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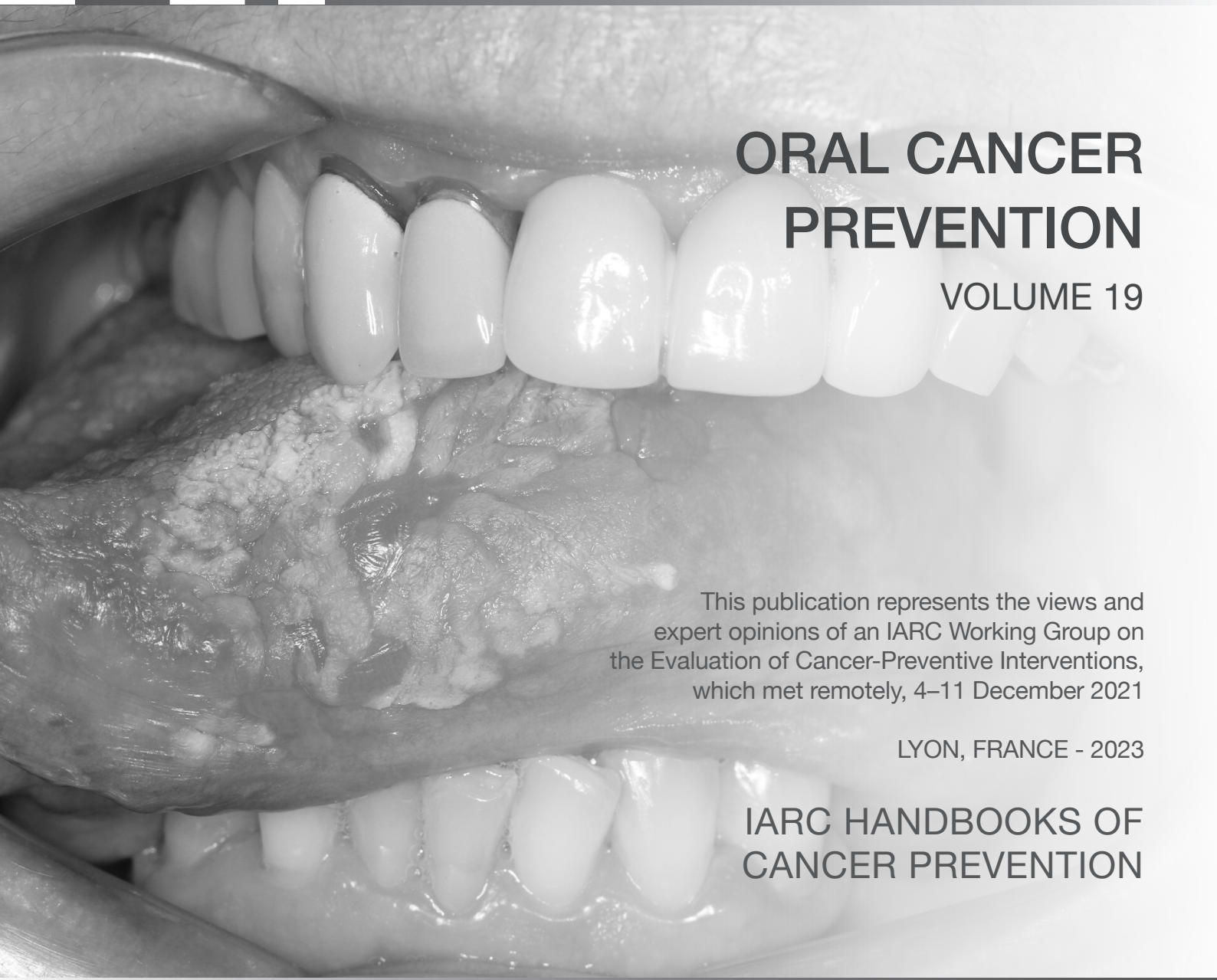

ORAL CANCER PREVENTION

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IARC HANDBOOKS OF CANCER PREVENTION

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4. SCREENING AND EARLY DIAGNOSIS OF ORAL CANCER

4.1 Screening methods and technologies

4.1.1 Clinical oral examination

The first-line approach to the identification of oral cancer and oral potentially malignant disorders (OPMDs) remains the standard clinical oral examination (COE). Traditionally, COE consists of a white-light visual examination and palpation of the oral cavity structures and the external facial and neck regions.

A routine can be established to examine each oral anatomical subsite in a consistent way. For example, one would first examine the lips/labial mucosae, the buccal mucosae, and the buccal aspects of the mandibular and maxillary gingivae, and then the lingual aspects of the mandibular gingivae, followed by examination of the palate (hard and soft), the floor of the mouth, the tongue, and the tonsils. A detailed description of how to examine the oral cavity for cancer is available in Ramadas et al. (2008b).

COE involves both a visual examination and a tactile examination (i.e. digital palpation). The neck is examined to identify enlarged lymph nodes or masses. There is no universally recognized, evidence-based determination of what constitutes an appropriate oral cancer screening examination. Li et al. (2013) described an expert consensus on what should be included in the cancer screening process for the general population in the USA. Abnormal oral mucosal findings indicative of oral cancer or OPMDs will lead to referral for further evaluation (Warnakulasuriya, 2020).

(a) Necessary training

Expertise in the screening and diagnosis of oral mucosal diseases varies substantially across different clinicians and community workers engaged in either organized or opportunistic screening activities, and these differences are linked to their different training backgrounds. A meta-analysis of eight studies comparing the knowledge, attitudes, and practices of dentists and physicians related to oral cancer and OPMDs concluded that dentists were better trained than physicians to perform COE and to recognize white or red lesions (Coppola et al., 2021). Educational requirements for competence in performing oral cancer screening are not universal, but they have been formalized in some countries, including the USA, where the Commission on Dental Accreditation has mandated that all graduating dentists be competent in performing screening for oral cancer. Such competencies are not mandated for medical school graduates, and the results from a survey showed variable training across medical schools in the United Kingdom (Carter et al., 2011).

The need to improve training for medical providers to perform COE was suggested long ago (Carter and Ogden, 2007; Shanks et al., 2011), and in one study most of the survey respondents indicated a desire for further education on the identification of oral cancer (Ni Riordain and McCreary, 2009). Interventions to train medical practitioners have been associated with improvements in knowledge, attitudes, and practices over the short term (Papadiochou et al., 2020). Web-based educational approaches seem feasible to facilitate teaching primary health-care workers to perform COE (Wee et al., 2016).

In terms of allied clinicians, dental hygienists may play a primary role in performing opportunistic COE at recall visits in dental offices (Clarke et al., 2018). Similar to the situation for medical education, nurses and nurse practitioners receive variable education on oral cancer screening (Carter et al., 2009). The perceived benefit of such education has been recognized (Patton et al., 2006; Li et al., 2020). In low-resource countries, there is evidence that community health-care workers can be successfully trained to perform oral cancer screening (Warnakulasuriya and Kerr, 2021).

Even though dentists receive training on performing COE and recognizing abnormalities, there is evidence to suggest that they often lack the skills to identify early lesions (Maybury et al., 2012) and that they may lack the decision-making skills to differentiate oral cancers and OPMDs from benign lesions (Kerr et al., 2020).

(b) Performance of COE

A recent analysis of nine studies (10 data sets) assessed the accuracy of COE to detect oral cancer and OPMDs (Walsh et al., 2021b). These studies varied widely in terms of the types of primary screeners performing COE (non-expert community health-care workers, dentists, physicians, or nurses), the settings in which the studies were performed, the definition of what constitutes a positive or negative finding, and the reference standard against which the results of COE performed by the primary screener were compared (clinical diagnosis by an expert and/or histological end-points). In all the studies, screeners were trained to perform COE. A negative COE finding was designated when the patients either had no discernible abnormality or had an abnormality that was deemed to be benign. Compared with the reference standard, non-expert screeners who designated the COE findings as negative performed very well (pooled specificity, 98%; 95% confidence interval [CI], 97–100%) (Table 4.1). The small overall false-positive rate (1 – specificity) was attributed to the large number of true-negative examinations (linked to the low prevalence of disease in the populations studied, which were mostly general populations). The ability of the screener to perform a risk assessment on detected abnormalities equated to the sensitivity of COE. A positive examination in patients with oral mucosal abnormalities showed heterogeneous sensitivity across studies, ranging from 50% (95% CI, 7–93%) to 99% (95% CI, 97–100%); the heterogeneity of the sensitivity prevented pooling of data. Compared with false-positive rates, the higher and heterogeneous overall false-negative rate (1 – sensitivity) was attributed to the relatively small number of patients with true-positive examinations in the general populations studied. The sensitivity and specificity outcomes were based on aggregate data of both oral cancer and OPMDs.

In an attempt to explore the performance of COE to detect oral cancer versus OPMDs, a re-analysis of the data was performed (Walsh et al., 2021b). In four of the data sets, no cancers were detected, and the performance of COE to detect OPMDs ranged from 60% to 81% for sensitivity and from 94% to 99% for specificity (Downer et al., 1995; Ikeda et al., 1995; Jullien et al., 1995). In one large data set in which only cancers were considered positive (i.e. OPMDs were considered negative) (Chang et al., 2011), 3 cancers were missed (i.e. false-negatives) out of

Table 4.1 Performance of COE for detection of oral cancer and OPMDs

Outcome measured	No. screened	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Reference
Oral cancer and OPMDs	2140	59 (39–78)	98 (97–99)	Mehta et al. (1986)
Oral cancer and OPMDs	1872	95 (92–97)	81 (79–83)	Warnakulasuriya and Pindborg (1990)
Oral cancer and OPMDs	3522	97 (96–98)	75 (73–77)	Warnakulasuriya and Nanayakkara (1991)
Oral cancer and OPMDs	2069	94 (90–97)	98 (98–99)	Mathew et al. (1997)
OPMDs	309	71 (44–90)	99 (98–100)	Downer et al. (1995)
OPMDs	985	61 (44–83)	99 (98–100)	Jullien et al. (1995)
OPMDs	1042	81 (64–93)	99 (98–99)	Jullien et al. (1995)
OPMDs	154	60 (32–84)	94 (88–97)	Ikeda et al. (1995)
Oral cancer	13 606	99 (97–100)	99 (99–99)	Chang et al. (2011)
Oral cancer	88	50 (7–93)	98 (92–100)	Sweeny et al. (2011)

CI, confidence interval; COE, conventional oral examination; OPMDs, oral potentially malignant disorders.
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a total of 285 cancers, yielding both sensitivity and specificity of 99%. Four of the data sets comprised both oral cancers and OPMDs (Mehta et al., 1986; Warnakulasuriya and Pindborg, 1990; Warnakulasuriya and Nanayakkara, 1991; Mathew et al., 1997), and among a combined total of more than 9000 people screened, only 1 cancer (out of 36; 2.8%) compared with 95 OPMDs (out of 2309; 4.1%) were falsely identified as screen-negative. [There was no stratification analysis of COE performance by outcome (cancer vs OPMDs). None of the studies specifically assessed whether health workers could adequately discriminate between oral cancers and OPMDs; nonetheless, the high sensitivity and specificity of COE to detect cancer would indicate that such discrimination could be successfully done by trained health workers.]

The overall certainty of the evidence underlying the reported accuracy of COE to detect oral cancer and OPMDs was rated as low (Walsh et al., 2021b).

(c) Mobile technology to improve the performance of COE

Over the past decade, advances in smartphones have enabled their use in health care. A novel approach to oral cancer screening is using mobile phone technology to transmit digital images from the field for specialists to review remotely. Three preliminary studies (two in India and one in Brazil) (Gomes et al., 2017; Birur et al., 2019; Vinayagamoorthy et al., 2019) were included in a recent systematic review exploring the accuracy of remote screening in low-resource settings (Walsh et al., 2021b). In data from 3600 remote screenings, the sensitivity ranged from 82% to 94%, and the specificity ranged from 72% to 100% (Table 4.2), although the overall certainty of the evidence was rated as very low.

