Appraisal of Screening for Oral Cancer

A report for the
UK National Screening Committee

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Contents

Introduction

1. This report reviews screening for oral cancer against the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (NSC 2003). It is based on a literature search conducted for the NSC in October 2014. Full details of the search strategy are set out in Appendix A.

2. Oral cancer is a group of cancers that includes cancer of the lip, tongue, mouth, oropharynx, piriform sinus, hypopharynx and other ill-defined sites of the lip, oral cavity and pharynx (Cancer Research UK 2014). Ninety percent of oral cavity and pharyngeal cancer are classified as squamous cell carcinoma (Moyer et al 2014).

3. Screening for oral cancer in adults was previously reviewed against the UK NSC criteria in 2010 (Speight & Warnakulasuriya 2010). The current NSC policy is that screening should not be offered[1].

4. The 2010 NSC review (Speight & Warnakulasuriya 2010) concluded that:

   "There is still considerable uncertainty regarding the natural history of the disease. In particular we are still unable to accurately predict which potentially malignant lesions will progress to cancer. Thus the criteria of a 'white patch, red patch or non-healing ulcer' are insufficiently specific to be used as a basis for referral to secondary care. Clear guidelines need to be developed for dentists to enable them to recognize the clinical features of those lesions that are most likely to progress. This may be helped by the development of point-of-care tests to identify which screen-detected lesions are most likely to progress [which] would alleviate this problem by allowing more accurate diagnosis and improving the specificity of lesions referred from primary care".

5. With regards to the management of potentially malignant lesions the 2010 NSC review concluded that:

   "There is no clear evidence-base for the management of potentially malignant lesions and recent studies have cast doubt on the current practice of surgical removal of all lesions deemed to be 'high risk' (moderate or severe dysplasia) as compared to 'watch and wait'."

6. This current review therefore focuses on these four questions:

   - Is the natural history understood, and has a biomarker suitable for screening been identified?
   - Has a reliable test suitable for use in primary care been identified? This may be an alternative or an adjunct to the visual examination.
   - Have any papers compared the 'watch and wait' approach with conventional active treatment (surgery and/or radiotherapy), for potentially malignant lesions?
   - Are there any large studies of other approaches to the management of potentially malignant lesions?

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[1] The UK NSC policy on Oral Cancer screening in adults
http://www.screening.nhs.uk/oralcancer

The Condition

The condition should be an important health problem

7. In 2011, around 6,800 people were diagnosed with oral cancer in the UK, making it the 16th most common cancer in the UK (Cancer Research UK 2014). More than 50% of people with oral and pharyngeal cancer have regional spread or distant metastasis at the time of diagnosis (Moyer et al 2014).

8. The five-year survival rate varies for different oral cancers. The five-year survival rate for people diagnosed with lip cancer between 1996 and 1999 is over 90% for men and women. For tongue and oral cavity cancers the five-year survival rate is about 45% for men and about 55% for women. For hypopharynx cancer the five-year survival rate is about 20% for men and women (Cancer Research UK 2014). The prognosis generally worsens with increasing inaccessibility of the tumour (Cancer Research UK 2014).

9. In the UK, oral cancer incidence rates have steadily risen since the 1980s. The English age-standardised incidence rate for oral cancer has risen from 6.6 per 100,000 in 2000 to 9.0 per 100,000 in 2011 (12.8 per 100,000 males and 5.4 per 100,000 females) (Cancer Research UK 2014). Mistry et al (2011) projected that cancers of the lip, mouth and pharynx will increase by 1% per year to 2030.

10. This criterion is met.

The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

11. Between 2009 and 2011, 71% of oral cancer cases were diagnosed in men aged 50 to 74 and 15% in men aged 75 years or more. In women the 50 to 74 age group accounted for 59% of cases, with a further 29% of cases in women aged 75 and over (Cancer Research UK 2014).

12. The main risk factor for oral cancer is smoking, with links in more than two-thirds of cases in men and more than half of cases in women. More than a third of oral cancers in men and about a sixth of oral cancers in women are linked to alcohol in the UK, with risk almost tripled in alcohol drinkers who also currently smoke tobacco (Cancer Research UK 2014). The previous 2010 NSC review stated that there is "good evidence that tobacco in all forms (both smoked and smokeless, including snuff) and betel quid[2] are carcinogenic in the upper aerodigestive tract, which includes the mouth. There is also convincing evidence that alcoholic drinks are carcinogenic and act synergistically with tobacco" (Speight & Warnakulasuriya 2010).

