cochrane Oral Health on the treatment of oral and oropharynx cancers (Bulsara 2018; Furness 2011; Glenny 2010) and oral leukoplakia (Lodi 2016), screening programmes for the early detection and prevention of OSCC (Brocklehurst 2013). This review was originally published in 2013 as clinical assessment to screen for the detection of oral cavity cancer and oral potentially malignant disorders in apparently healthy adults (Walsh 2013). In this updated Cochrane Review we have included contemporary studies irrespective of publication language and status, and assessed the body of evidence using GRADE (Schünemann 2020; Schünemann 2020a) to facilitate the production of summary of findings tables.

OBJECTIVES

To estimate the diagnostic test accuracy of index tests (conventional oral examination (COE), vital rinsing, light-based detection, mouth self-examination (MSE), remote screening, and biomarkers), used singly or in combination, for the early detection of oral potentially malignant disorders (OPMD) or oral squamous cell carcinoma (OSCC) in apparently healthy adults.

METHODS

Criteria for considering studies for this review

Types of studies

Eligible study designs were cross-sectional studies (or prospective consecutive series) and randomised controlled trials (RCTs) of test accuracy. Where randomised or paired comparative designs were available these were included in the review and analysed separately. We excluded case series and diagnostic case-control studies which have been shown to lead to inflated estimates of prevalence and test accuracy (Whiting 2004). We also excluded studies that reported in abstract form alone, uncontrolled reports, and randomised controlled trials of the effectiveness of screening programmes (intervention studies). Only studies reporting test accuracy data in the form of a 2 x 2 table or where a 2 x 2 table could be constructed from the information in the study report were included.

Participants

Apparently healthy adults not reporting symptoms of oral potentially malignant disorders (OPMD) or oral squamous cell carcinoma (OSCC), attending an organised screening or surveillance programme, or screened during attendance at a dental or physician examination. We did not exclude specific subgroups of patients in this review, such as high-risk cohorts or surveillance cohorts.

Index tests

Eligible index tests included:

- conventional oral examination (COE)/visual inspection by a dentist, physician, or other healthcare worker;
- vital staining or rinsing (e.g. toluidine blue, tolonium chloride);
- oral cytology (e.g. OralCDx brush biopsy, Cyte ID);
- light-based detection (e.g. VELscope, Orascoptic DK, Identafi 3000, ViziLite Plus, Microlux/DL);
- mouth self-examination;
- remote clinical examination (including telemedicine); and
- blood and saliva analyses.

Target conditions

Following the consensus views of the expert working group of the World Health Organization (WHO) Collaborating Centre for Oral Cancer/Precancer (Warnakulasuriya 2007; Warnakulasuriya 2021a), the following OPMDs and malignancies were considered as constituting a diseased classification: OSCC; OPMD represent a heterogeneous group of conditions including leukoplakia, erythroplakia, proliferative verrucous leukoplakia, oral lichen planus/oral lichenoid lesions, oral submucous fibrosis, and actinic keratosis (Warnakulasuriya 2007; Warnakulasuriya 2020). Where

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

10

studies evaluated COE by someone other than a dentist or physician, or mouth self-examination, the target condition of the index test was typically expressed as the presence or absence of an oral lesion.

Reference standards

The reference standard was examination and clinical evaluation by a clinician with specialist knowledge or training, working to the current diagnostic guidelines of their locality. At the most experienced level, this would be an oral and maxillofacial pathologist or oral medicine specialist, possibly utilising biopsy with histology where clinically appropriate. More commonly, this was expected to include general dentists in receipt of supplementary training in the detection and identification of OPMDs and OSCCs. We included studies where confirmation of individuals who were screened as negative by the index test was obtained from extended follow-up. To be eligible for inclusion in the review, at least a proportion of the screened negatives were required to be verified. For each study we noted the diagnostic protocol, guidelines or registry used for follow-up in the Characteristics of included studies table. Studies with confirmatory biopsy of individuals who were screened as negative by the index test were eligible for inclusion although ethically questionable (Downer 2004).

Where a histopathological reference standard was employed this review classified any level of dysplasia (mild, moderate, or severe) as disease-positive.

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches for diagnostic test accuracy studies in the following databases:

- Cochrane Oral Health's Trials Register (searched 20 October 2020) (Appendix 1);
- MEDLINE Ovid (1946 to 20 October 2020) (Appendix 2);
- Embase Ovid (1980 to 20 October 2020) (Appendix 3).

Searching other resources

The following trial registries were searched for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 20 October 2020) (Appendix 4);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 20 October 2020) (Appendix 5).

We sought to locate further studies through citation searches and reference lists of key articles.

For the previous version of this review, we searched the Cochrane Diagnostic Test Accuracy Register and the MEDION database on 30 April 2013. These databases were no longer available to search for this update. The search strategies for these two databases can be found in Appendix 6 .

Data collection and analysis

Selection of studies

Two review authors independently assessed the titles and abstracts of all articles identified from the searches. Full-text reports were obtained for those appearing to meet the inclusion criteria, or where a clear decision was unable to be made from scanning the title and abstract alone. Where disagreements occurred, these were resolved by discussion with the review team.

Data extraction and management

Two review authors independently extracted data using a piloted data collection form. Discrepancies were resolved through discussion with the review team. Study authors were contacted to obtain relevant missing data if these were not available in the printed report.

From each study, we extracted the following data.

- Sample characteristics (age, sex, socioeconomic status, risk factors (e.g. human papillomavirus status, tobacco use, betel quid and alcohol consumption), number of participants/ lesions).
- Setting (country, disease prevalence, type of screening).
- Type of index test(s) (category, positivity threshold).
- Study information (design, reference standard, case definition, training and calibration of personnel).
- Study results (true positive, true negative, false positive, false negative, any equivocal results, withdrawal or exclusions).

This information was documented in the Characteristics of included studies table for each study.

Assessment of methodological quality

We used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (Whiting 2011) to assess the quality of the included studies over four key domains: patient selection, index test, reference standard, and flow and timing of participants through the study. The QUADAS-2 tool was tailored specifically for this review (Additional Table 2). Review specific guidance was used to facilitate documentation of the pertinent descriptive information contained in the studies. Two core signalling questions were removed: 'Was a case-control design avoided?' (this study design was excluded from the review); and 'Did all patients receive a reference standard?' (this was a criterion for inclusion). Two additional signalling items relating to commercial funding and multiple index tests were added to the core signalling questions. Responses to the signalling questions, risk of bias, and applicability judgements are presented in the Characteristics of included studies tables and summarised graphically.

Statistical analysis and data synthesis

Data for the true-positive, true-negative, false-positive, and false-negative values for each test in each study was entered into Review Manager (Review Manager 2020). Estimates of diagnostic accuracy were expressed as sensitivity and specificity with 95% confidence intervals (CI) for each study and for each available data point if there were multiple index tests or lesions reported within a single study. Study estimates of sensitivity and specificity were plotted on coupled forest plots and in receiver operating characteristic (ROC) space.

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

11

Where studies directly evaluated the comparative accuracy of more than one index test with the reference standard, i.e. randomising individuals to different index tests, we planned to report the results of these studies separately.

For the primary analysis we had intended to undertake a meta-analysis to combine the results of the studies for each index test. However, the substantial diversity of characteristics of the included studies meant that this was not appropriate.

Investigations of heterogeneity

We planned to explore possible sources of heterogeneity through meta-regression including the following covariates:

- characteristics of the study sample (prevalence of OSCC or OPMD in the study (> 50% prevalence), inclusion of human papillomavirus (HPV) + adults, tobacco users/high alcohol consumption);
- target condition (OSCC alone or OSCC and potentially malignant disorders (PMD));
- aspects of study design (prospective organised or opportunistic);
- type of reference standard (examination and clinical evaluation by physician with specialist knowledge or extended follow-up) and operator (dentist, physician, or other healthcare workers).

Sensitivity analyses

No sensitivity analyses were planned.

Assessment of reporting bias

Tests for reporting bias were not conducted because current tests are misleading when applied to systematic reviews of diagnostic test accuracy (Leeflang 2008).

Summary of findings and assessment of the certainty of the evidence

We reported our results for the different index tests following GRADE methods (Schünemann 2020; Schünemann 2020a), and using the GRADEPro online tool (www.guidelinedevelopment.org). To enhance readability and understanding, we planned to present test accuracy results in natural frequencies to indicate numbers of false positives and false negatives. We assessed the certainty of the body of evidence with reference to the overall risk of bias of the included studies, the indirectness of the evidence, the inconsistency of the results, and the imprecision of the estimates. We categorised the certainty of the body of evidence as high, moderate, low, or very low.

R E S U L T S

Results of the search

Thirteen studies were included in the previous version of this review based on the original search date of 30 April 2013. 4970 references were retrieved in the search update up to 20 October 2020, and 4588 remained after the removal of duplicates. These were screened independently and in duplicate according to eligibility criteria. For this update 16 records were considered potentially eligible for inclusion, five new studies were included (Birur 2019; Furquim 2014; Ghani 2019; Gomes 2017; Vinayagamoorthy 2019), one study is ongoing, one previously ongoing study has not yet reported results and is awaiting classification, one study is awaiting classification pending further details of the study design from the authors. Eight studies were excluded (Figure 1).

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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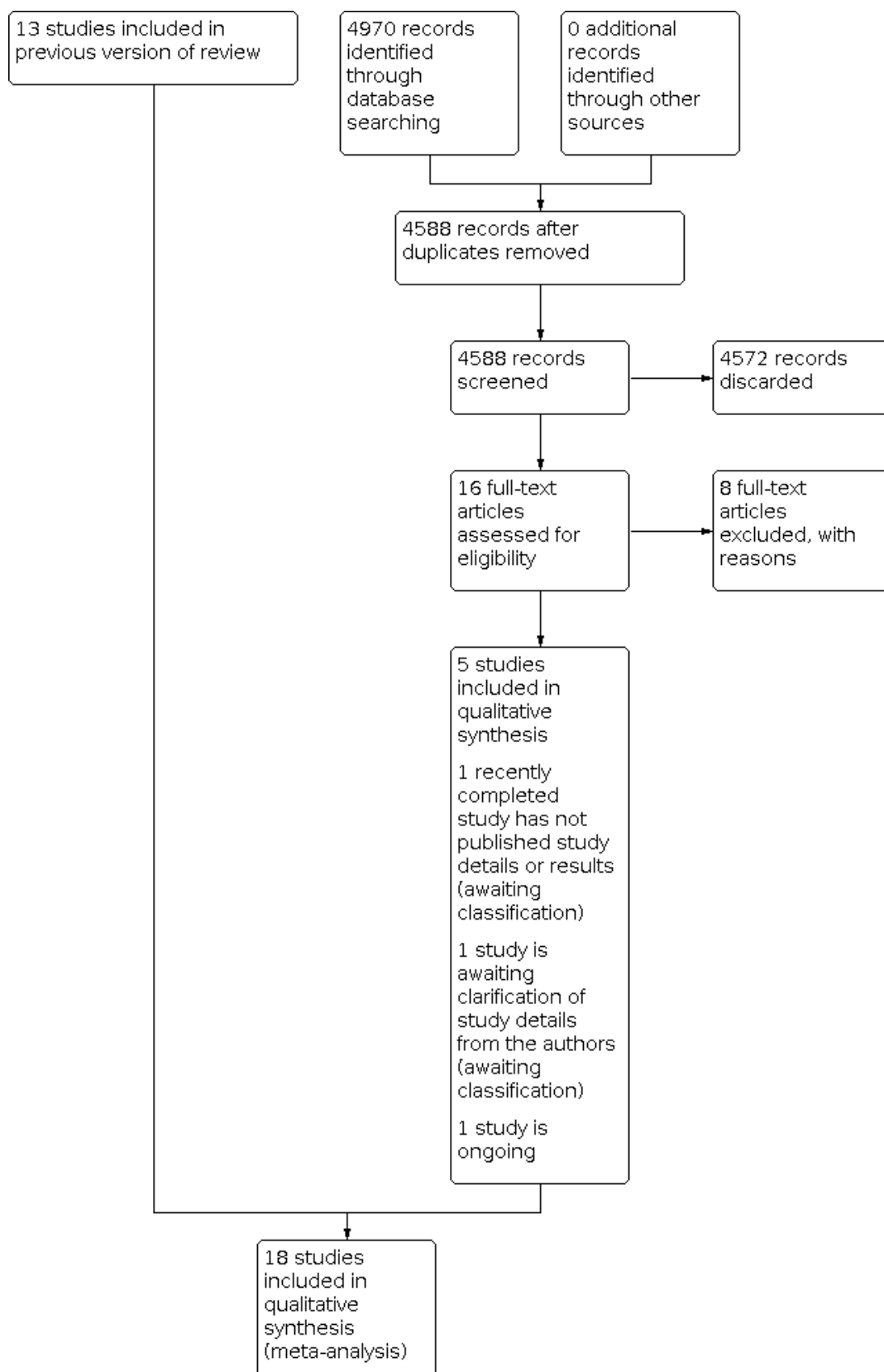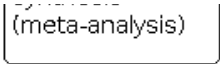
12

Figure 1. Study flow diagram.

Figure 1. (Continued)

(meta-analysis)

Methodological quality of included studies

The assessment of methodological quality is presented graphically
in Figure 2 and summarised by index test in Figure 3.

Figure 2. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

Figure 3.   Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.
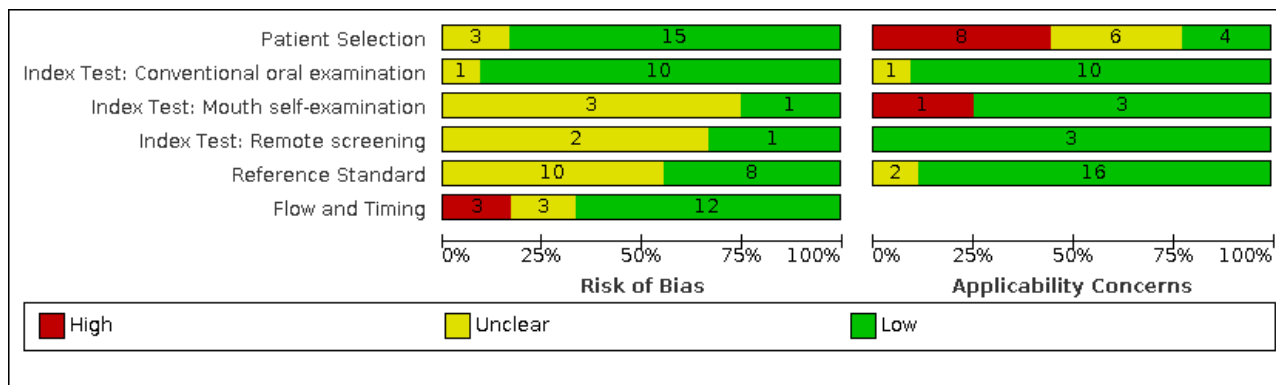
Conventional oral examination/visual inspection

No new eligible studies evaluating screening using conventional oral examination/visual inspection were included in this update.

The nature of the screening test accuracy studies have broadly been categorised as opportunistic screening (Chang 2011; Jullien 1995), organised screening programmes (Downer 1995; Jullien 1995a; Warnakulasuriya 1990; Warnakulasuriya 1991), validation as part of an organised screening programme or randomised controlled trial (Ikeda 1995; Mathew 1997; Mehta 1986), and screening as part of routine surveillance (Sweeny 2011).

The accuracy of detecting oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC) was evaluated in a variety of different settings. In Tokoname, Japan, all residents of 60 years of age were invited by mail to attend a dental screening programme at a health centre (Ikeda 1995). In Kerala, India, basic healthcare workers incorporated screening into their routine house visits (Mathew 1997; Mehta 1986) as in Sri Lanka (Warnakulasuriya 1990; Warnakulasuriya 1991). In the UK, the feasibility and accuracy of workplace screening was evaluated in one study (Downer 1995), of screening patients at a medical practice in another (Jullien 1995a), and opportunistically in patients attending a dental hospital for an outpatient appointment (Jullien 1995). In Taiwan, screening was offered to individuals attending a tertiary referral centre (Chang 2011). In the USA, screening was part of the routine surveillance visit of patients attending an otolaryngology clinic (Sweeny 2011).

Risk of bias for the patient selection domain was low for all studies with one exception (Julien 1995). This study was judged as unclear as the method of patient selection for this opportunistic screening study was not reported. Two studies were judged to be of low concern for applicability (Jullien 1995; Jullien 1995a); five studies of unclear applicability as a result of not fully reporting the participant characteristics or risk factors of the study sample or both (Downer 1995; Ikeda 1995; Mathew 1997; Warnakulasuriya 1990; Warnakulasuriya 1991). Three studies were selective in their sampling, targeting a 'high risk' population. These were all male patients attending the otolaryngology or dental department (Chang 2011), previous cancer patients attending the otolaryngology clinic for a routine surveillance visit (Sweeny 2011),

and individuals over 35 years of age with "tobacco habits" (Mehta 1986).

The conventional oral examination (COE) index test was carried out by clinicians (general dental practitioners, community dental officers, otolaryngologists) in six studies (Chang 2011; Downer 1995; Ikeda 1995; Jullien 1995; Jullien 1995a; Sweeny 2011), and by health workers in the studies in India and Sri Lanka (Mathew 1997; Mehta 1986; Warnakulasuriya 1990; Warnakulasuriya 1991). We assessed the risk of bias for this domain as low in nine studies. The index test was carried out prior to the reference standard and a positivity threshold for the target condition was specified a priori. One study (Sweeny 2011) was judged to be at unclear risk of bias as there was a lack of clear definition of the target condition and the positivity threshold. All studies were judged to be at low concern regarding applicability.

We judged four studies (Downer 1995; Ikeda 1995; Jullien 1995; Jullien 1995a) to be at low risk of bias for the reference standard domain. In these studies the reference standard was carried out by experienced specialist physicians and the results were interpreted without knowledge of the results of the index tests. For the remaining studies it was unclear whether the reference standard personnel were unaware of the results of the index test when interpreting the reference standard. One study (Sweeny 2011) was judged to be at unclear concern regarding applicability as the target definition was recurrence of head and neck cancer; all other studies were judged as low concern.

For the flow and timing domain, two studies were judged to be at high risk of bias as a result of attrition following positive screen (37.5% of screen positive) and differential verification (Chang 2011) and time from screen positive to receiving reference standard Warnakulasuriya 1990). Two studies were judged to be at unclear risk of bias (Sweeny 2011; Warnakulasuriya 1991), the remainder at low risk of bias (Downer 1995; Ikeda 1995; Jullien 1995; Jullien 1995a; Mathew 1997; Mehta 1986).

