Screening programmes for the early detection and prevention of oral cancer

Brocklehurst, Paul; Kujan, Omar; Glenny, Anne-Marie; Oliver, Richard; Sloan, Philip; Ogden, Graham

Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD004150.pub3

Publication date:
2010

Document Version
Publisher's PDF, also known as Version of record

Screening programmes for the early detection and prevention of oral cancer (Review)

Brocklehurst P, Kujan O, Glenny AM, Oliver R, Sloan P, Ogden G, Shepherd S

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 11

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Screening programmes for the early detection and prevention of oral cancer

Paul Brocklehurst[1], Omar Kujan[2], Anne-Marie Glenny[3], Richard Oliver[4], Philip Sloan[5], Graham Ogden[6], Simon Shepherd[6]

[1]Department of Dental Public Health & Primary Care, School of Dentistry, Manchester, UK. [2]Oral Pathology and Medicine, School of Dentistry, AlBaath University, Hama, Syrian Arab Republic. [3]Cochrane Oral Health Group, School of Dentistry, The University of Manchester, Manchester, UK. [4]School of Dentistry, The University of Manchester, Manchester, UK. [5]Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, UK. [6]Department of Oral Surgery & Medicine, School of Dentistry, University of Dundee, Dundee, UK

Contact address: Paul Brocklehurst, Department of Dental Public Health & Primary Care, School of Dentistry, The University of Manchester, Higher Cambridge Street, Manchester, M15 6FH, UK. paul.brocklehurst@hotmail.co.uk. paul.brocklehurst@postgrad.manchester.ac.uk.

Editorial group: Cochrane Oral Health Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2010.
Review content assessed as up-to-date: 5 October 2010.

Citation: Brocklehurst P, Kujan O, Glenny AM, Oliver R, Sloan P, Ogden G, Shepherd S. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 11. Art. No.: CD004150. DOI: 10.1002/14651858.CD004150.pub3.

ABSTRACT

Background

Oral cancer is an important global healthcare problem, its incidence is increasing and late-stage presentation is common. Screening programmes have been introduced for a number of major cancers and have proved effective in their early detection. Given the high morbidity and mortality rates associated with oral cancer, there is a need to determine the effectiveness of a screening programme for this disease, either as a targeted, opportunistic or population based measure. Evidence exists from modelled data that a visual oral examination of high-risk individuals may be a cost-effective screening strategy and the development and use of adjunctive aids and biomarkers is becoming increasingly common.

Objectives

To assess the effectiveness of current screening methods in decreasing oral cancer mortality.

Search methods

The following electronic databases were searched: the Cochrane Oral Health Group Trials Register (to 20 May 2010), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 2), MEDLINE via OVID (1950 to 20 May 2010), EMBASE via OVID (1980 to 20 May 2010) and CANCERLIT via PubMed (1950 to 20 May 2010). There were no restrictions regarding language or date of publication.

Selection criteria

Randomised controlled trials (RCTs) of screening for oral cancer or potentially malignant disorders using visual examination, toluidine blue, fluorescence imaging or brush biopsy.

Data collection and analysis

The original review identified 1389 citations and this update identified an additional 330 studies, highlighting 1719 studies for consideration. Only one study met the inclusion criteria and validity assessment, data extraction and statistics evaluation were undertaken by six independent review authors.

Main results

One 9-year RCT has been included (n = 13 clusters: 191,873 participants). There was no statistically significant difference in the age-standardised oral cancer mortality rates for the screened group (16.4/100,000 person-years) and the control group (20.7/100,000 person-years). A 43% reduction in mortality was reported between the intervention cohort (29.9/100,000 person-years) and the control arm (45.4/100,000) for high-risk individuals who used tobacco or alcohol or both, which was statistically significant. However, this study had a number of methodological weaknesses and the associated risk of bias was high.

Authors' conclusions

Although there is evidence that a visual examination as part of a population based screening programme reduced the mortality rate of oral cancer in high-risk individuals, whilst producing a stage shift and improvement in survival rates across the population as a whole, the evidence is limited to one study and is associated with a high risk of bias. This was compounded by the fact that the effect of cluster randomisation was not accounted for in the analysis. Furthermore, no robust evidence was identified to support the use of other adjunctive technologies like toluidine blue, brush biopsy or fluorescence imaging within a primary care environment. Further randomised controlled trials are recommended to assess the efficacy, effectiveness and cost-effectiveness of a visual examination as part of a population based screening programme.

PLAIN LANGUAGE SUMMARY

Screening programmes for the early detection and prevention of oral cancer

There is a need to understand whether screening programmes could detect oral cancer earlier and so reduce the number of deaths from this disease. Cancer of the mouth is becoming increasingly common and has a low survival rate, as many patients present with advanced disease. Screening the general population for oral cancer might make it possible to detect cases earlier. The most common method is visual inspection by a clinician, but other techniques include the use of a special blue "dye", the use of imaging techniques and measuring biochemical changes to normal cells. The review found that overall there is not enough evidence to decide whether screening by visual inspection reduces the death rate for oral cancer, and there is no evidence for other screening methods. However, there is some evidence that it might help reduce death rates in patients who use tobacco and alcohol, although the only included study may be effected by bias.

BACKGROUND

Oral cancer is the 6th most common cancer globally and represents a group of conditions with a range of sites and a varied aetiology. Its annual estimated incidence is approximately 275,000, but unlike many other cancers, its incidence is increasing (Warnakulasuriya 2009). There is a wide geographic variation in the incidence of the disease with two-thirds of the burden born by developing countries such as South and South-East Asia, Latin America and Eastern Europe. However, the incidence continues to rise in the West (IARC 2010) and the age standardised incidence of oral cancer in Western Europe has steadily increased over the past two decades (Boyle 2005). Within the EU countries the highest male incidence rates are found in France and Hungary, whilst the lowest rates are found in Greece and Cyprus (IARC 2010). India, Sri Lanka and Pakistan has the highest level of the disease, making it the most common cancer for men in these countries and accounts up to 30% of all new cases of cancer compared to 3% in the United Kingdom (UK) and 6% in France (Cancer Research UK). The age adjusted incidence rate from these countries cancer registries range from 3.4 to 13.8 per 100,000 in these countries (Ministry of Health 2005; Warnakulasuriya 2009). The incidence of oral cancer for men in Brazil is second only to France and India with an estimated crude

rate of 11 per 100,000. In the UK, the incidence of oral cancer is increasing (Conway 2006; Doobaree 2009) and 4926 cases of oral cancer were diagnosed in 2005 (Cancer Research UK). This represents a doubling of the number of cases seen in 1989 and represents a year on year increase of approximately 2.7% per year (Warnakulasuriya 2009). The incidence of oral cancer is strongly related to social and economic deprivation (Scully 2009; Conway 2010a), with the highest rates occurring in the most disadvantaged sections of the population. Across Europe, inequalities tend to be observed among men, particularly in the UK and Eastern Europe (Conway 2010b).

Important risk factors in the development of the disease are tobacco, betel quid, alcohol, age, gender and sunlight, although a role for candida and the human papilloma virus has also been documented (Scully 2009). Increased consumption of alcohol has been implicated in the increasing incidence of the disease in the UK (Hindle 2000) at a time when tobacco use is falling (Ogden 2005), despite the precise mechanism remaining unclear (Ogden 1998). When tobacco and alcohol use are taken together, the carcinogenic action of tobacco and alcohol is synergistic, with heavy drinkers and smokers having 38 times the risk of developing oral cancer compared to abstainers (Blot 1988). In addition, it is considered to be of particular importance in the development of malignancy in younger cohorts (Petti 2005), given the volume of spirits consumed in binge drinking. Historically the risk of developing oral cancer increased with age, however, the age band with the highest incidence (26.8%) in the United States of America from 2003 to 2007 was between 55 and 64 years of age (SEER 2010). In contrast, many patients from high-incidence countries are below the age of 40 years of age (Warnakulasuriya 2009) and the incidence of oral cancer diagnosed in men in their 40s and 50s has doubled in the UK (Cancer Research UK; Doobaree 2009) and in many countries in the European Union.

Of equal concern to the increasing incidence, is the relative stability of the age standardised mortality rates. This is unlike the falling rates for cancer of the breast and colon (Cancer Research UK), despite advances in surgical and management techniques. The 5-year survival rates for most countries is approximately 50% (Warnakulasuriya 2009). These have been estimated at 3 to 4 per 100,000 men and 1.5 to 2.0 per 100,000 for women respectively (Warnakulasuriya 2009). Mortality rates from oral cancer have also increased in certain European countries (La Vecchia 2004). Stage at diagnosis significantly affects 5-year survival, with survival rates approaching 80% for stage I disease dropping significantly for stage IV disease (Rusthoven 2010). This is further compounded by the inaccessibility of the tumour. In addition, the morbidity associated with surgery is high, the rate of second primary tumours in these patients is greater than any other type of cancer (3 to 7% per annum) (Day 1992) and is more often the cause of death (Lippman 1989). The most important determinant factor behind these dire statistics is diagnostic delay (Onizawa 2003; McLeod 2005), as over 60% of patients present with stage III and IV disease (Lingen 2008), meaning that their management is complex and multidisciplinary.

