UK National Screening Committee

SCREENING FOR ORAL CANCER IN ADULTS

An evidence map to outline the volume and type of evidence related to screening for oral cancer for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes. Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Contents

Summary

This document discusses the findings of the evidence map on screening for oral cancer*.

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Based on the findings of this evidence map overall, no further work on screening for oral cancer should be commissioned at the present time.

The UK National Screening Committee (UK NSC) will return to screening for oral cancer in 3-years' time.

* Cancer of the oral cavity and oropharynx

Introduction and approach

Background & Objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Screening for oral cancer is a topic currently due for an external review update. The term oral cancer in this document refers to cancers developing in a part of the mouth, such as the surface of the tongue, the inside of the cheeks, the roof of the mouth (palate), the lips or gums.

Previous review on screening for oral cancer

The UK NSC currently recommends against screening for oral cancer. The Committee based this recommendation on the evidence provided by the 2015 review carried out by Solutions for Public Health (1).

The 2015 UK NSC review identified several studies on the natural history of oral cancer and concluded that only a small percentage of potentially malignant disorders progressed to malignancy (between 1.1% and 17.8% in the studies cited). Potentially malignant disorders included in studies cited in the review encompassed oral lichen planus, oral lichenoid lesions, oral epithelial dysplasia and oral leukoplakia. The review also concluded that it was unclear which individuals with potentially malignant lesions progressed to oral cancer (1).

The 2015 UK NSC review identified a Cochrane review that considered the accuracy of screening tests for oral cancer or potentially malignant disorders in apparently healthy adults attending an organised screening programme or screened during attendance at a dental or other clinical appointment. The screening tests used in the included studies were conventional oral examination, mouth self-examination and conventional oral examination with vital rinsing. The reference standard was evaluation by a physician with specialist knowledge. It is to be noted that there was a lot of variability on how such tests were performed. Sensitivity scores reported ranged from 5% to 99%. Specificity scores ranged from 54% to 100%. An individual study published after the search date of the Cochrane review assessed the accuracy of conventional oral examination and Microlux/DL in a high risk population (tobacco users). The sensitivity reported was 100% but specificity was approximately 30%-35%. The 2015 UK NSC review concluded that

there was insufficient evidence to determine the accuracy of screening tests in the general UK population (1).

The 2015 UK NSC review also concluded that it was not clear which individuals detected through screening should be offered treatment (1). The effectiveness of early treatment for oral cancer in leading to better outcomes than late treatment had been established in a previous UK NSC review and was not revisited in 2015 (1).

Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

This evidence map has been developed to assess whether a more sustained review on screening for oral cancer should be commissioned in 2020 and to evaluate the volume and type of evidence on key issues related to screening for oral cancer.

The aim was to address the following questions:

1. Is the natural history of oral cancer understood (progression from potentially malignant disorders to malignancy)?
2. Are there any accurate screening tests for the detection of oral cancer?
3. Are there any studies looking at the effectiveness of treatment in screen detected (opportunistic or population programmes) oral cancers or potentially malignant lesions?

The findings of this evidence map will provide the basis for discussion to support decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on oral cancer in 2020. The aim of this document is to present the information necessary for the UK NSC to decide this.

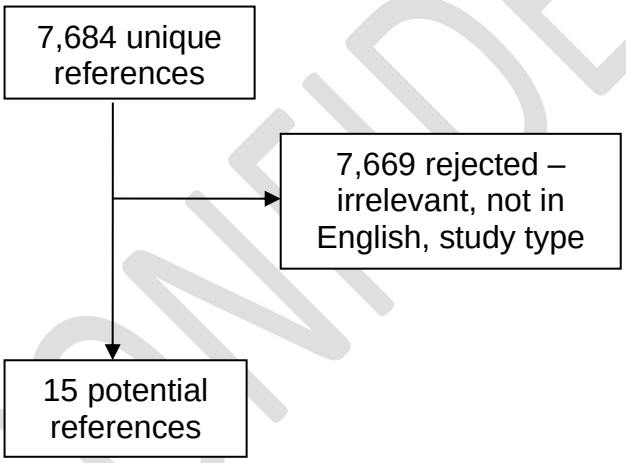
Search methods and results

The search was conducted on 7th April 2020 on 3 databases: [Medline, Embase and the Cochrane Library]. The search period was restricted to October 2014 – April 2020. The detailed search strategies, including exclusion and inclusion criteria are available in appendix 1. The search returned a total of 7,684 unique references which were initially sifted by an information scientist for potential relevance. One reviewer assessed 611 titles and abstracts for further appraisal and possible inclusion in the evidence map. Fifteen references were included in the final evidence map. These were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertainty.

A flow diagram summarising the number of studies included and excluded is presented in Figure 1.

Abstract reporting tables are available in appendix 2.

Figure 1: Summary of included and excluded publications



Summary of findings

Question 1: Is the natural history of oral cancer understood (progression from potentially malignant disorders to malignancy)?

Of the 15 potential references identified from the search, 14 met the criteria for inclusion for this question. The inclusion and exclusion criteria are summarised in appendix 1.

For this question we included studies about the progression of potentially malignant disorders, namely studies that reported malignant transformation rates for oral potentially malignant disorders (OPMD) and studies that reported risk factors for malignant transformation.

Six systematic reviews, 4 of which included meta-analysis, explored the progression of a number of different OPMD to oral cancer, with some also reporting risk factors for progression. A further 2 systematic reviews with meta-analysis focused on a risk factor for progression from OPMD to malignancy. Although there is likely to have been overlap in the studies and patients included in some of the systematic reviews, they considered different OPMD and considered different factors that may affect the risk of malignant transformation. As a recent systematic review (Iocca et al 2020) (2) included the malignant transformation of any OPMD, only individual studies published after the search date for this review (February 2019) were included. This identified an additional 6 studies. The details of these studies are briefly summarised here. Further information about the individual reviews and studies is provided in the abstract reporting tables in appendix 2.