We judged two studies (Chang 2011; Warnakulasuriya 1990) as being at overall high risk of bias resulting from the flow and timing domain; three studies were at overall low risk of bias (Downer 1995; Ikeda 1995; Jullien 1995a). For the remaining five studies an unclear risk of bias for at least one of the four domains resulted in an overall

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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16

risk of bias judgement of unclear (Jullien 1995; Mathew 1997; Mehta 1986; Sweeny 2011; Warnakulasuriya 1991).

Three studies (Chang 2011; Mehta 1986; Sweeny 2011) were judged as having high overall concerns regarding applicability, arising from patient selection of high-risk groups. Two studies (Jullien 1995; Jullien 1995a) were judged as having low overall concerns regarding applicability. For the remaining five studies an unclear concern regarding applicability in the patient selection domain resulted in an overall applicability judgement of unclear (Downer 1995; Ikeda 1995; Mathew 1997; Warnakulasuriya 1990; Warnakulasuriya 1991).

Mouth self-examination

Two additional studies evaluated mouth self-examination in this update (Furquim 2014; Ghani 2019). All four studies that evaluated mouth self-examination did so as part of an organised screening programme in India (Elango 2011), Malaysia (Ghani 2019), UK (Scott 2010), and Brazil (Furquim 2014). Risk of bias assessments for the patient selection domain was judged to be low for all studies. There was high concern for applicability in one study that recruited and evaluated participants with Fanconi anaemia (which carries an increased risk of oral cancer) in a hospital setting (Furquim 2014), and participants that were identified and invited to participate based on their physician assessed risk of oral cancer (smokers aged 45 years or older) (Scott 2010).

We gave a judgement of unclear risk of bias to three studies for the index test domain as it was not reported whether the results of the index test were interpreted without knowledge of the reference test in two studies (Elango 2011; Scott 2010), in one study there was insufficient information on the target condition and threshold in order to ascertain whether a pre-specified threshold was used (Furquim 2014). We gave a judgement of high concern regarding applicability for this domain to one study (Furquim 2014) where the mouth self-examination was undertaken without instruction, and low concern for the remaining three studies.

The risk of bias judgement for the reference standard domain was low for one study (Scott 2010), being evaluated by a dentist with specialist training and the reference test being carried out prior to the index test. We judged three studies to be at unclear risk of bias (Elango 2011; Furquim 2014; Ghani 2019) as there was a lack of information as to whether the reference standard was interpreted without knowledge of the index test. We judged three studies to be of low concern for the reference standard (Furquim 2014; Ghani 2019; Scott 2010) and one study that used general health workers specifically trained for the study to be of unclear concern (Elango 2011). The manuscript states that "the competence of the health workers [reference standard] was confirmed by a trained oral cancer specialist" but not reported. It is reasonable to assume that the implicit threshold for disease of the trained health workers would differ from that of an experienced oral medicine specialist.

Risk of bias was judged to be low for the flow and timing domain (Furquim 2014; Ghani 2019; Scott 2010) where there was (or could be assumed to be) an appropriate time interval between the index test and reference standard, all patients received the same reference standard, and all patients were included in the analysis. There was a significant number of withdrawals and exclusions for non-compliance in one study (Elango 2011) which we judged to be at high risk of bias for this domain.

The overall risk of bias for the studies that evaluated mouth self-evaluation was judged to be unclear (Furquim 2014; Ghani 2019; Scott 2010) and high (Elango 2011). Concern regarding the overall applicability of the studies to the review question was high for two studies (Furquim 2014; Scott 2010), unclear for one study (Elango 2011), and low for the remaining study (Ghani 2019).

Conventional oral examination compared to conventional oral examination plus vital rinsing (toluidine blue)

No new eligible studies evaluating screening using conventional oral examination were included in this update.

One study (Su 2010) that directly compared two index tests in a randomised controlled trial was judged to be at low risk of bias for patient selection and index test domains. We judged the trial to be of high concern regarding applicability for the patient selection domain as individuals who "lacked oral habits" such as smoking or betel quid chewing were ineligible for the trial.

We judged the study to be at unclear risk of bias whether this was interpreted without knowledge of the results of the index tests is unclear. There was low concern regarding applicability of the reference standard. Risk of bias for the flow and timing domain was judged as low.

Overall risk of bias for this study was judged as unclear, based on the interpretation of the reference standard. Concern regarding the overall applicability of the study was high, arising from patient selection.

Remote screening (mobile applications)

Three studies, new to this review, evaluated remote screening in India (Birur 2019; Vinayagamoorthy 2019) and Brazil (Gomes 2017). One study was an organised screening programme in a workplace setting (Birur 2019) and two studies (Gomes 2017; Vinayagamoorthy 2019) were smaller feasibility or pilot studies that focused on the use of the technology.

Risk of bias assessments for the patient selection domain was judged to be unclear for two studies that stated that a convenience sample was selected but with limited information on the methods for selecting participants (Gomes 2017; Vinayagamoorthy 2019), but low risk of bias for the organised screening programme study (Birur 2019). There was high concern for applicability in two studies where smokers made up a large majority or the total sample, where the participants were all male, or where most participants were over 60 years of age (Birur 2019; Gomes 2017). We judged the applicability of the patient selection domain as unclear where there was little detail on the characteristics of the convenience sample (Vinayagamoorthy 2019).

We gave a judgement of unclear risk of bias to two studies for the index test domain as the threshold for the target condition was not explicitly reported (Gomes 2017; Vinayagamoorthy 2019), and a low risk of bias for one study (Birur 2019). We judged all studies to be at low concern for applicability for the index test domain.

The risk of bias judgement for the reference standard were low for all three studies as the reference standard personnel were typically oral medicine specialists, and we judged all studies to be at low concern for applicability.

Risk of bias was judged to be low for the flow and timing domain (Birur 2019; Vinayagamoorthy 2019) where there was (or could be assumed) an appropriate time interval between the index test and reference standard, and unclear where this was not explicitly stated or could not be assumed (Ghani 2019). All participants received the same reference standard any exclusion from analysis was minimal and related to poor quality of images (Birur 2019; Vinayagamoorthy 2019).

The overall risk of bias was judged to be low (Birur 2019) and unclear (Gomes 2017; Vinayagamoorthy 2019). Concern regarding the overall applicability of the studies to the review question was high for two studies (Birur 2019; Gomes 2017) on account of patient selection and unclear for one study (Vinayagamoorthy 2019).

Findings

Conventional oral examination/visual inspection

No new studies of conventional oral examination/visual inspection were included in this update.

Ten studies (Chang 2011; Downer 1995; Ikeda 1995; Jullien 1995; Jullien 1995a; Mathew 1997; Mehta 1986; Sweeny 2011; Warnakulasuriya 1990; Warnakulasuriya 1991) provided data from

25,568 individuals. The prevalence varied widely across the studies from 1.4% (Mehta 1986) to 50.9% (Warnakulasuriya 1991), with a median prevalence of 5.1%. For many of the studies the sensitivity estimates were imprecise, often reflective of the low disease prevalence in the samples.

For the seven studies with low prevalence (10% or less) (Chang 2011; Downer 1995; Ikeda 1995; Jullien 1995; Jullien 1995a; Mehta 1986; Sweeny 2011):

- the sensitivity estimates were highly variable, and ranged from 0.50 (95% confidence interval (CI) 0.07 to 0.93) (Sweeny 2011) to 0.99 (95% CI 0.97 to 1.00) (Chang 2011);
- the specificity estimates were more consistent and ranged from 0.94 (95% CI 0.88 to 0.97) (Ikeda 1995) to 0.99 (95% CI 0.98 to 1.00) (Downer 1995; Jullien 1995), 0.99 (95% CI 0.98 to 0.99) (Jullien 1995a), 0.99 (95% CI 0.99 to 0.99) (Chang 2011).

For the three studies with higher prevalence (Mathew 1997; Warnakulasuriya 1990; Warnakulasuriya 1991) sensitivity estimates ranged from 0.94 to 0.97, and specificities ranged from 0.75 to 0.98 (Figure 4; Figure 5). For many of the studies the sensitivity estimates were imprecise, reflective of the low disease prevalence in the samples.

Figure 4.   Forest plot of 1. Conventional oral examination.

Study	TP	FP	FN	TN	Prevalence %	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Jullien 1995a	26	12	6	998	3.1	0.81 [0.64, 0.93]	0.99 [0.98, 0.99]		
Mehta 1986	16	35	11	1859	1.4	0.59 [0.39, 0.78]	0.98 [0.97, 0.99]		
Warnakulasuriya 1990	384	276	21	1191	21.6	0.95 [0.92, 0.97]	0.81 [0.79, 0.83]		
Warnakulasuriya 1991	1741	431	52	1298	50.9	0.97 [0.96, 0.98]	0.75 [0.73, 0.77]		
Ikeda 1995	9	9	6	130	9.7	0.60 [0.32, 0.84]	0.94 [0.88, 0.97]		
Downer 1995	12	2	5	290	5.5	0.71 [0.44, 0.90]	0.99 [0.98, 1.00]		
Jullien 1995	14	8	8	955	2.2	0.64 [0.41, 0.83]	0.99 [0.98, 1.00]		
Mathew 1997	200	31	12	1826	10.3	0.94 [0.90, 0.97]	0.98 [0.98, 0.99]		
Chang 2011	282	172	3	13149	2.1	0.99 [0.97, 1.00]	0.99 [0.99, 0.99]		
Sweeny 2011	2	2	2	82	4.6	0.50 [0.07, 0.93]	0.98 [0.92, 1.00]		

Figure 5. Summary receiver operating characteristic (ROC) plot of 1. Conventional oral examination.
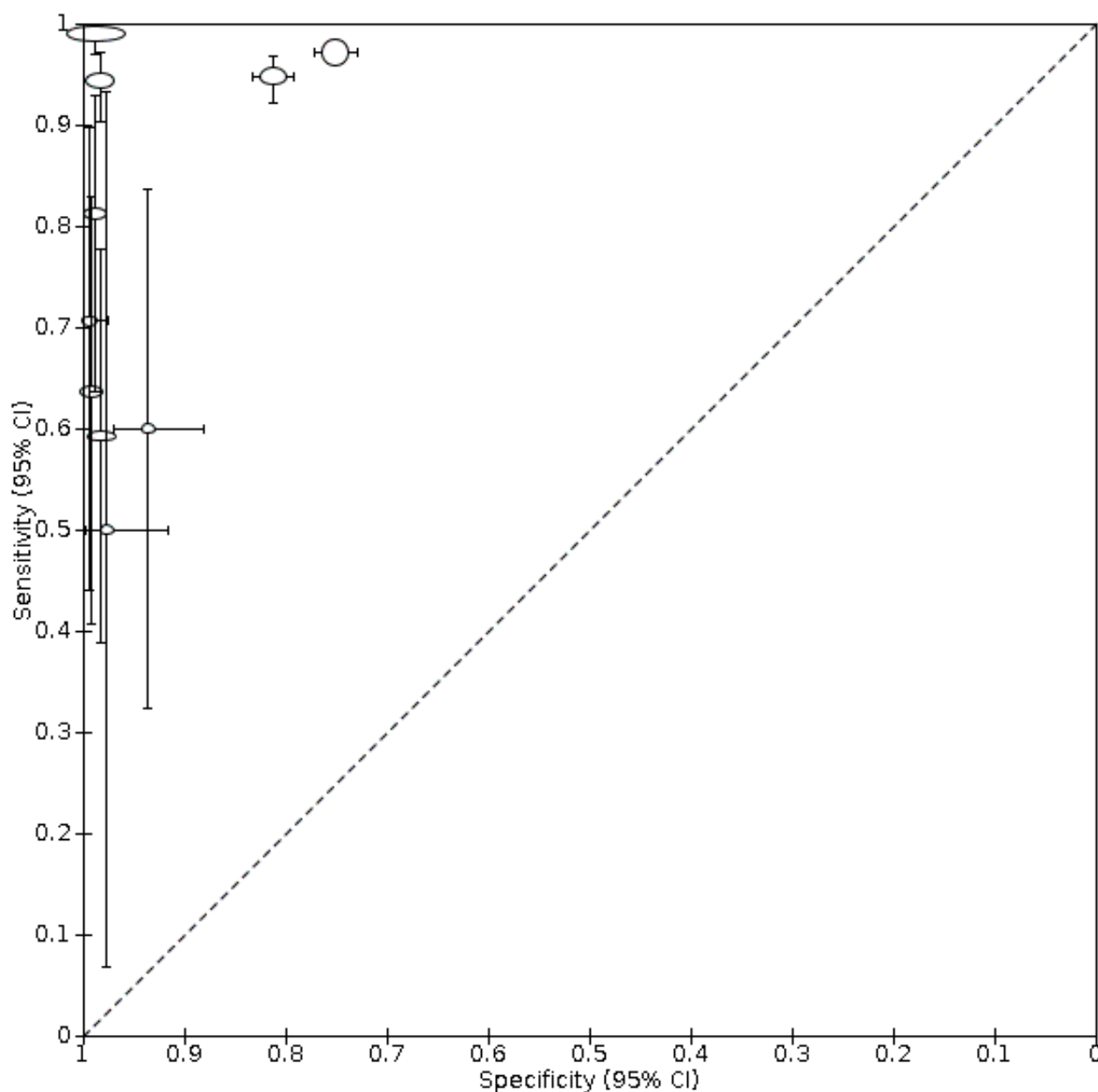
For the three studies with higher prevalence, from 10.3% to 50.9%:

- the sensitivity estimates ranged from 0.94 (95% CI 0.90 to 0.97) (Mathew 1997) to 0.97 (95% CI 0.96 to 0.98) (Warnakulasuriya 1991);
- the specificity estimates ranged from 0.75 (95% CI 0.73 to 0.77) (Warnakulasuriya 1991) to 0.98 (95% CI 0.98 to 0.99) (Mathew 1997).

Due to differences in region, setting, nature of the index test, and reference standard we elected not to pool the studies.

A summary is given in the Summary of findings 1. We judged the overall certainty of the evidence to be low, and downgraded for inconsistency and indirectness.

Mouth self-examination

Four studies (Elango 2011; Furquim 2014; Ghani 2019; Scott 2010) provided data from 35,059 individuals. The prevalence varied widely across the studies from 0.6% for the largest study (Elango 2011) to 63.6% for the smallest study (Furquim 2014).

In two studies the sensitivity estimates were much lower than the specificity estimates (Elango 2011; Ghani 2019) (sensitivity 0.18 (95% CI 0.13 to 0.24), specificity 1.00 (95% CI 1.00 to 1.00) and sensitivity 0.09 (95% CI 0.04 to 0.15), specificity 0.95 (95% CI 0.88 to 0.99), respectively). Sensitivity and specificity values were similar for two studies (Furquim 2014; Scott 2010) (sensitivity 0.43 (95% CI 0.24 to 0.63), specificity 0.44 (95% CI 0.20 to 0.70) and sensitivity

0.33 (95% CI 0.10 to 0.65), specificity 0.54 (95% CI 0.37 to 0.69), respectively) (Figure 6; Figure 7).

Figure 6. Forest plot of 2. Mouth self-examination.

Study	TP	FP	FN	TN	Prevalence %	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Elango 2011	39	15	180	34532	0.6	0.18 [0.13, 0.24]	1.00 [1.00, 1.00]		
Furquim 2014	12	9	16	7	63.6	0.43 [0.24, 0.63]	0.44 [0.20, 0.70]		
Ghani 2019	10	4	106	76	59.2	0.09 [0.04, 0.15]	0.95 [0.88, 0.99]		
Scott 2010	4	19	8	22	22.6	0.33 [0.10, 0.65]	0.54 [0.37, 0.69]		

Figure 7. Summary receiver operating characteristic (ROC) plot of 2. Mouth self-examination.
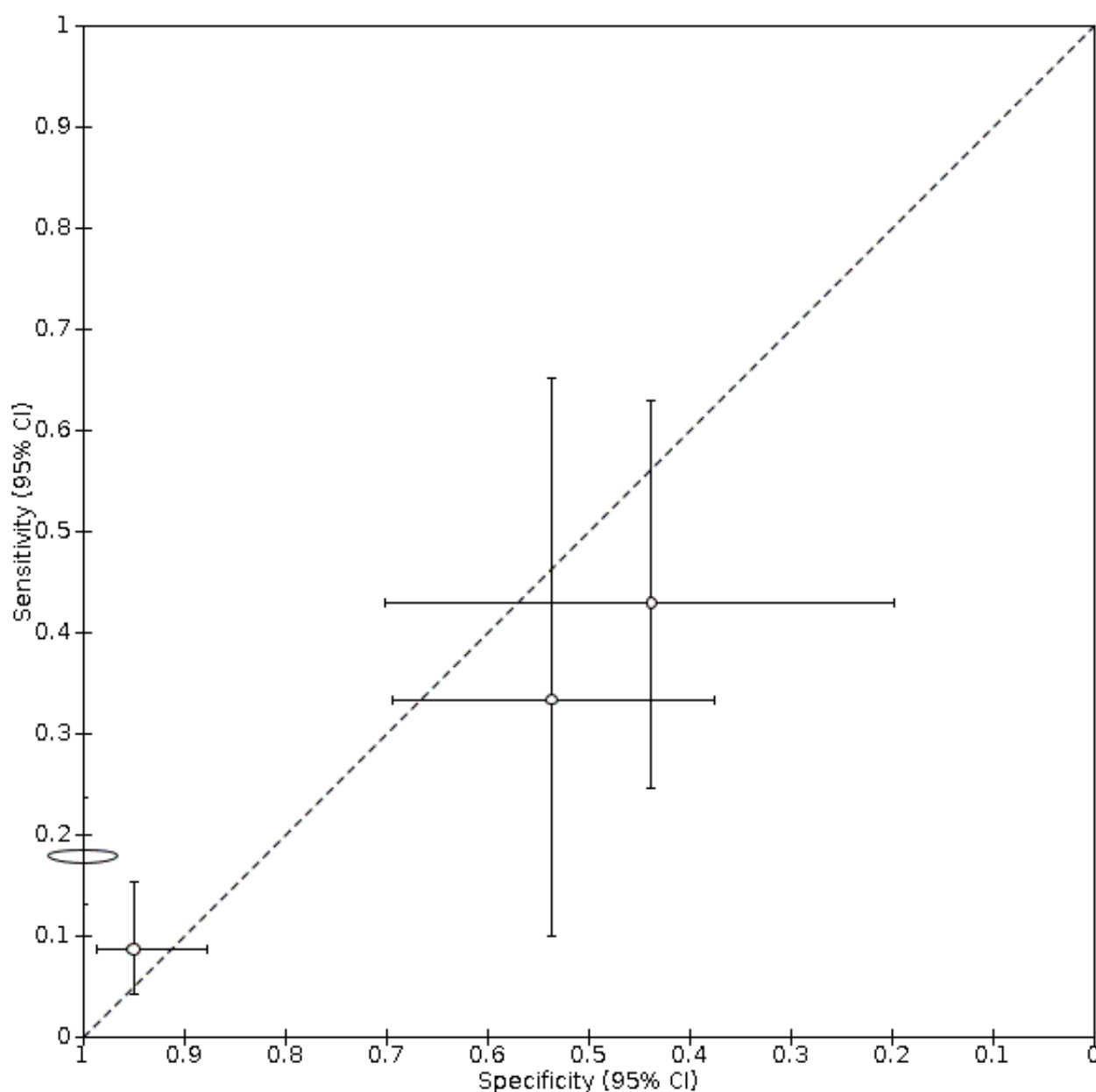
Due to differences in region, setting, training, and reference standard we elected not to pool the studies.