Subsequently, Haron et al. (2023) compared the accuracy of COE and the decision to refer (i.e. lesions suspicious for oral cancer or OPMDs) performed on site with those based on clinical images sent via the Mobile Mouth Screening Anywhere (MeMoSA) smartphone application. Non-specialists were trained to capture the digital images. For remote assessment and referral decision, the sensitivity was 94.0% and the specificity was 95.5%.

The feasibility of community health workers using a prototype mobile technology to perform oral cancer screening was evaluated in rural India (Bhatt et al., 2018). The screening process

Table 4.2 Performance of remote screening (with mobile phone technology) for detection of oral cancer and OPMDs

Outcome measured	No. screened	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Reference
Oral cancer and OPMDs	55	82 (57–96)	100 (91–100)	Gomes et al. (2017)
Oral cancer and OPMDs	3414	85 (81–88)	99 (99–100)	Birur et al. (2019)
Oral cancer and OPMDs	131	94 (70–100)	72 (63–80)	Vinayagamoorthy et al. (2019)

CI, confidence interval; OPMDs, oral potentially malignant disorders.
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was well accepted by this high-risk local population, which traditionally had limited access to specialized health-care providers; it also had a positive impact on the social standing of the community health workers using the prototype.

Collectively, these studies have shown opportunities to develop oral cancer screening programmes using technology based on mobile phone photography.

4.1.2 Mouth self-examination

The oral cavity is easily accessible for examination, and most OPMDs and oral cancers are readily visible (see Section 1.3.1), which facilitates mouth self-examination (MSE). Almost 50 years ago, Glass et al. (1975) recommended teaching MSE as part of cancer prevention programmes; after clinical examination, each patient was taught the technique under supervision and encouraged to repeat it every month. Worldwide, MSE is being taught to apparently healthy populations as part of numerous public awareness programmes to promote early detection of oral cancer, particularly in populations at high risk (tobacco smokers and/or alcohol drinkers) (Hussain and Sullivan, 2013; Jornet et al., 2015; Mishra and Bhatt, 2017; Shrestha and Maharjan, 2020).

(a) Description of the technique

To perform MSE, the person stands in front of a mirror under good light to visualize all parts of the oral cavity and the visible parts of the oropharynx. The procedure is a comprehensive examination, which is divided into eight steps: facial symmetry, lips, gingivae, buccal mucosae, tongue and floor of the mouth, palate, oropharynx, and lateral aspect of the neck. This is followed by digital palpation of these structures using the index finger in the same sequence as COE.

The main advantages of MSE are the low cost, the possibility of performing the examination in remote, low-resource areas without diagnostic infrastructure, and increased awareness about oral diseases. The disadvantages are the impact of overdiagnosis of oral diseases, unnecessary referrals, and potential false-negative findings.

(b) Compliance with and performance of MSE for screening

Mathew et al. (1995) were the first to assess the feasibility and performance of MSE in a large trial, in Trivandrum, Kerala, India. About 10 000 copies of a brochure describing risk factors for oral cancer, the appearance of OMPDs and oral cancer, and the method for MSE were distributed to 9000 households by college students in 9 villages over a period of 10 days. In some situations, the students also demonstrated the procedure to the villagers. One week later, a survey

was conducted. Of about 22 000 eligible individuals, only 8028 (36%) had read the brochure and performed MSE, of whom 247 identified an oral lesion and reported to a referral clinic. A benign lesion was diagnosed in 97 cases (39%), and 51 individuals (21%) had normal oral variations. [The accuracy of MSE against clinical diagnosis was not reported.]

Scott et al. (2010) reported the results of a pilot study of diagnostic accuracy of MSE in smokers aged ≥ 45 years who were recruited from a list of general practitioners in south-eastern London, United Kingdom. COE was performed by a dentist in 53 participants and identified OPMDs in 12 participants (22%). Without knowing the results of the dentist's examination, all of the participants received a leaflet on "how to spot mouth cancer early", with details of MSE, and were asked to proceed with self-examination in the room. Most of the participants (39; 74%) found MSE easy to perform. A total of 23 participants (43%) reported noticing one or more lesions. The sensitivity of MSE was 33%, and the specificity was 54%. [The Working Group noted the poor performance of the test, leading to a risk of false reassurance for those with false-negative results and unnecessary anxiety for those with false-positive results.]

Elango et al. (2011) analysed the effectiveness of MSE in coastal villages of Kerala, India, in a high-risk population of 57 704 individuals. A brochure was distributed with information on risk factors for oral cancer and the MSE technique, and instructions to report to an oral cancer screening clinic if any suspicious lesions were identified. Four weeks after the brochure was distributed, trained health workers performed COE on 34 766 available individuals. A total of 30 342 individuals (87%) had practised MSE; 987 (3%) reported not knowing how to perform MSE, 1751 (5%) reported disinterest, and 1580 (5%) did not report any reason. Of the available individuals, 791 (2%) refused to be examined by a health worker. Only 54 individuals identified a suspicious lesion by MSE (of which 39 were confirmed as OPMDs), whereas 219 individuals had a suspicious lesion detected by the health workers. The sensitivity of MSE was 18.0%, and the specificity was 99.9%.

In a study conducted in the Buksa tribal community in Dehradun District (India), out of 539 participants, 220 (40.8%) practised MSE. The prevalence of oral mucosal lesions identified by COE performed by a health worker was 213 (39.5%), whereas only 69 lesions (12.8%) were detected by MSE. The sensitivity was 24.6%, and the specificity was 87.4%. The sensitivity varied from 10.2% for white lesions to 72.7% for ulcers, and the specificity varied from 92.4% for difficulty in mouth opening to 99.3% for red lesions (Shah et al., 2020). In an MSE training programme conducted in this tribal community (Singh et al., 2017), 85 participants attended a health education lecture on MSE and oral cancer. The participants were then asked to perform MSE and report the presence of any abnormalities or oral lesions. Of the 77 study participants who performed MSE, 9 detected a lesion.

The efficacy of MSE was also tested as an alternative to follow-up hospital visits in treated patients with oral cancer (Vaishampayan et al., 2017). MSE is included in the contents of new technologies such as mobile apps for oral cancer awareness (Deshpande et al., 2019).

4.1.3 Adjunctive techniques

An adjunct is defined as a technique or test that if applied in a screening or diagnostic setting would facilitate the detection or assessment of an abnormal lesion. A screening adjunct is not the same as a diagnostic adjunct, and this distinction is important. A screening adjunct is applied to all apparently healthy individuals undergoing oral cancer screening (as part of a population screening programme, or opportunistically to patients attending dental offices) with the sole aim of improving the ability of a screener

to detect disease in a population. A diagnostic adjunct is typically applied only to patients with abnormal mucosal findings after COE, to better characterize such findings and guide clinical decisions.

In the hands of primary care clinicians, the distinction between a screening adjunct and a diagnostic adjunct is subtle. Hypothetical differences might be that occult or small lesions (i.e. disease that is not readily visible during COE) would be more likely to be detected when the technique is used as a screening adjunct (i.e. when COE and the adjunctive technique are used sequentially). In the hands of expert clinicians, such adjunctive techniques might be used in a diagnostic way to facilitate selection of the site of biopsy to aid in mapping or assessing the margins of disease for the purposes of excision. In addition, these techniques might be used in the surveillance setting to monitor patients with OPMDs or with a history of oral cancer who are at risk of malignant development or recurrence (Kerr, 2020).

The adjuncts used in a screening setting are typically point-of-care technologies that provide macroscopic or wide-field information about the entire mouth (i.e. when used as a screening adjunct) or about specific abnormal areas (i.e. when used to examine a lesion or lesions detected by COE) (Kerr, 2020). Table 4.3 compares the utility of adjunctive techniques.

(a) Visualization adjuncts

Visualization or optical adjuncts include devices or machines that expose tissues in vivo to various wavelengths of light, generating optical signals in real time. These adjuncts work on the premise that the optical properties of diseased tissues differ from those of normal tissue (Kerr, 2020).

(i) Tissue autofluorescence

Tissue autofluorescence devices are hand-held and generate violet-blue light (in the 400–450 nm range). This light excites naturally occurring tissue fluorophores, i.e. molecules such as flavin adenine dinucleotide (FAD) and reduced nicotinamide adenine dinucleotide (NADH) in the epithelium and collagen or elastin cross-links in the submucosa. The result is visible fluorescence emission, which enables clinicians to visually scan the mucosa in a darkened environment to detect disruptions in natural tissue autofluorescence (Poh et al., 2010). Two early case series of OPMDs harbouring carcinoma or high-grade dysplasia demonstrated that such lesions exhibited a characteristic loss of fluorescence visualization (fluorescence visualization loss [FVL]), in contrast to normal tissue, which shows normal fluorescence (fluorescence visualization retained [FVR]) (Lane et al., 2006; Poh et al., 2007; Fig. 4.1).

In a single, low-quality study, autofluorescence as a screening adjunct showed no difference compared with COE alone (Simonato et al., 2019). Autofluorescence has been evaluated almost exclusively as a diagnostic adjunct in accuracy studies. A recent meta-analysis of these studies reported a pooled sensitivity of 88% (95% CI, 80–93%) and a pooled specificity of 61% (95% CI, 44–75%) compared with histopathological outcomes, i.e. any grade of oral epithelial dysplasia (OED), carcinoma in situ, or oral squamous cell carcinoma (OSCC) was rated as a positive reference outcome (Table 4.4; Walsh et al., 2021b). The low specificity is attributed to the preponderance of benign lesions that demonstrate FVL (i.e. confounder lesions that yield false-positive outcomes), predominantly inflammatory lesions (such as geographic tongue or erythematous candidiasis), non-inflammatory vascular changes, or pigmented lesions, all of which absorb blue light. Specificity may be increased in primary dental settings through

Table 4.3 Comparison of adjunctive techniques for screening or diagnosis of oral cancer and OPMDs

Technique	Inherent advantages	Inherent disadvantages	Sensitivity	Specificity	Benefits for screening	Disadvantages for screening	Costs for screening	Costs for assessment	Relevance to screening	Current state of development
Autofluorescence	Non-invasive, real-time, hand-held	Requires darkened room; infection-control supplies needed	High	Low	Minimal	Challenging for field population screening; interpretation is challenging for non-experts	Single purchase of device; purchase of infection-control supplies	None, other than time for clinician if used in opportunistic setting	Unclear	Commercially available in some countries
Narrow-band imaging	Non-invasive, real-time	Large, expensive unit; endoscope requires sterilization between patients	High (small number of studies)	High (small number of studies)	Minimal	Impossible for field population screening	Prohibitively high cost for opportunistic screening	None, other than time for clinician if used in opportunistic setting	Not likely	Commercially available in some countries
Tissue reflectance	Non-invasive, real-time, hand-held	Requires darkened room; infection-control supplies needed; requires consumable supplies; requires rinsing steps	High	Very low	None	Interpretation is challenging for non-experts; significant overdiagnosis	Single purchase of device; purchase of infection-control supplies; purchase of rinse	None, other than time for clinician if used in opportunistic setting	Not relevant	Commercially available in some countries
Vital staining	Non-invasive, real-time	Uses consumable supplies; requires rinsing steps; can be messy (stains skin/clothing)	Intermediate	Intermediate	Minimal	Interpretation is challenging for non-experts	Purchase of kits	None, other than time for clinician if used in opportunistic setting	Not likely	Commercially available in some countries, or may be easily prepared from raw materials