The 8 systematic reviews included were:

- Iocca et al (2020) (2): systematic review and meta-analysis including 92 studies published up to February 2019 and 34,393 patients with any OPMD
- Idrees et al (2020) (3): systematic review and meta-analysis including 33 studies published up to January 2020 and 12,838 patients with oral lichen planus
- Akrish et al (2019) (4): systematic review including 35 studies published up to 2018 and 297 patients with oral proliferative verrucous leukoplakia
- Giuliani et al (2019) (5): systematic review including 21 studies published up to June 2017 and 6,559 patients with oral lichen planus and oral lichenoid lesions
- Gonzalez-Moles et al (2019) (6): systematic review and meta-analysis including 82 studies published up to November 2018 and 26,742 patients with oral lichen planus, oral lichenoid lesions and oral lichenoid reactions
- Saluja et al (2019) (7): systematic review including 12 studies published up to December 2017 and 1,659 patients with OPMD

- Alaizari et al (2018) (8): systematic review and meta-analysis including 5 studies on patients with OPMD (search date and number of patients not reported[†])
- Aghbari et al (2017) (9): systematic review and meta-analysis including 57 studies (search date not reported) and 20,095 patients with oral lichen planus and oral lichenoid lesions.

The 6 individual studies identified for inclusion were all retrospective cohort studies conducted in the US, Australia, China, Taiwan and the Netherlands. One study reported malignant transformation in patients with OPMD detected via a screening programme (Chiang et al 2020) (10), 4 studies considered malignant transformation for oral leukoplakia (Wils et al 2020 (11), Chaturvedi et al 2019 (12), Sherston et al 2019 (13), Wu et al 2019 (14)) and 1 considered oral lichenoid conditions (Shearston et al 2019) (15). Study sample sizes ranged from 84 to 4,886.

Cancer type was most commonly described as oral squamous cell carcinoma (7 studies) or oral cancer (3 studies). Other descriptions included invasive cancer (1 study) and verrucous or squamous oral cancer (1 study). Two studies did not provide a description of cancer type other than referring to the malignant transformation of OPMD.

The systematic review and meta-analysis by Iocca et al (2020) (2) reported an overall malignant transformation rate for any OPMD to invasive oral cancer of 7.9% (99%CI 4.9 to 11.5). The retrospective cohort study of patients with OPMD detected by screening by Chiang et al (2020) (10) reported an annual malignant transformation rate of 1.16%.

The malignant transformation rates for individual OPMD varied. The range of rates reported were:

- oral lichen planus: 0.44% to 1.4% (5 reviews (2,3,5,6,9))
- oral lichenoid lesions: 0% to 6.8% (4 reviews (2,5,6,9); 1 cohort study (15))
- oral leukoplakia: 1.3% to 30% (1 review (2); 5 cohort studies (10,11,12,13,14))
- proliferative verrucous leukoplakia: 50% (2 reviews (2,4))
- oral submucous fibrosis: 5.2% to 5.7% (1 review (2); 1 cohort study (10))
- oral erythroplakia: 33.1% (1 review (2))
- lichenoid reactions: 1.7% (1 review (6))
- candida hyperplasia: 13.6% (1 cohort study (10))
- verrucous hyperplasia: 21.3% (1 cohort study (10))

Several studies looked at the impact of definitions on malignant transformation rates. For example, one systematic review (3) reported that 1.2% of oral lichen planus cases were initially considered to have progressed to malignancy. However, after the application of

[†] The full text of this paper was not readily available

stricter inclusion criteria‡ the malignant transformation rate was 0.44%. Common features in other studies that explored the impact of definitions or inclusion/ exclusion criteria on the malignant transformation rates of OPMD were presence/ definition of dysplasia, use of clinical and histopathological criteria for diagnosis and duration of follow-up.

Many of the included reviews and studies also considered risk factors for malignant transformation. In 1 systematic review and meta-analysis (2), moderate/ severe dysplasia was associated with a greater risk of malignant transformation than mild dysplasia (odds ratio 2.4, 95%CI 1.5 to 3.8). Other studies that explored the risk associated with dysplasia also reported higher risk with more severe dysplasia. Other risk factors reported to be associated with a greater risk of malignant transformation included:

- smoking (3 reviews (3,6,9) and 1 cohort study (13))
- alcohol consumption (3 reviews (3,6,9) and 1 cohort study (13))
- testing positive for hepatitis C virus (3 reviews (3,6,9))
- displaying a red lichen planus subtype (2 reviews (3,5))
- tongue site (2 reviews (5,6) and 1 cohort study (13))
- female gender (1 review (5) and 1 cohort study (13))
- presence of atrophic-erosive lesions (1 review (6))
- heavy betel quid chewing (1 cohort study (10))
- refusal of surgery (1 cohort study (10)).

Two systematic reviews with meta-analysis focused on specific risk factors for progression from OPMD to malignancy. Saluja et al (2019) (7) reported a significant association between cancer stem cells and progression to malignancy in patients with OPMD (risk ratio 3.31, 95%CI 2.72 to 4.02). Alaizari et al (8) reported a significant association between DNA aneuploidy and progression to malignancy in patients with OPMD (risk ratio 3.12, 95%CI 1.86 to 5.24).

As with the 2015 UK NSC review (1), this evidence map has identified several studies on the natural history of oral cancer which vary in study design, size and focus. There is variation in the malignant transformation rates reported and these results may be sensitive to variations in definitions and study inclusion/ exclusion criteria. Some risk factors associated with progression to malignancy have been identified. It is not clear if any of the evidence is based on UK populations, therefore the applicability to the UK is unclear.

‡ These criteria included the presence of a properly verified diagnosis of lichen planus, a clear description of the cancerous lesion developing at the same site as the verified lichen planus lesion and a follow-up period of at least 6 months prior to carcinoma development.