Prevention strategies are important to meet the World Health Organisation's (WHO) resolution to incorporate oral cancer into national cancer control programs (Petersen 2009). Although it is important to continue to clarify the public health message and promote primary prevention, determining the feasibility of a national screening programme is an important step in the prevention of the disease. The National Screening Committe define screening as "a process of identifying apparently healthy people who may be at increased risk of a disease or condition" (NSC 2010). Programmes for major cancers, such as breast, cervical and now bowel cancer have effectively improved the mortality rates and helped to decrease the incidence of these cancers (Gøtzsche 2006; Hewitson 2007). Screening can be undertaken across the whole population, opportunistically, when individuals are attending for some other purpose, or selectively, where high-risk groups are targeted.

Screening is predicated on the idea that malignancy is preceded by clinically evident lesions, which if identified early and removed, can either prevent their malignant transformation or reduce their staging. The majority of oral carcinomas are preceded by visible lesions, known as potentially malignant disorders (PMDs) (Warnakulasuriya 2007; van der Waal 2009) that exhibit oral epithelial dysplasia associated with a number of different disease processes (Scully 2009). Table 1 highlights the different types of potentially malignant disorders (PMDs) that were considered by the WHO's Working Party on Oral Cancer and Precancer to be important (Warnakulasuriya 2007). The most common form of PMD is leukoplakia (Napier 2008), which has an estimated global prevalence of 2.6% (95% confidence interval (CI): 1.72 to 2.74%) (Petti 2003). However, the extent and rate of progression of dysplasia in leukoplakia is not uniform and can vary from site to site and within the same lesion (Napier 2008).

The overall malignant transformation rate for oral leukoplakia is approximately 5% (Scully 2009). These variations in the disease process and the extent of dysplastic change in PMDs mean that the natural history of oral cancer is not fully understood, although there remains a consensus in the literature that the majority of cancers are preceded by a detectable preclinical phase (Napier 2008).

Although there has been no randomised controlled trial (RCT) in any Western or low-prevalence population (Brocklehurst 2010a), Speight et al used simulation modelling and suggested that an oral examination of high-risk individuals may be a cost-effective screening strategy (Speight 2006). A systematic review of a visual examination demonstrated an overall sensitivity of 0.85 and specificity of 0.97 (Downer 2004) and the authors concluded that visual screening compares well with cervical screening and mammography, which had sensitivities and specificities in the order of

0.80 and 0.98, respectively. In addition, a visual screen is not surgically invasive, is painless and has been found to be acceptable. Other adjunctive and diagnostic aids can be grouped into visual staining (toluidine blue), oral cytology using brush biopsy and a number of light-based techniques (e.g. ViziLite [Zila Pharmaceuticals, AZ, USA] and VELscope [LED Dental Inc, BC, Canada]) (Brocklehurst 2010a).

The RCT provides the strongest level of evidence on which to base clinical decisions (Clarkson 2003) and so represent a level of rigor that is appropriate for assessing the effectiveness of any test or programme. As with other cancers, screening for oral cancer and PMD has potential advantages and disadvantages (Speight 1992). Screening and treatment may offer the opportunity to reduce the incidence of invasive lesions and also could help in decreasing the mortality rates associated with oral cancer. In addition, Speight et al demonstrated that targeting high risk groups could result in a pronounced increase in the Quality Adjusted Life Years saved and any associated stage shifts could produce significant cost savings (Speight 2006). However, screening also has the potential to generate false positives and false negatives (Wilson 1968). In a systematic review of the literature, Kujan et al concluded that there was insufficient evidence to support or refute the use of screening for oral cancer in the general population (Kujan 2005). As a result, the purpose of this update is to determine whether the evidence base has changed. An up-to-date systematic review of the research evidence was therefore undertaken.

OBJECTIVES

To assess the effectiveness of screening programmes in detecting oral cancer and potentially malignant disorders.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of screening programmes for the early detection of oral cancer or potentially malignant disorder (PMD).

Types of participants

Participants involved in mass, high-risk and opportunistic screening programmes were included.

Types of interventions

Any screening programme for the detection of oral cancer or PMD was considered, but they had to be compared to a control group which do not receive a screen. These included:

- visual screening;
- visual staining using toluidine blue;
- oral cytology using brush biopsies;
- fluorescence imaging and light based techniques.

As the review was not determining the diagnostic accuracy of the interventions per se, the exact definition of a positive case in each of these categories was not defined. To do so may have limited the number of studies reviewed. As a result, each study was assessed on an individual study by study basis.

Types of outcome measures

The primary outcome considered in this review will be oral cancer specific mortality.
Other outcomes included were:

- incidence of oral cancer or PMD;
- mortality at 3 or more years;
- stage at diagnosis;
- harms of screening (including adverse outcomes from false positive or false negative results on initial screen);
- cost data (where reported).

Search methods for identification of studies

Electronic searches

For the identification of studies included or considered for this review, detailed search strategies were developed for each database searched. These were based on the search strategy developed for MEDLINE (OVID) but revised appropriately for each database (see Appendix 1). The search strategies for MEDLINE and CANCERLIT used a combination of controlled vocabulary and free text terms. They were linked with the Cochrane Highly Sensitive Search Strategies (CHSSS) for identifying RCTs in MEDLINE: sensitivity maximising versions (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in boxes 6.4a and 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 (updated September 2009) (Higgins 2009). The search of EMBASE was linked to the Cochrane Oral Health Group filter for identifying RCTs.

Databases searched

The following electronic databases were searched.

- The Cochrane Oral Health Group's Trials Register (to 20 May 2010) (see Appendix 2).

- CENTRAL (*The Cochrane Library*, 2010, Issue 2) (see Appendix 3).
- MEDLINE via OVID (1950 to 20 May 2010) (see Appendix 1).
- EMBASE via OVID (1980 to 20 May 2010) (see Appendix 4).
- CANCERLIT via PubMed (1950 to 20 May 2010) (see Appendix 5).

Searching other resources

Two high yield journals, Community Dental Health and Community Dentistry and Oral Epidemiology were handsearched. In addition, the following journals were handsearched from the date of the last review (2006 to 2010).

- Oral Oncology
- British Dental Journal
- Cancer
- Cancer Research

Language

There were no non-English papers that required translation. Had such trials been identified they would have been translated through The Cochrane Collaboration.

Unpublished trials

The bibliographies of included papers and relevant review articles were checked for studies not identified by the search strategies above. The authors of identified and included studies were also contacted to identify unpublished or ongoing trials.

Data collection and analysis

Selection of studies

The titles and abstracts obtained from initial electronic searches were scanned for relevance independently by two of the review authors (Paul Brocklehurst (PRB), Anne-Marie Glenny (AMG)). Reports from the studies that fulfilled the inclusion criteria were obtained. When there was insufficient data in the study title to determine whether a study fulfilled the inclusion criteria, the full report was obtained and assessed independently by the same review authors. Disagreement was resolved by discussion.

Data extraction and management

All studies meeting the inclusion criteria underwent data extraction and an assessment of risk of bias was made. Studies rejected at this and subsequent stages were recorded in the table of excluded studies. Data from each included study was extracted independently using the tool developed and reported in Kujan 2005. Differences were again resolved by discussion. If a single publication reported two or more separate studies, then each study was extracted separately. If the findings of a single study were spread across two or more publications, then the publications were extracted as one. For each study with more than one control or comparison group for the intervention, the results were extracted for each intervention arm. For each trial the following data were recorded.

- Year of publication, country of origin and source of study funding.
- Details of the participants including demographic characteristics and criteria for inclusion.
- Details on the type of intervention and comparisons.
- Details on the study design.
- Details on the outcomes reported, including method of assessment.

Assessment of risk of bias in included studies

For the studies included in this review assessment of risk of bias was conducted by four review authors (PRB, AMG, Simon Shepherd (SS) and Graham Ogden (GO)) using the Cochrane risk of bias assessment tool. The domains that were assessed for each included study were: sequence generation, allocation concealment, blinding, completeness of outcome data, risk of selective outcome reporting and risk of other potential sources of bias.
A description of the domains was to be tabulated for each included trial, along with a judgement of low, high or unclear risk of bias. For example, criteria for risk of bias judgements regarding allocation concealment are given below as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.2 (Higgins 2009).

- Low risk of bias - adequate concealment of the allocation (e.g. sequentially numbered, sealed, opaque envelopes or centralised or pharmacy-controlled randomisation).
- Unclear risk of bias - unclear about whether the allocation was adequately concealed (e.g. where the method of concealment is not described or not described in sufficient detail to allow a definite judgement).
- High risk of bias - inadequate allocation concealment (e.g. open random number lists or quasi-randomisation such as alternate days, date of birth, or case record number).

A summary assessment of the risk of bias for the primary outcome (across domains) across studies was undertaken (Higgins 2009). Within a study, a summary assessment of low risk of bias was given when there was a low risk of bias for all key domains, unclear risk of bias when there was an unclear risk of bias for one or more key domains, and high risk of bias when there is was a high risk of bias for one or more key domains. Across studies, a summary

assessment was rated as low risk of bias when most information was from studies at low risk of bias, unclear risk of bias when most information was from studies at low or unclear risk of bias, and high risk of bias when the proportion of information was from studies at high risk of bias sufficient to affect the interpretation of the results.