13. A number of recent studies were identified in the literature search for this review considering other risk factors associated with oral cancer. For example:

    *   The combination of low consumption of fruits and vegetables and high consumption of meat with high tobacco and alcohol use was associated with a 10-20 fold excess risk of oral cavity and pharyngeal cancer (Bravi et al 2013)

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[2] a mixture of ingredients including areca nut, slaked lime with or without added tobacco, which is wrapped in a betel leaf and chewed

- Occupational exposure to asbestos was associated with a increased risk of pharyngeal cancer (OR 1.41, 95%CI 1.01 to 1.97) (Langevin 2013)
- Personal history of oral candidiasis (a fungal infection) was associated with an increased risk of oral cavity cancer (OR 5.0, 95%CI 2.1 to 12.1) (Radoi et al 2013)
- History of head and neck cancer among first-degree relatives was associated with oral cavity cancer (OR 1.9, 95%CI 1.2 to 2.8) (Radoi et al 2013)
- Periodontal (gum) disease was associated with oral cancer (OR 3.53, 95%CI 1.52 to 8.23) (Yao et al 2014)
- A systematic review of 418 studies found that the prevalence of human papilloma virus (HPV) was 48.5% in oropharyngeal cancer, 32.5% in oral cancer, 30.7% in laryngeal cancer and 33.3% in unselected head and neck squamous cell carcinoma cases (Liu et al 2013).

14. One of the questions for this current review asks 'Is the natural history understood, and has a biomarker suitable for screening been identified?'

15. The previous 2010 NSC review concluded that the natural history of oral cancer is only partly understood, with the authors concluding that "it is clear that oral squamous cell carcinoma (OSCC) is preceded by changes in the oral mucosa, but the extent or nature of these changes is uncertain" (Speight & Warnakulasuriya 2010). It was also noted that "the majority of cancers are preceded by a detectable preclinical phase manifested as potentially malignant disorders … most often present as white lesions of unknown cause (leukoplakia), but may also be red patches or erythroplakia". However, it was also noted that "only about 5% of these lesions will progress to malignancy and although some clinical features are associated with higher risk (e.g. non-homogenous, speckled or red lesions) there are still no reliable ways to predict which individuals or lesions will develop OSCC" (Speight & Warnakulasuriya 2010).

16. In the literature search for the current review we identified a number of studies that have considered the natural history of premalignant oral lesions.

17. A systematic review on the malignant transformation of oral lichen planus (OLP) and oral lichenoid lesions (OLL) (Fitzpatrick et al 2014) identified 16 studies. Of 7,806 patients with OLP, 85 (1.1%) developed squamous cell carcinoma and of 125 with OLL, 4 (3.2%) developed squamous cell carcinoma. The rate of transformation in individual studies ranged from 0% to 3.5% and the mean time from diagnosis of OLP or OLL to malignant transformation was 51.4 months.

18. A retrospective review (Arduino et al 2009) included 207 patients with oral epithelial dysplasia and follow-up of at least 12 months, with 133 patients having received active treatment[3]. During the follow-up period 15 (7.2%) developed squamous cell carcinoma, 39.4% of lesions disappeared, 19.7% remained stable and 33.7% showed a new dysplastic event after treatment. No statistically significant differences were found between treated and untreated patients[4]. The authors concluded that the risk of malignant development did not seem to be predictable. The only statistically significant finding was that patients who continued to be exposed to risk factors (smoking and alcohol use) had a higher chance of recurrence (OR 2.43; 95%CI 1.99 to 5.93).

19. The literature search identified four studies exploring various means of predicting the progression of premalignant oral conditions. The key findings are summarised in Table 1:

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[3] Lesions with moderate or severe grades of dysplasia, or that were located on the lateral boarder or ventral surface of the tongue were usually offered treatment. Some patients refused surgical treatment for personal reasons.
[4] The authors did not separately report the results of patients who had, or had not, received intervention.