Table 4.4 Performance of autofluorescence for detection of oral cancer and OPMDs

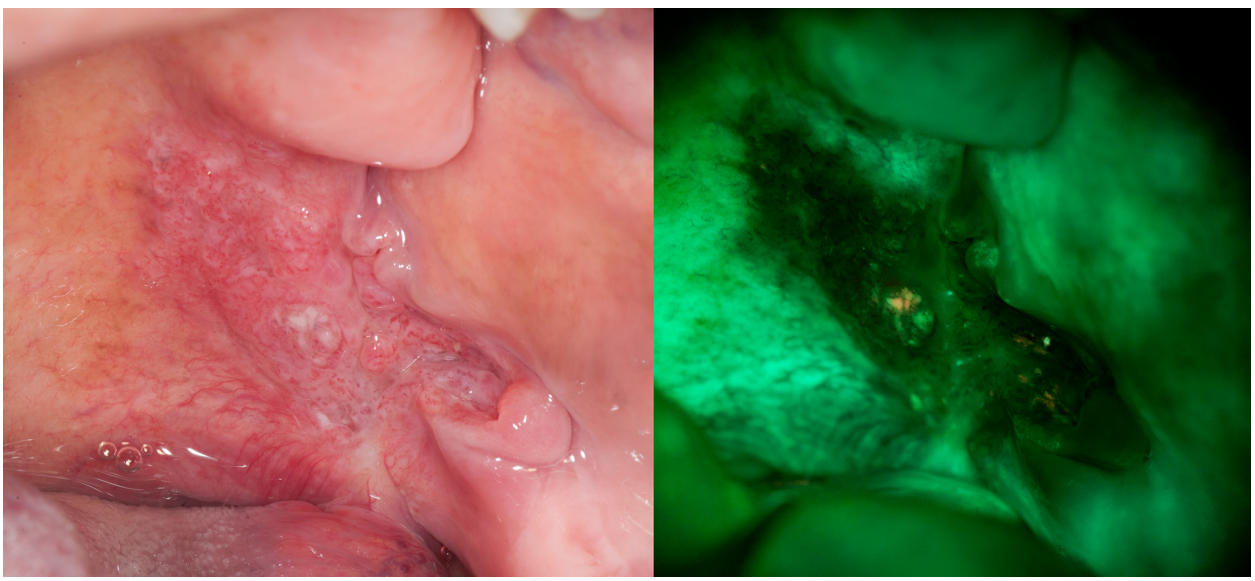
Reference	No. of studies	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Walsh et al. (2021b)	16	2140	OED (any grade), CIS, OSCC	88 (80–93)	61 (44–75)

CI, confidence interval; CIS, carcinoma in situ; OED, oral epithelial dysplasia; OPMDs, oral potentially malignant disorders; OSCC, oral squamous cell carcinoma.

adequate training and/or by reassessing patients with FVL lesions to rule out benign inflammatory lesions (Bhatia et al., 2014; Laronde et al., 2014). False-negative outcomes may occur in patients with dysplastic OPMDs, largely in homogeneous leukoplakias with histopathological evidence of mild OED, but in rare cases even in OSCCs (Truelove et al., 2011). Occult lesions (i.e. lesions not detected by COE) have been detected with autofluorescence, and a small fraction of them harboured OED (Truelove et al., 2011). These results, coupled with the fact that most of the accuracy studies were not generalizable to a primary care dental setting, led an expert panel to recommend against the use of tissue autofluorescence devices by frontline clinicians as screening or diagnostic adjuncts for OPMDs (Lingen et al., 2017a).

One issue that deserves consideration is the mucosal changes associated with chewing of smokeless tobacco or areca nut products. These changes can cause substantial hyper-reflectance (i.e. a bright white signal) as a result of the effect of surface debris on the mucosa (i.e. betel chewers' mucosa), keratosis (such as smokeless tobacco keratosis), or increased collagen deposition (i.e. oral submucous fibrosis). False-positives are also common due to the preponderance of reactive pigmented lesions (i.e. melanosis) in users of smokeless tobacco or areca nut products. Collectively, these findings can make interpretation challenging, and there are no validated

Fig. 4.1 Oral squamous cell carcinoma involving the left retromolar trigone



The image on the left is under white light. The image on the right displays fluorescence visualization loss (FVL).
Courtesy of Alexander Ross Kerr.

Table 4.5 Performance of narrow-band imaging for detection of oral cancer and OPMDs

Reference	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Piazza et al. (2010)	97	Oral and oropharyngeal SCC	96[a]	98[a]
Yang et al. (2013)	317	OED (any grade), CIS, SCC	87 (78–96)	94 (91–97)

CI, confidence interval; CIS, carcinoma in situ; OED, oral epithelial dysplasia; OPMDs, oral potentially malignant disorders; SCC, squamous cell carcinoma.
[a] 95% CI not reported.

objective measures to record or document autofluorescence outcomes.

(ii) Narrow-band imaging

Narrow-band imaging (NBI) is an endoscopic adjunctive technique that is used in the aerodigestive tract to evaluate the surface texture and vascular patterns of the mucosa. NBI units simultaneously emit two distinct narrow bands of light: one in the blue-green range (400–430 nm), which helps delineate superficial vasculature (blood vessels appear brown), and the other in the green range (525–555 nm), which delineates thicker vessels in the submucosa (they appear cyan). The endoscopic NBI unit also facilitates the photographic capture of images. Compared with healthy tissues, OSCC and OED may exhibit abnormal neovascular (angiogenic) patterns; this is the premise for the utility of NBI in the oral cavity.

Based on two studies (Piazza et al., 2010; Yang et al., 2013), the sensitivity and specificity compared with histopathological outcomes (i.e. any grade of OED, carcinoma in situ, or OSCC as a positive reference outcome) ranged from 87% to 96% and from 94% to 98%, respectively (Table 4.5). In both studies, NBI was significantly more accurate than white-light evaluation alone. [The studies were of low quality.]

A commercially available and comparatively inexpensive hand-held multimodal visualization adjunctive device sequentially uses three lights: a white light, a 405 nm violet light to detect autofluorescence, and a 545 nm green light, which is of a similar wavelength to the green light used in NBI. The green light was incorporated into the device to better identify changes in vascularity of OPMDs. Two accuracy studies reported data on the green light compared with histopathological outcomes. They demonstrated low sensitivity and specificity: a sensitivity of 40.0% (95% CI, 24.9–56.7%) and a specificity of 71.0% (95% CI, 63.8–78.0%) (Lalla et al., 2016) and a sensitivity of 78.4% (95% CI, 61.8–90.2%) and a specificity of 15.4% (95% CI, 4.4–34.9%) (Sharma et al., 2021). [The results showed wide heterogeneity, suggesting that this device is not a surrogate for an NBI unit.]

[An NBI unit is a sophisticated and expensive piece of equipment, unlikely to be used for screening by frontline clinicians or in low-resource settings.]

(iii) Tissue reflectance

This diagnostic adjunct was first developed for the evaluation of cervical neoplasia and then adapted for use in the oral cavity (Kerr et al., 2006). The proposed basis for its use in the oral cavity is that OPMDs harbouring OSCC or OED have a differential tissue reflectance compared with normal mucosa. The evaluation of OPMDs is performed in two steps: topical application of an acetic acid solution, followed by direct illumination using a low-wavelength (blue-white) light source. In some of these platforms, the light is generated by a chemical reaction (hence the term "chemiluminescence"), whereas in others the source is a light-emitting diode (LED).

Table 4.6 Performance of tissue reflectance for detection of oral cancer and OPMDs

Reference	No. of studies	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Lingen et al. (2017b)	4	307	Clinically evident, suspicious lesions	81 (71–89)	69 (63–75)
Walsh et al. (2021b)	6	432	OED (any grade), CIS, SCC	94 (35–99)	19 (3–67)

CI, confidence interval; CIS, carcinoma in situ; OED, oral epithelial dysplasia; OPMDs, oral potentially malignant disorders; SCC, squamous cell carcinoma.

A recent meta-analysis of five accuracy studies (Walsh et al., 2021b) yielded poor specificity compared with histopathological outcomes of OED or OSCC, with a pooled sensitivity of 94% (95% CI, 35–99%) and a pooled specificity of 19% (95% CI, 3–67%) (Table 4.6). This technology is currently marketed for use in combination with toluidine blue vital staining. Based on four studies, the combined use of these two adjuncts led to improvements in the pooled sensitivity to 81% (95% CI, 71–89%) and in the pooled specificity to 69% (95% CI, 63–75%) (Lingen et al., 2017b). The studies were considered to have serious issues of risk of bias and indirectness of evidence, which downgraded the quality level of the evidence to very low.

Collectively, these findings led an expert panel to recommend against the use of tissue reflectance devices by general dentists (Lingen et al., 2017a).

(b) Vital staining

Vital staining involves the topical application of a dye to the entire oral mucosa as a screening adjunct, or more commonly as a diagnostic adjunct to assess abnormal mucosal lesions. Most of the research on vital staining is related to the use of toluidine blue and Lugol's iodine.

(i) Toluidine blue

The use of toluidine blue vital staining as a diagnostic adjunct for assessing OPMDs was first reported more than 50 years ago by Niebel and Chomet (1964). The mechanism of action of toluidine blue remains unclear, but it is probably related to its affinity for nuclear material in the context of increased cellular permeability in OSCC and high-grade OED. Toluidine blue stain may be prepared as a 1% or 2% solution or is available commercially in pre-prepared packages or bottles. It is used in conjunction with a 1% acetic acid solution; acetic acid is applied first, followed by toluidine blue, and then acetic acid again (Kerr, 2020). A positive test is commensurate with dark blue staining (Fig. 4.2).

Toluidine blue was tested as a screening adjunct in a community-based randomized controlled trial (RCT) in 7975 people at high risk for oral cancer. Those identified as test-positive (i.e. with positive toluidine blue staining) had a 21% lower incidence rate of OSCC at 5 years compared with the control group (COE only); this result was not statistically significant (Su et al., 2010). In a later systematic review, this study was judged to have high concerns regarding applicability, due to patient selection, and unclear risk of differential verification bias related to the use of a national cancer registry as a reference standard (Walsh et al., 2013).