Measures of treatment effect

For dichotomous outcomes, the estimate of effect of an intervention was expressed as risk ratios together with 95% confidence intervals (CIs). For continuous outcomes, mean differences and 95% CIs were used to summarise the data for each group.

Unit of analysis issues

Where cluster randomised trials were included, analysis was to be undertaken, whenever feasible, at the same level as randomisation, or at the individual level accounting for the clustering.

Assessment of heterogeneity

The significance of any discrepancies in the estimates of the treatment effects from the different trials was to be assessed by means of Cochran's test for heterogeneity and heterogeneity would have been considered significant if $P < 0.1$ (Higgins 2009). The I^2 statistic, which describes the percentage total variation across studies that is due to heterogeneity rather than chance, was used to quantify heterogeneity with I^2 over 50% being considered substantial heterogeneity (Higgins 2009).

Assessment of reporting biases

If there had been sufficient numbers of trials (more than 10) in any meta analysis, publication bias would have been assessed according to the recommendations on testing for funnel plot asymmetry as described in the Cochrane Handbook (Higgins 2009).

Data synthesis

Where appropriate, meta-analysis was applied to the outcomes (minimum of three RCTs). Risk ratios were to be combined for dichotomous data, and mean differences for continuous data using a random-effects model, if data had allowed.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The original search of MEDLINE via OVID (1966 to September 2002) that the first Cochrane review undertook revealed 1389 citations and the search conducted for the update revealed 1719 studies (to June 2010). However, initial screening of these titles only revealed 32 potentially relevant articles which were selected for review. Following the screening of these abstracts only one study met the inclusion criteria, which had been identified earlier by the original review (Sankaranarayanan 2000).

Searches of EMBASE, CANCERLIT, The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010), the Cochrane Oral Health Group's Trials Register and bibliographies of review articles did not reveal any further relevant studies that had not been identified by the MEDLINE search. Similarly, handsearching for oral cancer screening in the identified journals did not identify any further studies. The principal investigator of the included trial (Dr Sankaranarayanan) was also contacted and no other trials were identified that had mortality due to oral malignancy as its outcome measure.

The included study was designed to have an 80% power at the 5% significance level to detect a 35% reduction in the cumulative mortality rate of oral cancer in 12 years of enrolment between the intervention and the control groups. The study commenced in October 1995 and three rounds of screening at 3-year intervals were planned for the study. The first round was completed in May 1998 and the second was completed in June 2002. The final (third) round was completed in October 2004.

In this project (Trivandrum Oral Cancer Screening Study) all participants (n = 191,873) were apparently healthy residents aged 35 years or older living in 13 clusters in rural areas of Trivandrum city, Kerala, India. Those who were bedridden, suffering from open tuberculosis or other debilitating diseases and those diagnosed with oral cancer prior to entry into the study were excluded. In each cluster the number of eligible participants varied from 8000 to 18,500. These clusters were allocated into an intervention arm (n = 7) and a control arm (n = 6) by blocked randomisation.

The intervention group in the third round of screening consisted of 96,517 persons, 41,540 of whom were male, and 54,977 female (Table 2). The participation rate for screening at least once was 91%, males (86%) and females (94%). Of the screened subjects 5.9% (n = 5145) had referable lesion. 63% (3218) of the screen positive subjects complied with referral (Table 3).

The control group consisted of 95,356 persons. Health workers were initially trained and provided with two simple published manuals on oral visual examination with colour photographs and descriptions of various oral lesions. Eligible participants were interviewed and information relating to demographic, social and personal habits including the use of paan, tobacco, alcohol and dietary supplements was recorded. Tobacco and alcohol cessation advice was provided as appropriate.

Oral visual inspections were performed in daylight with the help

of a flashlight. All the intraoral sites were carefully examined and palpated and the neck was also palpated to detect enlarged lymph nodes. The findings were recorded as normal, non-referable lesions and referable lesions.

Participants who had a positive screen were then referred to be examined by dentists or physicians for confirmation of the positive screen, although it is unclear whether these clinicians were also trained in the recognition of oral cancer or potentially malignant disorders. Oral biopsies were performed in those with clinically confirmed homogeneous leukoplakias, non-homogeneous leukoplakias, oral submucous fibrosis and oral cancers. Surgical excision was carried out for leukoplakia wherever possible. All potentially malignant disorders were regularly reviewed concerning the possibility of surgical excision and to assess any regression or progression. Oral cancer mortality was reported as the main outcome measure.

The control group clusters were also visited by a "control health worker" for baseline recruitment, who recorded the same sociodemographic information and measured height, weight, blood pressure and respiratory peak flow measurements. However, the control health workers were not trained in how to undertake a visual oral inspection.

Risk of bias in included studies

Allocation

Sequence generation

The randomisation procedure was conducted using restricted block randomisation. The exact detail of this process was not provided, although the clusters were grouped into blocks of four and allocated at random to screening or non-screening groups from the six possible combinations available to each block of four. Clustering was not accounted for in the analysis in accordance with the guidance from Cochrane (Section 16.3.3, Higgins 2009).

Allocation concealment

No detail of allocation concealment was provided, although the principal investigator confirmed that this was not undertaken.

Blinding

Blinding of outcome assessment

No blinding was described in the study, but the review authors judge that the outcome and its measurement are unlikely to be influenced by this. As a result, the risk of bias based on the lack of blinding is considered to be low.

Incomplete outcome data

Withdrawals and drop-outs were not described clearly in this study and this missing data will have increased the risk of bias. Of those who were referred with positive-screen lesions, 63% of individuals complied with referral, males (1604: 60%) and females (1614: 65%) (Table 3). However, the analysis was carried out on an intention-to-treat (ITT) basis.

Selective reporting

The study protocol was not made available, but it appears that the published reports include all the expected and pre-specified outcome measures.

Other potential sources of bias

Positive cases were referred to General Practitioners and General Dental Practitioners to make a diagnosis, but it is unclear whether standardised criteria were used by these clinicians or whether they had received any formal training or standardisation in the identification of positive lesions.

It is stated that subjects with confirmed oral cancer and potentially malignant disorders (PMDs) were biopsied and those with confirmed oral cancer were referred. However, although not detailed in the first cycle, only 26.4% of subjects with a potentially malignant disorder (PMD) had a biopsy in the second cycle and only 26% in the third cycle. It is not clear whether all suspected oral cancer cases did receive a biopsy, but given the definition of "interval cases" in the third paper, it would appear not. In addition, it is stated in the third paper that the reference investigation for final diagnosis was clinical examination by doctors or histology or both. As it is not possible to diagnose early malignancy by visual appearance alone, this may have led to substantial underreporting of oral cancer. The lack of a histological diagnosis for many of the PMDs also makes it difficult to accurately assess the correct diagnosis and true prevalence of these disorders.

Prevalence of PMD and mortality data is only provided in detail for the first two cycles only. The third paper presents the results over the three cycles from 1996 to 2004 and so does not provide individual detail about the results of the third cycle. It is not clear why this was the case.

In the included study the health workers reported on 24 baseline variables including multiple age strata, occupation, education, income, household belongings such as television and personal habits of chewing, smoking, and drinking. The intervention and control cohorts appear to have been well matched for the stratified variable age at the baseline. However, the distribution of income, education, use of tobacco and alcohol varied across the intervention and control groups, with the former demonstrating higher

levels of consumption Table 2. Men smoked and drank alcohol more than females in both groups, but the prevalence of chewing tobacco was not as marked across gender differences. Although, such differences in baseline variables might be expected to occur in cluster randomised studies, the differences between the numbers who used tobacco and alcohol need to be borne in mind when interpreting the results.

Effects of interventions

The included study reported data on oral cancer incidence, disease specific-mortality, and stage at diagnosis after 9-years follow-up. Data on quality of life and all cause mortality was not reported.

Oral cancer incidence

Among the 87,829 participants screened in the intervention group, 5145 (5.9%) were found to have referable lesions. Of these, 3218 (63%) complied with the referral criteria for confirmatory examination by dentists or medical officers in special clinics. Healthy mucosa or benign lesions were found in 835 (26%). The number of PMDs was 2252 (70%) (lichen planus (n = 51), homogenous leukoplakia (n = 795) and submucous fibrosis (n = 509)) and oral cancer 131/3218 (4%). The detection rate of PMD and oral cancer in the first, second and third rounds of screening were 28.0, 11.6 and 11.3 per 1000 screened subjects respectively. Examination of the Trivandrum cancer registry recorded 363 patients with oral cancer. Two hundred and five patients were in the intervention group and 158 in the control group. The crude incident rate of oral cancer was 43.7 per 100,000 person-years in the intervention arm and 37.6 per 100,000 person-years in the control group (Table 4).

Test performance

Across the nine years of the programme, the reported sensitivity of the visual examination in detecting oral cancer was 64% (131/205) (Table 4). No information on the specificity or the positive predictive value of the programme was recorded. However, the latter was calculated based on the published data from the study as the number of screen-selected oral cancers as a proportion of total screen positive subjects (confirmed by biopsy), which was 74% for oral cancer.

Oral cancer mortality

There was no statistically significant difference in the mortality rate for oral cancer between the intervention group and control. Over the 9-year period, 77 of 205 subjects with oral cancer in the intervention group and 87 of the 158 cases in the control group died, which represents a mortality rate of 16.4 and 20.7 per 100,000 person years respectively (Table 4).