Table 1: Factors predicting the progression of premalignant oral conditions

Study	Premalignant condition (n)	Malignant cases	Predictive factors
Liu et al 2012 Retrospective review of clinicopathological factors	Oral leukoplakia n=320	**Developed OSCC:** 57 (17.8%) **Mean follow-up:** 5.1 years	Independent significant indicators for malignant transformation (multivariate analysis): • Age > 60 years • Non-homogenous lesion • Lesion located at lateral/ ventral tongue • High grade dysplasia
Xu et al 2013 Retrospective review of ALDH1 expression	Oral lichen planus n=101	**Developed oral SCC:** 12 (11.9%) **Mean follow-up:** 5 years	ALDH1 expression significantly associated with a 6.71-fold increased risk of malignant transformation (95%CI 1.64 to 27.42) (multivariate analysis)
Siebers et al 2013 Retrospective review of chromosome instability using DNA image cytometry (ICM) and FISH analysis	Oral leukoplakia n=102	**Developed oral SCC or carcinoma in situ:** 16 (15.7%) **Minimum follow-up:** 6 months **Median follow-up:** 91.5 months	Hazard ratios[5] (HR) for significant markers of progression (multivariate analysis): Chromosome instability (adjusted for histopathology): • DNA ICM (HR 5.4; 95%CI 1.8 to 15.8) • FISH (HR 4.4; 95%CI 1.5 to 13.1)
Smith et al 2009 Systematic review on the use of biomarkers to predict the transformation of oral dysplasia into cancer	Oral dysplasia 13 studies identified (all longitudinal design[6])	**N/a**	Factors associated with significant risk of progression to cancer from pooled analysis: • Loss of heterozygosity[7] (RR 17.60; 95%CI 2.77 to 108.37) • Survivin (RR 30; 95%CI 4.25 to 197.73) • MMP 9 (RR 19.00; 95%CI 1.56 to 209.38) • DNA content (RR 12.00; 95%CI 1.17 to 82.10) Other markers identified in the review that did not predict progression were p53[8], p73[8], MMP1 and 2 and cathepsin L mRNA

ALDH1 – aldehyde dehydrogenase (a cancer stem cell marker); ICM – image cytometry; FISH – fluorescence in situ hybridization; HR – hazard ratio; MMP – Matrix metalloproteinase; mRNA – messenger RNA; OSCC – oral squamous cell carcinoma; RR – relative risk

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[5] The chances of an event occurring within a group at a particular time

[6] Described as mainly small, single centre, retrospective studies. All included studies had less than 100 participants

[7] Loss of heterozygosity is caused by a deletion mutation or loss of a chromosome from a chromosome pair. At locations showing loss of heterozygosity, two alleles are observed in normal cells, while only one allele is detected in tumour cells (Kasamatsu et al 2011)

[8] A tumour encoded by the p53 or p73 gene

20. The question to be addressed in this review is: 'Is the natural history understood, and has a biomarker suitable for screening been identified?' Studies on the natural history of oral cancer published since the 2010 NSC review, including a systematic review of almost 8,000 patients, reinforced the earlier conclusion that only a small percentage of potentially malignant disorders progress to malignancy. The studies in Table 1 explored whether any factors can be identified to predict which potentially malignant disorders will progress to malignancy. However, there are many limitations to the evidence base. The studies were typically generating rather than testing hypotheses about which biomarkers might be useful. Sample sizes were small, the numbers of cases or oral cancer were very small and the confidence intervals for estimates of test performance were correspondingly wide. The performance metrics used were relative risk or hazard ratios; the performance of these biomarkers for predicting progression to malignancy has not been expressed using the metrics generally used in a screening programme (i.e. sensitivity, specificity and predictive values). Overall the evidence is currently insufficient to conclude that a biomarker suitable for screening has been identified.

21. This criterion is not currently met.

22. The remaining NSC criteria relating to 'the condition' are not considered further at this time.

The Test

23. The previous NSC review reported a sensitivity of 74% and a specificity of 99% for the detection of lesions that might possibly progress to oral cancer (white or red patches or non-healing ulcers) through the systematic visual examination of oral soft tissues in UK studies. However, the authors of the 2010 NSC review noted that (Speight & Warnakulasuriya 2010):

    "Most of these studies have evaluated an oral examination for potentially malignant disorders – essentially for the presence of leukoplakia, or lesions suspicious for early cancer. As such, all suffer from the fact that the malignant transformation rate of these lesions is low, resulting in an inherent low specificity for the detection of lesions that will truly progress."