There is a large volume of evidence on the natural history of OPMD. This includes systematic reviews with meta-analyses considering a variety of different OPMD and risk factors. The volume and type of evidence available on the natural history of oral cancer is sufficient for more detailed consideration in an evidence summary.

Question 2: Are there any accurate screening tests for the detection of oral cancer?

Of the 15 potential references identified from the search, 1 met the criteria for inclusion for this question (Simonato et al 2019) (16). The inclusion and exclusion criteria are summarised in appendix 1.

The 1 study that met the inclusion criteria provided information on the diagnostic accuracy of conventional oral examination and fluorescence visualization to detect oral squamous cell carcinoma (16). This study was based on the results of a screening programme run in 18 primary health care centres in Brazil between 2014 and 2015 (n=1,765). The screening was conducted by a general dentist practitioner and any suspicious lesions were referred for diagnosis by a specialist in oral medicine. High risk lesions were biopsied. Two cases of oral cancer were detected by screening. Conventional oral examination and fluorescence visualization both had a sensitivity of 100% and specificities of 90.4% and 90.8% respectively. Positive predictive values were 3.6% and 3.7% and both had a negative predictive value of 100%.

This study included a small number of participants and was set in Brazil. The applicability of the results to a UK population is unclear. Although all suspicious lesions were referred for diagnosis by a specialist it is not clear if all were biopsied or if patients were followed-up to determine if further oral cancer cases developed.

The UK NSC's current position is that there is insufficient evidence to determine the accuracy of potential screening tests for oral cancer in a general UK population. At present there is insufficient new evidence in this key area to justify commissioning an evidence summary. The volume and type of evidence identified is unlikely to lead to a change in the UK NSC's current position.

Question 3: Are there any studies looking at the effectiveness of treatment in screen detected (opportunistic or population programmes) oral cancers or potentially malignant lesions?

No studies were identified that met the criteria for inclusion for this question. The inclusion and exclusion criteria are summarised in appendix 1.

No studies were identified that met the inclusion criteria for this question.

Conclusions

A large volume of evidence was identified on the natural history of oral cancer. In contrast there was only a single paper that met the inclusion criteria for key question 2 and none for key question 3. The limited evidence suggests that an evidence review of these 2 questions is unlikely to impact on current recommendations on screening for oral cancer. With this in mind it is unclear whether commissioning a full, more sustained review on the natural history of oral cancer would be justified at the current time.

Recommendations

On the basis of this evidence map, the volume and type of evidence related to screening for oral cancer overall is currently insufficient to justify an update review at this stage and so should be re-considered in 3-years' time.

Appendix 1 — Search strategy for the evidence map

Question 1 – Natural history

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: October 2014 to 7th April 2020

SEARCH STRATEGIES:

Medline			**Embase**		
1	((oral* or mouth*) adj3 "potentially malignant lesion?").ti,ab,kw.	94	1	((oral* or mouth*) adj3 "potentially malignant lesion?").ti,ab,kw.	122
2	exp Mouth Neoplasms/	68249	2	exp mouth cancer/	60444
3	((oral or oropharyn* or hypopharyn* or lip or tongue or lingual or mouth* or piriform sinus) adj3 (cancer* or neoplas* or carcinoma* or tumo?r? or malignan*)).ti,ab,kw.	48690	3	((oral or oropharyn* or hypopharyn* or lip or tongue or lingual or mouth* or piriform sinus) adj3 (cancer* or neoplas* or carcinoma* or tumo?r? or malignan*)).ti,ab,kw.	60806
4	2 or 3	90211	4	2 or 3	92078
5	risk factors/	810337	5	*risk factor/	77068
6	disease progression/	159395	6	*disease course/ or cancer growth/ or illness trajectory/	164332
7	epidemiology/	12323	7	*epidemiology/	45240
8	(risk* or progress* or epidemiolog* or trend? or natural history or transform*).ti,ab,kw.	4122788	8	(risk* or progress* or epidemiolog* or trend? or natural history or transform*).ti,ab,kw.	5705769
9	5 or 6 or 7 or 8	4404539	9	5 or 6 or 7 or 8	5787463
10	Oral Ulcer/ or Leukoplakia, Oral/	5428	10	mouth lesion/ or exp mouth ulcer/ or Leukoplakia/	25256
11	Precancerous Conditions/	27786	11	Precancer/	20568
12	(((mouth or oral) adj3 (lesion? or ulcer? or lichen? or fibrosis)) or leukoplakia? or erythroplakia?).ti,ab,kw.	19159	12	(((mouth or oral) adj3 (lesion? or ulcer? or lichen? or fibrosis)) or leukoplakia? or erythroplakia?).ti,ab,kw.	23302
13	((precancer* or pre-cancer* or premalignan* or pre-malignan*) adj3	12114	13	((precancer* or pre-cancer* or premalignan* or pre-malignan*) adj3	17006