However, for individuals that used tobacco, alcohol or both, there was a significant reduction of 43% in mortality rates for men from 42.9 per 100,000 person years in the control group to 24.6 per 100,000 person years in the intervention group (Table 5). For women, there was a 22% reduction, from 50.7 to 39.4 per 100,000 person years, but this did not reach significance (Table 5).

Survival

The authors also examined survival rates by comparing the proportion of patients alive 5 years after diagnosis across the two groups. A significantly higher 5-year survival rate was reported in the intervention group (50%) than in the control group (34%) (P = 0.009).

Stage shift at diagnosis

There was a statistically significant stage shift in the cancers that were diagnosed in the intervention group, based on the criteria of the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) clinical TNM stage was available. In the intervention group, 42% of the cases were in stage I or II, as opposed to 24% of cases in the control group (P = 0.004) (Table 6). On the other hand, 66% of cases in the control group were in the stage III or IV compared to 41% of cases in the intervention group (Table 6).

Cost effectiveness

The costs associated with the study were reported in a later study (Subramanian 2009) (Table 7). The benefit produced by a screen was 269.31 life years saved per 100,000 for all the individuals and 1437.64 for those at high risk. The incremental cost per life-year saved was US$835 for all individuals, which reduced to US$156 for high-risk individuals. This fulfils the target set by the World Health Organisation (WHO) Commission on Macroeconomics and Health (WHO 2001), who define an intervention as being cost effective when its cost-effectiveness ratio is less than a country's gross domestic product per capita. Subramanian argues that this provides good evidence that opportunistic screening of high-risk groups may be feasible and cost effective (Subramanian 2009), but there has been no randomised controlled trial in any Western or low-prevalence population and the risk of bias of the included study is high.

DISCUSSION

The incidence of oral cancer is increasing in both developed and developing countries (Warnakulasuriya 2009). Delays in diagnosis and management persist (Onizawa 2003; McLeod 2005) and are associated with a dramatic deterioration in 5-year survival rates.

Effective primary and secondary prevention strategies are critical in delivering the World Health Organisation's (WHO) resolution that oral cancer should be an integral part of national cancer control programs (Petersen 2009).

Given that the majority of oral carcinomas are preceded by visible lesions (Scully 2009), determining the efficacy and effectiveness of screening warrants attention, whilst balancing the potential benefits with any potential negative consequences of any programme (Wilson 1968).

The most recent meta-analysis of visual screening found a weighted and pooled sensitivity of 84.8% (95% confidence interval (CI) 73.0 to 91.9) and specificity of 96.5% (95% CI 93.0 to 98.2) (Downer 2004). In this systematic review, only prospective population level studies with gold standard verification were selected and reports were excluded if at least one of the six inclusion criteria were not met. Nine databases were searched and out of 481 papers, only eight papers met this standard. However, there was considerable heterogeneity in these studies, due to differences in the size of the target populations, in the numbers of patients screened and verified and the type of clinician used. Despite this, meta-analysis regression showed no difference (P = 0.99) in the discriminatory ability between these groups, although the authors highlight the low number of studies and reported a lack of independence in two of these eight papers.

These values of sensitivity and specificity for visual examination have not been surpassed by any other type of method, such as vital staining (toluidine blue), oral cytology or light-based techniques (Lingen 2008; Patton 2008). More importantly, visual screening is the only method that has been evaluated in primary care using a randomised controlled trial design, on patients who are apparently free from the disease (Lingen 2008). In Patton's systematic review, 23 studies met the inclusion criteria, yet there remained insufficient evidence to support or refute the use of adjunctive techniques to the visual examination (Patton 2008). In another review, Lingen found that the majority of the published studies had employed these techniques on patients who had already received a diagnosis and that they did not improve upon the sensitivity or specificity of the visual examination.

The aim of this Cochrane systematic review was to examine whether screening for oral cancer reduced the mortality associated with the disease. The original review identified 1389 citations and this update identified an additional 330 studies (1719 studies to June 2010). However, only one study (Sankaranarayanan 2000) met the inclusion criteria, which had been identified earlier by the original review.

As highlighted by Kujan, the Sankaranarayanan 2000 study was found to have a number of methodological weaknesses that may have introduced bias (Kujan 2005). These included a lack of detail about the process of sequence generation to ensure random assignment, no analysis of the impact of clustering on the results and no detail about allocation concealment. In addition, the there was no blinding of the outcome assessment and withdrawals and drop-outs were not described. More importantly, of those who were referred with screen-positive lesions, only 63% of individuals complied with referral and it was unclear whether the clinicians who saw these patients followed any standardised criteria. Finally, only 26.4% and 26.0% of subjects had a biopsy in the second or third cycle, respectively, with no detail being provided from the first cycle. As it is not possible to diagnose early malignancy by visual appearance alone, this may have led to substantial underreporting of oral cancer and the lack of a histological diagnosis makes it difficult to accurately assess the correct diagnosis and true prevalence of these disorders. Kujan also argues that the small number of randomised clusters may have resulted in heterogeneity across the intervention and control groups and the close geographical proximity of the clusters may have led to contamination (Kujan 2005).

The study reported a sensitivity of the visual examination in detecting oral cancer was 64% and Kujan calculated a positive predictive value of 74% for the programme was recorded. Overall, there was no statistically significant difference in the mortality rate for oral cancer between the intervention group and control over the 9-year period. However, when high-risk individuals that used tobacco, alcohol or both were compared with low-risk individuals, there was a significant reduction of 43% in mortality rates for men who had received a visual screen. Although substantial, the 22% reduction in high-risk women was not significant. When these results are combined with the significant stage shift and survival rate in the intervention group, it would appear that visual examination could be effective at reducing mortality rates for oral cancer when used within a targeted screening programme. However, this statement needs to be read with caution given the potential sources of bias identified above. In addition, it is also possible that the improvement in survival rates with early stage oral cancer was due to lead-time bias i.e. increasing the length of time that the individual knows about their condition, without any effective increase in survival. Without subtracting this period from the overall survival time for screened patients, early detection merely increases the duration of the patients' awareness of their disease without reducing their mortality or morbidity. Numerous cancer-screening procedures were thought to improve survival until lead-time bias was addressed (Kay 1991).

Given the natural history of oral cancer and the variation in the reduction in mortality rates between the intervention and control groups in each of the three individual cycles (Sankaranarayanan 2000; Ramadas 2003; Sankaranarayanan 2005) it is also critical to ensure that any future studies are undertaken over a sufficient time scale to ensure there is adequate statistical power to detect the effect size in mortality reduction.

The cost effectiveness of the Sankaranarayanan 2000 study was reported in a later paper (Subramanian 2009). Again, the targeted

approach was more effective, with 1437.64 life years saved per 100,000 high-risk individuals and an incremental cost per life-year saved of US$156. According to the authors, this fulfils the target set by the WHO Commission on Macroeconomics and Health, who define an intervention as being cost effective when its cost-effectiveness ratio is less than a country's gross domestic product per capita. The results also need to be read in context, given the higher prevalence of the disease in the developing world. To date, there has been no randomised controlled trial in any Western or low-prevalence population, although Petti did not establish a statistically significant difference in prevalence of PMD between developing and developed nations (Petti 2003). Napier & Speight argue that this may be due to the global use of tobacco (Napier 2008) and Lim also found a similar prevalence of PMD in a General Dental Practice setting in the United Kingdom (Lim 2003).

The consideration of both the benefits and harms of screening is an essential component of any programme (Wilson 1968) and is fundamental to the satisfactory introduction of any technology into daily practice (Duffy 2001). The sensitivity reported in the Sankaranarayanan 2000 study was relatively low (64%) compared to Downer's systematic review (Downer 2004) and false positives may have unintended psychological consequences on the population being screened, for example, increased levels of anxiety from the false positive and along with the associated trauma of any unnecessary investigations. However, these could be reduced by careful patient management and by educating screened patients about the positive benefits of screening (Speight 1992). Recent studies by Brocklehurst, highlighted the need to train General Dental Practitioners to discuss positive findings (Brocklehurst 2010b) and the need for standardised criteria to avoid both under and over-referral in clinical practice (Brocklehurst 2010).

The purpose of healthcare is to improve both the quantity and quality of life (Kaplan 2005). The evidence from the Sankaranarayanan 2000 study is that visual screening can impact upon the former in high-risk individuals and can produce a significant stage shift and survival rate. This is important as advances in the management of the disease is more effective and cost effective for early stage disease (Speight 2006; Rogers 2009).

AUTHORS' CONCLUSIONS

Implications for practice

Our results suggest that there is insufficient evidence to recommend inclusion or exclusion of screening for oral cancer using a visual examination in the general population, in addition to that, no robust evidence exists for adjunctive methods of screening, toluidine blue, fluorescence imaging and brush biopsy, to be either included or excluded. The data need to be supplemented by further randomised controlled trials to provide the highest level of evidence for practice.

In the meantime, as an alternative for a national based screening programme, regular opportunistic screening by visual examination applied by qualified healthcare providers for a high-risk group might be effective in achieving an improvement outcome. Systematic examination of the oral cavity by the general dental practitioner or physician should remain an integral part of their routine daily work.