Most of the literature available for toluidine blue is about its use as a diagnostic adjunct. A recent meta-analysis of 20 accuracy studies, predominantly using toluidine blue as a single stain, reported a pooled sensitivity of 86% (95% CI, 79–90%) and a pooled specificity of 68% (95% CI, 58–77%) compared with histopathological end-points (i.e. any grade of OED or OSCC); the certainty of the evidence was rated as low to very low (Table 4.7; Walsh et al., 2021b). There was broad heterogeneity in accuracy, which may be

Table 4.7 Performance of vital staining for detection of oral cancer and OPMDs

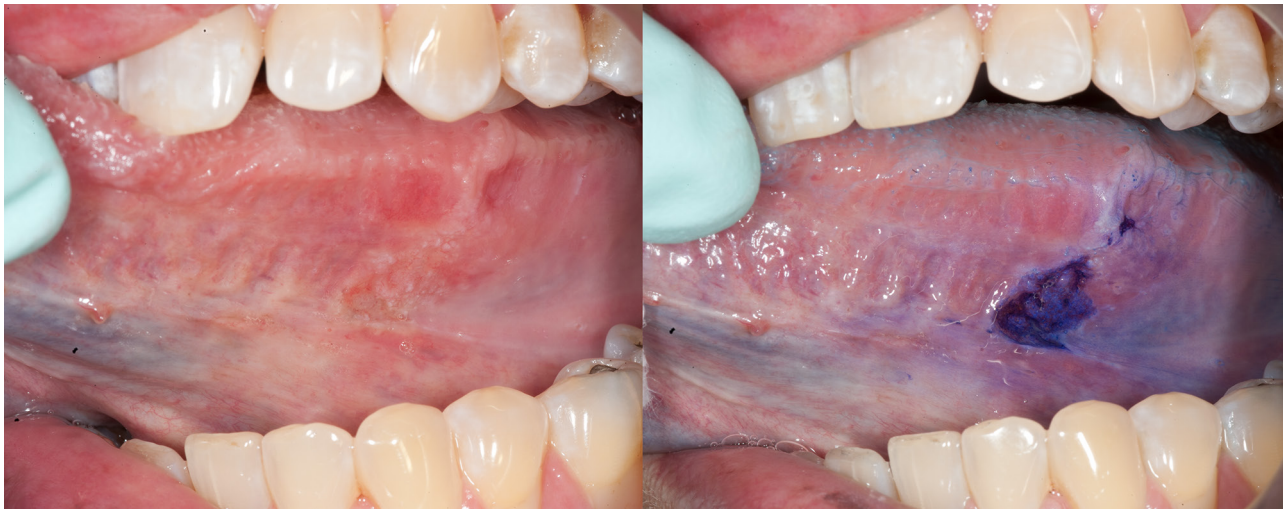
Reference	No. of studies	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Walsh et al. (2021b)	21	1780	OED (any grade), CIS, SCC	86 (79–90)	68 (58–77)

CI, confidence interval; CIS, carcinoma in situ; OED, oral epithelial dysplasia; OPMDs, oral potentially malignant disorders; SCC, squamous cell carcinoma.

attributed to several factors, including the diversity of OPMDs tested (i.e. a higher percentage of high-grade OED, carcinoma in situ, or OSCC will lead to higher sensitivity) (Chainani-Wu et al., 2015) and variability both in the testing protocols and in the interpretation of light or equivocal staining patterns.

Vital staining has potential for both false-positives and false-negatives, and the clinician's experience is critical. False-positives may occur because toluidine binds to benign inflammatory, ulcerative, or regenerating tissues. In addition, the dye may be mechanically retained in the crevices of rough or fissured lesions and the filiform papillae. False-negatives may be due to the inability of the dye to penetrate through thick hyperkeratotic lesions (e.g. homogeneous leukoplakia). In most of the study populations, there is a lower ratio of traumatic and inflammatory oral lesions to OPMDs or OSCCs than would be expected in a general population. Given that primary care clinicians and healthcare workers will encounter a blend of mucosal abnormalities that reflects the general population, even higher false-positive and false-negative rates may be anticipated. Training in the use of toluidine blue may reduce the number of false-positive and false-negative outcomes (Li et al., 2019), and a follow-up visit for repeated staining after allowing sufficient time for traumatic and inflammatory lesions to resolve has long been recommended to improve specificity (Mashberg, 1980).

Fig. 4.2 Oral squamous cell carcinoma involving the left lateral border of the tongue



The image on the left is under white light. The image on the right displays positive toluidine blue staining (royal blue). Note the small satellite of blue staining superiorly.
Courtesy of Alexander Ross Kerr.

Collectively, these findings led an expert panel to recommend against the use of vital staining as a diagnostic adjunct for OPMDs by general dentists (Lingen et al., 2017a).

(ii) Lugol's iodine and other vital stains

Lugol's iodine, named after the French physician Lugol, stains for glycogen content. Therefore, normal non-keratinized oral mucosa will preferentially retain the stain.

Given the contrasting staining effects of Lugol's iodine and toluidine blue, the two agents have been tested in combination to improve the specificity of toluidine blue staining in diagnostic accuracy studies for oral cancer and OPMDs (Epstein et al., 1992; Nagaraju et al., 2010; Chaudhari et al., 2013).

A few other vital stains, such as methylene blue and rose bengal, have a similar staining profile and performance to toluidine blue (Chen et al., 2007; Du et al., 2007).

4.1.4 Cytology and quantitative DNA cytometry

(a) Cytology

The use of cytology was introduced by Papanicolaou and Traut (1943) to detect cervical cancer. Since the 1950s, exfoliative cytology and then brush biopsy cytology were increasingly used as practical, low-risk, and low-cost diagnostic tools for the initial evaluation of OPMDs and oral cancer (Silverman, 1959; Sciubba, 1999; Böcking et al., 2011; Koch et al., 2011; Nanayakkara et al., 2016).

Oral cavity samples are collected with a wooden or metallic spatula (scrape biopsy or exfoliative biopsy), a curette, or a cytological brush (cytobrush biopsy), which is rubbed or scraped (in the case of a spatula) or rotated (in the case of the cytobrush) on the surface of the lesion and then spread onto a glass slide for analysis. Exfoliative cytology collects only superficial cells, whereas cytobrushes can collect superficial, intermediate, and even basal cells (i.e. transepithelial sampling). The malignant or benign nature of the oral lesion is usually evaluated with computer-assisted analysis (Sciubba, 1999; Acha et al., 2005). Epithelial cells collected with a wooden or metallic spatula are usually scarce and can exhibit nuclear and cytoplasmic distortion (Ogden et al., 1992). Cytobrushes improve the capacity to harvest oral mucosa cells and the quality of smears. Although transepithelial sampling can cause some discomfort to the patient, the brush must penetrate deeper (indicated by pinpoint bleeding) in order to collect basal cell layers. This is necessary because dysplastic and early invasive cancer cells are first detected in the basal cell layer (Acha et al., 2005).

Usually, slides are immediately fixed with 95% ethyl alcohol (96° GL), which enables further staining with routine staining methods, such as Papanicolaou, haematoxylin and eosin (H&E), periodic acid–Schiff (PAS), or Feulgen techniques, among others (Pérez-de-Oliveira et al., 2020).

Subsequent laboratory processing methods include simple centrifugation, cytocentrifuge preparation, or cell blocks. The cytocentrifuge approach, which was developed to overcome the issues of insufficient material when using simple centrifugation, enables better results in processing specimens. Fresh samples are collected in anticoagulant vials, loaded into an automated cytospin machine, and centrifuged. Slides containing smears prepared by the cytospin technique are then fixed in 95% ethyl alcohol for 20–30 minutes and stained with H&E, Papanicolaou, or PAS techniques (Qamar et al., 2018). A modified Papanicolaou staining procedure can be carried out in clinical settings that require faster decision-making processes (Thakur and Guttikonda, 2017).

In liquid-based cytology, the cytobrush-collected specimen is placed into a vial containing preservative fluid before transportation to the

laboratory where the specimen is processed, i.e. with cytospin and staining (modified Papanicolaou, or Feulgen in the case of DNA ploidy; see below) or for flow cytometry (Hutchinson et al., 1994; Khandelwal and Solomon, 2010; Olms et al., 2018). In the CDx system, the cytology results are reported as positive (for dysplasia or carcinoma), atypical (cellular changes of uncertain diagnosis), negative (normal cells), or inappropriate (incomplete sample) (Sciubba, 1999; Mehrotra et al., 2011; Nanayakkara et al., 2016). In other reporting systems, the categories may be different.

Cytology with exfoliative biopsy yields high false-negative rates (up to 31%) (Folsom et al., 1972). Modified liquid-based cytology with brush biopsy improves the diagnostic accuracy of cytology for OPMDs and oral cancer (Delavarian et al., 2010; Navone et al., 2011; Deuerling et al., 2019). When the preparation methods of conventional cytology (transfer procedure to glass slides) and liquid-based cytology are compared, liquid-based preparations show a more uniform distribution and less cellular overlapping, cellular deformation, mucus, microbial colonies, and debris compared with those of conventional cytology (Olms et al., 2018). Liquid-based platforms also have technical advantages, including (i) enabling immediate fixation of cells while removing unwanted harvested material (e.g. mucus and debris), (ii) producing thin layers with a clear background and producing more homogeneous samples than conventional smears, and (iii) reducing the proportion of unsatisfactory samples (Hayama et al., 2005; Deuerling et al., 2019); however, the higher cost can be a substantial problem in low-resource settings.

The exfoliative and brush biopsy techniques were compared in a prospective study of patients with leukoplakia (116 lesions) and lesions with a suspicion of malignancy (76 lesions) (Nanayakkara et al., 2016). When only positive results were considered ["high-risk" lesions defined as smears with any degree of dysplasia or malignant cells], compared with histopathological end-points of OSCC, the brush technique had a sensitivity of 89.6% and a specificity of 100%, and the exfoliative technique had a sensitivity of 60.4% and a specificity of 95.2%. When the histopathological end-points included moderate dysplasia or worse, the accuracy increased.

Recent reviews of the performance of cytology for detection of oral cancer and OPMDs are presented in Table 4.8. In a review and meta-analysis of 16 studies (Lingen et al., 2017b), cytology in patients with OPMDs had the highest accuracy among all reviewed adjuncts, with a sensitivity of 92% (95% CI, 86–98%) and a specificity of 94% (95% CI, 88–99%).

A recent review of 24 data sets compared the accuracy of cytology when using a cytobrush (n = 16) or scraping (n = 3) to harvest cells. The overall sensitivity was 90% (95% CI, 82–94%), and the specificity was 94% (95% CI, 88–97%). For cytobrush, the sensitivity was 91% (95% CI, 81–96%) and the specificity was 94% (95% CI, 87–97%); for scraping, the sensitivity was 93% (95% CI, 87–96%) and the specificity was 92% (95% CI, 81–97%) (Walsh et al., 2021a).

Table 4.8 Performance of cytology for detection of oral cancer and OPMDs

Reference	No. of studies (data sets)	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Lingen et al. (2017b)	16	2148	Clinically evident, suspicious lesions	92 (86–98)	94 (88–99)
Walsh et al. (2021a)	24	1950	Oral cancer and OPMDs	90 (82–94)	94 (88–97)

CI, confidence interval; OPMDs, oral potentially malignant disorders.

Table 4.9 Performance of DNA cytometry for detection of oral cancer and OPMDs

Reference	No. of patients	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Maraki et al. (2004)	98	98	Oral cancer	100[a]	97.4[a]
Ng et al. (2012)	171	199	Oral cancer and OPMDs	89.3[a]	96.5[a]
Walsh et al. (2021a)[b]	216	525	Oral cancer and OPMDs	76 (68–82)	98 (72–99)

CI, confidence interval; OPMDs, oral potentially malignant disorders.
[a] 95% CI not reported.
[b] Meta-analysis with 5 studies.

In a prospective trial, Sciubba (1999) analysed the accuracy of brush biopsy with computer-assisted sample analysis. Of the 298 cases with lesions judged to be clinically suspicious that underwent brush and scalpel biopsy [excisional biopsy], 102 were malignant. The sensitivity of brush biopsy was 100%, and the specificity was 100% for positive results [definitive cellular evidence of epithelial dysplasia or carcinoma] and 92.9% for atypical results [abnormal epithelial changes of uncertain diagnostic significance].

To evaluate the feasibility of oral brush biopsy in resource-constrained settings, Mehrotra et al. (2008) evaluated 94 patients with OPMDs or oral cancer using a baby toothbrush followed by scalpel biopsy, and the specimens were analysed without computer-assisted analysis. The specimens were adequate in 74 cases, with a sensitivity of 76.8% and a specificity of 93.3%.

Experts from the American Dental Association recommend the use of cytology as a triage tool in primary care settings or if the patient refuses a tissue biopsy (Lingen et al., 2017a).

(b) Quantitative DNA cytometry

DNA cytometry, which is used to detect the cytometric equivalent of chromosomal aneuploidy, was developed as an adjunctive technique to improve the accuracy of cytology. Aneuploidy is defined as an alteration of the chromosome number that is not a multiple of the haploid complement (Williams and Amon, 2009). Because aneuploidy is frequent in cancer cells, DNA cytometry has been used in the context of early diagnosis of oral cancer and OPMDs (Tong et al., 2009).