    The previous review also identified a number of adjunctive techniques that had been advocated as potential screening tests, such as vital staining (toluidine blue), oral cytology using brush biopsy and a number of light based techniques (Speight & Warnakulasuriya 2010). At the time of the previous NSC review none of these adjunctive tests had been evaluated as screening tests in primary care settings in patients who were otherwise apparently healthy.

24. One of the questions for this current review is 'has a reliable test suitable for use in primary care been identified? This may be an alternative or an adjunct to the visual examination.' Potential adjunct tests include:

    - Vital rinsing or staining (Toluidine blue, Tolonium chloride)
    - Light-based detection (e.g. ViziLite and ViziLite Plus, Microlux/DL, VELscope, Orascoptic DK, Identafi 3000)
    - Mouth self-examination
    - Blood and saliva analysis.

25. Biopsy with histopathology is the gold standard used to confirm a diagnosis of oral cancer.

There should be a simple, safe, precise and validated screening test. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

26. A Cochrane review (Walsh et al 2013) considered conventional oral examination, vital rinsing, light-based detection, biomarkers and mouth self examination, used singly or in combination, for the early detection of potentially malignant disorders (PMD) or cancer of the lip or oral cavity in apparently healthy adults attending an organised screening programme or screened during attendance at a dental or other clinical practice examination. Databases were searched up to 30th April 2013 and 13 studies (n=68,362) were included. Included studies were randomised controlled trials or cross-sectional (or consecutive series) studies of test accuracy.

27. Ten of the 13 included studies evaluated conventional oral examination, two studies evaluated mouth self examination and one study evaluated conventional oral examination with vital rinsing. No eligible studies were identified evaluating light-based detection or blood or salivary sample analysis (testing for the presence of biomarkers).The reference standard was 'examination and clinical evaluation by a physician with specialist knowledge or training, working to the current diagnostic guidelines of their locality' (Walsh et al 2013). Studies where confirmation of a negative screen was done by extended follow-up were included. It was not possible to conduct meta-analysis due to the 'diversity of characteristics of the included studies', including variation in the nature of the screening test, the experience of people undertaking the test, the verification of screen positive and screen negative individuals and the prevalence of PMD or oral cancer (Walsh et al 2013). The results of this review are summarised in Table 2.

Table 2: Summary of the results from Walsh et al (2013)

Test	Participants	Prevalence[9] of PMD or oral cavity cancer	Sensitivity	Specificity
Conventional oral examination	10 studies (n=25,568)	Ranged from 1.4% to 50.9%	**For 8 studies with prevalence ≤10%:** Estimates ranged from 5% (95%CI 7% to 93%) to 99% (95%CI 97% to 100%) **For 1 study with prevalence 21.6%:** 95% (95%CI 92% to 97%) **For 1 study with prevalence 50.9%:** 97% (95%CI 96% to 98%)	**For 8 studies with a prevalence ≤10%:** Estimates all around 98% (95%CI 97% to 100%) **For 1 study with prevalence 21.6%:** 81% (95%CI 79% to 83%) **For 1 study with prevalence 50.9%:** 75% (95%CI 73% to 77%)
Mouth self-examination	2 studies (n=34,819)	Ranged from 0.6% to 22.6%	**For prevalence of 0.6%:** 18% (95%CI 13% to 24%) **For prevalence of 22.6%:** 33% (95%CI 10% to 65%)	**For prevalence of 0.6%:** 100% (95%CI 100% to 100%) **For prevalence of 22.6%:** 54% (95%CI 37% to 69%)
Conventional oral examination (COE) plus vital rinsing (toluidine blue)	1 study[10] (n=7,975)	**For COE alone:** 0.15% (for oral cancer) **For COE with vital rinsing:** 0.13% (for oral cancer)	**For COE alone:** 50% (95%CI 12% to 88%) **For COE with vital rinsing:** 40% (95%CI 5% to 85%)	**For COE alone:** 92% (95%CI 91% to 93%) **For COE with vital rinsing:** 91% (95%CI 90% to 91%)

COE – conventional oral examination; PMD – potentially malignant disorders

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[9] When the screening test relies on human judgement rather than a biomarker one might expect test performance, especially sensitivity, to be lower in low prevalence than in high prevalence contexts, because the human observer will rarely see a positive case and be more likely to miss one when it occurs.

[10] This study was an RCT comparing the performance of COE alone, with COE plus vital rinsing, with biopsy and long-term follow up through a National Cancer Registry. The results cited are the estimates of sensitivity and specificity when the two trial arms were considered independently.

28. Walsh et al judged the overall quality of the included studies to be variable, with many studies not fully reporting the characteristics and risk factors of the study sample, which introduces uncertainty about the applicability of the findings to a UK population screening context. Additionally, it was stated that in five studies the participants could be considered high risk individuals which also raises questions about the applicability of the findings to a UK screening context. The authors concluded that conventional oral examination for potentially malignant disorders and oral cancer has a variable sensitivity (ranging from 5% to 95%, generally with very wide 95% confidence intervals), but a consistently higher specificity (98% for studies with prevalence of 10% or less). The authors explored the included studies for sources of variation, but were not able to identify any single factor that consistently influenced the accuracy of the screening test. The one study that considered conventional oral examination with vital rinsing reported similar specificity for oral examination with and without vital rinsing. However, the prevalence of oral cancer in this study was low and the confidence intervals around the sensitivity values were very wide. For mouth self-examination, Walsh et al concluded that there was insufficient evidence to determine its accuracy as part of an organised screening programme.

29. It should be noted that the ability of a test to detect potentially malignant disorders is distinct from its ability to detect those that would progress to cancer cases. An important consideration within the Cochrane review is that it included studies exploring the sensitivity and specificity of tests to detect potentially malignant disorders or oral cancer cases. As discussed in the previous section the rate of transformation for potentially malignant disorders to oral cancer is low.

30. Although two studies in the Cochrane review reported a combination of high sensitivity and reasonably high specificity (Mathew et al 1997, Chang et al 2011), these studies were conducted in India and Taiwan respectively, both of which are high prevalence areas and are therefore not applicable to a UK screening context. The study reported by Mathew et al (1997) was conducted in south India in a population with a high prevalence of oral cancer, and the study reported Chang et al (2011) was conducted opportunistically in a tertiary referral centre in Taiwan among patients with a high prevalence of oral cancer.

31. We identified one additional study assessing screening tests for oral cancer published after the search date of the Cochrane review.

32. Ibrahim et al (2014) considered the effectiveness of Microlux/DL (a light-based detection test) in screening for potentially malignant and malignant oral lesions. Participants were 599 tobacco users in Saudi Arabia recruited from the general population. All participants were assessed by conventional oral examination (COE) and Microlux/DL with and without toluidine blue, with the MicroLux/DL assessor blinded to the results of the COE test. Fifty-three patients with suspicious lesions[11] were offered a biopsy (scheduled to take place two weeks after the clinical examination), however only 39 completed the biopsy (in nine cases the patient refused the biopsy or failed to attend for follow-up and in five cases the lesion disappeared). Five cancer cases were identified through biopsy. The authors did not report on any treatments received by patients. The results are summarised in Table 3:

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[11] For any lesions detected, the size, ease of visibility, border distinctiveness and presence of satellite lesions was recorded

Table 3: Summary of the results from Ibrahim et al (2014)

Test	Suspicious lesions detected	Sensitivity[12]	Specificity[12]	PPV	NPV
COE	53	100%	29.4%	17.2%	100%
Microlux DL	52	100%	32.4%	17.9%	100%
Microlux DL with toluidine blue	51	100%	35.3%	18.5%	100%

COE – conventional oral examination; PPV – positive predictive value; NPV – negative predictive value

33. There are several limitations to the study by Ibrahim et al. It used a high risk population (tobacco users) that differs from a UK screening population. Although a sensitivity of 100% was claimed, only people with suspicious lesions were offered a biopsy and the authors did not report any follow-up of patients, so it is possible that additional oral cancer cases were not detected by screening. The positive predictive values were low, suggesting that a high proportion of false positive results would be obtained in using these tests to screen for oral cancer.

34. Two further studies were identified that considered the use of a potential screening test in a relevant population, but did not report findings that can be used to understand their performance as a screening test. These are summarised briefly below with an explanation about why the results do not tell us anything about their performance as a screening test.

- Bhatia et al (2014) assessed the effectiveness of VELscope (a light-based detection test) in addition to conventional oral examination in detecting potentially malignant disorders in 305 patients presenting for general dental treatment. This study identified 222 lesions, with 23[13] referred to a specialist and ten biopsied. Although sensitivity and specificity were reported, referral to a specialist was used as the gold standard so this study assesses the ability for the test to detect people for further assessment but does not tell us anything about the ability of VELscope to detect cancer cases in a screening programme.
- Laronde et al (2013) evaluated the use of fluorescence visualisation (FV) (a light-based detection test) using a VELscope imaging device by community dental practitioners as an adjunct to clinical evaluation. Whilst this study involved a potential screening test with a population relevant to screening, the authors did not report sensitivity and specificity results or the number of cancers identified, and instead focused on whether FV was associated with persisting lesions. This study does not therefore allow assessment of the effectiveness of FV as a screening test.

35. We did not identify any studies examining the use of blood or saliva analysis in a screening population of apparently healthy adults.

36. The question posed at the outset of this section was 'has a reliable test suitable for use in primary care been identified?' We agree with the conclusion of the Cochrane review by Walsh et al (2013) that there is insufficient evidence to determine the screening test accuracy of conventional oral examination, vital rinsing, light-based detection, biomarkers or mouth self examination, used singly or in combination. The only relevant study (Ibrahim et al 2014) published after the Cochrane review claimed 100% sensitivity for conventional oral examination with or without light-based detection and vital rinsing, but since the study design could not reliably ascertain cases of oral cancer that were missed by screening (i.e they only offered biopsy to people with suspicious lesions and did not report any follow-up

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[12] Using histopathology as the gold standard
[13] Lesions which displayed loss of autofluorescence with no blanching on VELscope were recommended for referral to a specialist; lesions which were suspicious for dysplasia on oral examination were recommended for referral to a specialist.

of non-suspicious lesions), this claim is not robust. Additional limitations with Ibrahim et al's study include the small sample size and high risk population (tobacco users) that differs from a UK screening population. In conclusion, although studies considering the use of screening tests in a screening population were identified the results of these studies do not provide sufficient evidence to conclude that a reliable screening test has been identified.

37. This criterion is not met.

38. The remaining NSC criteria relating to the test are not considered further as they are not the focus of this review.

The Treatment

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

39. The 2010 NSC review reported that "early detection and treatment of lesions while they are small (Stage 1) may result in a 30-50% improvement in survival". The 2010 review also stated that "surgical management of small lesions may obviate the need for radiotherapy and will result in significantly less morbidity, especially with respect to facial appearance, eating and speaking" (Speight & Warnakulasuriya 2010).

40. This criterion was met in the 2010 review and is not considered further in this review.

There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

41. The 2010 review found "no clear evidence for management of potentially malignant lesions" (Speight & Warnakulasuriya 2010). In this review we considered the two questions:

- Have any papers compared the 'watch and wait' approach with conventional active treatment (surgery and/or radiotherapy), for potentially malignant lesions?
- Are there any large studies of other approaches to the management of potentially malignant lesions?

42. Although the literature review identified two papers describing a watch and wait approach (Flach et al 2013; Kohler & Kowalski 2011) these related to the management of patients with early stage oral cancer, not the management of potentially malignant lesions. The literature search did not reveal any studies comparing the 'watch and wait' approach with conventional active treatment for potentially malignant lesions. The literature search did not identify any large studies of other approaches to the management of potentially malignant lesions.

43. This criterion is not met.

44. The remaining NSC criteria relating to treatment are not considered further as they are not the focus of this review.

The Screening Programme

There should be evidence from high quality Randomised Controlled Trials (RCT) that the screening programme is effective in reducing mortality or morbidity

45. The previous NSC review identified an RCT (Sankaranarayanan et al 2005) which evaluated the visual examination for screening of oral cancer and showed improved survival and a significant stage shift to diagnosis of early stage disease. However, it was noted that this RCT used a high prevalence population and that it's generalisability to a Western population was uncertain (Speight & Warnakulasuriya 2010).

46. A 2013 Cochrane review assessing the effectiveness of current screening methods in decreasing oral cancer mortality (Brocklehurst et al 2013) only identified the same RCT (Sankaranarayanan et al 2005).

47. A further publication from this 2005 RCT was identified in the literature search for this current review (Sankaranarayanan et al 2013). This reported the results of a 15-year follow-up from the original trial and found a sustained reduction in oral cancer mortality with larger reductions in those who adhered to repeated screening rounds. However, this screening study was conducted in south India (a high-incidence area) and a statistically significant reduction in mortality was found only in users of tobacco and / or alcohol; the reduction in mortality from oral cancer when all individuals were considered did not reach statistical significance. The authors interpreted their findings as support for the introduction of population-based screening programs targeting (i.e. limited to) users of smoking or chewing tobacco or alcohol or both in high-incidence countries, but did not recommend the introduction of a screening programme in low-incidence countries such as the UK.

48. No further RCTs on screening for oral cancer were identified.

49. The rest of the NSC criteria are not considered further at this time as the key criteria covered by the questions posed for this review have not been met.

Implications for Policy

This review considered four questions with regards to screening for oral cancer, which are considered in turn below.

- Is the natural history understood, and has a biomarker suitable for screening been identified?

In 2010 the NSC review concluded that "there is still considerable uncertainty regarding the natural history of the disease". The literature search for this review identified additional studies on the natural history of oral cancer, however, the evidence does not yet seem sufficient to identify which individuals with potentially malignant lesions will progress to oral cancer. A range of potential biomarkers for the progression of potentially malignant conditions have been identified, but their value has not yet been established for use within a general population screening programme.

- Has a reliable test suitable for use in primary care been identified? This may be an alternative or an adjunct to the visual examination.

Studies considering the use of screening tests in a screening population were identified in the literature search for this review. This included ten studies on conventional oral examination, two studies on mouth self-examination, one study on vital rinsing and one study on light-based detection. No studies evaluating blood or salivary samples to test for the presence of biomarkers in a screening population were identified. The sensitivity, specificity and positive predictive values reported in the studies identified varied considerably and the reasons for the variation were not clear. Other limitations in the identified studies included wide confidence intervals around sensitivity estimates and the use of high risk populations with limited relevance to a UK screening context. Estimates of the positive predictive values associated with the range of prevalence, sensitivity, and specificity scores presented in the identified studies were around 20% or lower, which suggests that a high proportion of false positive results might be achieved in population screening.

The previous NSC review noted the low specificity for the detection of lesions that will truly progress associated with oral examination. The 2013 Cochrane review and a subsequently published study identified in the literature search for this review confirmed that there is insufficient evidence to determine the screening test accuracy of conventional oral examination, vital rinsing, light-based detection, biomarkers or mouth self examination, used singly or in combination. At present, the evidence identified is not sufficient to conclude that a reliable screening test for oral cancer has been identified.

- Have any papers compared the 'watch and wait' approach with conventional active treatment (surgery and/or radiotherapy), for potentially malignant lesions?
- Are there any large studies of other approaches to the management of potentially malignant lesions?

The 2010 NSC review concluded that "there is no clear evidence-base for the management of potentially malignant lesions". The literature search for this review did not identify any additonal studies comparing the 'watch and wait' approach with conventional active treatment for potentially malignant lesions or any large studies of other approaches to the management of potentially malignant lesions.

Implications for Research

Areas of interest for research include:

- Establishing whether any of the potential biomarkers identified in this review, used alone or in combination, could improve the sensitivity and specificity of population screening for oral cancer in the UK to a level where it might be viable
- An RCT of active surgery for potentially malignant lesions, compared with surveillance.

Appendix A

NSC Oral cancer literature search, Bazian, 17th October 2014

BACKGROUND:

This review should be structured around the issues previously raised by Speight and Warnakulasuriya in 2010, which focussed on the natural history and lack of a suitable testing strategy. The NSC will only take into consideration screening for SCC due to the rareness of oral cancer, and the predominance of SCC among oral cancer patients.

The key points made were:
1. The natural history of oral cancer is not understood
2. A reliable testing strategy which can be implemented within a primary care setting is required.
3. An RCT of active surgery for potentially malignant lesions, compared with surveillance, is required.
4. Opportunistic screening for high-risk individuals in general dental and medical practice may be an alternative to whole population screening but requires evaluation; eg clinical effectiveness, cost effectiveness and feasibility.

The literature search should cover the following headings:

- The condition- focussing on natural history
  - For example have any biomarkers determining which lesions are most likely to progress been identified
- The test – focussing on testing candidates providing an alternative to the visual examination
  - For example brush biopsy cytology samples, and other techniques for oral cancer detection (including toluidine blue, and light based techniques)
- The treatment
  - For example has an RCT comparing active treatment for potentially malignant lesions, with surveillance been undertaken
- The screening programme
  - Any RCTs in UK/Western low prevalence countries.

SOURCES SEARCHED: Medline and Medline In-process, Embase, Cochrane Library
DATES OF SEARCH: January 2009 – October 2014
LANGUAGE: English

SEARCH STRATEGY:
Population terms
1. Exp Mouth Neoplasms/
2. Exp Pharyngeal Neoplasms/
3. Exp Carcinoma, Squamous Cell/ AND (oral or mouth).ti,ab.
4. ((oral or mouth or lip$ or tongue$ or gum$ or gingiv$ or oropharyn$ or pharyn$ or palate or cheek$) adj5 (cancer$ or pre-cancer$ or precancer$ or carcinoma$ or neoplas$ or tumor$ or tumour$ or dysplasia$ or malignan$ or pre-malignan$ or premalignan$)).ti,ab.
5. (leukoplakia or erythroplakia).ti,ab.

6. Or/1-6

Screening terms
1. Mass Screening/
2. Early Detection of Cancer/
3. Early Diagnosis/
4. screen$3.ti,ab.
5. Population Surveillance/
6. surveillance.ti,ab.
7. ((early adj3 diagnos$) or detect$).ti,ab.
8. (test or tests or testing).ti,ab.
9. visual examination.ti,ab.
10. (biops* or cytology or imaging or "toluidine blue" or fluorescence).ti,ab.
11. Exp Biological markers/
12. marker$.ti,ab.
13. Exp Risk factors/
14. Or/1-13

SIGN systematic review, RCT and diagnostic studies filters
http://www.sign.ac.uk/methodology/filters.html

Epidemiological studies filter developed for this project
1. Epidemiology/
2. Incidence/
3. exp Mortality/
4. exp disease progression/
5. (ep or di or mi or mo or pc or sn).fs.
6. (incidence or epidemiolog* or mortality or prevention or "natural history").ti,ab.
7. Or/1-6

These search strategies will be combined with methodological filters to retrieve systematic reviews, randomised controlled trials, epidemiological and diagnostic accuracy studies.

Similar searches also carried out in Embase, PsycINFO, Cinahl, and Cochrane Library.

Inclusions and exclusions

A total of 2800 studies were identified. This was reduced to 415 references that were deemed to be relevant using the following criteria:

Scope
- Focused on developed Western countries with UK emphasis
- Excluded epidemiological studies in developing and high risk countries i.e. China, Brazil, Thailand, Malaysia
- Excluded studies on prognostic markers after diagnosis (unless systematic review)

Study design
- Excluded non-empirical research, e.g. letters, editorials, overviews, and excluded conference abstracts
- Systematic reviews stating at least two bibliographic search sources in abstract, or state prisma compliance, or giving sufficient methodological detail to sound like a systematic review, and not a selective review or overview
- Focussed on clinical studies (rather than laboratory only), excluded animal studies

- RCT's and observational studies: minimum 100 participants.
- RCT's Phase III and above

The study design search filters used were SR, RCT, DTA and epidemiological studies. Only high-level studies on treatment were included (i.e. on the whole topic, e.g. Cochrane review or other systematic reviews).

415 references were passed to the reviewer for consideration.

Appendix B

Table A1 gives examples, of the positive and negative predictive values associated with the range of prevalence, sensitivity and specificity scores that were presented in the Cochrane review. It should be noted that the information used for these estimates is from studies that looked at ability to detect either potentially malignant disorders or oral cancer and the Cochrane review did not distinguish between test performance for these two purposes:

Table A1: Example positive and negative predictive values

Prevalence	Sensitivity	Specificity	PPV	NPV
0.15%	50%	98%	3.6%	99.9%
0.6%	18%	100%	100%	99.5%
10%	5%	98%	21.7%	90.3%
10%	99%	98%	84.6%	99.9%
21.6%	95%	81%	57.9%	98.3%
22.6%	33%	54%	17.3%	73.4%
50.9%	97%	75%	80.1%	96.0%

NPV – negative predictive value; PPV – positive predictive value

Low PPVs suggest that screening may result in a high proportion of false positives. A lower NPV suggests that some positive cases may be missed by the screening test.

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