Implications for research

Given the high risk of bias in the study included in this review, a lack of randomised controlled studies associated with adjunctive methods (e.g. brush biopsy, fluorescence imaging) and a lack of understanding of the natural history of oral cancer, further randomised controlled trials are recommended. These should ensure the method of randomisation is accounted for in the analysis, that there is adequate allocation concealment and standard interventions for screening based on standardised criteria. In addition, the use of fully qualified and trained teams, a clear follow-up procedure and blinding of the outcome assessment should be utilised as far as possible.

ACKNOWLEDGEMENTS

We would like to thank Dr Sankaranarayanan for answering the queries of the review group. We would also like to thank Anne Littlewood (Cochrane Oral Health Group) for her help with preparing the searches for this update. We are also grateful to Professor Helen Worthington for her assistance on the development of the initial review and the Editors at the Cochrane Oral Health Group for their valuable comments.

REFERENCES

References to studies included in this review

Sankaranarayanan 2000 *{published data only}*

Ramadas K, Sankaranarayanan R, Jacob BJ, Thomas G, Somanathan T, Mahe C, et al.Interim results from a cluster randomized controlled oral cancer screening trial in Kerala, India. *Oral Oncolgy* 2003;**39**(6):580–8.

* Sankaranarayanan R, Mathew B, Jacob BJ, Thomas G, Somanathan T, Pisani P, et al.Early findings from a community-based, cluster-randomized, controlled oral cancer screening trial in Kerala, India. *Cancer* 2000;**88**(3): 664–73.

Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, et al.Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet* 2005;**365**(9475):1927–33.

References to studies excluded from this review

Allen 1998 *{published data only}*

Allen CM. Toluidine blue: proceed with caution?. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 1998;**86**(3):255.

Chamberlain 1993 *{published data only}*

Chamberlain J. Evaluation of screening for cancer. *Community Dental Health* 1993;**10 Suppl**(1):5–11.

Chen 2004 *{published data only}*

Chen TH, Chiu YH, Luh DL, Yen MF, Wu HM, Chen LS, et al.Community-based multiple screening model: design, implementation, and analysis of 42,387 participants. *Cancer* 2004;**100**(8):1734–43.

Cheng 2003 *{published data only}*

Cheng B, Yang L. The clinical evaluation of Oratest in detecting oral mucosal lesions. *Hua Xi Kou Qiang Yi Xue Za Zhi* 2003;**21**(2):124–6.

Eliezri 1988 *{published data only}*

Eliezri YD. The toluidine blue test: an aid in the diagnosis and treatment of early squamous cell carcinomas of mucous membranes. *Journal of American Academy of Dermatology* 1988;**18**(6):1339–49.

Garrote 1995 *{published data only}*

Frenandez Garrote L, Sankaranarayanan R, Lence Anta JJ, Rodriguez Salva A, Maxwell Parkin D. An evaluation of the oral cancer control program in Cuba. *Epidemiology* 1995;**6** (4):428–31.

Gray 2000 *{published data only}*

Gray M, Gold L, Elley A, Bursla A. *The effectiveness of Toluidine Blue dye as adjunct to oral cancer screening in general dental practice*. Birmingham: University of Birmingham, Department of Public Health & Epidemiology, 2000.

Gupta 1986 *{published data only}*

Gupta PC, Mehta FS, Pindborg JJ, Aghi MB, Bhonsle RB, Daftery DK, et al.Intervention study for primary prevention of oral cancer among 36 000 Indian tobacco users. *Lancet* 1986;**1**(8492):1235–9.

Gupta 1992 *{published data only}*

Gupta PC, Mehta FS, Pindborg JJ, Bhonsle RB, Murti PR, Daftary DK, et al.Primary prevention trial of oral cancer in India: a 10-year follow-up study. *Journal of Oral Pathology & Medicine* 1992;**21**(10):433–9.

Ikeda 1991 *{published data only}*

Ikeda N, Ishii T, Iida S, Kawai T. Epidemiological study of oral leukoplakia based on mass screening for oral mucosal diseases in a selected Japanese population. *Community Dentistry and Oral Epidemiology* 1991;**19**(3):160–3.

Ikeda 1995 *{published data only}*

Ikeda N, Downer MC, Ishii T, Fukano H, Nagao T, Inoue K. Annual screening for oral cancer and precancer by invitation to 60-year-old residents of a city in Japan. *Community Dental Health* 1995;**12**(3):133–7.

Lavelle 2005 *{published data only}*

Lavelle CL, Scully C. Criteria to rationalize population screening to control oral cancer. *Oral Oncology* 2005;**41**(1): 11–6.

Martin 1998 *{published data only}*

Martin IC, Kerawala CJ, Reed M. The application of toluidine blue as a diagnostic adjunct in the detection of epithelial dysplasia. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 1998;**85**(4): 444–6.

Miller 1988 *{published data only}*

Miller RL, Simms BW, Gould AR. Toluidine blue staining for detection of oral premalignant lesions and carcinomas. *Journal of Oral Pathology* 1988;**17**(2):73–8.

Moyer 1986 *{published data only}*

Moyer GN, Taybos GM, Pelleu GB Jr. Toluidine blue rinse: potential for benign lesions in early detection of oral neoplasms. *Journal of Oral Medicine* 1986;**41**(2):111–3.

Mullhaupt 2004 *{published data only}*

Mullhaupt B, Jenny D, Albert S, Schmid S, Fried M. Controlled prospective evaluation of the diagnostic yield of a laryngopharyngeal screening examination during upper gastrointestinal endoscopy. *Gut* 2004;**53**(9):1232–4.

Nagao 2000 *{published data only}*

Nagao T, Warnakulasuriya S, Ikeda N, Fukano H, Fujiwara K, Miyazaki H. Oral cancer screening as an integral part of general health screening in Tokoname City, Japan. *Journal of Medical Screening* 2000;**7**(4):203–8.

Nagao 2000a *{published data only}*

Nagao T, Ikeda N, Fukano H, Miyazaki H, Yano M, Warnakulasuriya S. Outcome following a population screening programme for oral cancer and precancer in Japan. *Oral Oncology* 2000;**36**(4):340–6.

Nagao 2003 *{published data only}*

Nagao T, Warnakulasuriya S. Annual screening for oral cancer detection. *Cancer Detection and Prevention* 2003;**27** (5):333–7.

Patton 2003 *{published data only}*
Patton LL. The effectiveness of community-based visual screening and utility of adjunctive diagnostic aids in the early detection of oral cancer. *Oral Oncology* 2003;**39**(7): 708–23.

Sankaranarayanan 1997 *{published data only}*
Sankaranarayanan R. Health care auxiliaries in the detection and prevention of oral cancer. *Oral Oncology* 1997;**33**(3): 149–54.

Sankaranarayanan 2002 *{published data only}*
Sankaranarayanan R, Fernandez Garrote L, Leuce Anta J, Pisani P, Rodriguez Salva A. Visual inspection in oral cancer screening in Cuba: a case-control study. *Oral Oncology* 2002;**38**(2):131–6.

Silverman 1984 *{published data only}*
Silverman S Jr, Migliorati C, Barbosa J. Toluidine blue staining in the detection of oral precancerous and malignant lesions. *Oral Surgery, Oral Medicine, and Oral Pathology* 1984;**57**(4):379–82.

Vahidy 1972 *{published data only}*
Vahidy NA, Zaidi SH, Jafarey NA. Toluidine blue test for detection of carcinoma of the oral cavity: an evaluation. *Journal of Surgical Oncology* 1972;**4**(5):434–8.

Zhang 2005 *{published data only}*
Zhang L, Williams M, Poh CF, Laronde D, Epstein JB, Durham S, et al.Toluidine blue staining identifies high-risk primary oral premalignant lesions with poor outcome. *Cancer Research* 2005;**65**(17):8017–21.

Additional references

American 1992
American Cancer Society. Update January 1992: The American Cancer Society guidelines for the cancer-related checkup. *CA: a Cancer Journal for Clinicians* 1992;**42**:44–5.

Begg 1996
Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al.Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996; **276**(8):637–9.

Blot 1988
Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al.Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Research* 1988;**48**(11):3282–7.

Boyle 2005
Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Annals of Oncology* 2005;**16**(3):481–8.

Brocklehurst 2010
Brocklehurst PR, Baker SR, Speight PM. A qualitative study examining the experience of primary care dentists in the detection and management of potentially malignant lesions. 2. Mechanics of the referral and patient communication. *British Dental Journal* 2010;**208**(2):E4.

Brocklehurst 2010a
Brocklehurst PR, Baker SR, Speight PM. Oral cancer screening: what have we learnt and what is there still to achieve?. *Future Oncology* 2010;**6**(2):299–304.

Brocklehurst 2010b
Brocklehurst PR, Baker SR, Speight PM. Factors which determine the referral of potentially malignant disorders by primary care dentists. *Journal of Dentistry* 2010;**38**(7): 569–78.

Cancer Research UK
Cancer Research UK. http://info.cancerresearchuk.org/cancerstats/types/oral (accessed 14 April 2010).

Clarkson 2003
Clarkson J, Harrison JE, Ismail AI, Needleman I, Worthington H. *Evidence Based Dentistry for Effective Practice*. London: Taylor & Francis Group, 2003.