A recent review included 24 data sets, of which 5 used DNA cytometry. The pooled sensitivity was 76% (95% CI, 68–82%), and the pooled specificity was 98% (95% CI, 72–99%) (Walsh et al., 2021a) (Table 4.9).

In a series of 98 cytobrush and scalpel biopsies of clinically evident lesions, 75 samples were cytologically and histologically negative (the cut-off for true positive was severe dysplasia or carcinoma). The remaining 23 samples, which had positive (15 cases), suspicious (4 cases), or doubtful (4 cases) cytological results, underwent DNA cytometry, and 19 of the 23 cases showed aneuploidy (a sensitivity of 100% and a specificity of 97.4%) (Maraki et al., 2004).

In a retrospective review of 171 patients with 199 suspicious oral lesions who underwent biopsy and quantitative cytology, 28 patients had OPMDs with OED or OSCC, of whom 25 had positive quantitative cytology. False-positive quantitative cytology was observed in 5 of the 143 patients with negative histology; the sensitivity was 89.3%, and the specificity was 96.5% (Ng et al., 2012).

4.1.5 Liquid biopsy

Liquid biopsy is a non-invasive, convenient, and low-cost method, and it is easy to collect liquid samples (Mali and Dahivelkar, 2021). Tumour DNA was detected in 100% of

saliva samples from patients with oral cancer, suggesting that saliva is preferentially enriched with tumour DNA from tumours at this site (Wang et al., 2015). The diagnostic and prognostic applications of "salivaomics" (Wong, 2012) for oral cancer have been extensively explored, with the identification of many potential biomarkers: minerals, peptides, proteins, DNA, messenger RNA (mRNA), microRNA (miRNA), long coding RNA, oxidative stress-related molecules, glucocorticoids, glycosylation-related molecules, telomerase activity, and the microbiome (Li et al., 2004; Jou et al., 2011; Cheng et al., 2014; Yu et al., 2016; Amer et al., 2017; Kaczor-Urbanowicz et al., 2017; van Ginkel et al., 2017; Payne et al., 2018, 2019; Chen and Zhao, 2019; Rapado-González et al., 2019; Hofmann et al., 2020). However, saliva testing has not yet been incorporated into commercial products or clinical practice (Masthan et al., 2012; Walsh et al., 2021a).

The role of cytokines and other proteins as promising salivary biomarkers for oral cancer has been shown consistently in numerous studies. In a large study that included five cohorts (169 cases and 226 controls), interleukin 8 (IL-8) and SAT mRNA had the highest predictive values (Elashoff et al., 2012). In a single study, the combination of the three biomarkers IL-8, SAT, and H3F3A increased the sensitivity and specificity to predict the presence of oral cancer compared with each of the biomarkers separately (Li et al., 2004).

In one systematic review, high sensitivity and specificity were observed for IL-8, choline, pipecolinic acid, L-phenylalanine, and S-carboxymethyl-L-cysteine; however, the combination of different biomarkers did not improve sensitivity or specificity (Guerra et al., 2015). In another systematic review, the proteins found most frequently were IL-8, CD44, matrix metalloproteinase-1 (MMP-1), and MMP-3 (Gualtero and Suarez Castillo, 2016). Recent systematic reviews and a meta-analysis showed that numerous cytokines, such as IL-6, IL-8, and tumour necrosis factor α (TNF-α), are present at significantly higher concentrations in the saliva of patients with oral cancer compared with that of healthy people (Rezaei et al., 2019; Ferrari et al., 2021). Another systematic review also identified IL-8 mRNA as a potential candidate (Gaba et al., 2021).

The most recent systematic review of salivary diagnostic biomarkers for oral cancer and OPMDs, which included 295 articles (Piyarathne et al., 2021), included proteomic biomarkers, cytokines, growth factors, angiogenic factors, antigens, cytokeratin, cell surface receptors, enzymes, and silencing of tumour suppressor genes via promoter hypermethylation. From the reported data, IL-1β, IL-6, and IL-8 were selected as the most suitable salivary biomarkers for early detection of OSCC and OPMDs. [Most of the studies were graded with fair quality and moderate risk of bias.]

Matrix metalloproteinases are also promising saliva biomarkers. Stott-Miller et al. (2011) observed that the concentrations of MMP-1 and MMP-3 were higher in later stages of oral cancer compared with controls, cases with dysplasia, and early-stage tumours, with an area under the curve (AUC) of the receiver operating characteristic (ROC) curve of 0.845 for MMP-1 and 0.877 for MMP-3. Chang et al. (2020) also identified MMP-1 as the most promising candidate from a panel of proteins, with a sensitivity of 76.6% and a specificity of 86.8%. In a systematic review, Hema Shree et al. (2019) observed a high sensitivity for MMP-9 (95%; 95% CI, 88–100%) and chemerin (100%; 95% CI, 78–100%), with a specificity of 100% for both MMP-9 and chemerin. In a systematic review of six studies (with a total of 775 participants), high performance rates were reported for MMP-9 and for CYFRA 21-1 (Gualtero and Suarez Castillo, 2016; AlAli et al., 2020).

Several reviews and meta-analyses have highlighted the diagnostic accuracy of miRNAs in differentiating patients with oral cancer from

healthy controls (Tian et al., 2015; Arantes et al., 2018; Al Rawi et al., 2021; Liu et al., 2021). The most recent meta-analysis, which included 1106 patients and 732 controls, found a pooled sensitivity of salivary miRNAs of 70%, a pooled specificity of 82%, and an AUC of 0.80 (Liu et al., 2021). A previous meta-analysis based on 23 studies found a pooled sensitivity of 75.9%, a pooled specificity of 77.3%, and an AUC of 0.83 (Tian et al., 2015). Among a panel of miRNAs in saliva samples from patients with head and neck cancer (comprising cancers of the oral cavity, oropharynx, larynx, and pharynx) and from healthy controls, miR-9, miR-191, and miR-154 had excellent discriminatory power, with an AUC of 0.85, 0.74, and 0.98, respectively (Salazar et al., 2014). Momen-Heravi et al. (2014) performed a genome-wide evaluation of miRNA patterns in saliva samples from patients with oral cancer, patients with oral lichen planus, and healthy controls and observed that miR-27b had a sensitivity of 85.7% and a specificity of 100% for detection of oral cancer (AUC, 0.96; 95% CI, 0.88–1.05).

Aberrant methylation of tumour suppressor genes is an important epigenetic mechanism of carcinogenesis. Several genes have been found to be more frequently hypermethylated in saliva samples from patients with oral cancer than in those from controls (Carvalho et al., 2008; Arantes et al., 2018; Rapado-González et al., 2021a, b). In a meta-analysis of 18 studies, the frequency of methylation was higher in patients with head and neck cancer (comprising mostly cancers of the oral cavity) than in healthy controls (odds ratio, 8.34; 95% CI, 6.10–11.39); a significant association between methylation of specific tumour-related genes and risk of head and neck cancer [not otherwise specified] was observed for *p16*, *MGMT*, *DAPK*, *TIMP3*, and *RASSF1A* (Rapado-González et al., 2021b).

Finally, changes in the microbiome have been associated with risk of oral cancer (Perera et al., 2016). In dysplastic leukoplakia, the most enriched species were *Fusobacterium*, *Leptotrichia*, *Campylobacter*, and *Rothia* species; severe dysplasia was associated with specific microbial enrichments (*Leptotrichia* spp. and *Campylobacter concisus*) (Amer et al., 2017).

[Despite the great potential of saliva biomarkers in the diagnosis of OPMDs and oral cancers, and the rapidly evolving knowledge in the field and the consistently high accuracy of some of the biomarkers in a research setting, there is a lack of clinical validation regarding this approach in oral cancer screening settings.]

4.1.6 Use of emerging technologies in the primary screening setting

(a) Artificial intelligence for identification of OPMDs

Artificial intelligence (AI) is defined as the process by which a computer is able to learn by continuously incorporating new data into an existing statistical model (Deo, 2015). A promising new approach to improve the detection and diagnosis of OPMDs is to engage the interest of mathematicians with expertise in AI or machine learning to apply these techniques to improve the clinical diagnosis of oral cancer and OPMDs (Kar et al., 2020; García-Pola et al., 2021).

Several groups have investigated the use of AI to improve the efficacy of COE (García-Pola et al., 2021; Ilhan et al., 2021), and the preliminary findings have been promising.

(b) Optical coherence tomography

Optical coherence tomography (OCT) is an optical technology that uses back scattered signals from different layers of tissue to construct in vivo cross-sectional images of tissue with high resolution (Huang et al., 1991; Machoy et al., 2017). This technology is similar to that used in ultrasound, but whereas ultrasound uses sonic signals to generate tissue images, OCT uses optical signals.

OCT has been used for many years for the evaluation and diagnosis of retinal lesions (Fujimoto, 2003). Wilder-Smith et al. (2009) evaluated the use of OCT for diagnosis of oral cancer and OPMDs in 50 patients and found strong agreement between the diagnosis based on OCT images and that based on histology. Heidari et al. (2019) developed a portable OCT system and used it to evaluate oral lesions in 20 patients and 10 healthy individuals. Whereas previous studies had compared the qualitative evaluation of OCT images and histological images, in this small study the researchers developed an objective algorithm to differentiate between normal and abnormal oral mucosa based on the OCT images. They reported a sensitivity and specificity of this algorithm for differentiating between healthy and cancerous or dysplastic mucosa of 95% and 100%, respectively, and a sensitivity and specificity for differentiating between cancer and dysplasia of 91% and 100%, respectively.

James et al. (2021) provided validation of a point-of-care OCT diagnostic device based on an automated algorithm, which was used to examine 232 individuals across a spectrum ranging from normal mucosa to OPMDs and oral cancer. The process included first imaging the lesion and then providing the image to the algorithm for further interpretation. The algorithm score was compared with standard histopathological diagnoses if biopsy was indicated. The algorithm score was unable to distinguish between the grades of dysplasia, but it accurately differentiated oral cancers (OSCC, with a sensitivity of 93%) and OPMDs (with a sensitivity of 95%) from benign lesions and normal mucosa. To provide the delineation of high-grade dysplastic lesions (moderate or severe dysplasia) from low-grade lesions (mild dysplasia, benign, or normal), the research team implemented the use of an artificial neural network, which reached a sensitivity of 83% (James et al., 2021).

(c) In vivo microscopy

Whereas OCT provides a cross-sectional image of the oral mucosa and submucosa, reflectance microscopy and fluorescence microscopy provide images of the oral mucosal surface (Muldoon et al., 2012). Emerging reflectance microscopy technologies, including those that can analyse vascular patterns in the oral submucosa, are adequate to visualize oral tissue without use of contrast agents. However, most fluorescence microscopy approaches require the use of an optical contrast agent, either applied topically or administered intravenously.

Muldoon et al. (2012) described a new high-resolution optical microscopy (high-resolution microendoscope [HRME]), fluorescence microscope (Yang et al., 2018b), which could provide real-time images of the nuclear morphology of the oral mucosa. To enable visualization of the nuclei, topical application of the fluorescent dye proflavine was required. The images obtained could be saved for further analysis of the size and shape of the nuclei by an automated computer algorithm (Yang et al., 2018b). Autofluorescence (see Section 4.1.3) has low specificity for identifying benign lesions. To boost the specificity, a multimodal approach was suggested of merging autofluorescence with HRME technology (Yang et al., 2018b). Subsequent studies that used the HRME instrument, alone and in combination with wide-field autofluorescence imaging devices, have documented the ability of this technology to objectively identify abnormal and dysplastic mucosa with high sensitivity and specificity (Yang et al., 2018a, 2019, 2020). However, this HRME technology is not yet available for clinical use.