	(symptom? or sign? or lesion?)).ti,ab,kw.			(symptom? or sign? or lesion?)).ti,ab,kw.	
14	10 or 11 or 12 or 13	54044	14	10 or 11 or 12 or 13	66034
15	((progression or "progress to" or "progressed to" or "progressing to") adj5 (cancer* or neoplas* or carcinoma* or tumo?r? or malignan*)).ti,ab,kw.	138063	15	((progression or "progress to" or "progressed to" or "progressing to") adj5 (cancer* or neoplas* or carcinoma* or tumo?r? or malignan*)).ti,ab,kw.	197336
16	4 and 15	2967	16	4 and 15	4657
17	4 and 9 and 14	3658	17	4 and 9 and 14	3526
18	exp Mouth Neoplasms/ep [Epidemiology]	3911	18	exp mouth cancer/ep	2274
19	1 or 16 or 17 or 18	9489	19	1 or 16 or 17 or 18	9627
20	limit 19 to (("systematic review" or systematic reviews as topic) and "reviews (maximizes specificity)")	85	20	limit 19 to "reviews (maximizes specificity)"	201
21	Epidemiologic studies/	8259	21	major clinical study/ or cohort analysis/	3932542
22	exp case control studies/	1067951	22	exp case control study/	171757
23	exp cohort studies/	1975209	23	exp longitudinal study/ or prospective study/ or retrospective study/	1563662
24	Case control.tw.	123096	24	Case control.tw.	160330
25	(cohort adj (study or studies)).tw.	199105	25	(cohort adj (study or studies)).tw.	290325
26	Cohort analy$.tw.	7807	26	Cohort analy$.tw.	12563
27	(Follow up adj (study or studies)).tw.	48705	27	(Follow up adj (study or studies)).tw.	62568
28	(observational adj (study or studies)).tw.	103318	28	(observational adj (study or studies)).tw.	162440
29	Longitudinal.tw.	239744	29	Longitudinal.tw.	322680
30	Retrospective.tw.	515904	30	Retrospective.tw.	859091
31	Cross sectional.tw.	342366	31	Cross sectional.tw.	448211
32	Cross-sectional studies/	323060	32	Cross-sectional studies/	214366
33	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	2954260	33	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	5485601
34	17 and 33	1066	34	17 and 33	1319
35	20 or 34	1134	35	20 or 34	1485
36	limit 35 to (english language and yr="2014 -Current")	416	36	limit 35 to (english language and yr="2014 -Current")	733
			37	conference*.pt.	4514886
			38	36 not 37	587

Question 2 – Screening tests

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: October 2014 to 7th April 2020

SEARCH STRATEGIES:

Medline			**Embase**		
1	((oral* or mouth*) adj3 "potentially malignant lesion?").ti,ab,kw.	94	1	((oral* or mouth*) adj3 "potentially malignant lesion?").ti,ab,kw.	122
2	exp Mouth Neoplasms/	68254	2	exp Mouth cancer/	60444
3	((oral or oropharyn* or hypopharyn* or lip or tongue or lingual or mouth* or piriform sinus) adj3 (cancer* or neoplas* or carcinoma* or tumo?r? or malignan*)).ti,ab,kw.	48711	3	((oral or oropharyn* or hypopharyn* or lip or tongue or lingual or mouth* or piriform sinus) adj3 (cancer* or neoplas* or carcinoma* or tumo?r? or malignan*)).ti,ab,kw.	60806
4	2 or 3	90234	4	2 or 3	92078
5	Mass Screening/ or "Early Detection of Cancer"/	120564	5	cancer screening/ or screening test/ or screening/ or mass screening/ or early cancer diagnosis/	365864
6	screen*.ti,ab,kw.	734520	6	screen*.ti,ab,kw.	1037911
7	Physical Examination/ or Self-Examination/	41505	7	Physical Examination/ or Self Examination/	214417
8	light/ or exp luminescence/	149790	8	luminescence/	26089
9	Tolonium Chloride/	1801	9	Tolonium Chloride/	4680
10	Saliva/an, cy [Analysis, Cytology]	4404	10	saliva analysis/	8741
11	Hematologic Tests/	9191	11	blood examination/	14126
12	((rins* or stain*) adj5 (diagnos* or detect* or test* or vital)).ti,ab,kw.	32966	12	((rins* or stain*) adj5 (diagnos* or detect* or test* or vital)).ti,ab,kw.	45874
13	(toluidine blue or tolonium chloride).ti,ab,kw.	5319	13	(toluidine blue or tolonium chloride).ti,ab,kw.	6761
14	((oral or mouth) adj3 (examination or self-exam* or selfexam* or assessment)).ti,ab,kw.	6488	14	((oral or mouth) adj3 (examination or self-exam* or selfexam* or assessment)).ti,ab,kw.	7877
15	((physical or clinical) adj (exam* or assessment)).ti,ab,kw.	136802	15	((physical or clinical) adj (exam* or assessment)).ti,ab,kw.	224069

16	((light* or luminesc*) adj5 (diagnos* or detect* or test* or vital)).ti,ab,kw.	24357	16	((light* or luminesc*) adj5 (diagnos* or detect* or test* or vital)).ti,ab,kw.	29369
17	(vizilite* or microlux* or velscope or orascop* or identafi).ti,ab,kw.	103	17	(vizilite* or microlux* or velscope or orascop* or identafi).ti,ab,kw.	121
18	((blood or saliva*) adj2 (analys* or test* or diagnos* or detect*)).ti,ab,kw.	65957	18	((blood or saliva*) adj2 (analys* or test* or diagnos* or detect*)).ti,ab,kw.	103979
19	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1198719	19	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1659005
20	4 and 19	5862	20	4 and 19	8017
21	limit 20 to ("systematic review" or systematic reviews as topic or "reviews (maximizes specificity)")	165	21	limit 20 to "reviews (maximizes specificity)"	182
22	exp "Sensitivity and Specificity"/	576831	22	predictive value/ or diagnostic accuracy/ or "sensitivity and specificity"/	634540
23	(sensitiv* or specific* or predict* or ppv or npv or accura* or replicab*).ti,ab,kw.	5610735	23	(sensitiv* or specific* or predict* or ppv or npv or accura* or replicab*).ti,ab,kw.	7084854
24	22 or 23	5796025	24	22 or 23	7242173
25	20 and 24	1963	25	20 and 24	2873
26	1 and 19	22	26	1 and 19	35
27	21 or 25 or 26	2061	27	21 or 25 or 26	2974
28	limit 27 to (english language and yr="2014 -Current")	892	28	limit 27 to (english language and yr="2014 -Current")	1480
			29	conference*.pt.	4514886
			30	28 not 29	1107

Question 3 – Treatment

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: October 2014 to 7th April 2020

SEARCH STRATEGIES:

Medline			**Embase**		
1	((oral* or mouth*) adj3 "potentially malignant lesion?").ti,ab,kw.	94	1	((oral* or mouth*) adj3 "potentially malignant lesion?").ti,ab,kw.	122
2	exp Mouth Neoplasms/	68249	2	exp mouth cancer/	60444
3	((oral or oropharyn* or hypopharyn* or lip or tongue or lingual or mouth* or piriform sinus) adj3 (cancer* or neoplas* or carcinoma* or tumo?r? or malignan*)).ti,ab,kw.	48690	3	((oral or oropharyn* or hypopharyn* or lip or tongue or lingual or mouth* or piriform sinus) adj3 (cancer* or neoplas* or carcinoma* or tumo?r? or malignan*)).ti,ab,kw.	60806
4	1 or 2 or 3	90216	4	1 or 2 or 3	92085
5	Oral Surgical Procedures/	6277	5	oral surgery/	18840
6	exp Radiotherapy/	183177	6	exp *Radiotherapy/	206237
7	Watchful Waiting/	3651	7	Watchful Waiting/ or *conservative management/	13766
8	(therap* or manage* or treat* or radiotherap* or watchful waiting or "watch and wait").ti.	2506245	8	(therap* or manage* or treat* or radiotherap* or watchful waiting or "watch and wait").ti.	3031677
9	Treatment Outcome/	957835	9	5 or 6 or 7 or 8	3140855
10	5 or 6 or 7 or 8 or 9	3244941	10	4 and 9	20039
11	4 and 10	18094	11	exp mouth cancer/dt, rt, su, th	18908
12	exp Mouth Neoplasms/dt, rt, th [Drug Therapy, Radiotherapy, Therapy]	12004	12	10 or 11	31054
13	11 or 12	23172	13	limit 12 to "reviews (maximizes specificity)"	427
14	limit 13 to ("systematic review" or systematic reviews as topic or "reviews (maximizes specificity)")	311	14	limit 13 to "therapy (best balance of sensitivity and specificity)"	211
15	limit 14 to "therapy (best balance of sensitivity and specificity)"	94	15	cohort analysis/ or exp longitudinal study/ or prospective study/ or retrospective study/	1878118
16	exp cohort studies/	1975209	16	(cohort adj2 (stud* or analy*)).mp.	658876
17	(cohort adj2 (stud* or analy*)).mp.	406269	17	prospective stud*.mp.	681889
18	prospective stud*.mp.	605092	18	Retrospective stud*.mp.	944493
19	Retrospective stud*.mp.	855586	19	15 or 16 or 17 or 18	2066842
20	16 or 17 or 18 or 19	2147234	20	12 and 19	6700
21	13 and 20	6330	21	13 or 14 or 20	7066
22	14 or 15 or 21	6596	22	limit 21 to (english language and yr="2014 -Current")	4423

23	limit 22 to (english language and yr="2014 - Current")	2036	23	conference*.pt.	4514886
			24	22 not 23	3570

For all 3 questions

Cochrane	
#1	MeSH descriptor: [Mouth Neoplasms] explode all trees
#2	(((oral or oropharyn* or hypopharyn* or lip or tongue or lingual or mouth* or "piriform sinus") NEAR/3 (cancer* or neoplas* or carcinoma* or tumo* or malignan*))):ti,ab,kw
#3	(((oral* or mouth*) NEAR/3 "potentially malignant lesion*")):ti,ab,kw
#4	#1 or #2 or #3 with Publication Year from 2014 to 2020, with Cochrane Library publication date Between Jan 2014 and Jan 2020, in Trials

Results by database

Medline	**3344**
Embase	**5264**
Cochrane Library	**1489**
Total	**10,097**

After the exclusion of duplicates, 7,684 references remained.

Inclusions and exclusions

Publications not in the English language, case reports, conference abstracts, trial protocols and comment/editorials/letters were excluded.

Eligibility for inclusion in the map

Question 1

- population: adult population
- intervention: none
- comparator: none
- outcomes: cancer of the oral cavity and oropharynx
- study design: observational studies and systematic reviews of these

Question 2
Inclusion criteria:

- population: asymptomatic adults in the general population
- index tests: any test alone or in combination with another
- comparator: none or any
- reference standard: as defined in the papers
- outcomes: sensitivity, specificity, positive predictive value, negative predictive value, any incidental findings

- study design: prospective and retrospective studies where a consecutive or random sample of participants received both the index test(s) and the reference standard, or where participants are randomised to different index tests but all receive the reference standard, and assessment in a cross-sectional manner.

Exclusion criteria:

- Case control studies and studies with longitudinal assessment of the reference standard

Question 3

- population: adults with screen-detected (opportunistically or not) oral cancer or potentially malignant lesions
- intervention: any management strategy (including conventional active treatment such as surgery, radiotherapy or 'watch and wait'
- comparator: any including no treatment or placebo
- outcomes: primary outcome – mortality. Secondary outcomes – morbidity, quality of life, anxiety
- study design: randomised controlled trials, cohort studies and systematic reviews of the above

Appendix 2 – Abstract reporting tables

Question 1: Is the natural history of oral cancer understood (progression from potentially malignant disorders to malignancy)?

Systematic reviews

TITLE	
Citation	Idrees et al (2020) (3)
BACKGROUND	
Study type	Systematic review and meta-analysis 33 studies published up to January 2020 n=12,838
Objectives	To assess the malignant potential rate of oral lichen planus using strict inclusion criteria and to explore the influence of associated risk factors
Components of the study	*Population* – Studies reporting malignant transformation rates for patients with oral lichen planus with the following inclusion criteria: • presence of a properly verified diagnosis of oral lichen planus • a clear description of the cancerous lesion developing at the same site as the verified oral lichen planus • follow-up period of at least 6 months prior to carcinoma development *Intervention* – N/A *Control* – N/A *Outcomes* – Malignant transformation rate, association between malignant transformation and risk factors
RESULTS	
Results	Malignant transformation rate for oral lichen planus without strict inclusion criteria: 1.2% Malignant transformation rate for oral lichen planus with strict inclusion criteria: 0.44% Risk of malignant transformation was higher for: • patients who smoked: odds ratio (OR) 4.62 • patients who consumed alcohol: OR 3.22 • patients who were seropositive for hepatitis C virus: OR 3.77 • patients who displayed a red lichen planus subtype: OR 0.37
Conclusions	Malignant transformation rates for oral lichen planus were lower when strict clinical and histopathological inclusion criteria area were applied. Certain risk factors may increase the risk of malignant transformation