Conway 2006
Conway DI, Stockton DL, Warnakulasuriya KA, Ogden G, Macpherson LM. Incidence of oral and oropharyngeal cancer in United Kingdom (1990-1999) - recent trends and regional variation. *Oral Oncology* 2006;**42**(6):586–92.

Conway 2010a
Conway DI, McKinney PA, McMahon AD, Ahrens W, Schmeisser N, Benhamou S, et al.Socioeconomic factors associated with risk of upper aerodigestive tract cancer in Europe. *European Journal of Cancer* 2010;**46**(3):588–98.

Conway 2010b
Conway DI, McMahon AD, Smith K, Black R, Robertson G, Devine J, et al.Components of socioeconomic risk associated with head and neck cancer: a population-based case-control study in Scotland. *The British Journal of Oral & Maxillofacial Surgery* 2010;**48**(1):11–7.

Day 1992
Day GL, Blot WJ. Second primary tumors in patients with oral cancer. *Cancer* 1992;**70**(1):14–9.

Diniz-Freitas 2004
Diniz-Freitas M, Garcia-Garcia A, Crespo-Abelleira A, Martins-Carneiro JL, Gandara-Rey JM. Applications of exfoliative cytology in the diagnosis of oral cancer. *Medicina Oral* 2004;**9**(4):355–61.

Doobaree 2009
Doobaree IU, Landis SH, Linklater KM, El-Hariry I, Moller H, Tyczynski J. Head and neck cancer in South East England between 1995-1999 and 2000-2004: An estimation of incidence and distribution by site, stage and histological type. *Oral Oncology* 2009;**45**(9):809–14.

Downer 1998
Downer MC, Jullien JA, Speight PM. An interim determination of health gain from oral cancer and precancer screening: 3. Preselecting high risk individuals. *Community Dental Health* 1998;**15**(2):72–6.

Downer 2004
Downer MC, Moles DR, Palmer S, Speight PM. A systematic review of test performance in screening for oral cancer and precancer. *Oral Oncology* 2004;**40**(3):264–73.

Duffy 2001
Duffy S, Hill C, Esteve J. *Quantitative methods for the evaluation of cancer screening*. London: Arnold, 2001.

Duffy 2005
Duffy SW, Agbaje O, Tabar L, Vitak B, Bjurstam N, Bjorneld L, et al.Overdiagnosis and overtreatment of breast cancer: estimates of overdiagnosis from two trials of mammographic screening for breast cancer. *Breast Cancer Research* 2005;**7**(6):258–65.

Fletcher 1993
Fletcher SW, Black W, Harris R, Rimer BK, Shapiro S. Report of International Workshop on Screening for Breast Cancer. *Journal of the National Cancer Institute* 1993;**85** (20):1644–56.

Gøtzsche 2006
Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [Art. No.: CD001877. DOI: 10.1002/14651858.CD001877.pub2]

Hauck 1991
Hauck WW, Gilliss CL, Donner A, Gortner S. Randomization by cluster. *Nursing Research* 1991;**40**(6): 356–8.

Hewitson 2007
Hewitson P, Glasziou PP, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [Art. No.: CD001216. DOI: 10.1002/14651858.CD001216.pub2]

Higgins 2009
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. *The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org*.

Hindle 2000
Hindle I, Downer MC, Moles DR, Speight PM. Is alcohol responsible for more intra-oral cancer?. *Oral Oncology* 2000; **36**(4):328–33.

IARC 2010
IARC. Cancer incidence in five continents, vol IX. http://www-dep.iarc.fr/ (accessed 15 April 2010).

Kaplan 2005
Kaplan RM. Screening for cancer: are resources being used wisely?. *Recent Results in Cancer Research* 2005;**166**:315–34.

Kay 1991
Kay BR, Witte DL. The impact of cancer biology, lead time bias, and length bias in the debate about cancer screening tests. *Journal of Insurance Medicine* 1991;**23**(2):102–4.

Kujan 2005
Kujan O, Glenny AM, Duxbury AJ, Thakker N, Sloan P. Evaluation of screening strategies for improving oral cancer mortality: a Cochrane systematic review. *Journal of Dental Education* 2005;**69**(2):255–65.

La Vecchia 1997
La Vecchia C, Tavani A, Franceschi S, Levi F, Corrao G, Negri E. Epidemiology and prevention of oral cancer. *Oral Oncology* 1997;**33**(5):302–12.

La Vecchia 2004
La Vecchia C, Lucchini F, Negri E, Levi F. Trends in oral cancer mortality in Europe. *Oral Oncology* 2004;**40**(4): 433–9.

Lim 2003
Lim K, Moles DR, Downer MC, Speight PM. Opportunistic screening for oral cancer and precancer in general dental practice: results of a demonstration study. *British Dental Journal* 2003;**194**(9):497–502.

Lingen 2008
Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncology* 2008;**44**(1):10–22.

Lippman 1989
Lippman SM, Hong WK. Second malignant tumors in head and neck squamous cell carcinoma: the overshadowing threat for patients with early-stage disease. *International Journal of Radiation Oncology, Biology, Physics* 1989;**17**(3): 691–4.

McLeod 2005
McLeod NM, Saeed NR, Ali EA. Oral cancer: delays in referral and diagnosis persist. British Dental Journal 2005; Vol. 198, issue 11:681–4.

Ministry of Health 2005
Ministry of Health. National Cancer Control Programme, Sri Lanka. Cancer incidence data: Sri Lanka year 2000. 6th Publication. *National Cancer Control Programme, Sri Lanka. Cancer incidence data: Sri Lanka year 2000. 6th Publication*. Maharagama: NCCP, 2005.

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

Noonan 2005
Noonan VL, Kabani S. Diagnosis and management of suspicious lesions of the oral cavity. *Otolaryngologic Clinics of North America* 2005;**38**(1):21–35.

NSC 2010
NSC. National Screening Committee. Available at http://www.screening.nhs.uk/screening (accessed 14 April 2010).

Ogden 1998
Ogden GR, Wight AJ. Aetiology of oral cancer: alcohol. *The British Journal of Oral & Maxillofacial Surgery* 1998;**36** (4):247–51.

Ogden 2005
Ogden GR. Alcohol and oral cancer. *Alcohol* 2005;**35**(3): 169–73.

Onizawa 2003
Onizawa K, Nishihara K, Yamagata K, Yusa H, Yanagawa T, Yoshida H. Factors associated with diagnostic delay of

oral squamous cell carcinoma. *Oral Oncology* 2003;**39**(8): 781–8.

Paci 2004
Paci E, Warwick J, Falini P, Duffy SW. Overdiagnosis in screening: is the increase in breast cancer incidence rates a cause for concern?. *Journal of Medical Screening* 2004;**11** (1):23–7.

Parkin 2005
Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA: a Cancer Journal for Clinicians* 2005;**55** (2):74–108.

Patton 2008
Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. *Journal of the American Dental Association* 2008;**139**(7):896–905.

Petersen 2009
Petersen PE. Oral cancer prevention and control - the approach of the World Health Organization. *Oral Oncology* 2009;**45**(4-5):454–60.

Petti 2003
Petti S. Pooled estimate of world leukoplakia prevalence: a systematic review. *Oral Oncology* 2003;**39**(8):770–80.

Petti 2005
Petti S, Scully C. Oral cancer: the association between nation-based alcohol-drinking profiles and oral cancer mortality. *Oral Oncology* 2005;**41**(8):828–34.

Rogers 2009
Rogers SN, Brown JS, Woolgar JA, Lowe D, Magennis P, Shaw RJ, et al.Survival following primary surgery for oral cancer. *Oral Oncology* 2009;**45**(3):201–11.

Rusthoven 2010
Rusthoven KE, Raben D, Song JI, Kane M, Altoos TA, Chen C. Survival and patterns of relapse in patients with oral tongue cancer. *Journal of Oral and Maxillofacial Surgery* 2010;**68**(3):584–9.

Scully 2009
Scully C, Bagan J. Oral squamous cell carcinoma overview. *Oral Oncology* 2009;**45**(4-5):301–8.

SEER 2010
National Cancer Institute. SEER Cancer statistics review 1975-2004. http://seer.cancer.gov/statfacts/html/oralcav.html (accessed 14 April 2010).

Speight 1992
Speight PM, Zakrzewska J, Downer MC. Screening for oral cancer and precancer. *European Journal of Cancer* 1992;**28B** (1):45–8.

Speight 2006
Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, et al.The cost-effectiveness of screening for oral cancer in primary care. *Health Technology Assessment* 2006;**10**(14):1–144.

Stewart 2003
Stewart BW, Kleihues P. International Agency for Research on Cancer. World cancer report. *World cancer report*. Lyon: IARC Press, 2003.

Subramanian 2009
Subramanian S, Sankaranarayanan R, Bapat B, Somanathan T, Thomas G, Mathew B, et al.Cost-effectiveness of oral cancer screening: results from a cluster randomized controlled trial in India. *Bulletin of the World Health Organization* 2009;**87**(3):200–6.

Tarvainen 2004
Tarvainen L, Suuronen R, Lindqvist C, Malila N. Is the incidence of oral and pharyngeal cancer increasing in Finland? An epidemiological study of 17,383 cases in 1953-1999. *Oral Diseases* 2004;**10**(3):167–72.

van der Waal 2009
van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology* 2009;**45** (4-5):317–23.