Nathan et al. (2014) reported on a preliminary study of 21 participants with oral cancer or OPMDs, who underwent imaging of lesions with confocal laser endomicroscopy for in vivo evaluation of the oral mucosa before resection or excisional biopsy. To provide optical contrast,

the participants underwent intravenous injection of fluorescein before imaging. Qualitative analysis of the images by experts familiar with this technology was compared with histological diagnosis. The overall sensitivity was 80% for diagnosis of dysplasia versus non-dysplasia. Despite these initial positive findings, this technology has not yet been adopted for clinical evaluation of patients with oral mucosal lesions, possibly due to the need for intravenous injection of fluorescein before imaging.

(d) Spectroscopy

In contrast to optical imaging technologies such as OCT and microscopy, optical spectroscopy involves the objective detection and analysis of optical signals collected after tissue is exposed to light of various wavelengths. Basically, clinical spectroscopy is the analysis of how light interacts with tissue (Sahu and Krishna, 2017). Alterations in spectroscopic signals can be used to detect biochemical and architectural changes in oral tissue that are associated with neoplastic progression (Müller et al., 2003; Bigio and Bown, 2004). Several different types of spectroscopic analysis have been evaluated for use in the detection of oral cancer, including Raman spectroscopy, fluorescence spectroscopy, reflectance spectroscopy, elastic scattering spectroscopy, and time-resolved autofluorescence spectroscopy. The distinction between these spectroscopic technologies is based on multiple factors, including the type of light illumination delivered to the tissue and the type of optical signal detected after this illumination (Sahu and Krishna, 2017). These differences arise as a result of how light interacts with tissue. For example, fluorescence spectroscopy involves illumination of tissue at wavelengths that are known to stimulate autofluorescence by tissue components such as collagen, and collection of the autofluorescence light emitted from the illuminated tissue at specific wavelengths (Romano et al., 2021). Reflectance spectroscopy involves assessment of the light reflected from tissue.

Although the reflected light is usually the same wavelength as the illumination light source, in rare cases light is reflected at a different wavelength, due to inelastic scattering (Bigio and Bown, 2004; Sahu and Krishna, 2017). These inelastic reflectance signals, which are often called Raman signals, are very faint compared with fluorescence and standard reflectance signals. However, spectroscopic analysis of Raman signals can provide objective documentation of chemical changes in biological tissues (Bigio and Bown, 2004; Sahu and Krishna, 2017). Raman spectroscopy is a technology that enables non-invasive, molecular interrogation of the chemical composition of biological tissues, using optical interrogation. Four biological components contribute to Raman signals: nucleic acids, lipids, proteins, and water (Bigio and Bown, 2004). Several studies have investigated the potential efficacy of Raman spectroscopy to discriminate between oral cancer or OPMDs and benign or normal oral mucosa. These studies refer to the possible use of this technology both ex vivo, with the use of formalin-embedded tissues (Ibrahim et al., 2021) and biopsies (Matthies et al., 2021), and in vivo, with possible clinical use indicating a potential novel adjunctive diagnostic technique (Sahu et al., 2012).

In contrast, elastic scattering spectroscopy relies on gradients in the optical index of refraction after the light is scattered by specific organelles inside the cell (e.g. nuclei or mitochondria). This spectroscopic method depends on the differences in the densities of the organelles; the elastic scattering spectrum may change in cells undergoing carcinogenesis (Bigio and Bown, 2004).

Fluorescence and reflectance spectroscopy technologies have been used to evaluate oral mucosal lesions in vivo (Schwarz et al., 2008; Messadi et al., 2014). Although these preliminary studies have shown promise for the ability of these technologies to discriminate between normal or benign oral tissue and dysplastic or

cancerous oral tissue, they showed insufficient sensitivity and specificity.

(e) Molecularly targeted optical imaging agents

Given that the standard COE and radiographic imaging are insufficient to determine the extent of OSCC in many patients, several molecularly targeted optical imaging agents have been developed over the past decades to improve the surgeon's ability to delineate the anatomical extent of malignant tissue and high-grade dysplastic disease, before or during surgical resection (Fakurnejad et al., 2019; van Keulen et al., 2019; Steinkamp et al., 2021).

[Although these clinical trials may offer new techniques to improve surgical resection of oral cancer, it is unclear how these molecularly targeted optical imaging agents might improve the early detection and diagnosis of oral precancer and cancer in individuals at high risk, particularly in low-resource settings.]

4.2 Organized and opportunistic oral cancer screening activities

Worldwide, there are very few large-scale population-based organized or non-organized oral cancer screening programmes, and there is very little sporadic screening activity. This is despite the fact that most patients with oral cancer present in advanced stages with poor prognosis. Previous reviews of oral cancer screening have concluded that there is "insufficient evidence to recommend inclusion or exclusion of oral cancer screening" in the general population, and that opportunistic screening of populations at high risk might be effective and should be considered (Hawkins et al., 1999; Kujan et al., 2005; Brocklehurst et al., 2013).

A large-scale population-based oral cancer screening programme in people aged ≥ 15 years has been under way in Cuba since 1982. The programme requires that dentists provide oral visual inspection annually in community dental clinics and refer suspicious cases to the regional head and neck and maxillofacial surgical service for further management. A formal evaluation of the programme for the period 1984–1990 was carried out in collaboration with IARC (Fernández Garrote et al., 1995). The programme covered 12–26% of the target population annually, and less than 30% of the individuals with suspicious lesions complied with referral to the maxillofacial surgical service. The programme identified about 16% of the 4412 incident oral cancers in Cuba during 1984–1990. After the formal evaluation of the programme, the age threshold for the target group was increased to ≥ 35 years as part of reorganization efforts (González, 2014). No further formal evaluation of the reorganized programme has been done since 1995.

A nationwide population-based oral cancer screening programme, which conducts oral visual inspection every 2 years, has been running in Taiwan (China) since 2004. It targets residents aged ≥ 30 years with a history of cigarette smoking and/or betel quid chewing, and Indigenous people aged ≥ 18 years. In 2004–2009, about 55% of invited individuals (n = 4.2 million) participated in screening (Chuang et al., 2017). More than 4.6 million individuals with the exposure of betel quid chewing and/or cigarette smoking have attended the biennial oral cancer screening. A nationwide online information system for breast cancer, colorectal cancer, and oral cancer screening was successfully developed to support health professionals and health decision-makers for planning, delivery, management, and evaluation in the population-based cancer screening programme (Lin, 2018).

India accounts for the largest contribution to the burden of oral cancer globally (Ferlay et al., 2020). Although the Government of India has issued guidelines for oral cancer screening

for all individuals in the age group 30–65 years (National Health Mission of India, 2021), these have yet to be implemented systematically on a large scale and have mostly resulted in sporadic screening. The draft national oral health policy released in February 2021 by the Ministry of Health and Family Welfare of India (Ministry of Health and Family Welfare, 2021) also emphasizes the need for screening, but it provides no clear direction or roadmap on how to achieve this. The Government of Tamil Nadu State in India has organized an oral cancer screening programme since 2016 through public health services. This programme targets people aged ≥ 18 years who are users of tobacco and/or alcohol (National Health Mission Tamil Nadu, 2021). It is supported by an information system, but no data have yet been published from this programme. In an opportunistic oral cancer screening activity, 1 061 088 people in 265 272 houses were surveyed in Kannur District, Kerala, India (Philip et al., 2018).

Sporadic oral cancer screening involving small numbers of individuals has been conducted both in India and in Sri Lanka, demonstrating the feasibility of MSE and/or home-based screening by community health workers, but such activities do not resemble sustained programmatic efforts (Amarasinghe et al., 2016; Philip et al., 2018; Basu et al., 2019). Guidelines have been developed by the National Cancer Control Programme of Sri Lanka for oral cancer screening and management of oral lesions, targeting users of tobacco and areca nut (National Cancer Control Programme, 2020); however, these have not resulted in a sustained programmatic activity.

There has been very little oral cancer screening activity in Central and South America. Since 2001, the São Paulo State Health Secretariat has coordinated oral cancer screening with annual COE, combined with the national campaign for influenza immunization of the population aged ≥ 60 years in São Paolo State, Brazil (Almeida et al., 2012). In 2001–2008, 2 229 273 individuals were screened, with an increase in coverage from 4.1% in 2001 to 16% in 2008, a decrease in the percentage of suspicious lesions from 9% in 2005 to 5% in 2008, and a decrease in the rate of confirmed cases of oral cancer per 100 000 examinations from 20.9 in 2001 to 10.4 in 2008.

No population-based oral cancer screening programmes have been reported in Europe, North America, or Oceania.

4.3 Determinants of participation in screening for oral cancer

The World Health Assembly adopted the first resolution related to oral cancer diagnosis in 2007, and the World Health Organization has formally provided guidance for oral health (WHO, 2007, 2013, 2021). Despite this, most countries have not widely adopted or reported oral cancer screening. In addition, the literature on the determinants of participation in oral cancer screening is scarce.

It is critical to identify and monitor the factors that positively and negatively influence cancer screening programmes and their outcomes, in order to facilitate translation of the scientific evidence of benefit to the clinical setting. The predictors of participation in cancer screening, adherence to follow-up screening rounds, and compliance with referrals for diagnosis and treatment are well established in the literature (Solar and Irwin, 2010). They consist of (a) drivers that influence the process at the level of (i) the individual, (ii) health-care providers, (iii) health-care systems, and (iv) health-care policies, and (b) interventions to increase participation in screening (Table 4.10).

Table 4.10 Determinants of participation in screening for oral cancer

Category of determinant	Facilitator	Barrier	Reference	Location
Individual level				
Risk factors				
		Smoking	Talamini et al. (1994)	Italy
	Smoking		Chang et al. (2011)	Taiwan (China)
	Smoking		Ramadas et al. (2008a)	India
	Betel quid chewing		Chang et al. (2011)	Taiwan (China)
	Alcohol consumption		Nagao and Warnakulasuriya (2003)	Japan
	Alcohol consumption		Ramadas et al. (2008a)	India
Age and sex				
	Age (45–54 years)	Age (> 65 years)	Ramadas et al. (2008a)	India
	Age (40–60 years)	Age (< 40 years and > 60 years)	Chang et al. (2011)	Taiwan (China)
	Middle-aged (55–64 years)	Younger and elderly (< 55 years and ≥ 65 years)	Talamini et al. (1994)	Italy
	Elderly women	Young and middle-aged women	Mishra et al (2021)	India
	Female sex		Ramadas et al. (2008a)	India
		Female sex	Talamini et al. (1994)	Italy
Socioeconomic factors				
	Hindu religion		Mishra et al. (2021)	India
	Marathi mother tongue		Mishra et al. (2021)	India
	High secondary school education		Mishra et al. (2021)	India
	Owning mass media devices (television and/or radio)		Ramadas et al. (2008a)	India
	Larger household size		Ramadas et al. (2008a)	India
Medical factors				
		Absence of symptoms	Talamini et al. (1994)	Italy
	Family history of cancer		Mishra et al. (2021)	India
Health-care system level				
		Inadequate patient referral	Warnakulasuriya et al. (1984)	Sri Lanka

4.3.1 Individual level

(a) Risk factors

Populations at high risk (i.e. individuals with risk factors for oral cancer, such as tobacco use, areca nut use, and alcohol consumption) were found to be more likely to adhere to oral cancer referral consultations and procedures, compared with individuals without these risk factors (Nagao and Warnakulasuriya, 2003; Ramadas et al., 2008a; Chang et al., 2011), except in one study (Talamini et al., 1994), in which smoking habits were negatively associated with compliance with referral.

(b) Age and sex

In three studies, middle-aged patients were more likely to comply with screening procedures, compared with elderly patients and younger patients (Talamini et al., 1994; Ramadas et al., 2008a; Chang et al., 2011). In contrast, Mishra et al. (2021) reported that elderly women were more likely to participate in oral cancer screening, followed by younger women and middle-aged women.

Inconsistent findings describe female sex as a positive predictor (Ramadas et al., 2008a) and a negative predictor (Talamini et al., 1994) of participation in oral cancer screening. In the study of Ramadas et al. (2008a), accrual of individuals was based on home visits in India, and the authors argued that their finding may be explained by the fact that in the population evaluated, women are more likely to be at home during home visits than their male partners. [It is not clear whether women are more likely than men to attend screening.]

[Although age and sex were important predictors in the above-mentioned studies (Talamini et al., 1994; Ramadas et al., 2008a; Mishra et al., 2021), these determinants were not consistent within and between the studies; this may be explained by confounders, biases in analysis, and study design.]

(c) Socioeconomic factors

Mishra et al. (2021) evaluated socioeconomic determinants of participation in oral cancer screening by women with current smoking habits or previous smoking habits (for ≥ 3 consecutive years) in an organized population-based screening programme in Mumbai, India. High secondary school education level, Hindu religion, and Marathi mother tongue were all positive factors associated with participation in oral cancer screening. In addition, Ramadas et al. (2008a) identified larger household size and owning mass media devices (television and/or radio) as socioeconomic factors associated with higher participation rates.

(d) Medical factors

In a study of screening for head and neck cancer (including oral cancer), patients with upper aerodigestive tract symptoms (Talamini et al., 1994) or a family history of cancer (Mishra et al., 2021) were more likely to attend screening than those who were asymptomatic.

4.3.2 Health-care provider level

Trained health-care providers are more likely to promote oral cancer screening. For instance, in a study in Ernakulam District, Kerala, India, about 53 basic health workers were trained by dentists to examine the oral cavity of individuals at high risk and recognize suspicious cancerous and precancerous lesions. Within a 1-year period, screening participation of the target population increased to 33.5% (Mehta et al., 1986). In addition, 45% of individuals were correctly referred, with a sensitivity of 59%. Thus, the training of basic health workers specifically for oral cancer screening through active recruitment dramatically changed the participation rate.

4.3.3 Health-care system level

Warnakulasuriya et al. (1984) recognized that in Sri Lanka only 50% of individuals with a suspicious lesion detected by primary health-care workers were re-examined by skilled professionals at the university referral centre. The authors concluded that the low compliance of the community with follow-up at the referral centre may have been due to lack of awareness about oral cancer and the value of the screening programme, and possibly an inadequate understanding between the individuals and the health workers about referral.

4.3.4 Health-care policies

Only a few countries, such as Cuba, India, Malaysia, Sri Lanka, and Taiwan (China), have adopted oral cancer screening on a large scale. However, the determinants of participation have most often not been reported. Overall, the above-mentioned countries promote distinct screening programmes in terms of target population, coverage, design, and framework; these differences pose challenges for harmonization and comparison of data in terms of not only the health impact but also the determinants of participation in screening (Warnakulasuriya et al., 1984; López Cruz et al., 2003; Sankaranarayanan et al., 2013; Moyer et al., 2014).

4.3.5 Strategies to increase participation in oral cancer screening

Studies have reported on various endeavours to increase participation in oral cancer screening, including individual invitations through billboards, radio advertisements, newspaper advertisements, toll-free hotlines, letters, home visits, educational leaflets, and phone calls (Jedele and Ismail, 2010; Pivovar et al., 2017). However studies designed to specifically evaluate the efficacy of these interventions are scarce and have biases.

Pivovar et al. (2017) described an e-health strategy to increase the selection of individuals at high risk, followed by an active home-based invitation to schedule oral cancer screening. Selecting individuals at high risk through an electronic database enabled improved efficiency and reduced the percentage of potential participants to 1.4% of the total population. [The Working Group noted that no comparison arm was provided to evaluate the magnitude of the impact associated with such an intervention. The study was also sex-biased, by excluding women at high risk.]

Jedele and Ismail (2010) conducted a 2-year oral cancer awareness and screening campaign that targeted African-American men aged ≥ 40 years. The number of billboards and radio advertisements was positively correlated with the number of calls received on the campaign's toll-free hotline number. Also, the calls to the toll-free number resulted in scheduled appointments and screening of patients.

4.4 Effectiveness of screening

In 2013, Brocklehurst et al. (2013) conducted the most recent systematic review of RCTs on screening for oral cancer or OPMDs using COE, toluidine blue vital staining, fluorescence imaging, or brush biopsy. Based on the only RCT that met the inclusion criteria (Sankaranarayanan et al., 2000, 2013), they concluded that as an alternative to a national-based screening programme, opportunistic oral cancer screening by visual examination in a population at high risk might be effective in reducing oral cancer mortality.

4.4.1 Preventive effects of screening

To ascertain the effect of screening on oral cancer incidence and/or mortality, a search was performed for experimental and observational studies that used "no screening" as the control group and that reported incidence of advanced

and/or early oral cancer and mortality from oral cancer. The Working Group identified one experimental study, from which the outcomes observed with the longest follow-up were extracted. No current experimental studies targeted at measuring incidence of advanced oral cancer and mortality from oral cancer were identified. In addition, three observational studies reporting the primary end-points for performance of oral cancer screening for the screening and control groups were identified.

(a) Randomized controlled trials

In the Trivandrum Oral Cancer Screening Study, in Kerala, India, healthy residents aged ≥ 35 years from 13 rural administrative units, considered as clusters, were randomized into an intervention arm (n = 7) and a control arm (n = 6) (Sankaranarayanan et al., 2000, 2005, 2013; Ramadas et al., 2003). Eligible individuals were identified through interviews during home visits; they provided information about their demographic characteristics and individual habits related to risk factors for oral cancer (i.e. tobacco use and alcohol consumption). The longest reported follow-up of this trial was 15 years (until December 2010) (Sankaranarayanan et al., 2013; Table 4.11). All intervention health workers were taught about cancer and trained in oral cancer screening. Of the 96 517 eligible individuals in the intervention arm, 25 144 (26.1%) underwent one round of screening, 22 382 (23.2%) underwent two rounds, 22 008 (22.8%) underwent three rounds, and 19 288 (20.0%) underwent four rounds. Eligible individuals in the control arm received routine care in 1996–2005 and were offered screening in 2006–2008, in which 43 992 (46.1%) of 95 356 individuals participated. Participants with positive screening results were referred for further clinical examination by a specialist (either a dentist or an oncologist). Examinations for all invasive oral cancers included both COE and histological investigation.

After four rounds of screening in the intervention arm, there was a statistically non-significant (12%) overall reduction in oral cancer mortality compared with the control arm (Table 4.12). However, in users of tobacco and/or alcohol, per-protocol analysis showed a statistically significant (24%; 95% CI, 3–40%) reduction in oral cancer mortality and a statistically significant (21%; 95% CI, 5–35%) reduction in incidence of advanced oral cancer (clinical stages III and IV). The reduction in both incidence of advanced oral cancer and mortality from oral cancer increased with the number of rounds of screening (Sankaranarayanan et al., 2013). To adjust an imbalance in risk of oral cancer between the two arms in this study, an intention-to-treat analysis was recently performed based on the 9-year follow-up; this analysis demonstrated a 27% reduction in oral cancer mortality due to screening (hazard ratio, 0.73; 95% CI, 0.54–0.98) (Cheung et al., 2021).

[The Kerala trial has multiple limitations, in particular related to a high non-compliance rate in screen-positive individuals, i.e. only 59% of screen-positive individuals complied with the clinical assessment by the physicians. The publication does not describe well whether and how the interval cancers were followed up. The cancers that developed in the non-compliant individuals were included in the no-screening group, which assumes per-protocol analysis instead of intention-to-treat analysis; however, the intention-to-treat analysis performed later reached a similar conclusion. No formal training certificate was issued to the health workers; however, all the health workers underwent an examination at the end of the training to test their skills in completing the questionnaire and also in identifying the relevant lesions in the oral cavity. Those whose performance was poor were retrained. It is possible that the health workers' lack of a certificate was perceived as indicating a low qualification and may have resulted in the low follow-up rate of screen-positive individuals.]

Table 4.11 Description of the cluster-randomized trial of the efficacy of oral cancer screening (Sankaranarayanan et al., 2013)

Location Randomization	No. of participants	Participation rate	Accrual period for screening		Age at entry (years)	Description of the intervention	Follow-up for screen-positive individuals	Follow-up rate for screen-positive individuals	Screening interval (years)	No. of rounds of screening Follow-up (years)
			Invited group	Control group						
Kerala, India Cluster-randomized (at the municipal level)	191 872 recruited; 96 517 in the intervention group; 77% men	Intervention arm (at least one screen): 92%; at first round: 79% Control arm: 46.1%	1996–2008	Routine care in 1996–2005, screened in 2006–2008	≥ 35 Mean, 49 (SD, 0.7)	Clinical oral examination by non-medical health worker	Clinical examination by a specialist (dentist or oncologist)	59%	3	4 15

SD, standard deviation.

Table 4.12 Results of the cluster-randomized trial of the efficacy of oral cancer screening (Sankaranarayanan et al., 2013)

Outcome	Population group	No. of participants (screened/control group)	Outcome per 100 000 person-years (screened/control group)	RR (95% CI)
Incidence of oral cancer				
	General population	895 310/898 280	31.2/27.2	1.14 (0.91–1.44)
	Users of tobacco and/or alcohol	429 620/377 350	59.2/61.6	0.97 (0.79–1.19)
Incidence of stages III and IV oral cancer				
	General population	895 310/898 280	16.4/17.7	0.92 (0.72–1.17)
	Users of tobacco and/or alcohol	429 620/377 350	32.2/40.9	0.79 (0.65–0.95)
Mortality from oral cancer				
	General population	895 310/898 280	15.4/17.1	0.88 (0.69–1.12)
	Users of tobacco and/or alcohol	429 620/377 350	30.0/39.0	0.76 (0.60–0.97)

CI, confidence interval; RR, relative risk.

(b) Observational studies

Two cohort studies, both based on a nationwide population-based biennial oral cancer screening programme in Taiwan (China), and one case–control study, evaluating the national oral cancer screening programme in Cuba, compared oral cancer screening attenders with non-attenders in terms of oral cancer incidence and/or mortality.

A cohort of 4 234 393 adults (≥ 18 years) who smoked cigarettes and/or chewed betel quid underwent biennial oral screening by dentists or physicians in 2004–2009 in Taiwan (China). The individuals were followed up until 2012, with a median follow-up of 4.5 years (Table 4.13; Chuang et al., 2017). Screen-positive individuals were referred to specialists in hospitals for histopathological examinations. The study was linked to the National Cancer Registry to enable precise recording of oral cancer cases in attenders and non-attenders in the screening programme. The expected incidence and mortality rates of non-attenders were estimated based on previous findings that about 90% of oral cancer cases were attributed to cigarette smoking and/or betel quid chewing. The participation rate at the first screening in the invited population was 55.1%. There was a 21% (95% CI, 18–24%) reduction in the incidence of advanced oral cancer and a 26% (95% CI, 23–28%) reduction in oral cancer mortality in the screened group compared with the non-screened group (Table 4.13). [The lower incidence rate of oral cancer in the screened group compared with the non-screened group may be due to an imbalance in risk of oral cancer between attenders and non-attenders, considering the low participation rate.]

[To assess the transferability of the conclusions on effectiveness of oral cancer screening to other settings, the following biases should be considered. First, enrolment of the participants was conducted in communities and in hospitals, with an unclear distribution between these two settings. Enrolment of participants in hospitals is likely to increase selection bias. Selection bias also increases with the retrospective choice of the controls related to the outcome of interest. Second, the participation rate of < 60% means that there is a high risk of non-response bias. Third, because the nationwide oral cancer screening programme in Taiwan (China) included an initial survey on the risk factors, this could potentially lead to contamination of the control group, which would lead to an underestimation of the benefits of screening.] A retrospective analysis of the at-risk cohorts invited to the oral cancer screening programme in Taiwan (China) was subsequently conducted by Ho et al. (2019). The study used the databases of the National Cancer Registry, the Nationwide Oral Mucosal Screening Program, and the National Death Registry. The duration of follow-up was calculated from the date of cancer diagnosis to the date of death or to the end of the follow-up period (until 2017). A total of 18 625 patients with oral cancer were identified from the National Cancer Registry during 2012–2015. The screened status was defined as having no records, records without a previous positive result, or records with a previous positive result. Of this cohort, 8165 patients (43.8%) attended at least one screening round and had a previous positive result, 3560 patients (19.1%) had a negative result on screening or no previous positive result, and 6900 patients (37.0%) had no records of attending the screening. Among the patients with cancer, most of the screened patients were diagnosed with cancer at earlier stages compared with the non-screened patients (Table 4.14). The 3-year survival rates were 71.4% for screened patients with positive results, 68.7% for screened patients with negative results, and 63.5% in the non-screened group; this showed a survival benefit of screening.

[The study of Ho et al. (2019) has several limitations. Although the oral cancer screening programme included individuals aged ≥ 18 years, this study limited the cohort to ages ≥ 30 years.

Table 4.13 Prospective cohort study of the effectiveness of oral cancer screening

Reference Location	Description of the cohort	Description of the controls	Accrual and follow-up periods	Participation rate and follow-up rate for screen-positive individuals	Detection rate	Cancer incidence/ mortality RR (95% CI)	Comments
Chuang et al. (2017) Taiwan (China)	4 234 393 high-risk invitees (cigarette smokers and/or betel quid chewers), followed up until the end of 2012; median follow-up, 4.5 years (National Cancer Registry)	Non-attenders; incidence and mortality rates were adjusted to attribute 90% of cases to a high-risk population; 86% men	10.5 million person-years of follow-up	Participation rate: 55.1% Referral follow-up rate: first screening, 91.1%; subsequent screening, 92.6%	*First screening:* Screen-positive, 18 116 (0.8%) Precancer, 11 051 (0.5%) Cancer, 4110 (0.2%) *Subsequent screening:* Screen-positive, 5825 (1.0%) Precancer, 3782 (0.6%) Cancer, 791 (0.1%)	*Incidence* Cancer: 0.83 (0.81–0.86) Advanced cancer: 0.79 (0.76–0.82) *Mortality* 0.74 (0.72–0.77)[a]	Reports also by age groups. The highest detection rate for men was in the age group 50–69 years and for women was in the age group ≥ 70 years

CI, confidence interval; RR, relative risk.

[a] Adjusted for self-selection bias.

Table 4.14 Retrospective cohort and case–control studies of the effectiveness of oral cancer screening

Reference Location	Description of the cohort/ cases	Description of the controls	Established programme: year of start, screening age, screening interval	Oral cancer or precancer end-point	Proportion of patients with events	Cancer incidence/ mortality RR (95% CI)
Ho et al. (2019) Taiwan (China)	Retrospective cohort of patients with oral cancer (2012–2015); high-risk invitees (cigarette smokers and/or betel quid chewers); 95.4% men	Patients without previous screening records; 82.1% men	Population-based biennial programme since 2004 targeting population aged ≥ 30 years	Early-stage diagnosis Survival Mortality	*Stage 0–I diagnosis:* Screened positive, 34.3% Screened negative, 34.3% Not screened, 27.8% *3-Year survival:* Screened positive, 71.4% Screened negative, 68.7% Not screened, 63.5%	Mortality in 3 years: HR[a]: 0.78 Stage 0–I diagnosis: HR[a]: 1.23
Sankaranarayanan et al. (2002) Cuba	Cases: 200 patients with oral cancer (77% men); median age, 65 years	Controls: 3 per case, matched on age, sex, and residence; 77% men	Population-based annual programme via oral inspection since 1984 in population aged ≥ 15 years; screening is mainly opportunistic	Incidence of advanced cancer	Screened cases: 56.0% Screened controls: 49.7%	Incidence of advanced cancer OR: Adjusted, 0.78 (0.53–1.15) Not adjusted, 0.67 (0.46–0.95)

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

[a] Calculated from the probability of having an event in 3 years in the screened positive and not screened groups.

The retrospective design carries a risk of misclassification and information bias. The screened cohorts included only a population at high risk, whereas the proportion of cigarette smokers and/or betel quid chewers among the screening non-attenders was unclear. The higher proportion of women in the non-screened group (17.9%) than in the screened group (4.6%) suggests a risk of bias. The comparison is done between five groups, none of which included the "all screened" population (i.e. with either a positive or a negative screening result). The lower hazard ratio for oral cancer mortality in all the groups in the reported Cox regression analysis (e.g. in those with a confirmed cancer and in those who had a positive screening result but did not complete confirmation of diagnosis) compared with those who were not screened suggests a possible risk of bias.]

A case–control study was conducted to evaluate the effectiveness of the national oral cancer screening programme in Cuba (Sankaranarayanan et al., 2002). The cases were 200 individuals with incident oral cancer of stages III and IV registered in 1994–1997. Three controls of apparently healthy individuals were matched to each case on sex, age (± 5 years), and residence (within a 200 m radius of the household of the case). A total of 462 (77%) males and 138 (23%) females provided data on socioeconomic factors and individual risk factors for oral cancer. The proportion of screened individuals was higher in cases than in controls (56.0% vs 49.7%). The odds ratio for advanced oral cancer in cases screened 3 months before diagnosis was 0.67 (95% CI, 0.46–0.95). After adjustment for the frequency of cigarette smoking to address selection bias, the odds ratio was 0.78 (95% CI, 0.53–1.15) (Table 4.14). A time series analysis compared incidence of early oral cancer and mortality from oral cancer in Cuba in 1983–1990 and concluded that the proportion of stage I cases increased from 24% in 1983 to 49% in 1990, without an impact on mortality rates (Fernández Garrote et al., 1995).

[The Working Group noted that the low coverage of the programme and the poor compliance with referral contribute to selection bias. Given the study design, there is also a possible risk of reporting bias. Another risk is recall bias and differential reporting of exposure in cases and controls due to the timing of the event. Furthermore, the definition of the intervention, which was "any visit to a community dentist", may lead to a possible overestimation of exposure in the controls. Finally, the number of cases may be too small to detect a difference in outcomes with an opportunistic screening programme.]

Several studies have assessed the impact of oral cancer screening on oral cancer incidence (Fernández Garrote et al., 1995; Sankaranarayanan et al., 2013; Chuang et al., 2017; Morikawa et al., 2021). Chuang et al. (2017) reported a statistically significant decrease of 17% in the oral cancer incidence rate. All other studies reported no impact.

4.4.2 Harms of screening

Although screening must by definition be beneficial, it may be associated with some harms. The harms related to screening for cancer at other sites have been reviewed extensively (e.g. Welch and Black, 2010; Woolf and Harris, 2012; Marmot et al., 2013).

The potential harms of screening include factors associated with false-positive tests, false-negative tests, overdiagnosis, and overtreatment. A false-positive test result is a positive test result in an individual who does not have cancer in the further assessment. A false-positive test result can lead to unnecessary psychological distress and anxiety, unnecessary additional investigations to rule out disease, side-effects, unnecessary treatment, and additional costs. A false-negative test result is a negative test result in an individual who has the disease. A

false-negative test leads to false reassurance of not having disease and consequent increased risk of advanced disease, with poor treatment outcome and poor cosmesis and functional outcomes. Overdiagnosis is the diagnosis of a cancer as a result of screening that would not have been diagnosed in the patient's lifetime if screening had not taken place. Although the concept of overdiagnosis is often discussed in the context of screening asymptomatic people, there is no agreement on how to estimate overdiagnosis. Estimates of overdiagnosis are highly heterogeneous and vary depending on the analytical approach. Overall, the harms are worse when the quality of the test is poor.

No studies have reported on harms from the oral cancer screening test itself (COE), from false-positive or false-negative screening test results, or from overdiagnosis. However, several studies have reported the detection rates and screening performance in various oral cancer screening programmes (see Section 4.1.1).

Diagnostic harms are primarily related to the side-effects and complications of biopsy for suspected oral cancer or its potential precursors. Although oral cancer screening can detect OPMDs, it is unclear which OPMDs regress spontaneously and which lesions persist or progress further to malignancy (see Section 1.3.1) (Moyer et al., 2014). The treatment of some screen-detected OPMDs is limited by a field cancerization effect due to the entire oral mucosa being exposed to carcinogens. Moreover, surgical and ablative treatments of OPMDs may lead to unwanted side-effects, such as severe pain, infection, and bleeding due to complications of treatment.

4.5 Risk-based model for screening

Cancer screening has historically been based on age and applied for all eligible individuals without any assessment of their exposure to known risk factors. However, the risk of developing cancer varies among individuals. Restricting screening to only individuals at high risk may improve the efficiency and effectiveness of screening while minimizing the harms. A risk-based screening strategy has been tested in several model-based studies and cohorts (Amarasinghe et al., 2010; Shieh et al., 2017; Cheung et al., 2019; Willoughby et al., 2019; de Koning et al., 2020; Harkness et al., 2020; Ten Haaf et al., 2021). Recently, several studies have reported that incorporating genomic information along with other individual risk factors can help in screening for breast cancer, prostate cancer, and lung cancer (Torkamani et al., 2018; Callender et al., 2019; Roberts et al., 2021).

The Trivandrum Oral Cancer Screening Study showed that the benefit of screening is limited to the individuals at high risk, i.e. those who use tobacco and/or consume alcohol (Sankaranarayanan et al., 2005). A reanalysis of the Trivandrum study using a risk-based screening strategy showed that the absolute benefits of screening increased significantly with increasing model-predicted risk of oral cancer (Cheung et al., 2021). The difference in the oral cancer mortality rate between the intervention arm and the control arm increased from 0.5 per 100 000 in the lowest quartile of oral cancer risk to 13.4 per 100 000 for individuals in the highest quartile. Similarly, among ever-users of tobacco and/or alcohol, the difference in the oral cancer mortality rate between the intervention arm and the control arm increased from 1.0 per 100 000 in the lowest quartile of oral cancer risk to 22.5 per 100 000 for individuals in the highest quartile. In a population similar to that in the Kerala trial, screening of 100% of eligible individuals (ages ≥ 35 years) would lead to a 27.1% reduction in oral cancer mortality at a number needed to screen of 2043. Restricting screening to ever-users of tobacco and/or alcohol with no additional risk stratification (43.4% of the population) would substantially increase efficiency (23.3% reduction in oral cancer mortality at a number needed to screen of 1029). Screening the

50% of ever-users of tobacco and/or alcohol at highest risk based on the risk-prediction model (21.7% of the population) would further enhance efficiency with little loss in programme sensitivity (19.7% reduction in oral cancer mortality at a number needed to screen of 610) (Cheung et al., 2021).

[This study provided the first proof of principle that a risk-based tailored approach may enhance the efficiency of screening, reduce harms, and be more cost-effective. However, the magnitude of risk associated with each risk factor may vary in different populations and countries (see Section 2.1) (Winn et al., 2015). This aspect should be considered before implementing a risk-based approach for a particular country. The risk-based approach may be appropriate for resource-limited countries with a high incidence of oral cancer (Cheung et al., 2021; D'Cruz and Vaish, 2021). However, the implementation of a risk-based screening programme faces several challenges in selecting the high-risk group without negatively influencing the trade-off between individual benefits and harms.]

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