A summary is given in the Summary of findings 2. We judged the overall certainty of the evidence to be very low, and downgraded for indirectness, inconsistency, and imprecision.

Conventional oral examination compared to conventional oral examination plus vital rinsing (toluidine blue)

We included one randomised controlled trial which directly compared the performance of conventional oral examination (COE) alone (3895 individuals) with COE plus vital staining (4080 individuals) with biopsy and long-term follow-up through a National Cancer Registry (Su 2010).

When we considered the trial arms independently, the estimates of sensitivity and specificity for the target condition of oral cancer in the trial arm of COE alone were 0.50 (95% CI 0.12 to 0.88) and 0.92 (95% CI 0.91 to 0.93) with a prevalence of 0.15%; the corresponding sensitivity and specificity values for the COE with

vital rinsing adjunct were 0.40 (95% CI 0.05 to 0.85) and 0.91 (95% CI 0.90 to 0.91) with a prevalence of 0.12%.

A summary is given in the Summary of findings 3. We judged the certainty of the evidence as moderate, and downgraded one level due to indirectness in patient selection.

Remote screening (mobile applications)

Three studies (Birur 2019; Gomes 2017; Vinayagamoorthy 2019), all published after the initial systematic review (Walsh 2013), provided data from 3600 participants. The prevalence varied across the studies from 12.2% (Vinayagamoorthy 2019) to 30.9% (Gomes 2017). Findings were encouraging with sensitivity and specificity values as follows: sensitivity 0.85 (95% CI 0.81 to 0.88), specificity 0.99 (95% CI 0.99 to 1.00) (Birur 2019); sensitivity 0.82 (95% CI 0.57 to 0.96), specificity 1.00 (95% CI 0.91 to 1.00) (Gomes 2017); and sensitivity 0.94 (95% CI 0.70 to 1.00), specificity 0.72 (95% CI 0.63 to 0.80) (Vinayagamoorthy 2019) (Figure 8; Figure 9).

Figure 8. Forest plot of 3. Remote screening (mobile app).

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Birur 2019	376	15	68	2955	0.85 [0.81, 0.88]	0.99 [0.99, 1.00]		
Gomes 2017	14	0	3	38	0.82 [0.57, 0.96]	1.00 [0.91, 1.00]		
Vinayagamoorthy 2019	15	32	1	83	0.94 [0.70, 1.00]	0.72 [0.63, 0.80]		
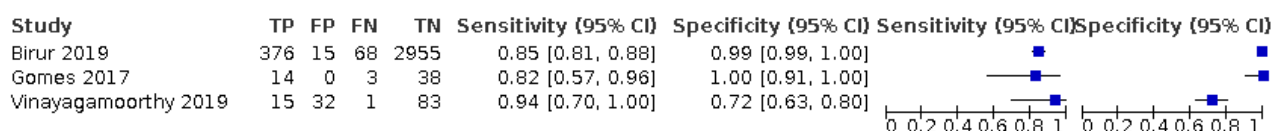
Figure 9. Summary receiver operating characteristic (ROC) plot of 3. Remote screening (mobile app).
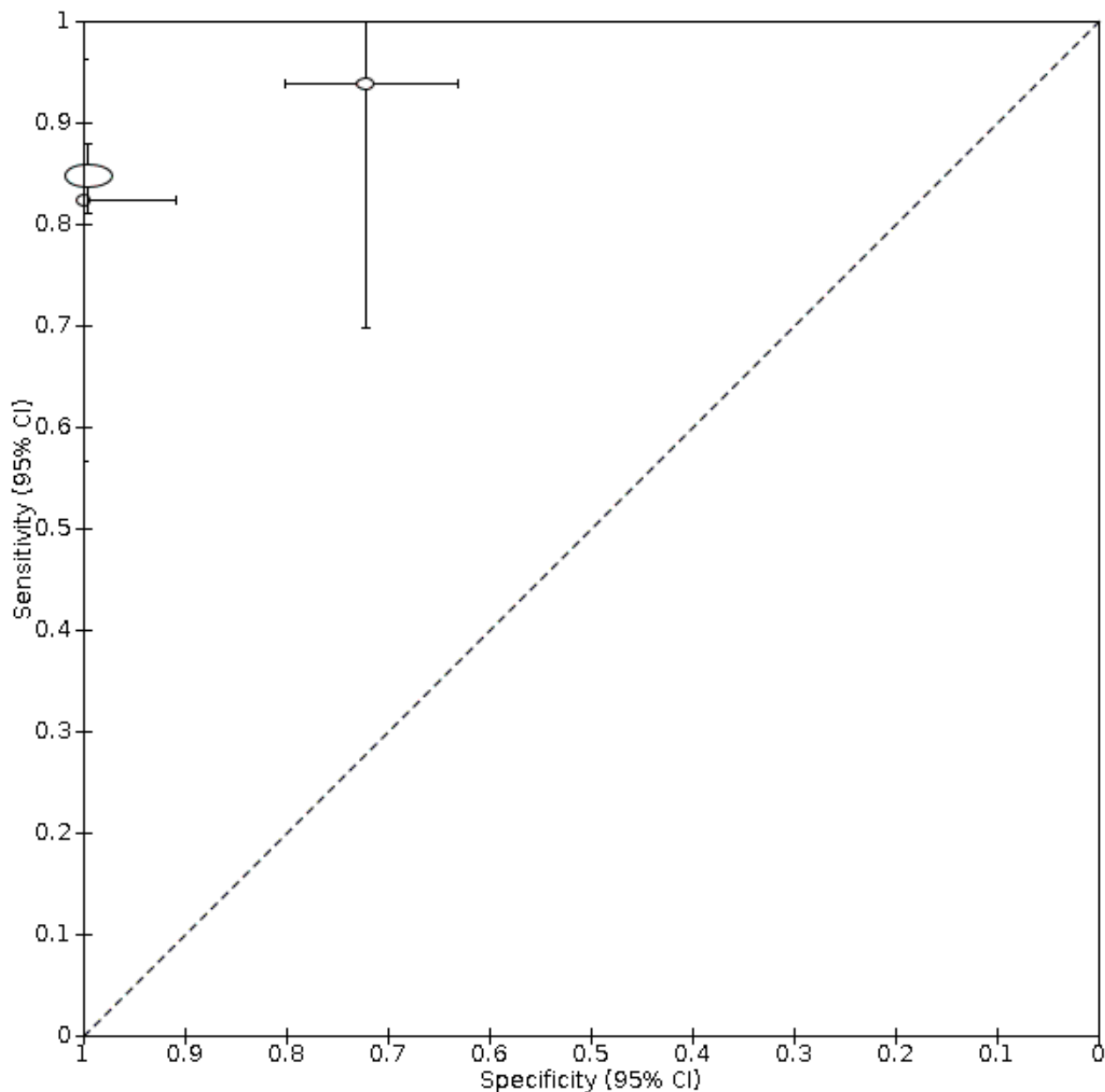
Due to differences in region, setting, and lack of information on case definition in some studies we elected not to pool the studies.

A summary is given in the Summary of findings 4. We judged the certainty of the evidence as very low, and downgraded two levels due to indirectness (applicability of the study sample) and for inconsistency.

DISCUSSION

Summary of main results

Eighteen studies were identified for inclusion evaluating the diagnostic accuracy of conventional oral examination (COE)/visual inspection, mouth self-examination, vital staining, and remote screening with mobile applications. The studies were diverse in nature with substantial variations in sample prognostic risk factors, nature of the screening test, the clinical specialty of personnel conducting the index test, verification of screened-negative and screened-positive individuals, exclusion of individuals from the analysis, and large variation in incidence of disease (including registry-based studies) across included studies. Consequently, the decision was taken that a meta-analysis of the included studies by index test was inappropriate. This is in contrast to some previously published systematic reviews (Downer 2004; Moles 2002).

Taken as a body of evidence, the overall quality of the studies was variable both within and between index tests with only one study (Jullien 1995a) of COE being judged as overall low risk of bias

and overall low concern regarding applicability (Figure 2). Many of the studies did not fully report on the characteristics and risk factors of the study sample, which precluded us from assessing the applicability of the results to a general screening population. In eight studies the participants could be considered as 'high - risk' individuals and consequently their findings elicit high concern judgements for the applicability of participant sample to the review question.

Prevalence of oral potentially malignant disorders (OPMDs) or oral squamous cell carcinoma (OSCC) in the test accuracy study samples ranged from 1.4% to 59% over the different index tests. Estimates should be interpreted with respect to the diagnostic test accuracy study prevalence levels. A low prevalence of the target condition effectively results in a lower sample size for diseased participants and for the calculation of sensitivity.

For COE/visual inspection, sensitivity estimates were highly variable for study level prevalence analogous to those in the population, and ranged from 0.50 (95% confidence interval (CI) 0.07 to 0.93) to 0.99 (95% CI 0.97 to 1.00) for the largest study (Summary of findings 1). Lower specificity values were observed in the two studies where the disease prevalence was higher than would normally be observed (20% and 50%) in the general population, and can be explained at least in part by the higher prevalence. For the four studies that evaluated mouth self-examination, two studies exhibited low sensitivity but higher specificity: sensitivity 0.18 (95% CI 0.13 to 0.24), specificity 1.00 (95% CI 1.00 to 1.00) and sensitivity 0.09 (95% CI 0.04 to 0.15), specificity 0.95 (95% CI 0.88 to 0.99), respectively. For the remaining two studies sensitivity and specificity values were similar, but lower: sensitivity 0.43 (95% CI 0.24 to 0.63), specificity 0.44 (95% CI 0.20 to 0.70) and sensitivity 0.33 (95% CI 0.10 to 0.65), specificity 0.54 (95% CI 0.37 to 0.69) respectively (Summary of findings 2).

In the within-study, between-person study of COE plus vital staining versus COE alone, estimates of sensitivity was slightly higher for COE alone, but specificities were similar across the trial arms (Summary of findings 3). Remote screening shows promise in terms of performance, but the estimates were imprecise in two of the three studies as these were pilot/feasibility studies on very small samples (Summary of findings 4).

Index tests at a prevalence reported in the population (between 1% and 5%) were better at correctly classifying the absence of OPMD or OSCC in disease-free individuals than classifying the presence in diseased individuals. A false-negative result from a screening programme would mean that the individuals with OPMD or OSCC would not be referred for further investigations; a false-positive result would mean a number of individuals without OPMD or OSCC would receive a positive-screening result, and would typically be referred for further investigations, possibly resulting in further excisional investigations for the patient. Whereas the false-positive results could and would no doubt have financial and other resource implications following inappropriate referral, the false-negative results indicate that people with OPMD or OSCC will be missed, possibly to be diagnosed at a later date when the disease becomes more advanced.

For this update we were able to provide judgement of the certainty of the evidence using a GRADE assessment. We judged the certainty of the evidence to be moderate for the within-study, between-person randomised controlled trial, low for COE/visual inspection, and very low for remote screening and mouth self-examination.

Strengths and weaknesses of the review

The utility of this review is limited in part by the number of included studies. A number of potentially eligible studies of sizeable organised screening programmes were excluded on the basis that the screened-negative individuals were not confirmed by a reference standard, or the results of the reference standard for the screened-negative individuals were not reported. Consequently, the number of false negatives could not be determined. In large screening programmes establishing a reference standard for all screened-negative individuals may not be possible. In such instances researchers could consider the possibility of a random subset of disease-free individuals to receive the index test.

We took the decision to exclude case-control or 'two-gate' accuracy studies, where two (or more) sets of eligibility criteria are used to recruit participants, owing to the potential for over estimation of diagnostic accuracy estimates with this design. However, this has meant that the index tests evaluated in this review do not include those based on newer technologies. We would anticipate that those index tests showing promise at this present time, would be further evaluated with a more robust study design and therefore be eligible for inclusion in future updates of this review.

Following on from previous systematic reviews in this area (e.g. Downer 2004), a further five test accuracy studies have been identified and included in this review, along with one ongoing study and one study awaiting classification as the results have yet to be reported. A key strength of this review is the inclusion of studies that evaluated a range of index tests. With this update we have included studies that evaluated remote screening, as well as additional studies for mouth self-examination, along with existing studies that evaluated conventional oral examination usually by dental professionals and visual inspection by other healthcare professionals. Whilst the diverse nature of the studies within the different categories of index tests precluded pooling of the studies, the reader is provided with an overview of the body of evidence, including the methodological quality, of different tests to screen for OPMDs and malignancies. Simultaneous consideration of accuracy estimates along with methodological strengths and weaknesses is essential in making appropriate inferences from the primary studies.

Due to the substantial diversity in the nature of the included studies and the characteristics of the participants it was not appropriate to pool the data, even within each category of index test. Whilst this is not a weakness of the review, the failure to provide summary estimates of sensitivity and specificity, in contrast to previous systematic reviews, could be regarded as a limitation. The range of accuracy estimates observed in this review is reflective of the considerable clinical and methodological heterogeneity across the included studies. In future updates should more homogeneous studies be included in the review, it would be informative to evaluate the influence of risk factors on estimates of diagnostic accuracy. However, we acknowledge that there was a lack of reported detail in a number of the included studies regarding the presence or absence of important risk factors such as smoking, betel quid chewing, and alcohol consumption.

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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23

The methods of recruitment and eligibility criteria differed widely across the included studies. The World Health Organization defines screening as "the application of a test or tests to people who are apparently free from the disease in question in order to distinguish between those that have the disease from those who probably do not" (Wilson 1968). A difficulty with a number of the included studies was determining how representative the screened population was, given the settings for recruitment such as company headquarters, hospital outpatient departments, and tertiary treatment centres. It could be argued that the latter sample represents a distinct population with a much higher risk of developing new disease and one where clinicians are likely to encounter disease with a higher index of suspicion. Prevalence of the included studies was in line with what would be expected; Napier 2008 argues that most authorities agree that this lies between 1% and 5%. However, the sample prevalence was particularly high in two studies of COE (Mathew 1997 10.3%, Ikeda 1995 9.7%) where a larger proportion of the population consumed tobacco (and engaged in other risk factors), and one study of mouth self-examination (Scott 2010 22.6%). In two studies of COE (Warnakulasuriya 1990; Warnakulasuriya 1991) the sample prevalence calculated from the 2 x 2 tables evaluating the test accuracy was particularly high at 21.6% and 50.9%. The screened-positive prevalence for these studies was more in line with population prevalence at 4.2% and 6.2%.

The use of cancer registries or other registries as a reference standard (e.g. Chang 2011; Su 2010) can be methodologically problematic, particularly if there is a mismatch in the target condition being evaluated and the outcome documented in the registry. For example, cancer registries are unlikely to hold data on OPMDs that have not undergone malignant transformation, inducing a disconnect in the target condition being detected by the index test and the outcome recorded in the registry. Differential verification bias can occur if screened-positive participants receive biopsy as a reference standard whilst the screened-negative participants are assessed through a national cancer registry alone. If there is potential for malignant transformation within the duration of follow-up then follow-up through registry could be appropriate. Careful thought should be given to the target condition of the index and reference standard and whether this information will be adequately recorded in the registry.

Applicability of findings to the review question

Only three studies were judged to be at overall low concern for applicability across the three domains of patient selection, index test, and reference standard. Concerns regarding applicability arose from targeted patient selection of high-risk groups for the patient selection domain, where participants had either a previous history of head and neck cancer or other medical conditions that put them at increased risk compared to that in the general population, or were older, typically male, and tobacco smokers. For example, participants in one study conducted in a tertiary care clinic (Chang 2011) were all males; and another study recruited former head and neck cancer patients undergoing routine surveillance visits (Sweeny 2011). One study recruited participants with Fanconi anaemia (Furquim 2014), a condition where there is a significantly higher incidence of head and neck squamous cell carcinoma compared with that observed in the general population (Kutler 2003). Studies with unclear concerns over in this domain were those that had omitted important information on patient

or study characteristics which meant that we were unable to determine whether the participants and settings matched the review question. There was low concern regarding applicability for the index test domain for most studies. An unclear judgement for applicability of the reference standard was given to one study where six people had been identified from the target population to act as the reference standard (Elango 2011). Although exposed to training, it is questionable whether trained lay people could act as a reference standard, and there was some concern that the index test and reference test may have been conducted simultaneously for those who had not responded initially. A second study (Sweeny 2011) was also judged to be at unclear applicability on this domain. There was low concern regarding applicability for the remaining studies in this domain.

AUTHORS' CONCLUSIONS

Implications for practice

There are known clinical and methodological difficulties associated with screening for oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC) that include relatively low incidence rates, the reluctance of screened-positive individuals to attend for follow-up, a lack of linear transition between pre-malignant and malignant states (Reibel 2003), disagreement over disease management (Warnakulasuriya 2009), and the relative cost-effectiveness of mass, selective, and opportunistic screening programmes (Brocklehurst 2011).

The lack of any formal registry for reporting OPMDs, in contrast to malignancy, makes it challenging to estimate possible reductions in mortality due to a screening programme aimed at precursor lesions. A recent population-based cohort study using electronic medical records has followed patients with oral leukoplakia and estimated the short- and long-term progression to OSCC (Chaturvedi 2020). And the efficacy of the early management of OPMDs is controversial, where even if lesions are surgically removed, the risk of malignant change may remain since the lesion represents only a small area in a field of damaged mucosa, any part of which may progress to malignancy (Holmstrup 2007; Holmstrup 2009).

The results of this review suggest that using the conventional oral examination (COE) or visual inspection for screening for OPMD and OSCC has a variable degree of sensitivity (greater than 0.70 in six of the 10 studies), and a consistently high value for specificity (greater than 0.90 in eight studies). However, there was considerable clinical heterogeneity in the study participants, the application of the index test and reference standard, and the flow and timing of the process. Exploring the primary studies for sources of heterogeneity has not shown any single factor to consistently influence the accuracy of the screening test. Further, even though the evidence of accuracy is not consistently strong, there is some evidence (Cheung 2021) that implementing COE as a component of a population screening programme can reduce mortality and produce stage-shift in a high-risk population. Should similar findings be replicated in other studies then it could be argued that explicit evaluation of COE accuracy per se would no longer be necessary, given the positive outcomes on mortality. Emphasis could instead be placed on the effectiveness of screening programmes, of which COE is a component, in reducing morbidity and mortality. This should be supplemented with information on the consequences of false-negative and false-positive screens.

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

24

The potential for vital staining, brush cytology, or light-based devices to be used as an adjunct to the COE in screening to detect OPMDs and malignancies in apparently healthy individuals warrants further investigation (Moyer 2014). In the randomised controlled trial (RCT) of screening strategies, vital staining as an adjunct to COE was compared to COE alone, with a clinically important but not statistically significant difference observed in health outcomes (Su 2010), and therefore the cost-effectiveness of using adjunctive methods over and above the standard COE would need to be justified. The concept of combining technologies to improve test accuracy seems reasonable; however, it is not possible to support the combining of such tests as the data from this review were limited; more studies are needed. Ideally, the role of adjunctive tests is to reduce uncertainty in the diagnostic decision. With some tests this can be achieved by exploring different threshold levels. However, this is not possible with any of these tests as they all dichotomise patients as either diseased or healthy. As a result, threshold analysis and area under the curve could not be investigated. Currently, there is insufficient evidence to deviate from the conclusions of the American Dental Association. Oral healthcare professionals should remain vigilant for signs of OPMD and OSCC whilst performing routine oral examinations in practice (Lingen 2017a; Rethman 2010).

Following a review of the evidence, Galvão-Moreira 2017 recently stated in their 2017 publication that "current evidence does not support the use of MSE [mouth self-examination] as a strategy for OC [oral cancer] screening." There is little evidence in this Cochrane Review to refute that statement. With the advent of mobile health (mHealth), newer screening strategies such as remote evaluation of digital images by oral specialists collected during screening events hold more promise. The Global Observatory for eHealth, a component of the World Health Organization (WHO), has defined mHealth as "a component of eHealth, and involves the provision of health services and information via mobile technologies, such as mobile phones, tablet computers, and Personal Digital Assistants (PDAs)." The WHO oral mHealth handbook details the potential of mHealth for the early detection of oral cancer (WHO 2021). Advantages to remote screening for disease by clinical specialists include comprehensive multimedia information for easy access, and offers particular benefits for individuals living in remote areas who may have difficulty accessing healthcare or health education materials (Bradway 2017). There is hope from a recently published new study conducted with a mobile data app (MeMoSA®) that these benefits could be achieved for rural societies (Haron 2021).

Implications for research

It is clear that there are some methodological shortcomings in the studies included in this review. The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool has provided a robust means of assessing the methodological quality of the included studies. There is now an opportunity to use this framework to ensure that future studies are conducted in a robust manner, with particular attention paid to the design of the study in the four domains of the QUADAS-2 tool. It is imperative that studies are reported with sufficient information to allow judgement of the merits of the study and its applicability to the review being undertaken. Reporting according to the Standards for Reporting Diagnostic accuracy studies (STARD) checklist should facilitate this process. In particular, results have been promising in the workplace setting, and for some opportunistic screening studies.

The population and participant selection should be clearly stated and carried out to reduce the possibility of sampling bias, preferably using a consecutive sample. The study setting is particularly important as, for example, studies undertaken within an academic referral centre are rarely directly applicable to studies in a primary care setting. Only by undertaking studies in different settings with different assessors will we be able to attain a comprehensive picture of the diagnostic test accuracy of different testing mechanisms across different contexts. The index test should be undertaken by trained and calibrated screeners, whose threshold for agreement should be stated a priori.

The definition of the target condition as identified by the index test is crucial. Often this is recorded and reported as a 'suspicious lesion.' The term is ambiguous and is interpreted in the context of the assessor's experience. A suspicious lesion for a clinical specialist is one that has a high likelihood of malignancy or a high-grade dysplasia, and most oral medicine specialists are able to make a correct risk stratification on almost any mucosal abnormality. A suspicious lesion for a healthcare worker is any white patch. Remote evaluation of digital images by clinical experts largely overcomes this problem but does require intensive training of the screener to ensure that the images are of sufficient quality. The reference standard should be both accurate and pragmatic to account for the practical considerations involved in establishing the initial diagnostic test accuracy component of large population screening programmes. For such programmes it is not necessary to apply the reference standard to the entire programme's participants, rather an initial evaluation of test accuracy should be established on a sizeable number of participants prior to commencement of the screening programme proper. It is also important to utilise reference standards that capture all the target conditions under question, not just those that are likely to be identified through cancer registries. Finally, the flow and timing of the diagnostic test accuracy study should ensure that the reference standard is undertaken within a short-time frame after the index test, given the potential for pre-malignant disorders to undergo malignant transformation, and for it to be applied after the index test to avoid bias being introduced. Where long-term follow-up is used as a reference standard, measures should be taken to minimise attrition. Further research on ways to maximise initial participation rates and also follow-up rates for those who screen positive is warranted.

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Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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25

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Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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26

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32

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Birur 2019

Study characteristics	
Patient Sampling	Method of patient selection: workplace-based organised screening programme. Quote: "Before screening all employees attended an educative talk on the importance of prevention and early detection of oral cancer and were encouraged to participate in the screening program. All employees were potential participants in the screening"
Patient characteristics and setting	Results available for 3445 eligible participants, "the entire population screening"
	Age: ranged from 18 to 57 years
	Sex: 3445 male, 0 female
	SES: not stated
	Ethnicity: not stated
	Stated risk factors: tobacco habit and alcohol use 2420
	Previous history: not stated
	Location: India
Index tests	Index test: educative talk on importance of prevention and early detection of oral cancer followed by mobile phone-based oral cancer screening by community health workers (CHWs) and remote consultation by oral medicine specialist
	Description of positive case definition by index test as reported: quote: "suspicious oral lesions"
	Sequence of tests: index test followed by reference standard
	Training or calibration: comprehensive training for CHSWs. Quote: "The training for 3 days included a power point presentation, one-to-one discussion, and use of education modules through a clinical manual. ...They were trained to identify suspicious oral lesions and were educated on risk factors and importance of habit cessation. CHWs underwent training in a clinical setup that involved chair-side clinical examination of various subsites of oral cavity in identification of normal and tobacco-associated mucosal lesions by an oral medicine specialist"
	Blinding of examiners: index test followed by referral to onsite oral medicine specialist. Quote: "hyperkeratosis, mild, moderate, severe dysplasias, carcinoma in situ, and squamous cell carcinoma"
	Conflict of interests: authors declare no conflicts of interest. Financial support and sponsorship from Biocon Foundation
Target condition and reference standard(s)	Target condition: oral cancer and potentially malignant lesions

Birur 2019 *(Continued)*

<u>Reference standard</u>: clinical diagnosis of onsite oral medicine specialist with histopathological examination if deemed necessary by the specialist

<u>Description of positive case definition by reference test as reported</u>: not specified, quote: "positive oral lesions"

<u>Training or calibration</u>: not stated, quote: "onsite specialist"

<u>Blinding of examiners</u>: quote: "hyperkeratosis, mild, moderate, severe dysplasias, carcinoma in situ, and squamous cell carcinoma"

<u>Prevalence of the target condition on the sample</u>: 394/3445 participants 11.4%

Flow and timing	<u>Time interval and any interventions between index test(s) and reference standard</u>: not explicitly stated but assumed to be direct referral following CHW assessment
	<u>Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis</u>: for remote assessment by specialist only 3414/3445 photographs were available for assessment. Quote: "There were no images for 27 (0.8%) individuals, and 36 (1.1%) images were of poor quality"
	<u>Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician</u>: reference standard carried out by onsite oral medicine specialist
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Conventional oral examination)			
DOMAIN 2: Index Test (Mouth self-examination)			
DOMAIN 2: Index Test (Remote screening)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

34

Birur 2019 *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Fluorescence)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Low risk	

Chang 2011 *(Continued)*

Study characteristics	
Patient Sampling	Method of patient selection: optional screening programme at a tertiary referral centre in central Taiwan. Quotes: "All male patients who visited our clinic (Otolaryngology or Dental Department) aged 18 or older were eligible for enrolment in this study." "Those who were reluctant to undergo oral screening were excluded"
Patient characteristics and setting	13,878 patients enrolled from March 2005 to January 2010
	Age: mean age 54.6 years (SD 18.4, range 18 to 97 years)
	Sex: male population, reasons for single sex sample not stated
	SES: not stated
	Ethnicity: not stated
	Stated risk factors: 2844 habitual smokers; 943 habitual betel quid chewers; 1955 habitual drinkers
	Previous history: not stated
	Location: Taiwan
	Clinical setting: tertiary academic medical centre. Veterans General Hospital
Index tests	Index test: quote: "..visual screening of the oral cavity was performed by experienced oto-laryngologists or dentists under adequate lighting and with proper instruments"
	Description of positive case definition by index test as reported: quote: "A non-healing ul-cer for more than 2 weeks, a persistent white or red lesion, a lesion that bled easily, or an irregular surface lesion inside the oral cavity were regarded as positive findings." Positive lesions indicative of oral cavity cancer
	Sequence of tests: index followed by reference
	Training or calibration: not stated
	Blinding of examiners: not stated
	Conflict of interests: authors declare no conflict of interest
Target condition and reference standard(s)	Target condition: oral cavity cancer
	Reference standard: punch biopsy with histopathology of abnormal lesions. Quote: "If the patient did not agree to further biopsy, follow-up was strongly recommended." Follow-up of entire cohort. Quote: "We further crosslinked the entire screened cohort with the Taiwan Cancer Registry database"
	Description of positive case definition by reference test as reported: oral cavity cancer
	Training or calibration: not stated
	Blinding of examiners: not stated
	Prevalence of the target condition on the sample: 285/13,606 2.1%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: not reported
	Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: quotes: "A total of 272 participants (37.5%) with abnormal oral cavity lesions were lost to follow-up and no further pathological report

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

36

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Chang 2011 *(Continued)*

could be obtained." "In order not to confound further analyses, we excluded those with positive lesions/yet no further biopsy during the follow-up period. Although 272 participants were excluded from the final analysis, there was little impact on the power of the statistic analysis due to the large population size"

<u>Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician</u>: quote: "We further cross linked the entire screened cohort with the Taiwan Cancer Registry database." Not reported when this was done (follow-up time) for entire cohort

Comparative	
Notes	Sensitivity and specificity data reported for oral cavity cancer. Index test target condition clinically suspicious oral lesions; reference standard target condition oral cancer

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Conventional oral examination)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?			
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

37

Chang 2011 *(Continued)*

DOMAIN 2: Index Test (Mouth self-examination)		
DOMAIN 2: Index Test (Remote screening)		
DOMAIN 2: Index Test (Fluorescence)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	No	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Downer 1995

Study characteristics	
Patient Sampling	<u>Method of patient selection</u>: employees (40 years or over) in a workplace setting responding to a screening invitation. Screening programme was widely publicised through in-house magazine, information leaflets, video in hallway. Participation rate 53%
Patient characteristics and setting	292/553 (53%) of workers responded to the screening invitation. Additional 17 screened from a separate site
	<u>Age</u>: ≥ 40 years
	<u>Sex</u>: not stated
	<u>SES</u>: 31.8% lower occupational level, 68.2% management grade or above
	<u>Ethnicity</u>: not stated

Downer 1995 *(Continued)*

	<u>Stated risk factors</u>: HPV - not stated; smoking - smokers included in sample but proportions not specified; alcohol - drinkers included in sample but proportions not specified <u>Previous history</u>: not stated <u>Location</u>: commercial company. London, UK <u>Clinical setting</u>: onsite company dental practice
Index tests	<u>Index test</u>: systematic visual examination by 2 general dental practitioners <u>Description of positive case definition by index test as reported</u>: quote: "...if a white patch, red patch or ulcer of greater than two weeks duration was detected." Further qualified into lesions that should be regarded as malignant or pre-malignant (positive) and those to be regarded as negative <u>Sequence of tests</u>: index test followed by reference standard <u>Training or calibration</u>: quote: "...who had not received any specific training except for instruction in the screening procedure and the criteria for a positive or negative test." No specific training and standardisation of screeners nor calibration <u>Blinding of examiners</u>: index test completed before reference standard <u>Conflict of interests</u>: not stated
Target condition and reference standard(s)	<u>Target condition</u>: as for the index test: carcinoma, leukoplakia, erythroplakia, lichen planus, lupus erythematosus, submucous fibrosis, actinic keratosis <u>Reference standard</u>: visual examination by an oral medicine specialist with "...access to any relevant diagnostic aids, including biopsy if considered necessary" <u>Description of positive case definition by reference test as reported</u>: quote: "...if a white patch, red patch or ulcer of greater than two weeks duration was detected." Further qualified into lesions that should be regarded as malignant or pre-malignant (positive) and those to be regarded as negative <u>Training or calibration</u>: not stated <u>Blinding of examiners</u>: index test completed before reference standard, quote: "...who was unaware of the findings of the screener" <u>Prevalence of the target condition on the sample</u>: 17/309 5.5%
Flow and timing	<u>Time interval and any interventions between index test(s) and reference standard</u>: immediately following attendance at screening session, quote: "After screening..." <u>Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis</u>: quote: "A number of staff who were screened will not have been included in the evaluation since they were unable to attend at one of the dedicated sessions and were therefore not examined by the specialist diagnostician." Separate values for those attending the screening and reference standard examination not reported <u>Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician</u>: none
Comparative	
Notes	68.2% proportion of participants at management grade or above. 53% participation rate
Methodological quality	

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

39

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Downer 1995 (Continued)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Conventional oral examination)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?			
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Mouth self-examination)			
DOMAIN 2: Index Test (Remote screening)			
DOMAIN 2: Index Test (Fluorescence)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

40

Downer 1995 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	Low risk	

Elango 2011

Study characteristics	
Patient Sampling	Method of patient selection: quote: "The study population was distributed in two Panchayats (local administrative unit in villages) with 33 subunits. Brochures were sequentially distributed to all the houses in the subunits." After a lapse of 4 weeks "Health workers attempted to locate individuals up to a maximum of three times, incase they were unavailable during the first visit"
Patient characteristics and setting	Results available for 34,766/48,080 eligible participants. Quote: "48,080 (83.3%) subjects, above the age of 10 years, were eligible for the study" Age: median age band 30 to 39 years Sex: 17,158 male, 17,608 female SES: not stated Ethnicity: not stated Stated risk factors: tobacco smoking/chewing pan 10,644; alcohol consumption 3844 Previous history: not stated Location: Kerala, India. Quote: "It was carried out in a high-risk population of 57,704, in the coastal villages of Kerala, India, where there is a high incidence of oral cancer and prevalence of risk factors" Clinical setting: participants' own homes
Index tests	Index test: mouth self-examination in accordance with brochures specifically designed for this population. Quote: "A brochure was developed, which contained information on oral cancer, its risk factors and the methods to perform MSE. It also had instructions to report to the oral cancer-screening clinic, in case of identification of any suspicious lesions"

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

41

Elango 2011 *(Continued)*

Description of positive case definition by index test as reported: white patch, red patch, non-healing ulcers, difficulty in opening mouth, other oral symptoms (burning sensation)

Sequence of tests: index test followed by reference standard

Training or calibration: dedicated brochure instructed on mouth self-examination technique

Blinding of examiners: no description of timing or recording of mouth self-examination in relation to visit by health worker 4 weeks after screening exam (mouth self-examination could have been carried out concurrently)

Conflict of interests: none. Quote: "The project was supported by Government of India, Department of Science and Technology, research grant (SSD/SCP/060/2005)"

Target condition and reference standard(s)	Target condition: oral cancer and potentially malignant lesions
	Reference standard: quote: "Six health workers recruited from the population wherein the study was conducted..."
	Description of positive case definition by reference test as reported: quote: "The presence (including site and provisional diagnosis) and absence of potentially malignant oral lesions (ulcers, white or red patches, or lumps/swellings) were noted on a proforma"
	Training or calibration: quote: "Six health workers underwent one month training on oral cancer in a comprehensive cancer center, which coordinated the study. The training consisted of a didactic course on oral cancer, its risk factors, clinical findings of potentially malignant and malignant oral lesions, and methods to perform oral visual examination. WHO Guide to epidemiology and diagnosis of oral mucosal diseases and conditions was used as the reference manual. The competence of the health workers was confirmed by a trained oral cancer specialist." Calibration not stated
	Blinding of examiners: not stated
	Prevalence of the target condition on the sample: 219/34,766 0.63%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: quote: "After a lapse of 4 weeks, the trained health workers performed oral visual examination on all the members of the households above the age of 10 years"
	Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: from 48,080 participants initially eligible, 5761 unavailable for examination by reference standard, and a further 7553 "who did not comply with the study procedure were excluded from the study population." Results available for 34,766 participants (38% attrition)
	Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: reference standard carried out by a trained health worker
Comparative	
Notes	Possible bias introduced through exclusion of participants that did not comply with the procedure. Participants located in area of high prevalence of oral cancer and potentially malignant lesions

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Elango 2011 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias?	Low risk	

Are there concerns that the included patients and setting do not match the review question?		Low concern

DOMAIN 2: Index Test (Conventional oral examination)

DOMAIN 2: Index Test (Mouth self-examination)

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Was conflict of interest avoided?	Yes
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?	

Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (Remote screening)

DOMAIN 2: Index Test (Fluorescence)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear

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Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

Elango 2011 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk

Furquim 2014

Study characteristics	
Patient Sampling	Method of patient selection: quote: "Patients with FA aged at least 18 years who were being managed on an outpatient basis at the Bone Marrow Transplant Unit of the Federal University of Paraná Hospital, Curitiba, Paraná, Brazil, were invited to take part in this study during routine appointments." High risk of head and neck cancer
Patient characteristics and setting	Results available for 44/50 eligible participants Age: mean age 19.5 years (range 18 to 38 years) Sex: 18 male, 26 female SES: not stated Ethnicity: 19 white, 25 other Stated risk factors: tobacco use 2; alcohol consumption 9 Previous history: not stated, but patients with Fanconi anaemia Location: Curitiba, Paraná, Brazil Clinical setting: hospital
Index tests	Index test: mouth self-examination but no explicit training or instruction, quote: "...the participants were asked to wash their hands and perform MSE in front of a standard 1 m 30 cm mirror in an artificially illuminated room. Patients did not use any tool to aid the examination (such as gauze, penlight, or oral retractors)"

Furquim 2014 *(Continued)*

Description of positive case definition by index test as reported: not explicitly reported, presence or absence of abnormality, quote: "Immediately after MSE, participants were asked to answer questions about the presence and location of oral lesions"

Sequence of tests: index test followed by reference standard

Training or calibration: none provided until after the MSE, quote: "Finally, all participants were taught to perform MSE correctly using verbal and demonstrative instruction with the support of an educational banner and a pamphlet"

Blinding of examiners: can be assumed, quote: "Immediately after MSE, participants were asked to answer questions about the presence and location of oral lesions." This was followed by the clinical examination by the oral specialist

Conflict of interests: none, quote: "The authors thank the Brazilian Education Ministry (MEC) for providing financial support through the Tutorial Education Program (PET) and the Brazilian Support Agency for Superior Education (CAPES)"

Target condition and reference standard(s)	Target condition: potentially malignant oral lesions (ulcers, white or red patches, or lumps/swellings) Reference standard: clinical examination by an experienced oral medicine specialist Description of positive case definition by reference test as reported: quote: "The presence (including site and provisional diagnosis) or absence of potentially malignant oral lesions (ulcers, white or red patches, or lumps/swellings) was registered in the patients' clinical charts" Training or calibration: quote: "An experienced oral medicine specialist" Blinding of examiners: not stated Prevalence of the target condition on the sample: 28/44 participants with suspicious lesions 63.6%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: not explicitly stated but assumed to be at the same appointment Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: quote: "Three patients were excluded because 1 had oral cancer and was not able to perform the examination properly and 2 others did not complete all the questionnaires." Results available for 44 participants (6% attrition) Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: reference standard carried out by an oral medicine specialist
Comparative	
Notes	Study participants received no previous orientation/instruction prior to carrying out the test. Unlikely to be reflective of best practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Furquim 2014 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High

DOMAIN 2: Index Test (Conventional oral examination)

DOMAIN 2: Index Test (Mouth self-examination)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?			
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High

DOMAIN 2: Index Test (Remote screening)

DOMAIN 2: Index Test (Fluorescence)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	

Furquim 2014 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	Low risk	

Ghani 2019

Study characteristics	
Patient Sampling	Method of patient selection: quote: "Two villages were selected as the sampling frame by the local Health District Office, based on the prevalence of tobacco and betel quid chewing habit. Selection criteria was adults aged 18 years and above. Out of a total of 1,490 eligible participants, 100 respondents were recruited from each village"
Patient characteristics and setting	Results available for 200/1490 eligible participants Age: 54.83 years (16.54 SD) Sex: 78 male, 122 female SES: not stated Ethnicity: not stated Stated risk factors: quote: "High-risk indigenous population" Previous history: not stated Location: Malaysia Clinical setting: community hall
Index tests	Index test: mouth self-examination where participants were asked whether they had any white lesions, red lesions, ulcers, or swellings in their mouth. Quote: "Respondents were taught on the signs and symptoms using a series of pictures depicting the various oral mucosal lesions/conditions. Similarly, training on MSE was also provided by local dental surgeons who have been calibrated against the specialist. Respondents were taught how to correctly perform MSE using verbal and demonstrative instructions, aided by a mirror which has the six steps of MSE" Description of positive case definition by index test as reported: white lesions, red lesions, ulcers, or swellings in their mouth Sequence of tests: index test followed by reference standard

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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47

Ghani 2019 *(Continued)*

Training or calibration: training provided

Blinding of examiners: not stated but could be assumed as the participants were asked to complete the self-assessment prior to the examination by the oral specialist

Conflict of interests: none. Quote: "The authors would like to thank the University of Malaya Research Grant (UMRG Programme) - HTM (Wellness), RP045A-15HTM grant for supporting this study. The authors declare no conflict of interest"

Target condition and reference standard(s)	Target condition: oral mucosal lesions Reference standard: oral medicine specialist Description of positive case definition by reference test as reported: quote: "The presence of any oral mucosal lesions or abnormalities was recorded" Training or calibration: quote: "The specialist was trained and calibrated on the diagnoses of various oral mucosal lesions including OPMDs, and lesions that are suspicious of oral cancer using the criteria described by Zain et al" Blinding of examiners: not stated Prevalence of the target condition on the sample: 116/196 59.2%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: immediately after Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: results available for 196 participants (Table 7 all lesions) (2% attrition). Characteristics not provided Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: 0
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Conventional oral examination)			
DOMAIN 2: Index Test (Mouth self-examination)			

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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48

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Ghani 2019 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?			
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Remote screening)			
DOMAIN 2: Index Test (Fluorescence)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Low risk	

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

49

Gomes 2017

Study characteristics

Patient Sampling	Method of patient selection: quote: "We recruited 55 individuals from the healthcare system in the city of João Pessoa, northeastern Brazil, to participate in the study by collecting data and video using the app. This sample was chosen for convenience and all individuals were over 40 years old, of both sexes, and smokers." Unclear how the sample was selected. Population at high risk for oral cancer development
Patient characteristics and setting	55 "high-risk" participants from a healthcare system Age: over 40 years; 16 between 40 and 59 years, 33 between 60 and 79 years, 6 over 80 years Sex: 29 male, 26 female SES: not stated Ethnicity: not stated Stated risk factors: 37 cigarette smokers, 8 pipe, 9 roll, 1 straw; 8 smoked for less than 20 years, 15 smoked for 20 to 39 years, 32 smoked for more than 40 years Previous history: cases in family; 2 yes, 53 no Location: João Pessoa, Northeastern Brazil Clinical setting: houses, streets, or public places
Index tests	Index test: mobile phone app, includes a questionnaire collecting clinical characteristics, and allows for video and photographs to be captured and shared with a remote clinician Description of positive case definition by index test as reported: not clearly reported; the only description states "homogeneous/heterogeneous white lesions with malignancy potential" Training or calibration: examiners had at least 3 years experience in oral diagnosis and 8 hours of training with the app Blinding of examiners: remote examiners, quote: "blinded, trained examiners" Conflict of interests: no conflicts stated
Target condition and reference standard(s)	Target condition: homogeneous/heterogeneous white lesions with malignancy potential Reference standard: quote: "an examiner with experience in oral pathology" examined the participants in natural light to simulate a population based survey Description of positive case definition by reference test as reported: homogeneous/heterogeneous white lesions with malignancy potential Training or calibration: quote: "an examiner with experience in oral diagnosis" Blinding of examiners: not explicitly stated but reference standard of clinical examination undertaken prior to the index test by blinded examiners, so can be assumed Prevalence of the target condition on the sample: 17/38; 31%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: not reported

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

50

Gomes 2017 *(Continued)*

Characteristics and proportion of individuals who did not receive the index test(s) and/ or reference standard or excluded from analysis: none

Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: none

Comparative	
Notes	Data from examiner 1 were used for analysis

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Conventional oral examination)			
DOMAIN 2: Index Test (Mouth self-examination)			
DOMAIN 2: Index Test (Remote screening)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?			
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Fluorescence)			

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

51

Gomes 2017 *(Continued)*

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk

Ikeda 1995

Study characteristics	
Patient Sampling	<u>Method of patient selection</u>: postal invitation to 60-year old residents to participate in an annual mass screening programme
Patient characteristics and setting	154 from last screening exercise (5187 eligible during reported 7 years of the programme from 1986 to 1993) <u>Age</u>: 60 years of age <u>Sex</u>: not stated <u>SES</u>: not stated <u>Ethnicity</u>: not stated <u>Stated risk factors</u>: not stated <u>Previous history</u>: not stated <u>Location</u>: Japan <u>Clinical setting</u>: city health centre
Index tests	<u>Index test</u>: standard visual examination carried out by 4 general dental practitioners. Quote: "Lesions were recorded on a standard WHO form modified for local conditions"

Ikeda 1995 *(Continued)*

<table>
<tr>
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<td>

<u>Description of positive case definition by index test as reported</u>: quote: "The screen was recorded as positive for oral cancer or precancer if the examiner considered a carcinoma, erythroplakia, lichen planus or chronic candidosis was present." Types of lesion categorised as malignancy, malignant potential, benign characterisation or absence

<u>Sequence of tests</u>: index followed by reference. Quote: "Following screening individual consultation was provided on site for all those examined..."

<u>Training or calibration</u>: trained according to WHO guidelines. Calibration for the 4 dentists was reported. Kappa scores were slight to moderate (0.08 to 0.44) for classification of lesions and moderate to substantial (0.39 to 0.78) for identifying the presence/absence of lesions

<u>Blinding of examiners</u>: index test completed prior to reference

<u>Conflict of interests</u>: not stated
</td>
</tr>
<tr>
<td>Target condition and reference standard(s)</td>
<td>

<u>Target condition</u>: as for index test

<u>Reference standard</u>: quote: "..assessed by an oral medicine specialist"

<u>Description of positive case definition by reference test as reported</u>: presence or absence of malignant or pre-malignant oral lesions and classification of lesions

<u>Training or calibration</u>: previously calibrated, details not reported

<u>Blinding of examiners</u>: not explicitly stated but "...independent clinical diagnoses of the instructor carried out concurrently"

<u>Prevalence of the target condition in the sample</u>: 15/154 9.7%
</td>
</tr>
<tr>
<td>Flow and timing</td>
<td>

<u>Time interval and any interventions between index test(s) and reference standard</u>: quote: "Following screening..." consultation undertaken on same day

<u>Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis</u>: all received index and reference (data fully reported for results of most recent screening exercise only)

<u>Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician</u>: screened positive did receive biopsy but data taken from table of clinical diagnosis of specialist (Table 1)
</td>
</tr>
<tr>
<td>Comparative</td>
<td></td>
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<tr>
<td>Notes</td>
<td>

Definition of positive threshold could underestimate accuracy

802/5187 eligible residents presented for screening during reported 7 years of the programme from 1986 to 1993
</td>
</tr>
</table>

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

53

Ikeda 1995 *(Continued)*

Could the selection of patients have introduced bias?	Low risk	
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (Conventional oral examination)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Was conflict of interest avoided?	Yes	
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?		
Could the conduct or interpretation of the index test have introduced bias?	Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (Mouth self-examination)		
DOMAIN 2: Index Test (Remote screening)		
DOMAIN 2: Index Test (Fluorescence)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	

Ikeda 1995 *(Continued)*

Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Jullien 1995

Study characteristics

Patient Sampling	<u>Method of patient selection</u>: participants recruited "...by the screener or the specialist from the various outpatient departments of the hospital." Method of selection of participants at the dental hospital is unclear
Patient characteristics and setting	1042 participants (total population not reported)
	Participant characteristics are reported across both studies
	<u>Age</u>: 40 years or over; mean 56 years
	<u>Sex</u>: 892 male, 1135 female
	<u>SES</u>: not stated
	<u>Ethnicity</u>: not stated
	<u>Stated risk factors</u>: 162 heavy smoker, 608 moderate smoker, 1257 non-smoker; 61 heavy drinker, 527 moderate drinker, 1439 light drinker
	<u>Previous history</u>: not stated
	<u>Location</u>: UK
	<u>Clinical setting</u>: outpatient departments of a dental hospital
Index tests	<u>Index test</u>: thorough visual examination of the surface of the oral mucosa according to the British Postgraduate Medical Federation, 1991, by either a general dental practitioner, a community dental officer, or a junior hospital dentist (24 screeners)
	<u>Description of positive case definition by index test as reported</u>: quotes: "A lesion was defined as positive when a white patch, red patch, or an ulcer of longer than two weeks duration was detected." "The screeners were also instructed to include lesions of lupus erythematosus, submucous fibrosis or actinic keratosis as positive." All types of lichen planus were also regarded as positive
	<u>Sequence of tests</u>: index followed by reference
	<u>Training or calibration</u>: quote: "..screeners advised of diagnostic criteria which should result in a positive or negative screen ...no formal training or standardisation was undertaken"
	<u>Blinding of examiners</u>: index test completed before reference
	<u>Conflict of interests</u>: supported by grant from the Department of Health, UK
Target condition and reference standard(s)	<u>Target condition</u>: oral cancer and pre-cancer

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

55

Jullien 1995 *(Continued)*

	Reference standard: visual examination by second dental specialist who was able to refer subjects for further tests or review as appropriate (single specialist)
	Description of positive case definition by reference test as reported: as for index test. Quotes: "A lesion was defined as positive when a white patch, red patch, or an ulcer of longer than two weeks duration was detected." "The screeners were also instructed to include lesions of lupus erythematosus, submucous fibrosis or actinic keratosis as positive." All types of lichen planus were also regarded as positive
	Training or calibration: not stated but quoted as "a specialist." Single examiner so no calibration
	Blinding of examiners: index test completed before reference. Quotes: "The results were also recorded on a standard form which was collated with the screeners' form only after completion." "All subjects were examined by a specialist who provided an independent definitive diagnosis"
	Prevalence of the target condition on the sample: 32/1042 3.1%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: not explicit, however, reasonable to assume both conducted on same visit
	Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: none
	Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: none
Comparative	
Notes	Participant characteristics reported for Jullien 1995 and Jullien 1995a together

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Conventional oral examination)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it prespecified?	Yes		

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56

Jullien 1995 *(Continued)*

Was conflict of interest avoided?	Yes

Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?	

Could the conduct or interpretation of the index test have introduced bias?	Low risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (Mouth self-examination)

DOMAIN 2: Index Test (Remote screening)

DOMAIN 2: Index Test (Fluorescence)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes

Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	

Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes

Did all patients receive the same reference standard?	Yes

Were all patients included in the analysis?	Yes

Could the patient flow have introduced bias?	Low risk	

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

57

Jullien 1995a

Study characteristics

Patient Sampling	Method of patient selection: list of registered medical practice patients obtained and postal invitation to participate in screening sent
Patient characteristics and setting	985 participants (total population not reported) Participant characteristics are reported across both studies Age: 40 years or over Sex: 892 male, 1135 female SES: not stated Ethnicity: not stated Stated risk factors: 162 heavy smoker, 608 moderate smoker, 1257 non-smoker; 61 heavy drinker, 527 moderate drinker, 1439 light drinker Previous history: not stated Location: UK Clinical setting: inner city medical practice
Index tests	Index test: thorough visual examination of the surface of the oral mucosa according to the British Postgraduate Medical Federation, 1991, by either a general dental practitioner, a community dental officer or a junior hospital dentist (24 screeners) Description of positive case definition by index test as reported: quotes: "A lesion was defined as positive when a white patch, red patch, or an ulcer of longer than two weeks duration was detected." "The screeners were also instructed to include lesions of lupus erythematosus, submucous fibrosis or actinic keratosis as positive." All types of lichen planus were also regarded as positive Sequence of tests: index followed by reference Training or calibration: quote: "..screeners advised of diagnostic criteria which should result in a positive or negative screen .....no formal training or standardisation was undertaken" Blinding of examiners: index test completed before reference Conflict of interests: supported by grant from the Department of Health, UK
Target condition and reference standard(s)	Target condition: oral cancer and pre-cancer Reference standard: visual examination by second dental specialist who was able to refer subjects for further tests or review as appropriate (single specialist) Description of positive case definition by reference test as reported: As for index test. Quotes: "A lesion was defined as positive when a white patch, red patch, or an ulcer of longer than two weeks duration was detected." "The screeners were also instructed to include lesions of lupus erythematosus, submucous fibrosis or actinic keratosis as positive." All types of lichen planus were also regarded as positive Training or calibration: not stated but quoted as "a specialist". Single examiner so no calibration Blinding of examiners: index test completed before reference. Quotes: "The results were also recorded on a standard form which was collated with the screeners' form only after

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58

Jullien 1995a *(Continued)*

	completion." "All subjects were examined by a specialist who provided an independent definitive diagnosis"
	<u>Prevalence of the target condition on the sample</u>: 22/985 2.2%
Flow and timing	<u>Time interval and any interventions between index test(s) and reference standard</u>: not explicit, however, reasonable to assume both conducted on same visit
	<u>Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis</u>: none
	<u>Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician</u>: none
Comparative	
Notes	Participant characteristics reported for Jullien 1995 and Jullien 1995a together

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Conventional oral examination)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it prespecified?	Yes		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?			
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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59

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

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DOMAIN 2: Index Test (Mouth self-examination)

DOMAIN 2: Index Test (Remote screening)

DOMAIN 2: Index Test (Fluorescence)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

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DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	

Mathew 1997

Study characteristics

Patient Sampling	<u>Method of patient selection</u>: re-examination of 2069 eligible participants from the 9000 participants recruited in January to May 1996, shortly after commencement of the study. Quote: "Subjects were selected by choosing densely inhabited areas to allow re-examination of as many subjects as possible in two weeks." Study looking at the reproducibility and validity of oral visual inspection by health workers within a randomised controlled intervention trial of visual screening
Patient characteristics and setting	2069 participants

Mathew 1997 *(Continued)*

Age: mean 47.7 years, SD 9.1 years (range 35 to 64 years)

Sex: 678 males, 1391 females

SES: recorded but not reported

Ethnicity: recorded but not reported

Stated risk factors: details on smoking and alcohol were recorded but not reported

Previous history: recorded but not reported

Location: Kerala, India

Clinical setting: participants' homes

Index tests	Index test: systematic oral visual examination by trained health workers (n = 14) in the inspection and detection of oral lesions
	Description of positive case definition by index test as reported: quote: "...homogeneous leucoplakia, ulcerated leucoplakia, verrucous leucoplakia, erythroplakia, nodular leukoplakia, submucous fibrosis, and oral cancer"
	Sequence of tests: initial screen by health worker followed by second screen (the index test) by same health worker (1 to 6 months later) to establish reliability. 2069 received the index test (second screen by health worker) and this formed the sample for the sensitivity and specificity calculations
	Training or calibration: quote: "Training sessions spread over 6 weeks composed of lectures, practical demonstrations and field work conducted by Faculty... At the end of training sessions written and practical tests were conducted identifying the best health workers.... They were also given manuals and photographic documentation to identify different types of oral lesions." The "best performing" health workers were retained for the study
	Blinding of examiners: index test completed before reference
	Conflict of interests: supported by a grant from the Association of International Cancer Research, Scotland, UK
Target condition and reference standard(s)	Target condition: as for index test, quote: "...homogeneous leukoplakia, ulcerated leukoplakia, verrucous leukoplakia, erythroplakia, nodular leukoplakia, submucous fibrosis, and oral cancer"
	Reference standard: visual examination by a specialist physician (decision made by single physician, 1 of 3). Quote: "....comparison with pathological findings is not possible as biopsy has not been performed for most case. Biopsy is performed for cases of nodular leukoplakias, erythroplakias and suspicious growths only, and this is currently being undertaken"
	Training or calibration: 100 participants formed the basis of comparability of findings evaluation. Kappa value of 0.85 was reported for the findings of the 3 physicians
	Blinding of examiners: reference test undertaken immediately after index test. Both health worker and specialist in participants' home at the same visit
	Prevalence of the target condition on the sample: 212/2069 10.3%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: quote: "This was immediately followed by an independent examination of the same subject by one of three physicians"
	Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: none

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61

Mathew 1997 *(Continued)*

<u>Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician</u>: none

Comparative
Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Conventional oral examination)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it prespecified?	Yes		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?			
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Mouth self-examination)			
DOMAIN 2: Index Test (Remote screening)			
DOMAIN 2: Index Test (Fluorescence)			

Mathew 1997 *(Continued)*

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes

Could the patient flow have introduced bias?	Low risk

Mehta 1986

Study characteristics

Patient Sampling	<u>Method of patient selection</u>: for the screening study, a basic health worker visited each household to report on health status in an area of high oral cancer prevalence. Quote: "Four adjacent blocks, two as study area I (pop 218728) and two as study area II (pop 250,399) were selected for this investigation." Field checking of the diagnosis of the health worker by the study dentist was initiated after 6 months and completed for 40 health workers. For each of the health workers' lists "A house with a lesion case was selected as a nodal point and all the available individuals from nearby houses who figured in the list were examined." Carried out on high risk individuals within a household "..i.e. people aged 35 years and above with tobacco habits"
Patient characteristics and setting	2063 'high risk' participants (out of 39,331 screened) <u>Age</u>: 35 years and above <u>Sex</u>: not stated <u>SES</u>: not stated <u>Ethnicity</u>: not stated

Mehta 1986 *(Continued)*

	<u>Stated risk factors</u>: all participants had tobacco habits, HPV and alcohol use not reported
	<u>Previous history</u>: not stated
	<u>Location</u>: Kerala, India
	<u>Clinical setting</u>: participants' homes
Index tests	<u>Index test</u>: standard visual examination by basic health worker working to a reference manual
	<u>Description of positive case definition by index test as reported</u>: referable lesions were "nodular leukoplakia, submucous fibrosis, and ulcers and growths suggestive of oral cancer." Non-referable lesions included "homogenous leukoplakia, oral lichen planus, smoker's palate and central papillary atrophy of the tongue papillae." Definition of positive threshold may over-estimate accuracy values (homogenous leukoplakia considered to be test negative)
	<u>Sequence of tests</u>: index followed by reference
	<u>Training or calibration</u>: yes. Training provided by dentists, members of the research team. Quote: "The final performance of the trainees was judged as satisfactory"
	<u>Blinding of examiners</u>: index test completed before reference
	<u>Conflict of interests</u>: none stated. Study was supported by a grant from the National Institutes of Health
Target condition and reference standard(s)	<u>Target condition</u>: referable lesion
	<u>Reference standard</u>: standard visual examination by dentist (member of research team) in participants' home
	<u>Description of positive case definition by reference test as reported</u>: referable lesions were "nodular leukoplakia, submucous fibrosis, and ulcers and growths suggestive of oral cancer." Non-referable lesions included "homogenous leukoplakia, oral lichen planus, smoker's palate and central papillary atrophy of the tongue papillae." Definition of positive threshold may over-estimate accuracy values (homogenous leukoplakia considered to be test negative)
	<u>Training or calibration</u>: the research team of dentists "...was experienced in conducting house to house surveys for oral cancer and precancerous lesions in rural areas of Ernakulam district for 16 years"
	<u>Blinding of examiners</u>: unclear whether the dentists were aware of the screening results. Quote: "The list contained the categorization indicated by the BHW"
	<u>Prevalence of the target condition on the sample</u>: 27/1921 1.41%
Flow and timing	<u>Time interval and any interventions between index test(s) and reference standard</u>: at the same visit. Quote: "One day was devoted to rechecking for each of the 40 BHW"
	<u>Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis</u>: 142 were falsely reported to have been examined by the basic health worker, and they were excluded from further analysis. Exclusions are unlikely to introduce bias
	<u>Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician</u>: none
Comparative	
Notes	Data presented for field check only, not full screening programme
Methodological quality	

Mehta 1986 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Conventional oral examination)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?			
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Mouth self-examination)			
DOMAIN 2: Index Test (Remote screening)			
DOMAIN 2: Index Test (Fluorescence)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowl-	Unclear		

Mehta 1986 *(Continued)*
edge of the results of the index
tests?

Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?	Low risk	

Scott 2010

Study characteristics	
Patient Sampling	Method of patient selection: quote: "Participants were recruited from a general practitioner's list in South East London, UK. Patients who were at risk of oral cancer (aged 45 years or older and who smoked) were identified as potential participants by their general practitioner." Recruitment was by invitation letter to 243 eligible patients. 53 patients participated
Patient characteristics and setting	53/243 eligible patients
	Age: mean age 54 years (SD 5.9 years, range 45 to 64 years)
	Sex: 36 male, 17 female
	SES: 24 no/compulsory education; 25 beyond compulsory education
	Ethnicity: 37 white, 14 other
	Stated risk factors: 40 hazardous drinking (AUDIT-C), 11 alcohol dependent; 41 current smoker, 12 used to smoke; 27 regular attenders, 10 irregular attenders, 15 emergency or never
	Previous history: not stated
	Location: South East London, UK
	Clinical setting: quote: "Research room"
Index tests	Index test: mouth self-examination in accordance with a patient leaflet, at the same location. Quote: "The leaflet had been specifically developed for and piloted with heavy smok-

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66

ers and drinkers and has a reading age of 10 to 12 years and a Flesch reading ease score of 79%, indicating it can be read and understood with ease"

<u>Description of positive case definition by index test as reported</u>: red patches, white patches, ulcers and lumps or swellings

<u>Sequence of tests</u>: reference followed by index test

<u>Training or calibration</u>: conducted mouth self-examination in accordance with specifically developed patient leaflet

<u>Blinding of examiners</u>: reference preceded index test. Quotes: "After the dentist's examination (yet before the results of the examination were revealed to the participant)…" "The dentist remained in the room but did not assist the participant in conducting the mouth self examination"

<u>Conflict of interests</u>: the study was funded by a Cancer Research UK Pilot Project Award (C19770/A8554), but no conflict of interest

Target condition and reference standard(s)	<u>Target condition</u>: red patches, white patches, ulcers and lumps or swelling <u>Reference standard</u>: examination by single dentist (member of research team). Protocol for examination reported <u>Description of positive case definition by reference test as reported</u>: quote: "The presence (including site and provisional diagnosis) and absence of potentially malignant oral lesions (ulcers, white or red patches, or lumps/swellings) were noted on a pro forma" <u>Training or calibration</u>: experience and training not reported <u>Blinding of examiners</u>: yes. Reference standard proceeded index test <u>Prevalence of the target condition on the sample</u>: 12/53 22.6%
Flow and timing	<u>Time interval and any interventions between index test(s) and reference standard</u>: reference test immediately followed index test <u>Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis</u>: none <u>Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician</u>: none
Comparative	
Notes	Low response rate for participation 53/243 eligible patients recruited from an "at risk" group

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

67

Scott 2010 *(Continued)*

Could the selection of patients have introduced bias?	Low risk	
Are there concerns that the included patients and setting do not match the review question?		High
DOMAIN 2: Index Test (Conventional oral examination)		
DOMAIN 2: Index Test (Mouth self-examination)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Was conflict of interest avoided?	Yes	
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?		
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (Remote screening)		
DOMAIN 2: Index Test (Fluorescence)		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		

Scott 2010 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Su 2010

Study characteristics	
Patient Sampling	<u>Method of patient selection</u>: community-based randomised controlled trial of toluidine blue for the detection and incidence of oral cancer. Mass screening programme (eligible at 15 years old or over) aimed at detecting 5 prevalent neoplasms (cervical, breast, hepatocellular, colorectal, and oral cancer) and 3 chronic diseases (hypertension, diabetes, and hyperlipidaemia). From the mass screening programme individuals were ineligible for the randomised controlled trial if they "lacked oral habits such as cigarette smoking or chewing betel quid." Randomised to either visual examination plus toluidine blue (experimental group) or to visual examination alone (control group)
Patient characteristics and setting	Analysis of data of 7975 participants enrolled into the randomised controlled trial during 2000 <u>Age</u>: mean 44.9 years, SD 14.4; mean 44.6 years, SD 15.3 <u>Sex</u>: male 3719 and 3550, female 361 and 345 <u>SES</u>: not stated <u>Ethnicity</u>: not specified <u>Stated risk factors</u>: participants were smokers or betel quid chewers, HPV or alcohol consumption not reported <u>Previous history</u>: not stated <u>Location</u>: Taiwan <u>Clinical setting</u>: randomised controlled trial as part of community-based screening programme
Index tests	<u>Target condition</u>: asymptomatic oral pre-malignant lesions (OPML) and oral cancer. Oral submucous fibrosis, homogenous leukoplakia, non-homogeneous leukoplakia, erythroplakia, and oral cancer <u>Index test (2)</u>: - visual examination by dentist plus toluidine blue (experimental group) - visual examination by dentist alone (control group)

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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69

Su 2010 *(Continued)*

Description of positive case definition by index test as reported: quote: "The presence of any visible lesion in the oral cavity was recorded as screen-positive." Information reported for screen positive rate and detection rate

Sequence of tests: index test followed by reference standard

Training or calibration: training given to dentists was carried out by a senior oral pathologist. No calibration was reported

Blinding of examiners: index test followed by reference standard. Placebo dye

Conflict of interests: none declared

Target condition and reference standard(s)	Target condition: any visible lesion (detection), oral cancer (incidence rate of oral cancer, diagnostic accuracy) Reference standard: only screened positives referred for biopsy; entire cohort (screened positive or screened negative) assessed through national cancer registry Description of positive case definition by reference test as reported: as indicated by national cancer registry Training or calibration: quote: "Diagnostic criteria, examination procedures, and documentation formats were discussed, taught, and calibrated in advance for all personnel participating in the study" Blinding of examiners: all personnel were unaware of group allocation Prevalence of the target condition on the sample: 0.12% and 0.15% in each trial arm
Flow and timing	Time interval and any interventions between index test(s) and reference standard: screened positive participants were referred for a definite clinical diagnosis within 10 to 14 days. 5-year follow-up of oral cancer development through linkage to the national cancer registry Characteristics and proportion of individuals who did not receive the index test(s) and/ or reference standard or excluded from analysis: none Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: all. Quote: "We retrieved the occurrence of oral cancer, survival status, and causes of death of the studied participants by linking the entire cohort with the National Cancer Registry and the National Household Registry until December 31, 2004"
Comparative	
Notes	Estimates of sensitivity and specificity of the index tests are based on the outcome of oral cancer as indicated by the national cancer registry. Results presented for detection rate ratio for oral pre-malignant lesions and malignant lesions and incidence rate of oral cancer

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Su 2010 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High

DOMAIN 2: Index Test (Conventional oral examination)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

DOMAIN 2: Index Test (Mouth self-examination)

DOMAIN 2: Index Test (Remote screening)

DOMAIN 2: Index Test (Fluorescence)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	No	

Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk

Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	No	
Were all patients included in the analysis?	Yes	

Could the patient flow have introduced bias?		Low risk

Sweeny 2011

Study characteristics

Patient Sampling	Method of patient selection: quote: "...a prospective study was performed at the University of Alabama at Birmingham. Consecutive patients who presented to the Otolaryngology clinic between November 2009 and October 2010 for follow-up (n = 88) following management of primary head and neck cancer"
Patient characteristics and setting	88 participants
	Age: mean 64 years (range 41 to 85 years)
	Sex: 65 male, 23 female
	SES: not reported
	Ethnicity: 54 Caucasian
	Stated risk factors: 58 alcohol consumption; 71 history of tobacco use
	Previous history: quotes: "All patients had undergone a previous treatment for head and neck cancer." "All patients evaluated during routine surveillance visits"

Sweeny 2011 *(Continued)*

Location: Alabama, USA

Clinical setting: otolaryngology clinic

Index tests	Index test (3): quotes: "..sites were initially screened by a registered nurse and then by a fellowship trained head and neck surgeon using visualization with white light illumination (traditional exam light) followed by visualization of tissue autofluorescence and tissue reflectance. The Trimira® Identafi® 3000 ultra, multi-spectral oral cavity screening system was used." "Patients were evaluated by direct visualization of the oral cavity with white light (traditional exam light), tissue autofluorescence and tissue reflectance." Only the results of visualisation examination with white light are included in this analysis as the autofluorescence and reflectance data are not presented as adjuncts but as independent tests
	Description of positive case definition by index test as reported: quote: "oral cavity cancer." Abnormality/lesion with concern for malignancy or recurrence. Not explicitly stated
	Sequence of tests: index followed by reference
	Training or calibration: not stated but index test conducted by registered nurse followed by head and neck surgeon
	Blinding of examiners: not stated but index tests preceded reference test. No information of blinding after successive index tests
	Conflict of interests: this work was supported by a grant from the National Institute of Health (2T32 CA091078-09), but no conflict of interest
Target condition and reference standard(s)	Target condition: head and neck cancer recurrence
	Reference standard: quote: "Screening results were compared to histological biopsy results or a three month follow-up screening. Any area of abnormality found by visualization with traditional white light illumination and/or by tissue autofluorescence or reflectance was biopsied and evaluated by a pathologist using standard histopathologic analysis"
	Description of positive case definition by reference test as reported: quote: "Positive disease"
	Training or calibration: not stated
	Blinding of examiners: not stated
	Prevalence of the target condition on the sample: 4/88 4.6%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: not explicitly stated. Follow-up screening visit at 3 months
	Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: none
	Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: biopsy for screened positive participants. Reference standard by follow-up visit for some participants (number of participants not specified)
Comparative	
Notes	Quote: "Our study was unique in that it evaluated the population most likely to benefit from screening." Participants attending for routine surveillance

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

73

Sweeny 2011 *(Continued)*

DOMAIN 1: Patient Selection

Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High

DOMAIN 2: Index Test (Conventional oral examination)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
Was conflict of interest avoided?	Yes		
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?			
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear

DOMAIN 2: Index Test (Mouth self-examination)

DOMAIN 2: Index Test (Remote screening)

DOMAIN 2: Index Test (Fluorescence)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Sweeny 2011 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	No	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Unclear risk	

Vinayagamoorthy 2019

Study characteristics	
Patient Sampling	<u>Method of patient selection</u>: quote: "... a convenience sample of participants of oral screening programs in different areas of Udupi District, Karnataka"
Patient characteristics and setting	131 participants (655 images) <u>Age</u>: mean 37.34 years (SD 11.31 years) <u>Sex</u>: 84 male, 29 female <u>SES</u>: not reported <u>Ethnicity</u>: not reported <u>Stated risk factors</u>: 13% tobacco users <u>Previous history</u>: not reported <u>Location</u>: Udupi District, Karnataka, India <u>Clinical setting</u>: oral screening programme
Index tests	<u>Index test</u>: series of 5 photographs captured using a mobile phone and transferred to remote clinician for assessment <u>Description of positive case definition by index test as reported</u>: diagnosed with OP-MD <u>Sequence of tests</u>: reference standard completed prior to index test <u>Training or calibration</u>: clinicians practiced in a pilot study

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

75

Vinayagamoorthy 2019 *(Continued)*

	Blinding of examiners: unclear but appears same examiner was included in index test and reference standard with a washout period, quote: "five images of the oral cavity of each individual, were sent through the messenger to both the examiners (1 and 2) after a washout period of 2 months." Can assume that washout period was sufficient Conflict of interests: authors declare they have no conflicts of interest
Target condition and reference standard(s)	Target condition: OPMD including tobacco pouch keratosis, leukoplakia, oral sub-mucous fibrosis and post-inflammatory hyperpigmentation Reference standard: clinical oral examination by a trained and calibrated examiner, under natural light using a mirror and explorer Description of positive case definition by reference test as reported: results described as normal/abnormal Training or calibration: quote: "trained and calibrated examiner" yes but details not reported Blinding of examiners: suspected to be involved in index test but reference standard was reported and preceded index test by 2 months so assume blinded. Further, 655 images were of the oral cavity and sequentially numbered Prevalence of the target condition on the sample: 16/131, 12.2%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: 2-month washout period, but oral examination and photographs captured on the same day Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: 5 images Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: none
Comparative	
Notes	Request to authors for data to support Table 1 and 2 was made in March 2021

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Conventional oral examination)			

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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76

DOMAIN 2: Index Test (Mouth self-examination)

DOMAIN 2: Index Test (Remote screening)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Unclear	
Was conflict of interest avoided?	Yes	
Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?		
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (Fluorescence)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Low risk	

Warnakulasuriya 1990

Study characteristics

Patient Sampling	Method of patient selection: screening programme at a rural location, Kadugannawa, Sri Lanka. Quote: "The PHC workers carried out an examination….of people over the age of 20 years in their area;….voters lists were used to identify and record the persons examined and those who were referred"
Patient characteristics and setting	Population of 87,277 adults (> 20 years of age) of whom 29,295 were screened during study periods of 52 weeks. From this number 1872 received both the index test and the reference test. Patient characteristic information reported only for those screened positive and attending the referral centre
	Age: 20 to 39 years n = 182, 40 to 59 years n = 315, > 60 n = 163
	Sex: 480 male, 180 female
	SES: not stated
	Ethnicity: not stated
	Stated risk factors: not stated
	Previous history: not stated
	Location: Sri Lanka
	Clinical setting: participants' own homes
Index tests	Index test: examination of the lining mucosa of the oral cavity in natural daylight using dental mirrors by primary healthcare (PHC) workers comprising midwives, public health inspectors, and public health nurses
	Description of positive case definition by index test as reported: quote: "The PHC workers identified positive cases on the basis of simple, explicitly stated criteria. The diagnosis criteria included the presence of a white or red lesion on the oral mucosa with a smooth, corrugated or nodular surface which cannot be scraped of using the dental mirror head. Elevated and ulcerated areas with co-existing red or white lesions were also referable"
	Sequence of tests: index followed by reference
	Training or calibration: quote: "…participated in a two-day training programme which provided a clinical demonstration of oral cancer and precancer, instructions regarding the screening methods and referral mechanisms"
	Blinding of examiners: index test preceded reference test
	Conflict of interests: authors declare no conflict of interest. Work was supported by the Cancer Control Programme of Sri Lanka
Target condition and reference standard(s)	Target condition: oral cancer/pre-cancer (for purposes of accuracy of examination). Leukoplakia, erythroplakia, or carcinoma
	Reference standard: re-examination by the project dentist
	Description of positive case definition by reference test as reported: oral cavity cancer
	Training or calibration: not stated but carried out by experienced dentists
	Blinding of examiners: unclear. Re-examination of screened positive cases took place at the referral centre, quote: "(all screened positives were referred); a sample of screened negative participants were randomly selected from PHC files by the project dentist visiting each field area"

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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78

Warnakulasuriya 1990 *(Continued)*

	Prevalence of the target condition on the sample: 405/1872 21.6% (sample for diagnostic test accuracy assessment), 660/29,295 screened positive referable lesions 2.25%
Flow and timing	Time interval and any interventions between index test(s) and reference standard: re-examination of "660 cases who arrived at the referral centre within 18 months (January 1981 to June 1982) after case detection." Quote: "...negative cases randomly selected from PHC files.. were re-examined, during the three month period of initial PHC examinations"
	Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: 87,277 adults were eligible for the screening programme of whom 29,295 were screened. Quotes: "All referred (screened positive) participants who arrived at the referral centre were re-examined by the project dentist to validate the PHC diagnosis." "A sample of negative cases was randomly selected from PHC files (in whom PHC workers had not recorded a lesion) were re-examined, during the three month period of initial examination. A minimum of 30 negative cases from each PHC file were thus re-examined." 1872 received both the index test and the reference test
	Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: none
Comparative	
Notes	Only 660 screened positive participants arrived at the referral centre within 18 months after screen positive detection; 54.1% of detected cases in the field
	Index test target condition "white or red lesion that cannot be scraped off"; reference standard for accuracy of screening "correctly referred cases who, on examination, had oral cancer or precancer"
	Prevalence in sample for diagnostic test accuracy assessment was high 21.6%

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Conventional oral examination)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

Warnakulasuriya 1990 *(Continued)*

Was conflict of interest avoided?	Yes

Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?	

Could the conduct or interpretation of the index test have introduced bias?	Low risk	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

DOMAIN 2: Index Test (Mouth self-examination)

DOMAIN 2: Index Test (Remote screening)

DOMAIN 2: Index Test (Fluorescence)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk	

Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	No

Did all patients receive the same reference standard?	Yes

Were all patients included in the analysis?	No

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review) 80

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Warnakulasuriya 1990 *(Continued)*

Could the patient flow have introduced bias?	High risk

Warnakulasuriya 1991

Study characteristics	
Patient Sampling	Method of patient selection: optional screening programme at a rural location, Galle, Sri Lanka. Primary healthcare (PHC) workers carried out a visual oral examination of people over the age of 20 years in their geographical area. The 1981 electoral list was used to identify eligible individuals
Patient characteristics and setting	Population of 72,867 adults (> 20 years of age) of whom 57,124 were examined during 1 year by primary healthcare workers. From this number 3543 received both the index test and the reference test
	Age: participants were 20 years of age or older
	Sex: not stated
	SES: not stated
	Ethnicity: not stated
	Stated risk factors: not stated
	Previous history: not stated
	Location: Sri Lanka
	Clinical setting: participants' own homes
Index tests	Index test: examination of the lining mucosa of the oral cavity in natural daylight using dental mirrors by primary healthcare workers
	Description of positive case definition by index test as reported: quote: "The PHC workers identified positive cases on the basis of simple, explicitly stated criteria. The diagnosis criteria included the presence of a white or red lesion on the oral mucosa with a smooth, corrugated or nodular surface which cannot be scraped of using the dental mirror head. Elevated and ulcerated areas with co-existing red or white lesions were also referable"
	Sequence of tests: index test followed by reference test
	Training or calibration: participated in a 2-day training programme which provided a clinical demonstration of oral cancer and pre-cancer, instructions regarding the screening methods and referral mechanisms, as in the pilot study (Warnakulasuriya 1990)
	Blinding of examiners: index test followed by reference test
	Conflict of interests: authors declare no conflict of interest. Work was supported by funds from the National Cancer Control Programme of Sri Lanka
Target condition and reference standard(s)	Target condition: oral cancer/pre-cancer (for purposes of accuracy of examination)
	Reference standard: re-examination by the project dentist. Quotes: "The hospital dental surgeon reexamined all referred subjects to revalidate the diagnosis given by the PHCW." "Biopsies were obtained from all cases suggestive of oral cancer and a representative sample of precancers was also made by incision biopsy"
	Description of positive case definition by reference test as reported: oral cavity cancer

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Warnakulasuriya 1991 *(Continued)*

Training or calibration: quote: "A hospital dentist attached to a local hospital and who had received special training in oral cavity examinations was assigned to supervise the project"

Blinding of examiners: unclear. Re-examination of screened positive cases took place at the referral centre (all screened positives were referred); a sample of screened negative participants were randomly selected from PHC files by the project dentist visiting each field area

Prevalence of the target condition on the sample: 1797/3543 50.7% (sample for diagnostic test accuracy assessment); 3559/57,124 6.23% screened positive (oral lesions)

Flow and timing	Time interval and any interventions between index test(s) and reference standard: not stated
	Characteristics and proportion of individuals who did not receive the index test(s) and/or reference standard or excluded from analysis: 72,867 adults were eligible for the screening programme of whom 57,124 were screened. Re-examination of 2193 participants who arrived at the referral centre out of 3559 who screened positive. Field checking of 1350 screened negative cases was undertaken (random sample from electoral list). 21 excluded from analysis due to non-diagnosis from primary healthcare worker. 3543 participants received both the index test and the reference test
	Characteristics and proportion of individuals who received a reference standard other than examination and clinical evaluation by a specialist physician: none
Comparative	
Notes	Only 2193 screened positive participants arrived at the referral centre; 62% of detected cases in the field
	Prevalence in sample for diagnostic test accuracy assessment was very high 50.7%

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Conventional oral examination)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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82

Warnakulasuriya 1991 *(Continued)*

Was conflict of interest avoided?	Yes

Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?	

Could the conduct or interpretation of the index test have introduced bias?	Low risk

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern

DOMAIN 2: Index Test (Mouth self-examination)

DOMAIN 2: Index Test (Remote screening)

DOMAIN 2: Index Test (Fluorescence)

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk

Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Unclear

Did all patients receive the same reference standard?	Yes

Were all patients included in the analysis?	No

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

Warnakulasuriya 1991 *(Continued)*

Could the patient flow have introduced bias?	Unclear risk

HPV = human papillomavirus; OPMD = oral potentially malignant disorder; SD = standard deviation; SES = socioeconomic status.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bhalang 2008	Patients suspected of oral squamous cell carcinoma
Bowles 1973	Patients suspected of cancer
Chen 2007	Presenting with lesions
Csépe 2007	Prevalence data and risk factors
Farah 2019	Not a DTA study
Fernández Garrote 1995	Data on referral, incidence, and stage
Hapner 2011	Prevalence data
Huber 2004	Exploration of oral soft tissue under chemiluminescent illumination
Huff 2009	Inappropriate study design
Krishna Rao 2016	Not a DTA study
Leocata 2007	Prevalence data
Lim 2003	Prevalence data
McNamara 2012	No information provided on patients without lesions. Unable to construct a 2 x 2 table
Nagao 2000	Participation rates and prevalence data; no screen negatives verified
NCT04487938	Not a DTA study
Oh 2007	Outcomes measured on a lesion level. Unable to construct a cross-tabulation table
Pivovar 2017	Unable to construct a 2 x 2 table, no follow-up of screened negatives
Pivovar 2017a	Children and adolescents
Poh 2007	Prevalence data
Skandarajah 2017	Sampled consisted of clinically suspicious lesions only
Srivastava 1971	Chronic ulcerative lesions
Uthoff 2018	Sampled consisted of clinically suspicious lesions only
Vahidy 1972	Presenting with lesions

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

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84

Study	Reason for exclusion
Warnakulasuriya 2010	Prevalence data

DTA = diagnostic test accuracy.

Characteristics of studies awaiting classification [ordered by study ID]

CTRI/2018/02/012257

Patient Sampling	-
Patient characteristics and setting	General public chosen in a set of village in the community; 18 to 70 years old
Index tests	-
Target condition and reference standard(s)	-
Flow and timing	-
Comparative	-
Notes	www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=22747

Simonato 2019

Patient Sampling	Quote: "Recruitment of patients was carried out by mass communication (radio, newspaper, television and internet) and by alternative means (folders and banners). In total, 18 primary healthcare centers (PHCC) participated in the study. Patients were neither selected nor excluded based on social habits or medical/dental history"
Patient characteristics and setting	Patients screened as part of the Oral Cancer Prevention Campaigns 2014 and 2015, Brazil. No further details provided
Index tests	Conventional oral examination by a general dentist; fluorescence visualization (EVINCE)
Target condition and reference standard(s)	Suspicious oral lesion (OPMD, dysplasia, carcinoma) Biopsy was performed for high-risk cases (clinical suspicion of OPMD or OSCC, and in lesions detected by fluorescence visualization but not by conventional oral examination), and the presence of epithelial dysplasia or malignancy was assessed
Flow and timing	Quote: "Patients who had any oral mucosa lesion, either by COE or by FV, were referred to a specialist in oral diagnosis and oral pathology at a second level healthcare center. This professional conducted the final diagnosis process applicable for each case"
Comparative	-
Notes	Awaiting clarification from the authors of reference standard for the screened negative participants

COE = conventional oral examination; FV = fluorescence visualization; OPMD = oral potentially malignant disorders; OSCC = oral squamous cell carcinoma.

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

85

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2019/02/017623

Study name	Developing an efficient and cost effective method for screening of oral cancer in India
Target condition and reference standard(s)	-
Index and comparator tests	-
Starting date	1 March 2019
Contact information	Dr Kunal Oswal, koswal@tatatrusts.org
Notes	www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=29546

D A T A

Presented below are all the data for all of the tests entered into the review.

Table Tests.   Data tables by test

Test	No. of studies	No. of participants
1 Conventional oral examination	10	25568
2 Mouth self-examination	4	35059
3 Remote screening (mobile app)	3	3600
4 Fluorescence	1	0

Test 1.   Conventional oral examination

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chang 2011	282	172	3	13149	0.99 [0.97, 1.00]	0.99 [0.99, 0.99]
Downer 1995	12	2	5	290	0.71 [0.44, 0.90]	0.99 [0.98, 1.00]
Ikeda 1995	9	9	6	130	0.60 [0.32, 0.84]	0.94 [0.88, 0.97]
Jullien 1995	14	8	8	955	0.64 [0.41, 0.83]	0.99 [0.98, 1.00]
Jullien 1995a	26	12	6	998	0.81 [0.64, 0.93]	0.99 [0.98, 0.99]
Mathew 1997	200	31	12	1826	0.94 [0.90, 0.97]	0.98 [0.98, 0.99]
Mehta 1986	16	35	11	1859	0.59 [0.39, 0.78]	0.98 [0.97, 0.99]
Sweeny 2011	2	2	2	82	0.50 [0.07, 0.93]	0.98 [0.92, 1.00]
Warnakulasuriya 1990	384	276	21	1191	0.95 [0.92, 0.97]	0.81 [0.79, 0.83]
Warnakulasuriya 1991	1741	431	52	1298	0.97 [0.96, 0.98]	0.75 [0.73, 0.77]

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86

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Test 2.   Mouth self-examination

Mouth self-examination

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Elango 2011	39	15	180	34532	0.18 [0.13, 0.24]	1.00 [1.00, 1.00]		
Furquim 2014	12	9	16	7	0.43 [0.24, 0.63]	0.44 [0.20, 0.70]		
Ghani 2019	10	4	106	76	0.09 [0.04, 0.15]	0.95 [0.88, 0.99]		
Scott 2010	4	19	8	22	0.33 [0.10, 0.65]	0.54 [0.37, 0.69]		

Test 3.   Remote screening (mobile app)

Remote screening (mobile app)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Birur 2019	376	15	68	2955	0.85 [0.81, 0.88]	0.99 [0.99, 1.00]		
Gomes 2017	14	0	3	38	0.82 [0.57, 0.96]	1.00 [0.91, 1.00]		
Vinayagamoorthy 2019	15	32	1	83	0.94 [0.70, 1.00]	0.72 [0.63, 0.80]		

Test 4.   Fluorescence

Fluorescence

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Su 2010	0	0	0	0	Not estimable	Not estimable		

ADDITIONAL TABLES

Table 1.   Screening tests for potentially malignant disorders (PMDs) and oral cavity cancer

Test	Characteristics	Classification of response	Other information
Conventional oral examination (COE)	A standard visual and tactile examination of the oral mucosa under normal (incandescent) light	The presence of an oral mucosal abnormality is classified as a positive test result; the absence of any oral mucosal abnormalities is classified as a negative test result	Traditionally been used as an oral cancer screen, but its utility is debated (Lingen 2008) **Advantages:** quick and easy once trained, minimally invasive **Disadvantages:** oral mucosal abnormalities are not necessarily clinically or biologically malignant; only a small percentage of leukoplakias are progressive or become malignant; COE cannot distinguish between those that are or are not; some pre-cancerous lesions may exist within oral mucosa that appears clinically normal by COE alone (Lingen 2008)
Vital rinsing (e.g. toluidine blue, tolonium chloride)	Vital rinsing refers to the use of dyes such as toluidine blue or tolonium chloride to stain oral mucosa tissues for PMD or malignancy (Lestón 2010; Lingen 2008; Patton 2008). The procedure is as follows:	The result of the test is classified as positive if tissue is stained and negative if no tissue is stained, or equivocal if no definitive result can be obtained	**Advantages:** ability to define areas that could be malignant or abnormal but cannot be seen; assess the extent of the PMD for excision **Disadvantages:** benign inflammatory lesions subject to stain; failure of some cancerous lesions to stain; variation in test performance depending on how thorough the test procedures

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87

Table 1.   Screening tests for potentially malignant disorders (PMDs) and oral cavity cancer *(Continued)*

<table>
<tr>
<td></td>
<td>

pre-rinse with acetic acid
rinse with water
apply toluidine blue
post-rinse with acetic acid
rinse with water
observe mucosa to check for staining

</td>
<td></td>
<td>are followed; contraindicated in those who are known to be allergic to iodine</td>
</tr>
<tr>
<td>Light-based detection (e.g. ViziLite and ViziLite Plus, Microlux/DL, VELscope, Identafi 3000)</td>
<td>Light-based systems to identify pre-malignant and malignant lesions, and to highlight their presence through tissue autofluorescence or reflectance (Lestón 2010; Lingen 2008; Patton 2008) e.g. using ViziLite Plus or Microlux/DL. The procedure is as follows (Lingen 2008):

pre-rinse with acetic acid
use blue-light source to visually assess the oral cavity

ViziLite Plus also provides a tolonium chloride solution (TBlue) to aid in the marking of the lesion for biopsy once the light source is removed</td>
<td>The result of the test is classed as negative if the appearance of the epithelium is lightly bluish white and positive if the appearance of the epithelium is distinctly white (acetowhite)

For systems based on autofluorescence the result of the test is classed as negative if fluorescence is maintained and positive if fluorescence is lost</td>
<td>**Advantages:** simple to use; non-invasive; do not require consumable re-agents; provide real time results; can be performed by a wide range of operators after a short training period
Disadvantages: the necessity of a dark environment; high initial set up (for VELscope) or recurrent costs (for ViziLite in low-income countries); lack of permanent record unless photographed; inability to objectively measure visualisation results</td>
</tr>
</table>

Table 2.   Indicators for the assessment of methodological quality

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods of patient selection. Describe included patients (characteristics, prior testing, presentation, intended use of index test and setting)	Describe the index test and how it was conducted and interpreted. Describe the sequence of tests, any training or calibration of assessors (levels of agreement should be reported. Where this is measured by the kappa statistic[*], acceptable values range from 0.61 (moderate agreement) to 1.00 (almost perfect agreement) (Landis 1977)), any procedures taken to ensure blinding of examiners, post-hoc or a priori threshold specification, any conflict of interest or commercial funding

[*]This statistic is a measure of inter-rater agreement of observations measured at a categorical level | Describe the reference standard and how it was conducted and interpreted. Any measures taken to ensure assessors were blinded to the results of the index tests should be documented, along with the sequence of reference and index tests | Describe the characteristics and proportion of patients who did not receive the index test(s) and/or reference standard, who received a reference standard other than examination and clinical evaluation by a specialist physician, or who were excluded from the 2 x 2 table (refer to flow diagram). Describe the time interval and any interventions between index test(s) and reference standard. The length of time between the index test and reference standard should be short in most cases. If the period elapsed between initial screening and reference standard (exami- |

Table 2. Indicators for the assessment of methodological quality *(Continued)*

			nation and clinical evaluation) is greater than 6 weeks, then this was considered an unacceptable delay

| Signalling questions (Yes/No/Unclear) | Was a consecutive or random sample of patients enrolled? Classify as **Yes** if consecutive patients or a random sample of individuals were recruited Classify as **No** if non-consecutive patients or a non-random sample of individuals were recruited Classify as **Unclear** if patient selection was not clearly described | Were the index test results interpreted without knowledge of the results of the reference standard? Classify as **Yes** if interpreters of index test results clearly do not know results of reference standard Classify as **No** if interpreters of index test results clearly know results of reference standard Classify as **Unclear** if study did not provide any information on whether interpreters of index tests were blinded to reference standard | Is the reference standard likely to correctly classify the target condition? The reference standard is an examination and clinical evaluation by a physician with specialist knowledge which if stated as such should be acceptable. Ideally this should be undertaken independently by more than one specialist. Alternatively an acceptable reference standard is extended follow-up Classify as **Yes** if the test is examination and clinical evaluation by a physician with specialist knowledge and/or training, or a non-specialist with dedicated training to an acceptable standard Classify as **No** if the test result is examination and clinical evaluation by a non-specialist physician in the absence of dedicated training Classify as **Unclear** if the study does not report the experience and training of those carrying out the reference standard | Was there an appropriate time interval between the index test(s) and reference standard? Classify as **Yes** if the delay between the index test(s) and reference standard is considered acceptable for the majority of participants Classify as **No** if the delay between the index test(s) and reference standard is considered unacceptable for the majority of participants Classify as **Unclear** if the delay between the index test(s) and reference standard is not explicitly stated |
| - | Did the study avoid inappropriate exclusions? Classify as **Yes** if the sample consisted of apparently healthy individuals Classify as **No** if only individuals with existing PMDs were recruited | If a threshold was used, was it pre-specified? Classify as **Yes** if the threshold was pre-specified Classify as **No** if the threshold was not pre-specified Classify as **Unclear** if it is unclear whether the threshold was pre-specified | Were the reference standard results interpreted without knowledge of the results of the index test? Classify as **Yes** if personnel clearly do not know index test results when performing the examination and clinical evaluation or evaluating follow-up data Classify as **No** if personnel clearly know index test results when performing the examination and clinical | Did all patients receive the same reference standard? Classify as **Yes** if the same reference standard was used in all participants Classify as **No** if the same reference standard was not used in all participants Classify as **Unclear** if it is unclear whether different reference standards were used |

Table 2. Indicators for the assessment of methodological quality *(Continued)*

	Classify as **Unclear** if exclusions were not clearly described		evaluation or evaluating follow-up data

Classify as **Unclear** if study did not provide any information on whether personnel were blinded to the index test results | |
| - | - | Where multiple index tests were used, were the results of the second index test interpreted without knowledge of the results of the first index test?

Classify as **Yes** if index test results were interpreted without knowledge

Classify as **No** if the index test results were interpreted with knowledge

Classify as **Unclear** if it is unclear whether the results of the second index test were interpreted without knowledge of the results of the first index test | - | Were all patients included in the analysis?

Classify as **Yes** if all patients were included in the analysis

Classify as **No** if only some patients were included in the analysis

Classify as **Unclear** if it is unclear whether all patients were included in the analysis |
| - | - | Were any conflicts of interest stated?

Classify as **Yes** if the study declared no conflict of interest

Classify as **No** if the study declared a conflict of interest

Classify as **Unclear** if there was no information on conflict of interest | - | - |
| Risk of bias (High/Low/Unclear) | Could the selection of individuals have introduced bias? | Could the conduct or interpretation of the index test have introduced bias? | Could the reference standard, its conduct, or its interpretation have introduced bias? | Could the patient flow have introduced bias? |
| Concerns regarding applicability (High/Low/Unclear) | Are there concerns that the included individuals do not match the review question? | Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Are there concerns that the target condition as defined by the reference standard does not match the review question? | - |

Assessment of overall risk of bias and applicability

An overall judgement of risk of bias and applicability to the review (high, low, or unclear) was undertaken based on the judgements given to each domain. If the answers to all signalling questions within a domain were judged as yes indicating low risk of bias, then the domain was judged to be at low risk of bias. A no response to a signalling question was taken as an indication of the potential for risk of bias and the authors considered this risk within the context of the study before making a decision on whether the study was a high/low risk of bias for that domain

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

90

Table 2. Indicators for the assessment of methodological quality *(Continued)*

If any of the 4 domains was judged to be at high risk of bias then the study was judged to have a high risk of bias overall. If any of the 3 applicability domains was judged to be at high concern regarding applicability then the study was judged to be of high concern regarding applicability overall

APPENDICES

Appendix 1. Cochrane Oral Health's Trials Register search strategy

Cochrane Oral Health's Trials Register is available via the Cochrane Register of Studies. For information on how the register is compiled, see oralhealth.cochrane.org/trials.

From April 2019, searches of Cochrane Oral Health's Trials Register were conducted using the Cochrane Register of Studies software and the search strategy below:

1 ((oral* or mouth* or bucca* or "oral cavit*" or "oral mucosa" or "mouth mucosa" or lip or lips or tongue* or gingiva* or palat* or cheek* or intra-oral* or intraoral* or gum or gums or labial*):ti,ab) AND (INREGISTER)
2 ((tumour* or tumor* or cancer* or carcinoma* or carcinogen* or neoplas* or malignan* or metasta* or dysplas* or lesion* or ulcer* or precancer* or pre- cancer* or premalignan* or precursor* or "lichen planus" or leukoplakia or "submucous fibrosis" or "actinic keratosis" or candidiasis or erythroplakia or erythroplas* or erythroleukoplakia or hyperplas* or hyperkerato*):ti,ab) AND (INREGISTER)
3 ((screen* or cytodiagnosis or cytophotometry or "brush biops*" or "oral cdx" or oralcdx or "modified liquid based cytology" or "exfoliat* cytolog*" or "tolonium chloride" or "toludine b*" or "toluidine b*" or tblue or t-blue or "toludine dye*" or "toludine rins*" or "toludine stain*" or "toludine wash*" or "toluidine dye*" or "toluidine rins*" or "toluidine stain*" or "toluidine wash*" or luminescence or fluorescen* or "light emitting diode*"):ti,ab) AND (INREGISTER)
4 (((blood or saliva) AND (analys* or inspect* or test or examin*)):ti,ab) AND (INREGISTER)
5 (("blue spectrum" or LED or luminous or "visual* adjunct*" or vizilite or microlux* or orascoptic or velscope or lumenoscope* or autofluorescen* or chemilumiescen* or spectrophotometr* or "acetic acid" or acetowhite or "tumor marker*" or "tumour marker*" or "neoplas* marker*"):ti,ab) AND (INREGISTER)
6 ((diagnos* AND (exam* or histolog* or check* or screen*)):ti,ab) AND (INREGISTER)
7 (#1 and #2) AND (INREGISTER)
8 (#3 or #4 or #5 or #6) AND (INREGISTER)
9 (#7 and #8) AND (INREGISTER)

Previous searches were conducted using the Procite software and the search strategies below:

((oral* or mouth* or bucca* or "oral cavit*" or "oral mucosa" or "mouth mucosa" or lip or lips or tongue* or gingiva* or palat* or cheek* or intra-oral* or intraoral* or gum or gums or labial*) AND (tumour* or tumor* or cancer* or carcinoma* or carcinogen* or neoplas* or malignan* or metasta* or dysplas* or lesion* or ulcer* or precancer* or pre-cancer* or premalignan* or precursor* or "lichen planus" or leukoplakia or "submucous fibrosis" or "actinic keratosis" or candidiasis or erythroplakia or erythroplas* or erythroleukoplakia or hyperplas* or hyperkerato*) AND (cytodiagnosis or cytophotometry or "brush biops*" or "oral cdx" or oralcdx or "modified liquid based cytology" or "exfoliat* cytolog*" or "tolonium chloride" or "toludine b*" or "toluidine b*" or tblue or t-blue or "toludine dye*" or "toludine rins*" or "toludine stain*" or "toludine wash*" or "toluidine dye*" or "toluidine rins*" or "toluidine stain*" or "toluidine wash*" or luminescence or fluorescen* or "light emitting diode*"))

((oral* or mouth* or bucca* or "oral cavit*" or "oral mucosa" or "mouth mucosa" or lip or lips or tongue* or gingiva* or palat* or cheek* or intra-oral* or intraoral* or gum or gums or labial*) AND (tumour* or tumor* or cancer* or carcinoma* or carcinogen* or neoplas* or malignan* or metasta* or dysplas* or lesion* or ulcer* or precancer* or pre-cancer* or premalignan* or precursor* or "lichen planus" or leukoplakia or "submucous fibrosis" or "actinic keratosis" or candidiasis or erythroplakia or erythroplas* or erythroleukoplakia or hyperplas* or hyperkerato*) AND ("blue spectrum" or LED or luminous or "visual* adjunct*" or vizilite or microlux* or orascoptic or velscope or lumenoscope* or autofluorescen* or chemilumiescen* or spectrophotometr* or "acetic acid" or acetowhite or "tumor marker*" or "tumour marker*" or "neoplas* marker*"))

((oral* or mouth* or bucca* or "oral cavit*" or "oral mucosa" or "mouth mucosa" or lip or lips or tongue* or gingiva* or palat* or cheek* or intra-oral* or intraoral* or gum or gums or labial*) AND (tumour* or tumor* or cancer* or carcinoma* or carcinogen* or neoplas* or malignan* or metasta* or dysplas* or lesion* or ulcer* or precancer* or pre-cancer* or premalignan* or precursor* or "lichen planus" or leukoplakia or "submucous fibrosis" or "actinic keratosis" or candidiasis or erythroplakia or erythroplas* or erythroleukoplakia or hyperplas* or hyperkerato*) AND (diagno* and (blood or saliva) and (analys* or inspect* or test* or examin*)))

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review) **91**

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((oral* or mouth* or bucca* or "oral cavit*" or "oral mucosa" or "mouth mucosa" or lip or lips or tongue* or gingiva* or palat* or cheek* or intra-oral* or intraoral* or gum or gums or labial*) AND (tumour* or tumor* or cancer* or carcinoma* or carcinogen* or neoplas* or malignan* or metasta* or dysplas* or lesion* or ulcer* or precancer* or pre-cancer* or premalignan* or precursor* or "lichen planus" or leukoplakia or "submucous fibrosis" or "actinic keratosis" or candidiasis or erythroplakia or erythroplas* or erythroleukoplakia or hyperplas* or hyperkerato*) AND (diagnos* AND (exam* or histolog* or check or inspect* or screen*)))

Appendix 2. MEDLINE Ovid search strategy

1. exp Mouth/
2. Cheek/
3. or/1-2
4. exp Carcinoma, squamous cell/di
5. exp Precancerous conditions/di
6. (tumor$ or tumour$ or cancer$ or carcinoma$ or carcinogen$ or neoplas$ or malignan$ or metasta$ or dysplas$ or lesion$ or ulcer$).tw,ot.
7. (pre-cancer$ or precancer$ or premalignan$ or precursor$ or "lichen planus" or leukoplakia or "submucous fibrosis" or (actinic adj2 keratosis) or candidiasis or erythroplakia or erythroplas$ or erythroleukoplakia or hyperplas$ or hyperkeratos$).tw,ot.
8. or/4-7
9. 3 and 8
10. exp Mouth neoplasms/di
11. Lichen Planus, Oral/di
12. Oral submucous fibrosis/di
13. Oral candidiasis/di
14. ((oral$ or mouth$ or bucca$ or "oral cavit$" or (oral adj mucosa$) or (mouth adj mucosa$) or lip or lips or tongue$ or gingiv$ or palat$ or cheek$ or "intra oral$" or intraoral$ or gum or gums or labial$) adj3 (tumor$ or tumour$ or cancer$ or carcinoma$ or carcinogen$ or neoplas$ or malignan$ or metasta$ or dysplas$ or lesion$ or ulcer$ or pre-cancer$ or precancer$ or premalignan$ or precursor$ or "lichen planus" or leukoplakia or "submucous fibrosis" or (actinic adj2 keratosis) or candidiasis or erythroplakia or erythroplas$ or erythroleukoplakia or hyperplas$ or hyperkerato$)).tw,ot.
15. or/10-14
16. 9 or 15
17. Cytodiagnosis/
18. Cytological techniques/
19. Cytophotometry/
20. (brush adj3 biops$).tw,ot.
21. ("oral cdx" or oralcdx).tw,ot.
22. ("modified liquid based cytology" or (exfoliat$ adj3 cytolog$)).tw,ot.
23. (brush$ and (cytodiagnosis or cytopathology)).tw,ot.
24. Tolonium chloride/
25. Coloring agents/du
26. ("tolonium chloride" or "tolu?dine blue" or "tolu?dine b" or tblue or t-blue).tw,ot.
27. (tolu?dine adj6 (dye$ or rins$ or stain$ or wash$)).tw,ot.
28. exp Luminescence/
29. Fluorescence/
30. Spectrometry, fluorescence/
31. exp Luminescent Agents/
32. Light/
33. Tomography, Optical Coherence/
34. (visual$ adj5 ("light emitting diode" or "blue spectrum" or LED or luminous$)).tw,ot.
35. (visuali?ation adj3 adjunct$).tw,ot.
36. (vizilite or microlux$ or orascoptic or velscope).tw,ot.
37. lumenoscop$.tw,ot.
38. ((tumor$ or tumour$ or cancer$ or carcinoma$ or neoplas$ or carcinogen$ or malignan$ or metata$ or lesion$ or ulcer$) adj5 (fluorescen$ or autofluorescen$ or luminescen$ or chemiluminescen$)).tw,ot.
39. (tissue adj3 reflect$).tw,ot.
40. Spectrophotometry/
41. Acetic acid/
42. (acetic acid adj3 (wash$ or rins$)).tw,ot.
43. acetowhite.tw,ot.
44. Saliva/an, ch
45. Tumor Markers, Biological/an
46. (("tumo?r marker$" or "neoplas$ marker$") adj3 (blood or saliva)).tw,ot.
47. ((analy$ or screen$ or test$ or examin$) adj3 (blood or saliva)).tw,ot.

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92

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48. Diagnosis, Oral/
49. Mass screening/
51. screen$.mp.
50. Physical examination/
51. ((oral$ or mouth$) adj5 (exam$ or histolog$ or check$ or inspect$)).tw,ot.
52. (visual$ adj3 (exam$ or inspect$ or screen$)).tw,ot.
53. or/17-52
54. 16 and 53

Appendix 3. Embase Ovid search strategy

1. exp Mouth/
2. Cheek/
3. or/1-2
4. exp Squamous cell carcinoma/di
5. exp Precancer/di
6. (tumor$ or tumour$ or cancer$ or carcinoma$ or carcinogen$ or neoplas$ or malignan$ or metasta$ or dysplas$ or lesion$ or ulcer$).tw,ot.
7. (pre-cancer$ or precancer$ or premalignan$ or precursor$ or "lichen planus" or leukoplakia or "submucous fibrosis" or (actinic adj2 keratosis) or candidiasis or erythroplakia or erythroplas$ or erythroleukoplakia or hyperplas$ or hyperkeratos$).tw,ot.
8. or/4-7
9. 3 and 8
10. exp Mouth tumor/di
11. Lichen planus/di
12. Thrush/di
13. ((oral$ or mouth$ or bucca$ or "oral cavit$" or (oral adj mucosa$) or (mouth adj mucosa$) or lip or lips or tongue$ or gingiv$ or palat$ or cheek$ or "intra oral$" or intraoral$ or gum or gums or labial$) adj3 (tumor$ or tumour$ or cancer$ or carcinoma$ or carcinogen$ or neoplas$ or malignan$ or metasta$ or dysplas$ or lesion$ or ulcer$ or pre-cancer$ or precancer$ or premalignan$ or precursor$ or "lichen planus" or leukoplakia or "submucous fibrosis" or (actinic adj2 keratosis) or candidiasis or erythroplakia or erythroplas$ or erythroleukoplakia or hyperplas$ or hyperkerato$)).tw,ot.
14. or/10-13
15. 9 or 14
16. Cancer cytodiagnosis/
17. Cytophotometry/
18. (brush adj3 biops$).tw,ot.
19. ("oral cdx" or oralcdx).tw,ot.
20. ("modified liquid based cytology" or (exfoliat$ adj3 cytolog$)).tw,ot.
21. (brush$ and (cytodiagnosis or cytopathology)).tw,ot.
22. Tolonium chloride/
23. Coloring agent/
24. ("tolonium chloride" or "tolu?dine blue" or "tolu?dine b" or tblue or t-blue).tw,ot.
25. (tolu?dine adj6 (dye$ or rins$ or stain$ or wash$)).tw,ot.
26. exp Luminescence/
27. Fluorescence/
28. Spectrofluorometry/
29. exp Luminescent Agents/
30. Light/
31. Tomography, Optical Coherence/
32. (visual$ adj5 ("light emitting diode" or "blue spectrum" or LED or luminous$)).tw,ot.
33. (visuali?ation adj3 adjunct$).tw,ot.
34. (vizilite or microlux$ or orascoptic or velscope).tw,ot.
35. lumenoscop$.tw,ot.
36. ((tumor$ or tumour$ or cancer$ or carcinoma$ or neoplas$ or carcinogen$ or malignan$ or metata$ or lesion$ or ulcer$) adj5 (fluorescen$ or autofluorescen$ or luminescen$ or chemiluminescen$)).tw,ot.
37. (tissue adj3 reflect$).tw,ot.
38. Spectrophotometry/
39. Acetic acid/
40. (acetic acid adj3 (wash$ or rins$)).tw,ot.
41. acetowhite.tw,ot.
42. Tumor Marker/
43. (("tumo?r marker$" or "neoplas$ marker$") adj3 (blood or saliva)).tw,ot.
44 ((analy$ or screen$ or test$ or examin$) adj3 (blood or saliva)).tw,ot.

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

93

45. Mass screening/
46. screen$.mp.
47. Physical examination/
48. ((oral$ or mouth$) adj5 (diagnos$ or exam$ or histolog$ or check$ or inspect$)).tw,ot.
49. (visual$ adj3 (exam$ or inspect$ or screen$)).tw,ot.
50. or/16-49
51. 15 and 50

Appendix 4. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) search strategy

Condition: oral cancer

Other terms: diagnosis or diagnose

Condition: oral cancer

Other terms: screen or screening

Appendix 5. World Health Organization International Clinical Trials Registry Platform search strategy

oral cancer AND diagnosis OR oral cancer AND diagnose OR oral cancer AND diagnostic

oral cancer AND screen OR oral cancer AND screening

Appendix 6. Search strategies used in the previous version of this review (April 2013)

Cochrane Diagnostic Test Accuracy Register search strategy

((oral* or mouth* or bucca* or "oral cavit*" or "oral mucosa" or "mouth mucosa" or lip or lips or tongue* or gingiva* or palat* or cheek* or intra-oral* or intraoral* or gum or gums or labial*) AND (tumour* or tumor* or cancer* or carcinoma* or carcinogen* or neoplas* or malignan* or metasta* or dysplas* or lesion* or ulcer* or precancer* or pre-cancer* or premalignan* or precursor* or "lichen planus" or leukoplakia or "submucous fibrosis" or "actinic keratosis" or candidiasis or erythroplakia or erythroplas* or erythroleukoplakia or hyperplas* or hyperkerato*)

MEDION search strategy

Searched using the code C (malignancies), and screened the results for oral cancer terms.

WHAT'S NEW

Date	Event	Description
16 December 2021	Amended	Additional external source of support added

HISTORY

Protocol first published: Issue 11, 2012
Review first published: Issue 11, 2013

Date	Event	Description
2 August 2021	New citation required but conclusions have not changed	Review update including 5 new studies bringing the total to 18 included studies. Conclusions remain unchanged
20 October 2020	New search has been performed	Searches updated to 20 October 2020

Clinical assessment for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)

94

CONTRIBUTIONS OF AUTHORS

Tanya Walsh, Saman Warnakulasuriya, Alexander R Kerr, Mark W Lingen, Graham R Ogden, Richard Macey, and Anne-Marie Glenny designed and wrote the review.

DECLARATIONS OF INTEREST

Tanya Walsh: none known. I am Statistical Editor for Cochrane Oral Health.
Saman Warnakulasuriya: none known.
Mark W Lingen: none known.
Alexander R Kerr: none known.
Graham R Ogden: none known.
Anne-Marie Glenny: none known. I am joint Co-ordinating Editor of Cochrane Oral Health.
Richard Macey: none known.

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External sources

- National Institute for Health Research (NIHR), UK

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- Cochrane Oral Health Global Alliance, Other

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- Centers for Disease Control and Prevention (CDC), USA

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have removed the index test training and calibration signalling question from the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) assessment of methodological quality. The diversity of index tests meant we were unable to uniformly apply this criterion to all the studies. For all index tests, we would expect that any training given would be reported and any diagnostic criteria followed in the index test assessment would have been piloted/validated. All study information pertaining to how the index test was carried out and interpreted is detailed in the Characteristics of included studies tables.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; *Carcinoma, Squamous Cell [diagnosis]; *Early Detection of Cancer; Mouth; Sensitivity and Specificity; United States

MeSH check words

Humans