Warnakulasuriya 2007
Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *Journal of Oral Pathology & Medicine* 2007;**36**(10):575–80.

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

WHO 2001
Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Geneva, 2001.

Wilson 1968
Wilson JM, Jungner YG. *Principles and practice of screening for disease. Public health paper number 34*. Vol. **Public health paper number 34**, Geneva: WHO, 1968.

Yellowitz 2000
Yellowitz JA, Horowitz AM, Drury TF, Goodman HS. Survey of U.S. dentist's knowledge and opinions about oral pharyngeal cancer. *Journal of the American Dental Association* 2000;**131**(5):653–61.

References to other published versions of this review

Kujan 2003
Kujan O, Glenny AM, Duxbury AJ, Thakker N, Sloan P. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [Art. No.: CD004150. DOI: 10.1002/14651858.CD004150]

Kujan 2006
Kujan O, Glenny AM, Oliver R, Thakker N, Sloan P. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [Art. No.: CD004150. DOI: 10.1002/14651858.CD004150.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Sankaranarayanan 2000

Methods	Randomised controlled trial, Kerala, India. First round: 1995 to 1998. Second round: 1998 to 2002. Final round: 2002 to 2004.
Participants	General population aged 35 years or older, all subjects 191,873 were apparently healthy residents were grouped into intervention (n = 7 clusters, 96,517) and control (n = 6 clusters, 95,356)
Interventions	Health workers interviewed the eligible subjects to extract specified information. Intervention group: visual examination of the oral mucosa. Control group: follow up to the end point (study is ongoing) The intervention and control cohorts are being followed up by the Trivandrum population-based cancer registry to determine the incidence and stage distribution of invasive oral cancer, treatment given and mortality
Outcomes	Oral cancer mortality was the major outcome. Further outcome measures were: 1. Participation: defined as "the number of eligible subjects screened as a proportion of the total eligible in the intervention arm". 2. Positivity rate: defined as "the proportion of screened subjects identified with referable lesions". 3. Detection rate: defined as "the number of subjects with lesions detected per 1000 screened subjects in the intervention group". 4. Compliance with referral: defined as "the proportion of screen positive subjects reporting for diagnostic confirmation by dentists or physicians". 5. Sensitivity, specificity, and positive predictive values 6. Program sensitivity and specificity: defined as "the number of screen-detected oral cancers as a proportion of the total oral cancers in the intervention group", "the proportion of screen true-negative subjects among the total non-cancer-eligible subjects" and "the number of screen-detected oral cancers as a proportion of total screen positive subjects" respectively. 7. Incidence rate of oral cancers 8. Characteristics of oral cancers in the study group including: the maximum dimension of lesions, regional lymph node involvement and International Union Against Cancer/ American Joint Committee on Cancer (UICC/AJCC) TNM stage grouping distribution. 9. Case fatality for oral cancer cases diagnosed during the study period: defined as "the number of deaths among the total number of cases"
Notes	

Sankaranarayanan 2000 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Subjects were allocated by block randomisation into 13 clusters but no detail is given about how this process was undertaken
Allocation concealment?	No	Author of the trial stated that there was no concealed allocation
Blinding? All outcomes	Yes	No blinding, but the review authors judge that the outcome and its measurement are unlikely to be influenced by this. Considered low risk
Incomplete outcome data addressed? All outcomes	No	Not all participants attended for biopsy after screen (only 63% of screened positive complied with referral to have a biopsy). This missing data will have increased the risk of bias
Free of selective reporting?	Yes	Protocol is not available, but it appears that the published reports include all expected and pre-specified outcomes
Free of other bias?	Unclear	Positive cases were referred to General Practitioners and General Dental Practitioners to make a diagnosis, but it is unclear whether standardised criteria were used by these clinicians or whether they had received any training in identification of positive lesions It is stated that subjects with confirmed oral cancer and potentially malignant disorders were biopsied and those with confirmed oral cancer were referred. However, although not detailed in the first cycle, only 26.4% of subjects with a potentially malignant disorder (PMD) had a biopsy in the second cycle and only 26% in the third cycle. It is not clear whether all suspected oral cancer cases did receive a biopsy, but given the definition of "interval cases" in the third paper, it would appear not. In addition, it is stated in the third paper that the reference investigation for final diagnosis was clinical examination by doctors or histology or

		both. As it is not possible to diagnose early malignancy by visual appearance alone, this may have led to substantial under-reporting of oral cancer. The lack of a histological diagnosis for many of the PMDs also makes it difficult to accurately assess the correct diagnosis and true prevalence of these disorders Prevalence of PMD and mortality data is only provided in detail for the first two cycles only. The third paper presents the results over the three cycles from 1996 to 2004 and so does not provide individual detail about the results of the third cycle. It is not clear why this was the case

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

Study	Reason for exclusion
Allen 1998	Letter to author.
Chamberlain 1993	Review study.
Chen 2004	Uncontrolled clinical mass screening study.
Cheng 2003	Randomised controlled trial (diagnostic use).
Eliezri 1988	Uncontrolled study (secondary care).
Garrote 1995	Uncontrolled study.
Gray 2000	Review.
Gupta 1986	Non randomised controlled study.
Gupta 1992	Non randomised controlled study.
Ikeda 1991	Uncontrolled study.
Ikeda 1995	Uncontrolled study.
Lavelle 2005	Review.
Martin 1998	Uncontrolled study.

(*Continued*)

Miller 1988	Study in hamsters.
Moyer 1986	Uncontrolled study (diagnostic only).
Mullhaupt 2004	Non-randomised controlled study.
Nagao 2000	Uncontrolled study.
Nagao 2000a	Uncontrolled study.
Nagao 2003	Uncontrolled mass screening study.
Patton 2003	Review.
Sankaranarayanan 1997	Review study.
Sankaranarayanan 2002	Observational, case control study.
Silverman 1984	Uncontrolled study.
Vahidy 1972	Uncontrolled study.
Zhang 2005	Observational study.

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Important Potentially Malignant Disorders

The following were identified as Potentially Malignant Disorders by the World Health Organisation's working group on Oral Cancer Warnakulasuriya 2007: Leukoplakia Erythroplakia Palatal lesion of reverse cigar smoking Oral lichen planus Oral submucous fibrosis Discoid lupus erythematosus Hereditary disorders such as dyskeratosis congenita and epidermolysis bullosa

Table 2. Comparison between the intervention and control groups after three cycles (1996 to 2004)

Study	Intervention group	Control group
Number of interviewed participants	n = 7 clusters (87,829: 91%)	n = 6 clusters (80,086: 84%)
Gender	35,687 male 52,142 female	31,281 male 48,805 female
Income (< 1500 rupees (US$35) per month)	42,415 (49%)	30,849 (40%)
Occupation (manual workers)	68,645 (78%)	55,811 (71%)
Education	68,263 (78%)	64,291 (78%)
Age (years; mean (SD, range))	49 (0.7, 48-50)	49 (0.8, 48-50)
No habits	10,933 male (27%) 39,923 female (73%)	13,996 male (33%) 42,361 female (79%)
Chewing habits	12,329 male (30%) 14,570 female (27%)	10,586 male (24.9%) 10,748 female (20%)
Smoking habits	26,133 male (63%) 1610 female (3%)	23,270 male (56%) 609 female (1%)
Drinking habits	17,738 male (43%) 133 female (0.2%)	15,472 male (37%) 127 female (0.1%)

Table 3. Screening history

Screening history	Male	Female	Total
Not screened	14% (5941)	5% (2921)	9% (8862)
Screened once	40% (16,744)	32% (17,599)	36% (34,343)
Screened twice	25% (10,274)	25% (13,936)	25% (24,210)
Screened thrice	21% (8581)	37% (20,521)	30% (29,102)
Number of subjects with referable lesions	2675	2470	5145
Subjects complied with referral	60% (1604)	65.7% (1614)	63% (3218)

Table 4. Number of oral cancers diagnosed and associated mortality rate

Kerala project	Intervention group	Control group
Number of oral cancers	205 (Male: 107 and Female: 98)	158 (Male: 104 and Female: 54)
Number of screen detected cases	131	N/A
Deaths of oral cancer	77	87
Total number of participants	87,829	80,086
Case fatality rate	37.5%	55.1%
Crude incidence rate of oral cancer per 100,000	43.7	37.6
Crude mortality rate from oral cancer per 100,000	16.4	20.7
Proportion of cancers at stage I/II[1]	41.5%	23.4%

[1]statistically significant P = 0.004

Table 5. Oral cancer experience in high-risk individuals after three cycles (1996 to 2004)

Kerala project	Intervention group		Control group	
	Male	Female	Male	Female
Person years of observation	150,702	83,703	128,102	59,179
Number of oral cancer diagnosed	99	91	104	52
Deaths of oral cancer	37	33	55	30
Case-fatality rate	37.3%	36.3%	52.9%	57.7%
Crude incidence rate of oral cancer per 100,000	65.7	108.7	81.2	87.9
Crude mortality rate from oral cancer per 100,000	24.6	39.4	42.9	50.7