TITLE	
Citation	Iocca et al (2020) (2)
BACKGROUND	
Study type	Systematic review and meta-analysis 92 studies published up to February 2019 n=34,393 (full text)
Objectives	To define malignant transformation rates to invasive cancer for oral potentially malignant disorders (OPMD) and the risk of development into cancer of mild vs moderate/severe oral dysplasia
Components of the study	*Population* – Studies reporting malignant transformation rates for patients with an OPMD or oral dysplasia *Intervention* – N/A *Control* – N/A *Outcomes* – Overall malignant transformation rate, malignant transformation rate for specific OPMD, association between dysplasia and malignant transformation
RESULTS	
Results	Overall malignant transformation rate for any OPMD: 7.9% (99%CI 4.9 to 11.5) Malignant transformation rates for specific OPMD: • oral lichen planus: 1.4% (99%CI 0.9 to 1.9) • oral leukoplakia: 9.5% (99%CI 5.9 to 14.0) • oral lichenoid lesions: 3.8% (99%CI 1.6 to 7.0) • oral erythroplakia: 5.2% (99%CI 2.9 to 8.0) • oral submucous fibrosis: 33.1% (99%CI 13.6 to 56.1) • oral proliferative verrucous leukoplakia: 49.5% (99%CI 26.7 to 72.4) Annual malignant transformation rates for specific OPMD: • oral lichen planus: 0.28% • oral leukoplakia: 1.56% • oral lichenoid lesions: 0.57% • oral erythroplakia: 2.7% • oral submucous fibrosis: 0.98% • oral proliferative verrucous leukoplakia: 9.3% Moderate/ severe dysplasia associated with a greater risk of malignant transformation than mild dysplasia (OR 2.4, 95%CI 1.5 to 3.8) (Oral erythroplakia annual malignant transformation rate obtained from full text. Other results from abstract)

Conclusions	The risk of malignant transformation varies for different OPMD. Moderate/ severe dysplasia has a higher risk of malignant transformation that mild dysplasia

TITLE	
Citation	Akrish et al (2019) (4)
BACKGROUND	
Study type	Systematic review 35 studies published between 1985 and 2018 n=297 (full text)
Objectives	To analyse oral proliferative verrucous leukoplakia, considering malignant transformation to verrucous carcinoma or squamous cell carcinoma and clinicopathologic features
Components of the study	*Population* – Studies with data on clinicopathologic features of oral proliferative verrucous leukoplakia in the premalignant and malignant stages *Intervention* – N/A *Control* – N/A *Outcomes* – Malignant transformation rate, clinical pathological features
RESULTS	
Results	Malignant transformation rate: 50% at an average of 57 months Most common locations for malignant transformation were: Gingiva, palate and buccal mucosa
Conclusions	Half of oral proliferative verrucous leukoplakia cases progressed to malignancy

TITLE	
Citation	Giuliani et al (2019) (5)
BACKGROUND	
Study type	Systematic review and meta-analysis 21 studies published up to June 2017 n=6,559 (full text)
Objectives	To assess the malignant potential rate to oral squamous cell carcinoma of oral lichen planus and oral lichenoid lesions
Components of the study	*Population* – Studies reporting malignant transformation rates for patients with oral lichen planus or oral lichenoid lesions *Intervention* – N/A *Control* – N/A *Outcomes* – Malignant transformation rate, risk factors for malignant transformation

RESULTS	
Results	Overall malignant transformation rate: 1.40% Overall annual malignant transformation rate: 0.2% Malignant transformation rate oral lichen planus: 1.37% Malignant transformation rate oral lichenoid lesions: 2.43% Female gender, red clinical forms and tongue site were reported to slightly increase the risk of malignant transformation
Conclusions	The malignant transformation rate was approximately 1 to 2% for oral lichen planus and oral lichenoid lesions. Certain risk factors may increase the risk of malignant transformation

TITLE	
Citation	Gonzalez-Moles et al (2019) (6)
BACKGROUND	
Study type	Systematic review and meta-analysis 82 studies published up to November 2018 n=26,742
Objectives	To assess the malignant transformation rate to oral squamous cell carcinoma of oral lichen planus, oral lichenoid lesions and oral lichenoid reactions and risk factors for cancer development (full text)
Components of the study	*Population* – Studies reporting malignant transformation rates for patients with oral lichen planus, oral lichenoid lesions and oral lichenoid reactions *Intervention* – N/A *Control* – N/A *Outcomes* – Malignant transformation rate, risk factors for malignant transformation
RESULTS	
Results	Malignant transformation rate: • oral lichen planus: 1.14% (95%CI 0.84 to 1.49) • oral lichenoid lesions: 1.88% (95%CI 0.15 to 4.95) • oral lichenoid reactions: 1.71% (95%CI 0.00 to 5.46) The malignant transformation rate was statistically significantly higher ($p<0.05$) when: • the exclusion criteria did not include presence of epithelial dysplasia • clinical and histopathological criteria were used for diagnosis • follow-up was at least 12 months • studies had a lower risk of potential bias

	Risk factors associated with malignant transformation: • tongue localization: relative risk (RR) 1.82 (95%CI 1.21 to 2.74), p=0.004 • presence of atrophic-erosive lesions: RR 4.09 (95%CI 2.40 to 6.9), p<0.001 • tobacco use: RR 1.98 (95%CI 1.28 to 3.05), p=0.002 • alcohol consumption: RR 2.28 (95%CI 1.14 to 4.56), p=0.02 • hepatitis C virus infection: RR 4.46 (95%CI 0.98 to 20.22), p=0.053
Conclusions	Malignant transformation rates were affected by study inclusion and exclusion criteria, study quality and follow-up period. Certain risk factors may increase the risk of malignant transformation

TITLE	
Citation	Saluja et al (2019) (7)
BACKGROUND	
Study type	Systematic review and meta-analysis 12 studies published up to December 2017 n=1,659 (full text)
Objectives	To assess the efficacy of cancer stem cells in predicting the risk of malignant transformation of OPMD to oral squamous cell carcinoma
Components of the study	*Population* – Studies reporting the prognostic significance of cancer stem cell markers in the malignant transformation of OPMD *Intervention* – N/A *Control* – N/A *Outcomes* – Risk of malignant transformation
RESULTS	
Results	Positive expression of cancer stem cell markers significantly associated with progression to oral squamous cell carcinoma (risk ratio 3.31, 95%CI 2.72 to 4.02) The authors concluded that variability in the cancer stem cell population makes it difficult to understand the exact biology of OPMD from a single cancer stem cell marker
Conclusions	Multi-marker panel investigations for cancer stem cells may be a prognostic indicator for risk of malignant transformation for OPMD

TITLE	
Citation	Alaizari et al (2018) (8)
BACKGROUND	
Study type	Meta-analysis 5 included studies (search date not stated in abstract)

	n not stated in abstract (full text not readily available)
Objectives	To assess the efficacy of DNA aneuploidy in predicting the risk of malignant transformation of OPMD to oral cancer
Components of the study	*Population* – Studies reporting the prognostic significance of DNA aneuploidy in the malignant transformation of OPMD *Intervention* – N/A *Control* – N/A *Outcomes* – Risk of malignant transformation
RESULTS	
Results	DNA aneuploidy significantly associated with progression to oral cancer (risk ratio 3.12, 95%CI 1.86 to 5.24)
Conclusions	DNA aneuploidy may be a prognostic indicator for risk of malignant transformation for OPMD

TITLE	
Citation	Aghbari et al (2017) (9)
BACKGROUND	
Study type	Systematic review and meta-analysis 57 studies (search date not reported) n=20,095 (full text)
Objectives	To assess the malignant transformation rate to oral squamous cell carcinoma of oral lichen planus and oral lichenoid lesions and risk factors for cancer development
Components of the study	*Population* – Studies reporting malignant transformation rates for patients with oral lichen planus and oral lichenoid lesions *Intervention* – N/A *Control* – N/A *Outcomes* – Malignant transformation rate, risk factors for malignant transformation
RESULTS	
Results	Overall malignant transformation rate for oral lichen planus (n=19,696): 1.1% (95%CI 0.9% to 1.4%) Malignant transformation rate for 14 studies using the 2003 World Health Organisation diagnostic criteria: 0.9% (95%CI 0.5% to 1.3%) Malignant transformation rate for oral lichenoid lesions (n=419): 2.5% (95%CI 1 to 4) Risk of malignant transformation was higher for: • smokers: OR 2 (95%CI 1.25 to 3.22)

	• alcoholics: OR 3.52 (95%CI 1.54 to 8.03) • patients with hepatitis C virus: OR 5 (95%CI 1.56 to 16.07)
Conclusions	Malignant transformation rates were affected by diagnostic criteria. Certain risk factors may increase the risk of malignant transformation

Individual studies

TITLE	
Citation	Chiang et al (2020) (10)
BACKGROUND	
Study type	Retrospective cohort study of patients detected through a screening programme, treated at 1 hospital in Taiwan between 2010 and 2012 n=617 Follow-up ≥5 years (to June 2018) (full text)
Objectives	To investigate the distribution and malignant transformation to oral cancer of OPMDs in people detected through screening
Components of the study	*Population* – Patients with oral cancer or OPMD detected through screening *Intervention* – N/A *Control* – N/A *Outcomes* –Malignant transformation rate, 5-year cumulative cancer-free interval rate, risk factors for malignant transformation
RESULTS	
Results	5-year cumulative cancer-free interval rate: 94.1% Annual malignant transformation rate: 1.16% Carcinoma development rate for different OPMDs: • candida hyperplasia: 13.6% • oral submucous fibrosis: 5.7% • homogenous leukoplakia: 4.6% • non-homogenous leukoplakia: 12.1% • verrucous hyperplasia: 21.3% Significant independent risk factors for transformation: • heavy betel quid chewing • verrucous hyperplasia • surgery refusal
Conclusions	Malignant transformation rates varied for different OPMD detected by screening. Certain risk factors may increase the risk of malignant transformation

TITLE	
Citation	Wils et al (2020) (11)
BACKGROUND	
Study type	Retrospective cohort study of patients treated at 1 centre in the Netherlands between 1997 and 2016 n=84 Follow-up ≥ 11 months (full text)
Objectives	To investigate whether assessing differentiated dysplasia besides World Health Organisation defined classic dysphasia improves risk assessment for the malignant transformation of oral leukoplakia to squamous cell carcinoma of the upper aerodigestive tract
Components of the study	*Population* – Patients with oral leukoplakia *Intervention* – N/A *Control* – N/A *Outcomes* – Malignant transformation rate, risk factors for malignant transformation
RESULTS	
Results	Malignant transformation rate: 30% (25/84) Risk of progression: • considering only classic dysphasia: Hazard ratio (HR) 3.26, p=0.002 • combining classic and differentiated dysplasia: HR 7.43, p=0.001 Loss of keratin 13 (CK13) combined with the presence of dysplasia was associated with greater risk of malignant progression (p=0.006)
Conclusions	Differentiated dysplasia was considered distinct from classic dysphasia and a prognostic histopathological marker for malignant transformation

TITLE	
Citation	Chaturvedi et al (2019) (12)
BACKGROUND	
Study type	Retrospective cohort study of patients treated between 1996 and 2012, recorded in a US healthcare organisation database n=4,886
Objectives	To investigate the risk of progression to oral cancer of oral leukoplakia and predictors of progression
Components of the study	*Population* – Patients with oral leukoplakia *Intervention* – N/A *Control* – N/A

	Outcomes – Oral cancer incidence, risk factors for malignant transformation
RESULTS	
Results	Oral cancer incidence was higher in patients with oral leukoplakia compared with the general population of patients recorded in the database (standardised incidence ratio 40.8, 95%CI 34.8 to 47.6) 5-year competing risk-adjusted absolute risk of progression from oral leukoplakia to oral cancer: • overall risk of malignant transformation: 3.3% (95%CI 2.7 to 3.9) • risk of malignant transformation with no dysplasia: 2.2% (95%CI 1.5% to 3.1%) • risk of malignant transformation with mild dysplasia: 11.9% (95%CI 7.1 to 18.1) • risk of malignant transformation with moderate dysplasia: 8.7% (95%CI 3.2 to 17.9) • risk of malignant transformation with severe dysplasia: 32.2% (95%CI 8.1 to 60.0)
Conclusions	Malignant transformation was higher in leukoplakia patients with dysplasia

TITLE	
Citation	Shearston et al (2019) (13)
BACKGROUND	
Study type	Retrospective cohort study of patients treated at 1 centre in Australia between 2006 and 2014 n=386 Mean follow-up not reported (full text)
Objectives	To investigate progression to oral squamous cell carcinoma for oral leukoplakia and risk factors for progression
Components of the study	*Population* – Patients with oral leukoplakia *Intervention* – N/A *Control* – N/A *Outcomes* – Malignant transformation rate, risk factors for malignant transformation
RESULTS	
Results	Malignant transformation rate: • patients with histopathological confirmation of oral leukoplakia (n=202): 1.49%. Average time to malignancy of 5.2 years • patients without histopathological confirmation of oral leukoplakia (n=184): 1.30%. Average time to malignancy of 4.9 years

	The authors reported that the groups that were more likely to transform to malignancy included: • older females • patients with a history of smoking • patients with a history of alcohol use • patients with leukoplakia on the tongue or floor of the mouth One third of patients who transformed to malignancy had oral epithelial dysplasia
Conclusions	Malignant transformation was slightly higher in patients who had histopathologically confirmed oral leukoplakia. Certain risk factors may increase the risk of malignant transformation

TITLE	
Citation	Shearston et al (2019) (15)
BACKGROUND	
Study type	Retrospective cohort study of patients treated at 1 centre in Australia between 2006 and 2014 n=218 Follow-up ≥18 months (full text)
Objectives	To investigate progression to oral squamous cell carcinoma for oral lichenoid conditions and risk factors for progression
Components of the study	*Population* – Patients with oral lichen planus, oral lichenoid lesions or oral lichenoid dysplasia *Intervention* – N/A *Control* – N/A *Outcomes* – Malignant transformation rate, risk factors for malignant transformation
RESULTS	
Results	Malignant transformation rate: • oral lichen planus (n=206): 0.49% • oral lichenoid lesions (n=31): 0% • oral lichenoid dysplasia (n=44): 6.81%. Average (±SD) time to malignancy of 4.6 ± 2.4 years
Conclusions	Oral lichenoid dysplasia lesions were at greater risk of malignant transformation than other lichenoid lesions

TITLE	
Citation	Wu et al (2019) (14)
BACKGROUND	
Study type	Retrospective cohort study of patients treated at 1 centre in China between 2000 and 2015

	n=2,628 Average follow-up 34.8 months (full text)
Objectives	To investigate risk factors for the malignant transformation of oral leukoplakia
Components of the study	*Population* – Patients with oral leukoplakia *Intervention* – N/A *Control* – N/A *Outcomes* – Malignant transformation rate, risk factors for malignant transformation
RESULTS	
Results	Malignant transformation rate: 1.7%. Mean interval to malignancy 26.7 months Independent prognostic factors for progression to malignancy: • nonhomogeneous lesions (p = 0.03) • high-risk dysplasia (p<0.01)
Conclusions	Malignant transformation rate was approximately 2%. Certain risk factors may increase the risk of malignant transformation

Question 2: Are there any accurate screening tests for the detection of oral cancer?

TITLE	
Citation	Simonato et al (2019) (16)
BACKGROUND	
Study type	Prospective cohort study of patients screened at 18 primary health care centres in Brazil between 2014 and 2015 n=1,765 (full text)
Objectives	To compare the detection of oral cancer by fluorescence visualization and conventional oral examination during population screening by general dental practitioners
Components of the study	*Population* – People receiving screening from a general dentist practitioner *Intervention* – In the first year: conventional oral examination. In the second year: conventional oral examination (all centres) plus fluorescence visualization (in 4/18 centres) *Reference standard* – Referral of any suspicious lesions, detected by any method, for diagnosis by a specialist in oral medicine. High risk lesions were biopsied *Outcomes* – Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) to detect oral squamous cell carcinoma (full text)
RESULTS	
Results	Two oral cancer cases were detected by screening Test performance of fluorescence visualization to detect oral squamous cell carcinoma: • sensitivity: 100% • specificity: 90.8% • PPV: 3.7% • NPV: 100% Test performance of conventional oral examination to detect oral squamous cell carcinoma: • sensitivity: 100% • specificity: 90.4% • PPV: 3.6% • NPV: 100% This study also reported test performance to detect oral potentially malignant disorders and epithelial dysplasia. These are not specified as

	outcomes of interest in the PICO for this question and are not reproduced (full text)
Conclusions	Test performance scores to detect oral squamous cell carcinoma were similar for fluorescence visualization and conventional oral examination

Question 3: Are there any studies looking at the effectiveness of treatment in screen detected (opportunistic or population programmes) oral cancer or potentially malignant lesions?

No studies were identified for this question.

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Question 1: Natural history (14 studies)

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Question 2: Screening tests (1 study)

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