High risk individuals were defined as those who used tobacco, alcohol or both

Table 6. Stage shift due to the intervention in Kerala

Stage	Intervention group				Control group
	Screen-detected	Interval	Non-responders	Total	
I	40 (31%)	9 (15%)	2 (13%)	51 (25%)	20 (13%)
II	23 (18%)	10 (17%)	1 (7%)	34 (17%)	17 (11%)
III	22 (17%)	12 (20%)	3 (20%)	37 (18%)	35 (22%)
IV	38 (29%)	24 (41%)	5 (33%)	67 (33%)	70 (44%)
Unknown	8 (6%)	4 (7%)	4 (27%)	16 (8%)	16 (10%)
Total	131 (100%)	59 (100%)	15 (100%)	205 (100%)	158 (100%)

Table 7. Cost effectiveness of the screening programme in Kerala

Detail		Cost of intervention less cost of control (US$)
Total cost per 100,000 individuals		224,964
Cost per additional cancer detected by the screen	All individuals	4817
Cost per additional cancer detected by the screen	High-risk individuals	9394
Cost per life-year saved by the screen	All individuals	835
Cost per life-year saved by the screen	High-risk individuals	156

Costs based on the calender year of 2004 (Subramanian 2009)

APPENDICES

Appendix 1. MEDLINE via OVID search strategy

1. exp MOUTH/
2. exp LIP/
3. exp GINGIVA/
4. exp TONGUE/
5. exp OROPHARYNX/
6. exp HYPOPHARYNX/
7. exp PALATE/
8. exp CHEEK/
9. (mouth or lip$ or tongue$ or gingiv$ or oropharynx or palate or cheek$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
10. or/1-9
11. exp MOUTH NEOPLASMS/
12. exp PRECANCEROUS CONDITIONS/
13. (tumor$ or tumour$ or cancer$ or carcinoma$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. malignan$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15. dysplasia$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16. (oral adj6 cancer$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. or/11-16
18. MASS SCREENING/
19. (visual$ adj screen$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. tolonium chloride.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. TOLONIUM CHLORIDE/
22. "toluidine blue".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

23. exp TOLUIDINES/
24. "toluidine dye".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. ("brush biopsy" or "exfoliate cytology").mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
26. "fluorescent imaging".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
27. ("fluorescent dye$" or "fluorescent antibody technique" or fluorescence).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
28. prevent$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
29. screen$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
30. (early adj3 detect$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
31. or/18-30
32. 10 and 17 and 31

The above subject search was linked to the the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of *The Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.0.2 [updated September 2009].

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 2. Cochrane Oral Health Group Trials Register Search Strategy

((tumor* or tumour* or cancer* or carcinoma* or malignan*) AND (screen* or tolonium or "brush biopsy" or "exfoliative cytology" or fluorescen* or "early detect*"))

Appendix 3. Cochrane Central Register of Controlled Clinical Trials (CENTRAL) Search Strategy

#1 MeSH descriptor MOUTH explode all trees
#2 MeSH descriptor LIP explode all trees
#3 MeSH descriptor GINGIVA this term only
#4 MeSH descriptor TONGUE explode all trees
#5 MeSH descriptor OROPHARYNX explode all trees
#6 MeSH descriptor HYPOPHARYNX explode all trees
#7 MeSH descriptor PALATE explode all trees
#8 MeSH descriptor CHEEK this term only
#9 (mouth* in All Text or lip* in All Text or tongue* in All Text or gingiv* in All Text or oropharnyx in All Text or palate* in All Text or cheek* in All Text)
#10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#11 MeSH descriptor MOUTH NEOPLASMS explode all trees
#12 MeSH descriptor PRECANCEROUS CONDITIONS explode all trees
#13 (tumor* in All Text or tumour* in All Text or cancer* in All Text or carcinoma* in All Text)
#14 malignan* in All Text
#15 dysplasia* in All Text
#16 (oral in All Text near/6 cancer* in All Text)
#17 (#11 or #12 or #13 or #14 or #15 or #16)

#18 MeSH descriptor Mass Screening explode all trees
#19 "visual* screen*" in All Text
#20 "tolonium chloride" in All Text
#21 MeSH descriptor TOLONIUM CHLORIDE this term only
#22 "toluidine blue" in All Text
#23 MeSH descriptor TOLUIDINES explode all trees
#24 "toluidine dye" in All Text
#25 ("brush biopsy" in All Text or "exfoliate cytology" in All Text)
#26 "fluorescent imaging" in All Text
#27 ("fluorescent dye*" in All Text or "fluorescent antibody technique" in All Text or fluorescence in All Text)
#28 prevent* in All Text
#29 screen* in All Text
#30 (early in All Text near/3 detect* in All Text)
#31 (#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
#32 (#10 and #17 and #31)

Appendix 4. EMBASE via OVID Search Strategy

1. exp MOUTH/
2. exp LIP/
3. exp GINGIVA/
4. exp TONGUE/
5. exp OROPHARYNX/
6. exp HYPOPHARYNX/
7. exp PALATE/
8. exp CHEEK/
9. (mouth or lip$ or tongue$ or gingiv$ or oropharynx or palate or cheek$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
10. or/1-9
11. exp MOUTH NEOPLASMS/
12. exp PRECANCEROUS CONDITIONS/
13. (tumor$ or tumour$ or cancer$ or carcinoma$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. malignan$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15. dysplasia$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16. (oral adj6 cancer$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. or/11-16
18. MASS SCREENING/
19. (visual$ adj screen$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. tolonium chloride.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. TOLONIUM CHLORIDE/
22. "toluidine blue".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
23. exp TOLUIDINES/
24. "toluidine dye".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. ("brush biopsy" or "exfoliate cytology").mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
26. "fluorescent imaging".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
27. ("fluorescent dye$" or "fluorescent antibody technique" or fluorescence).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
28. prevent$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
29. screen$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
30. (early adj3 detect$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

31. or/18-30
32. 10 and 17 and 31

The above subject search was linked to the Cochrane Oral Health Group filter for identifying RCTs in EMBASE via OVID:

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

Appendix 5. CANCERLIT via PubMed Search Strategy

#1 Search MOUTH [mh:exp]
#2 Search LIP [mh:exp]
#3 Search GINGIVA [mh:exp]
#4 Search TONGUE [mh:exp]
#5 Search OROPHARYNX [mh:exp]
#6 Search HYPOPHARYNX [mh:exp]
#7 Search PALATE [mh:exp]
#8 Search CHEEK [mh:exp]
#9 Search (mouth or lip* or tongue* or gingiv* or oropharynx or palate or cheek*)
#10 Search #1 or #2 or #3 pr #4 or #5 or #6 or #7 or #8 or #9
#11 Search MOUTH NEOPLASMS [mh:exp]
#12 Search PRECANCEROUS CONDITIONS [mh:exp]
#13 Search (tumor* or tumour* or cancer* or carcinoma*)
#14 Search malignan*
#15 Search dysplasia*
#16 Search “oral cancer*”
#17 Search #11 or #12 or #13 or #14 or #15 or #16
#18 Search MASS SCREENING [mh:exp]
#19 Search “visual* screen*”
#20 Search “tolonium chloride”
#21 Search TOLONIUM CHLORIDE [mh:noexp]
#22 Search “toluidine blue”
#23 Search TOLUIDINES [mh:exp]
#24 Search “toluidine dye”
#25 Search (“brush biopsy” or “exfoliate cytology”)
#26 Search “fluorescent imaging”
#27 Search (“fluorescent dye*” or “fluorescent antibody technique” or fluorescence)

#28 Search prevent*
#29 Search screen*
#30 Search "early detect*"
#31 Search #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30

The above subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.a of *The Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.0.2 [updated September 2009]:

#1 randomized controlled trial [pt]
#2 controlled clinical trial [pt]
#3 randomized [tiab]
#4 placebo [tiab]
#5 drug therapy [sh]
#6 randomly [tiab]
#7 trial [tiab]
#8 groups [tiab]
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 animals [mh] NOT humans [mh]
#11 #9 NOT #10

WHAT'S NEW

Last assessed as up-to-date: 5 October 2010.

Date	Event	Description
6 October 2010	New citation required but conclusions have not changed	New authorship.
6 October 2010	New search has been performed	New searches and methodology. Review text, background and references brought up to date

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 4, 2003

Date	Event	Description
18 June 2010	New search has been performed	Converted to new review format.
25 May 2006	New citation required but conclusions have not changed	This version includes a change in authors.
23 May 2006	New search has been performed	The current review reflects the results of an update search conducted in July 2005. No new trials were identified as meeting the review's inclusion criteria. However, a trial presenting the final analysis for the one, previously in-

(*Continued*)

		cluded trial was identified. The conclusions of the review remain the same

CONTRIBUTIONS OF AUTHORS

Development of protocol based on the latest Cochrane guidance: Paul Brocklehurst (PRB).

Identification of studies: PRB, Anne-Marie Glenny (AMG).

Data extraction: PRB, AMG, Graham Ogden (GO) and Simon Shepherd (SS).

Assessment of risk of bias: PRB, AMG, GO, SS.

Data input/synthesis: PRB, AMG.

Writing of conclusions: PRB, AMG, OK, RJO, GO, PS, SS.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The University of Manchester, UK.
- AlBaath University, Not specified.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Mass Screening [*methods]; Mouth Neoplasms [*diagnosis; mortality; prevention & control]; Physical Examination [methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans