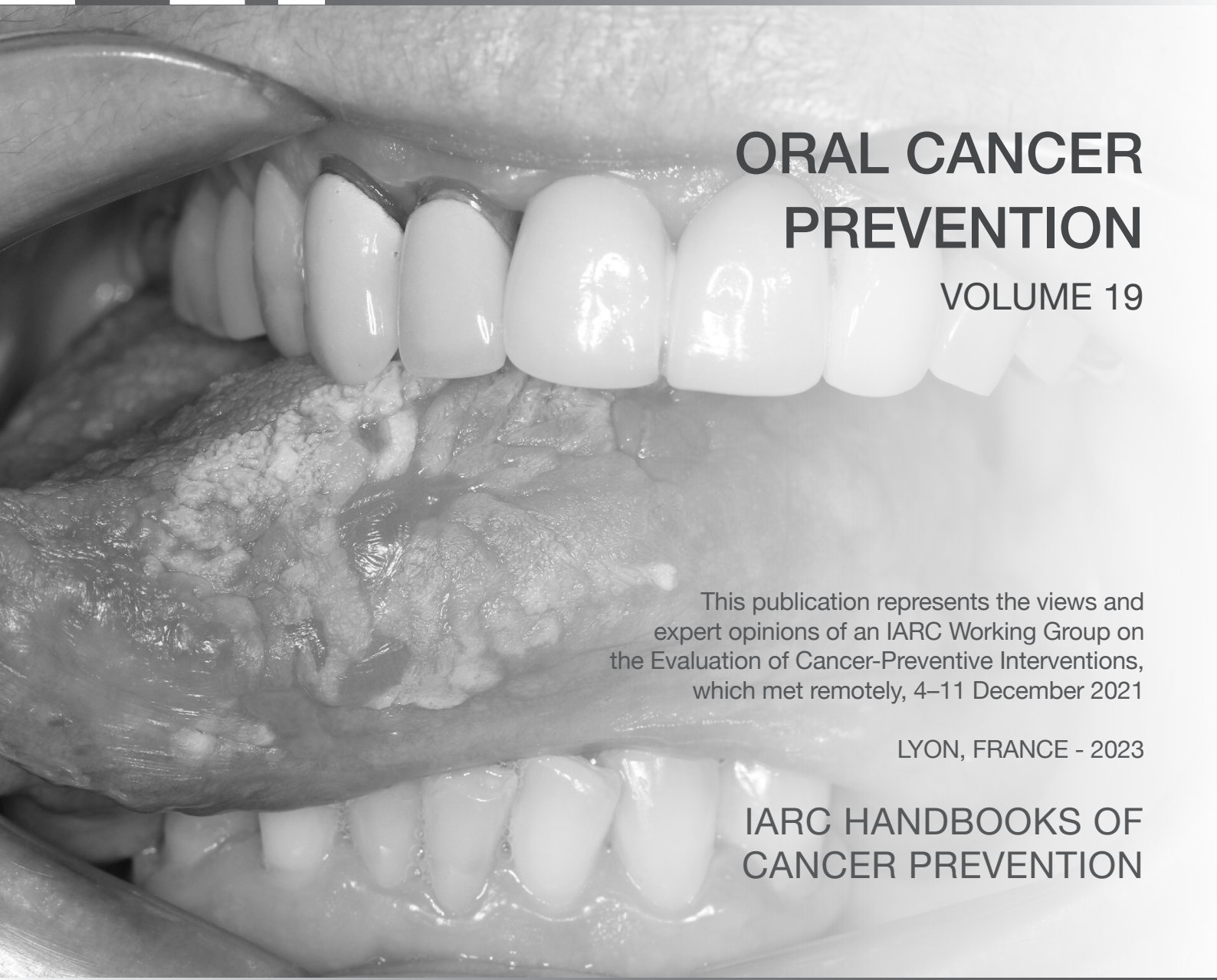
IARC HANDBOOKS



ORAL CANCER PREVENTION

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IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

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5. SUMMARY

5.1 Oral cancer and oral potentially malignant disorders

5.1.1 Anatomy of the oral cavity and the oropharynx

The oral cavity is the entrance to the gastrointestinal tract. It is bounded anteriorly by the lips, posteriorly by the faucial arches anterior to the tonsils, laterally by the cheeks (buccal mucosae), superiorly by the palate, and inferiorly by the muscular floor. The tongue occupies the floor of the oral cavity. The subsites of the oral cavity include the lips (mucosal surface or labial mucosae), oral commissures, buccal mucosae, tongue, gingivae (gums), floor of the mouth, and palate.

The oropharynx is a tube-shaped fibromuscular structure behind the oral cavity, continuous with the nasopharynx superiorly and the hypopharynx inferiorly. It extends from the lower surface of the soft palate to the upper border of the epiglottis and communicates with the oral cavity anteriorly. The palatine tonsils project from the lateral wall of the oropharynx, and the lingual tonsils are found on the posterior third (base) of the tongue.

5.1.2 Global burden

Cancer of the oral cavity is the most common cancer type in the head and neck region of the body, with about 380 000 new cases and 180 000 deaths worldwide in 2020. Cancer of the oropharynx is less common, with an estimated 98 412 new cases and 48 143 deaths worldwide in 2020. The estimated age-standardized incidence rates of oral cancer are highest in Melanesia and South Asia. The incidence rate of oropharyngeal cancer is highest in Europe. The incidence rate of oral cancer is highest in countries with medium levels of the Human Development Index, and the incidence rate of oropharyngeal cancer is highest in countries with very high levels of the Human Development Index; low socioeconomic status is associated with an increased risk of both cancer types. During the past two decades, the observed incidence rates of oral cancers have generally decreased, especially in North America, some countries in South-East Asia, and some countries in Europe. The incidence rates of oropharyngeal cancer appear to be increasing in most countries worldwide. Because of population growth, the burden of oral cancer and oropharyngeal cancer will increase in the next two decades.

5.1.3 Oral neoplasia

(a) Classification and natural history of OPMDs and oral cancer

An oral potentially malignant disorder (OPMD) is defined as any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer. OPMDs include leukoplakia, proliferative verrucous leukoplakia, erythroplakia, oral submucous fibrosis, oral lichen planus, oral lichenoid lesions, oral graft-versus-host disease, oral lupus erythematosus, actinic keratosis, palatal lesions in reverse smokers, and dyskeratosis congenita. OPMDs are a heterogeneous group of lesions, and the transformation rates to cancer vary from 1.4% to 49.5%; the presence of epithelial dysplasia is the most significant predictor. The highest-risk OPMDs are proliferative verrucous leukoplakia and erythroplakia, and the risk is lowest for oral lichen planus. The natural history of OPMDs is not always linear or predictable. They may persist unchanged, progress towards cancer, or even regress.

The clinical features of OPMDs vary according to the type of OPMD. The clinical features of oral cancer vary depending on the site and the stage of presentation. Early cancers may present as erythroleukoplakic lesions with red, white, or mixed red and white areas. As the disease advances, there is ulceration and/or nodularity (exophytic or endophytic tumours). Prognosis of oral cancer depends on multiple factors, including tumour-, host-, and treatment-related factors. Spread of cancer to the regional lymph nodes has a direct negative effect on prognosis.

(b) Stage at diagnosis and stage-related survival

Stage at diagnosis is one of the main factors that affects cancer prognosis. Most patients with cancers of the oral cavity are diagnosed with advanced disease. Besides staging, access to health-care systems, associated comorbidities, and the quality of treatment planning also affect the prognosis. The 5-year survival rate of oral cancer ranges from 0% to 64% across countries, with a median of 39%. The Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system (eighth edition) has recently been updated to enable improved staging and prediction of prognosis of patients with oral cancer.

(c) Treatment and management of OPMDs and oral cancer

OPMDs are a clinically diverse group of disorders, which require a careful clinicopathological evaluation and monitoring over long periods, and their clinical management is challenging. Consensus guidelines for clinical management of patients with leukoplakia or erythroplakia, oral submucous fibrosis, and oral lichen planus have recently been proposed. After clinical identification, the current reference standard is to perform a biopsy for histopathological diagnosis, treatment guidance, and prognostication based on the grade of epithelial dysplasia. Preventive strategies (modifying known risk factors) can reduce risk of oral cancer. Both topical or systemic agents and surgical excision or ablation of OPMDs have been proposed. No consensus exists about time intervals of serial follow-up, which remains important for monitoring and surveillance.

Management and treatment of oral cancer are multidisciplinary. Treatment pillars include combinations of surgery, chemotherapy, radiotherapy, and, more recently, immunotherapy, for early-stage and locally advanced disease.

5.2 Reducing incidence of cancer or precancer

5.2.1 Established risk factors

Tobacco smoking, alcohol consumption, smokeless tobacco use, chewing areca nut products (including betel quid) [hereafter referred to as "areca nut"] with or without tobacco, and infection with human papillomavirus type 16 (HPV16) are classified by the International Agency for Research on Cancer (IARC) *Monographs* programme as carcinogenic to humans (Group 1) and are established risk factors for cancers of the oral cavity. Tobacco smoking, alcohol consumption, and chewing areca nut with tobacco are also established risk factors for pharyngeal cancer. HPV16 infection is an established cause of oropharyngeal cancer.

(a) Tobacco smoking

In most countries, tobacco smoking is the leading cause of oral cancer and oral cancer death. The risk of oral cancer increases with increasing frequency (number of cigarettes smoked per day), duration (in years), and cumulative pack-years of smoking. The duration of smoking has a stronger effect on risk of oral cancer than the frequency of smoking does, but the elevated risk becomes significant at a low number of cigarettes smoked per day. For a given level of exposure, the risk of oral cancer conferred by tobacco smoking is similar by sex. Cigar, pipe, and bidi smoking are associated with a significantly increased risk of oral cancer. Tobacco smoking also causes oropharyngeal cancer, with a dose–response increase in risk. Worldwide, about one quarter to one third of oral cancers and 30–49% of oropharyngeal cancers are attributable to tobacco smoking alone. The main OPMDs caused by tobacco smoking are leukoplakia and erythroplakia.

(b) Alcohol consumption

Consumption of alcohol, particularly heavy alcohol consumption, is associated with an increased risk of oral cancer and oropharyngeal cancer. For the same cumulative exposure, higher alcohol intake for shorter duration confers a greater risk of oral cancer compared with lower alcohol intake for longer duration. Alcohol consumption also confers an elevated risk of OPMDs, particularly leukoplakia. Alcohol consumption increases synergistically in combination with tobacco smoking and accounts for 64% of the population attributable risk of oral cancer.

(c) Smokeless tobacco use

Use of smokeless tobacco (products containing tobacco but not including areca nut or betel quid) increases the risk of oral cancer in a dose-dependent manner with increasing frequency of use (times per day), duration of use (in months), and amount of time the product is retained in the mouth. The risk of oral cancer, after accounting for concurrent smoking, appears to be higher in women than in men. The fraction of oral cancers attributable to smokeless tobacco use is high (50–68%) in countries in South and South-East Asia and in the Sudan, and is much lower (1.6–6.6%) in North America. Smokeless tobacco use increases the risk of OPMDs, particularly leukoplakia.

(d) Chewing areca nut products (including betel quid) with added tobacco

Chewers of areca nut with added tobacco are at increased risk of oral cancer and oropharyngeal cancer compared with never-chewers. The effect is larger in women than in men. The risk of oral cancer increases with frequency (times per day) and duration (in years) of chewing. Chewers of areca nut with added tobacco also have increased risk of OPMDs compared with never-chewers, and the risk is highest for oral

submucous fibrosis, erythroplakia, and leukoplakia. The risk of OPMDs increases with the frequency of chewing (times per day), the duration of chewing (in years), and a younger age at the start of chewing. In India, the population attributable fraction of chewing betel quid with added tobacco for oral cancer was estimated to be higher in women (63.2%) than in men (44.7%). The population attributable risk for OPMDs was estimated to be 84% in Sri Lanka.

(e) Chewing areca nut products (including betel quid) without tobacco

Chewing areca nut without tobacco is predominant in Taiwan (China) but also occurs in other countries in South-East Asia, including Bangladesh, India, Myanmar, Sri Lanka, and Thailand. Chewers of areca nut without tobacco are at increased risk of oral cancer compared with never-chewers. The risk of oral cancer increases with the frequency (times per day) and the duration of chewing. Chewers of areca nut without tobacco also have increased risk of OPMDs compared with never-chewers; the highest risks have been reported for oral submucous fibrosis, erythroplakia, and leukoplakia. The risk of OPMDs increases with the frequency of chewing (times per day), the duration of chewing (in years), and a younger age at the start of chewing. In Taiwan (China), the population attributable fraction of chewing areca nut without tobacco was estimated to be 57.3% for oral cancer, 85.4% for oral submucous fibrosis, and 73.2% for leukoplakia.

(f) HPV16 infection

HPV infections are acquired primarily through sexual activity. HPV16 infection is associated with a < 5-fold increased risk of oral cancer and with a 14-fold to > 100-fold increased risk of oropharyngeal cancer. HPV16 infection causes ~2% of oral cancers worldwide. In contrast, there is wide geographical heterogeneity in attributable fractions of HPV for oropharyngeal cancers, ranging from about 40–50% in North America, Europe, Australia and New Zealand, Japan, and the Republic of Korea to < 15% in most other parts of the world. This heterogeneity may arise from a combination of differences in relevant sexual behaviours and the prevalence of exposure to other risk factors.

(g) Combined effects of established risk factors

Combined exposure to more than one of the risk factors confers a risk that is the sum of the individual risks for each of these carcinogens, and can confer a risk that exceeds the sum or the multiplication product of the individual risk estimates.

The relative risk of oral cancer in individuals who both smoke tobacco and consume alcohol is greater than multiplicative (i.e. the joint effect is greater than the multiplication product of the individual effects). The relative risk of oral cancer in individuals who smoke tobacco, consume alcohol, and chew areca nut with or without tobacco is greater than additive (i.e. the joint effect is greater than the sum of the individual effects).

(h) Additional potential risk factors

Other potential risk factors for oral cancer include second-hand smoke, indoor air pollution, low socioeconomic status (measured by education level, income, occupation), chronic mechanical irritation, and drinking hot maté. Other potential risk factors are dysbiosis of the oral microbiome; exogenous environmental, occupational, and infectious exposures; and poor oral hygiene or oral health, resulting in persistent or chronic inflammation.

5.2.2 Impact upon quitting

(a) Tobacco smoking

Since the *IARC Handbooks* Volume 11 evaluation (in 2006), two cohort studies, one meta-analysis of 17 case–control studies (including

3302 cases of oral cancer and 16 377 controls), and two additional case–control studies on incident oral cancer consistently showed a progressive reduction in the relative risk of oral cancer with increasing time since quitting smoking, with a statistically significant trend in four of these studies. The reduction in risk was evident in all studies within 10 years of smoking cessation. In the meta-analysis, the risk of oral cancer became significantly lower in former smokers compared with current smokers within 4 years after cessation (35% reduction), and the estimated relative risk in former smokers reached the relative risk in never-smokers after ≥ 20 years of smoking cessation, based on fully adjusted risk estimates taking into account frequency of alcohol consumption and cumulative smoking.

The body of evidence on oral cancer and smoking cessation included populations with a wide geographical distribution across North America, Central and South America, Europe, and Asia, including both men and women in four of five studies. The reported risk estimates were based mostly on former and current smokers of cigarettes but also included a minority of smokers of other tobacco products (cigars, pipes, and hand-rolled cigarettes).

Based on a single study that combined oral cancer and pharyngeal cancer, quitting smoking at any age was associated with a significant reduction in the risk of these cancers compared with current smokers, with a progressive and significant lowering of the risk with decreasing age at quitting.

Nine studies on smoking cessation and incidence or prevalence of OPMDs were identified, conducted in Brazil, India, Kenya, Puerto Rico, Sri Lanka, Taiwan (China), and the USA. In a large cohort study in India comparing former versus current bidi smokers after 10 years of follow-up, the incidence of leukoplakia decreased substantially (85% decrease) after smoking cessation. In addition, a large community-based case–control study nested within an intervention study in India reported a 70% increase in risk of leukoplakia in former smokers compared with never-smokers, in contrast to a > 3-fold increase in risk in current smokers. In case–control studies, estimates of the relative risk in former smokers compared with never-smokers ranged from 0.5 to 4.9; the 95% confidence interval often included 1, and the magnitude was mostly, but not always, markedly lower than the relative risk in current smokers (which ranged from 0.48 to 10.0).

(b) Alcohol consumption

Four studies were identified that reported estimates of the relative risk of oral cancer by time since cessation of alcohol consumption: one pooled analysis of case–control studies and three other, smaller case–control studies. In addition, two cohort studies were identified that had data on former alcohol drinkers relative to never-drinkers. The large international meta-analysis from 2010, which pooled data on 3302 cases of oral cancer from 13 case–control studies, found that the reduction in risk of oral cancer after alcohol cessation increases with time since cessation; the effects were more pronounced in former heavy drinkers (≥ 3 drinks per day), reducing the risk by > 50% by 20 years of quitting (odds ratio, 0.43; 95% confidence interval [CI], 0.28–0.67) for oral cancer, and were less clear for oropharyngeal and hypopharyngeal cancers combined. Of the three earlier smaller informative case–control studies, only the one in India reported data comparing former versus current drinkers, and found a tendency for reduction in the risk of oral cancer associated with ≥ 10 years of quitting (odds ratio, 0.62; 95% CI, 0.19–2.05).

No studies on the impact of duration of alcohol cessation on risk of OPMDs were identified. Based on data from seven case–control studies, risk estimates for OPMDs in former drinkers relative to never-drinkers were generally higher than for current drinkers relative to

never-drinkers, particularly for leukoplakia and erythroplakia.

(c) Smokeless tobacco use

A total of six studies were available that examined the association between former use compared with never use of smokeless tobacco and risk of oral cancer. (None of the studies considered current users of smokeless tobacco as the reference group, and none provided risk estimates by time since quitting use.) There were two large cohort studies, in Sweden and Norway, and four case–control studies, three in Sweden and one in Yemen. Neither of the two cohort studies found an association between use of oral snuff (former use or current use) and risk of oral cancer; they reported non-significant relative risk estimates for former users of 0.7–1.0. Although both cohort studies were well powered, exposure categories for smokeless tobacco use (as current, former, and never use) were defined at study entry only, with no reassessment of status of snuff use. In addition, neither of the studies adjusted for alcohol consumption. These limitations are particularly important given the long follow-up period of 12–35 years. The registry-based case–control study in Sweden, which included 128 cases of oral cancer and 756 matched controls, reported a 1.8-fold non-statistically significant increased risk of oral cancer in former oral snuff users after adjustment for potential confounding factors.

Data from eight studies on the association between former use of smokeless tobacco and risk of OPMDs were inconsistent, and all except one study lacked a definition of former users with regard to duration of cessation.

(d) Chewing areca nut products (including betel quid) with added tobacco

Evidence for reduction in risk of oral cancers or OPMDs with cessation of chewing areca nut with added tobacco comes from five published studies (three cohort studies and two case–control studies, all in India), one published meta-analysis, and two primary analyses undertaken by the Working Group (one cohort study and one case–control study, both in India). A primary intervention study in India assessed only OPMDs (leukoplakia) as the primary outcome.

Results from the published studies were inconsistent. Three out of five studies reported a non-significantly lower relative risk of oral cancer in former chewers compared with that in current chewers. The other two studies reported an increased risk, but the estimates were not adjusted for tobacco smoking and alcohol consumption, and the results could be due to reverse causation. Results from the meta-analysis did not show any inverse association. Nevertheless, primary analyses from the cohort study in India showed a reduction in risk of oral cancer in former chewers of 3% (95% CI, 1–4%) per year of cessation of chewing areca nut with added tobacco. In addition, results were consistent across studies for a reduction in the relative risk of OPMDs by duration of cessation of chewing areca nut with added tobacco. The primary prevention study showed strong reductions in the incidence of leukoplakia 5 years after the intervention, by 49% (95% CI, 7–72%) in men and 81% (95% CI, 70–89%) in women.

(e) Chewing areca nut products (including betel quid) without tobacco

Evidence for reduction in risk of oral cancers or OPMDs with cessation of chewing areca nut without tobacco comes from four published case–control studies (three in Taiwan [China] and one in Papua New Guinea), one published meta-analysis, and four primary analyses undertaken by the Working Group (three cohort studies and one case–control study, all in Taiwan [China]). Cessation of chewing areca nut without tobacco was consistently associated with a reduction in the relative risk of oral cancer in former chewers compared with current chewers; the inverse association was significant after long-term cessation

(≥ 15 years of quitting). Based on the primary data analyses, risk reductions per year of cessation ranged from 2.3% to 6.7%. Furthermore, risk reductions were generally larger for younger ages at cessation. In addition, results were consistent across studies for a reduction in the relative risk of OPMDs in former chewers compared with current chewers, and by duration of cessation of chewing areca nut without tobacco.

(f) HPV16 infection

Three types of vaccines against HPV infection are currently available: a bivalent vaccine, a quadrivalent vaccine, and a nonavalent vaccine. All three target HPV16, the type that causes most HPV-associated oral and oropharyngeal cancers. HPV vaccines are prophylactic (i.e. vaccination prevents future acquisition of infection) and not therapeutic (i.e. vaccination does not enable clearance of prevalent infection). Studies show strong evidence of reduction in the prevalence of oral and oropharyngeal HPV16 infection in vaccinated individuals compared with unvaccinated individuals. Because HPV vaccines were only approved recently (in 2006 for women and in 2011 for men in most countries worldwide), the impact of HPV vaccination will take several years or even decades to result in a reduction in incidence of oral cancer or oropharyngeal cancer. However, the anticipated reductions in the incidence of HPV-associated oral cancer and oropharyngeal cancer will depend on the extent of vaccination coverage in the population in any specific country.

5.2.3 Preventive dietary agents

Several studies have examined the protective effects of consuming coffee, tea, fruits and vegetables, and dietary fibre on the incidence of oral cancer. Several population studies have shown a significant inverse relationship between coffee intake and incidence of oral cancer. The effect of tea intake is unclear, with some studies showing a non-significant protective effect and others showing no benefit; it should also be noted that drinking very hot beverages (at temperatures > 65 °C) may increase risks of oral cancer and pharyngeal cancer. Studies examining consumption of fruits and vegetables found a general reduction in the relative risk of oral cancer associated with increasing consumption of fruits or vegetables. Consumption of dietary fibre has also been shown to have protective effects on development of oral cancer.

The effects of dietary agents on the development of OPMDs were examined in several population-based studies conducted in India and Sri Lanka, and a hospital-based study in Italy. In general, consumption of foods and nutrients rich in dietary fibre, vitamins A, C, E, and B12, β-carotene, lycopene, folate, retinol, α-tocopherol, and antioxidant mineral zinc has been found to be protective against the development of OPMDs. Also, biochemical studies were conducted on serum or plasma samples from patients with leukoplakia or oral submucous fibrosis. The available data indicate that the consumption of foods and nutrients rich in certain vitamins and antioxidants may inhibit the development of OPMDs.

5.3 Cessation of smokeless tobacco and/or areca nut use

5.3.1 Product definition and description

The term "smokeless tobacco" refers to a large variety of commercially available or non-commercially available products that contain tobacco as the principal constituent and that are used either orally (chewing, sucking, placing in the cheek or lip pouch, or drinking) or nasally, without combustion. Areca nut is the seed of *Areca catechu* L. and is used as a chewing substance, either alone or in combination with other substances. Areca nut is the primary component of betel quid, which may also be

consumed without tobacco. Smokeless tobacco and areca nut may be consumed separately or combined.

Smokeless tobacco or areca nut products are available as a myriad of products. The products vary substantially in their names and their use in each region; the greatest diversity is observed in South and South-East Asia.

Both smokeless tobacco and areca nut contain multiple carcinogens, and both have been classified as carcinogenic to humans (Group 1) by the *IARC Monographs* programme.

5.3.2 Prevalence of consumption

(a) WHO South-East Asia Region

The World Health Organization (WHO) South-East Asia Region has the highest prevalence of use of areca nut and smokeless tobacco products in adults worldwide, ranging from 2.1% in Thailand to 27.5% in Bangladesh. In 2019–2020, about 30% of men and about 13% of women in India were daily users of smokeless tobacco or areca nut products. In several countries (e.g. Bangladesh, Indonesia, and Thailand), the prevalence of use is higher in women than in men. The prevalence of use of smokeless tobacco or areca nut products is also high in young people in this region; Nepal has the highest reported prevalence in adolescents (16%). South-East Asia is culturally very diverse, and the forms in which these products are prepared and mixed are highly variable. Therefore, it is generally not possible to disaggregate data for areca nut and for smokeless tobacco. Commonly used products include *gutka*, *khaini*, *gul*, betel quid (with or without tobacco), and *supari*.

(b) WHO Western Pacific Region

The WHO Western Pacific Region is culturally extremely diverse. Consumption of areca nut is common in Hunan Province (China) and in Taiwan (China), where the prevalence of use is about 10% in men, but the prevalence is decreasing in older people. Use of areca nut and betel quid has spread from the Philippines across the Western Pacific islands over the past century; the prevalence of use is about 80% in Palau and the Solomon Islands. Smokeless tobacco use is not common. Initiation of use of areca nut products by young people is increasing, for example in Guam (USA).

(c) WHO European Region

In the WHO European Region, the overall prevalence of use of both areca nut and smokeless tobacco is low, with a prevalence of use in most countries of less than 2%. However, in four countries the prevalence exceeded the global average for smokeless tobacco use (6%). There is a marked use of specific types of smokeless tobacco (*snus*) by men, in Nordic countries and in populations in central Asia; also, people of Asian descent and immigrants from South Asia may have use patterns from those regions. The prevalence of use was highest in Sweden (14%) and Norway (18%), with a higher prevalence of use in men than in women. Areca nut, *gutka*, and *zarda* are imported and are used only by immigrant communities from Bangladesh, India, and Pakistan, in which a prevalence of use of about 7% is reported.

(d) WHO Region of the Americas

In the WHO Region of the Americas, the use of smokeless tobacco and areca nut is not culturally embedded, and only limited data are available about patterns of use in the general population. A relatively small spectrum of smokeless tobacco products (e.g. snuff, *snus*, *iqmik*, *chimó*, plug) is currently used by about 1.4% of the population (ranging from 0.2% in Argentina to 3.5% in Venezuela), with a higher prevalence of use in men (2.5%) than in women (0.3%). Several factors are involved in the prevalence of smokeless tobacco use in this region, such as immigrants from South Asia, military personnel, baseball players, middle and high

school students, and the *quilombola* community. Areca nut is not commonly used in this region, except in scattered populations in Hawaii (USA).

(e) WHO African Region

The WHO African Region has the second-highest prevalence of smokeless tobacco use in adults worldwide, with an estimated 15 million adult users. Most users of smokeless tobacco are men (8 million), but the prevalence of use in women is high in some countries. The prevalence of smokeless tobacco use ranges from 0.1% in women in Eritrea to 25% in men in Madagascar. Smokeless tobacco is commonly used without areca nut, through nasal or oral application. Some of the commonly used products are *shammah* (moist snuff), *taaba* (snuff), and *paraky*. Use of areca nut without tobacco by a minority population of South Asian descent has been reported in some countries (e.g. South Africa).

(f) WHO Eastern Mediterranean Region

In the WHO Eastern Mediterranean Region, there are about 21 million adult users of smokeless tobacco. The prevalence of use is much higher in men (~18 million) than in women (~3 million). The prevalence of use and the products used vary across countries. The most common smokeless tobacco products used in the region are *toombak* (especially in the Sudan) and *naswar* (a similar product that is common in the Arabian Peninsula). The prevalence of smokeless tobacco use ranges from 0.1% in women in Egypt to 34% in men in Afghanistan.

(g) Determinants of use

Determinants of use of smokeless tobacco and areca nut can be categorized into individual, social, and environmental factors.

Among individual factors, users' level of knowledge about the harmful health effects of use is a determinant of use of smokeless tobacco or areca nut. In addition, perceived positive effects such as relieving headaches, improving sleep quality, inducing relaxation, aiding decision-making, reducing boredom, and inducing a feeling of being energized are facilitators for use of smokeless tobacco and areca nut. Use of smokeless tobacco is associated with older age groups, and men generally have a higher likelihood of use.

The socioeconomic determinants of use of smokeless tobacco and areca nut are income level, employment, and education level. A large proportion of users of smokeless tobacco have low socioeconomic status, especially in unemployed people. Type of employment also determines use behaviour. The proportions of users of smokeless tobacco and areca nut are high in occupations that require long working hours or continuously repeated activities, such as in drivers and construction workers. With regard to education level, lower education levels are consistently associated with increased prevalence of smokeless tobacco use. The relatively low cost of the quid compared with smoked tobacco has been reported to be a socioeconomic determinant of areca nut use.

Socioculturally, influence from family members and peer pressure are important determinants of both smokeless tobacco use and areca nut use. Sharing of areca nut is a usual practice during social gatherings and is a significant cultural identifier, which reinforces social acceptance. It is also considered a symbol of love and marriage in many places, notably in India and in Taiwan (China). Sociodemographic factors for smokeless tobacco use include area of residence; there is a higher propensity for smokeless tobacco use in rural areas than in urban areas. Advertisements are another determinant of use of smokeless tobacco and areca nut.

5.3.3 Interventions for cessation of use

(a) Behavioural interventions

Nine intervention studies assessed the effects of behavioural interventions for cessation of use of smokeless tobacco or areca nut products in adults: six randomized controlled trials (RCTs) in the USA, one RCT in Sweden, and two large cohort studies in India. Interventions included dental examination; brief advice by physicians, dentists, or behavioural scientists, together with a written manual or leaflet; audiovisual support; follow-up telephone call; quitline support; and other forms of support. Controls received brief advice as in usual care, a written manual, and/or delayed intervention. Of the nine studies, four RCTs in the USA and the two cohort studies in India showed significant effects on the cessation rates, with relative risk ranging from 1.28 (95% CI, 1.09–1.50) to 25.70 (95% CI, 13.26–49.84) for the intervention arm compared with the control arm. The remaining three RCTs (two in the USA and one in Sweden) did not show significant effects; in addition, the numbers of smokeless tobacco users in both the intervention group and the control group were limited in the RCT in Sweden.

Five intervention studies assessed the effects of behavioural interventions for cessation of use of smokeless tobacco or areca nut products in youth: four RCTs in the USA and one large cohort study in India. Interventions included peer-led components, training by trained group leaders or athletes, further supported with tailored audiovisual meetings at periodic intervals. Controls received either no intervention or delayed intervention, general anti-tobacco education, or the general help of a support group. One RCT in the USA showed significant effects on the cessation rates in the intervention arm compared with the control arm, which received no intervention. The other four studies showed effects that were not statistically significant; of note, three of the studies included some sort of intervention in the control arm. One study reported a significant effect on the prevention of initiation of smokeless tobacco use in some of the participants in the intervention and control arms who were non-users at baseline.

(b) Pharmacological interventions

Three RCTs assessed the effects of pharmacological interventions for cessation of use of smokeless tobacco or areca nut products: two with nicotine replacement therapy (one with nicotine gum in India and one with nicotine lozenge in the USA) and one with antidepressants in Taiwan (China). Compared with the behavioural intervention received by the controls, neither nicotine gum nor nicotine lozenge had an effect on the cessation rates for use of smokeless tobacco and areca nut products. In the third study, use of both antidepressants showed significant effects on cessation rates compared with placebo for use of areca nut products (including betel quid) without tobacco (escitalopram: relative risk, 6.33; 95% CI, 1.53–26.14; moclobemide: relative risk, 6.17; 95% CI, 1.48–25.64 at 2 months).

(c) Combined pharmacological and behavioural interventions

A total of 16 RCTs were reviewed to assess the effects of pharmacological interventions in combination with behavioural interventions for cessation of use of smokeless tobacco or areca nut products. Two studies were on nicotine gum, four on nicotine patch, four on nicotine lozenge, three on bupropion (an antidepressant), and three on varenicline (a nicotinic receptor partial agonist). All of the studies were conducted in the USA, except for two studies on varenicline, of which one study was in Norway and Sweden and one study was in India. The study populations were users of smokeless tobacco alone (in the USA and in Norway and Sweden) or of smokeless tobacco or areca nut with tobacco products (in India). All studies performed intention-to-treat analyses or treated participants who withdrew and/or were

lost to follow-up as non-abstinent. Most studies (13 of 16) had a long follow-up (from 6 months to > 12 months). Nine of the 16 studies had at least 100 participants each in the intervention and control arms. In all studies except one, controls were provided with a combination of placebo plus behavioural therapy. Only two studies showed significant positive effects on cessation rates, one using varenicline (relative risk, 1.42; 95% CI, 1.08–1.79) and one using nicotine lozenge (relative risk, 1.27; 95% CI, 1.10–1.47); in both studies, the control arm also received the behavioural intervention. Most of the other studies showed non-significant positive effects; non-significant negative effects were found in three studies, and no effect was reported in one study.

5.3.4 Policies and their impacts

(a) Control policies for smokeless tobacco

Implementation of the articles of the WHO Framework Convention on Tobacco Control to control smokeless tobacco use is at an intermediate stage in the 182 countries that have acceded to the WHO Framework Convention on Tobacco Control.

Articles 4 and 5: Prevention of initiation of smokeless tobacco use in youth. In two studies in Bihar, India, school-based tobacco control policies showed positive effects in reducing the prevalence of smokeless tobacco use.

Article 6: Price and tax measures on smokeless tobacco. One study in the USA showed that taxation had reduced the prevalence of smokeless tobacco use. Four other studies, three in India and one in Bangladesh, showed that higher taxation would reduce the prevalence of use. A large meta-analysis of studies in five countries showed that a 10% price increase would reduce the demand for smokeless tobacco by 2.1%.

Article 11: Packaging and labelling of smokeless tobacco products. Three studies in India showed that large pictorial warnings on product packages are noticed by users and lead to motivation to quit and thinking about quitting.

Article 12: Education, communication, training, and public awareness on smokeless tobacco. Three studies in India and one study in Bangladesh showed that noticing anti-smokeless tobacco messages in the mass media is associated with intention to quit and attempts to quit.

Article 13: Ban on smokeless tobacco advertising, promotion, and sponsorship (TAPS). One study in India and one in the Sudan showed that restricting point-of-sale advertising near schools has an impact on the prevalence of smokeless tobacco use.

Article 14: Demand reduction measures concerning smokeless tobacco dependence and cessation. In one study in the USA and three studies in India, quitlines reported high cessation rates in the callers.

Article 16: Access to and availability of smokeless tobacco to minors. In Sri Lanka, enforcement of the policy of no sales to minors (aged < 18 years) led to a reduction in the prevalence of smokeless tobacco use by minors, as shown by two successive rounds of the Global Youth Tobacco Survey after this policy was adopted. However, in many places, adoption of a policy of no sales to minors has not been successful.

Bans on smokeless tobacco products. In three studies in India, bans have had some initial effect on prevalence of use. However, online sales and smuggling have been reported in Bhutan, India, Sri Lanka, and some European countries. One study in India showed that in view of the *gutka* ban, former users of *gutka* were turning to alternative, vendor-made mixtures (e.g. *mawa*) containing similar ingredients to *gutka*.

Article 20: Research, surveillance, and exchange of information on smokeless tobacco. In Bangladesh, India, and Thailand, a reduction in smokeless tobacco use was found in the second round of the Global Adult Tobacco

Survey after several control policies were implemented at the same time.

Overall, applying multiple key tobacco control policies simultaneously has an amplifying effect.

(b) Control policies for areca nut products (including betel quid)

Areca nut control policies are slowly emerging in countries where areca nut has traditionally been used. Taiwan (China) is the only country with an areca nut control programme; the prevalence of betel quid use has continued to decrease for more than 10 years.

Only a few countries have more than one policy. Taiwan (China) has the highest number of policies (six policies), followed by Myanmar (four policies) and India (three policies). The most commonly adopted policy is a ban on spitting in public places, as has been implemented in Bhutan, Myanmar, Papua New Guinea, and Taiwan (China), as well as in India (by the railways only) and in Hangzhou City (China).

The policies implemented in Taiwan (China) in 1997 are a ban on spitting in public places, a ban on chewing in certain workplaces and in the military, awareness programmes, a betel quid cessation programme, a plantation programme to help areca nut growers change to other crops, and an oral mucosal screening programme to monitor the effect of the policies. As a result, the prevalence of areca nut use in adults (aged ≥ 18 years) has decreased steadily, from about 45% in 2007 to about 5% in 2017. After having increased over several decades, the annual incidence rate of oral cancer has plateaued at about 42 per 100 000 people since 2009.

5.4 Screening and early diagnosis of oral cancer

5.4.1 Screening methods and technologies

(a) Clinical oral examination

Clinical oral examination is the only screening method for the detection of oral cancer and OPMDs that is routinely used. It consists of a visual inspection of the oral cavity and palpation of the neck to identify enlarged lymph nodes or masses. The specificity of clinical oral examination ranges from 75% to 99%, based on numerous studies conducted in Brazil, India, Japan, Portugal, Sri Lanka, Taiwan (China), and the United Kingdom. In contrast, the sensitivity of clinical oral examination for OPMDs and oral cancer was more heterogeneous across studies, ranging from 50% to 99%. Correct risk stratification of oral mucosal abnormalities detected by clinical oral examination is challenging, given the overlap in the signs and symptoms of OPMDs and oral cancer with those of benign mucosal diseases; therefore, primary screeners should be well trained. A limited number of studies on dental care workers have assessed the efficacy of training programmes. In low-resource settings, community health-care workers can be successfully trained to perform clinical oral examination.

Mobile phone technology platforms for remote screening (i.e. via the transmission of digital images for remote evaluation by an expert clinician) are currently being developed and tested.

(b) Mouth self-examination

The oral cavity is easily accessible for examination, and most OPMDs and oral cancers are readily visible. In mouth self-examination, individuals examine their own oral cavity to identify OPMDs or cancerous lesions. The accuracy of mouth self-examination for detection of OPMDs and early-stage cancer varies, from 8.6%

to 72.7% for sensitivity and from 54% to 99% for specificity; also, compliance with performing mouth self-examination varies from 36% to 88%. Several studies have assessed the detection rate of OPMDs.

(c) Adjunctive techniques

Visualization adjuncts and vital staining are techniques that aim to improve the performance of clinical oral examination to identify and/or risk-stratify patients with OPMDs and oral cancer. These adjuncts are rarely used in primary screening, and most of the evidence on their performance comes from secondary or tertiary care settings, against the reference standard of histopathology.

Visualization adjuncts include tissue autofluorescence, narrow-band imaging, and tissue reflectance. Tissue autofluorescence shows the highest performance, with a pooled sensitivity of 88% (95% CI, 80–93%) and a pooled specificity of 61% (95% CI, 44–75%). The low specificity is attributed to the preponderance of benign lesions, which yield false-positive outcomes. Consumption of smokeless tobacco or areca nut by the patient limits the interpretation of autofluorescence.

Vital staining with toluidine blue or Lugol's iodine involves the topical application of a dye directly to the oral mucosa to detect or highlight abnormal mucosa. A recent meta-analysis of 20 data sets assessing the accuracy of toluidine blue staining reported a pooled sensitivity of 86% (95% CI, 79–90%) and a pooled specificity of 68% (95% CI, 58–77%). The potential for false-positives is high because toluidine blue binds to benign inflammatory, ulcerative, or regenerating tissues. Toluidine blue staining has been tested as an adjunct to clinical oral examination in one screening study, showing a non-significant 21% reduction in cancer incidence.

(d) Cytology and liquid biopsy

Brush biopsy cytology may be used as a practical, low-risk, and low-cost diagnostic adjunct in patients with OPMDs and oral cancer. Brush biopsy showed the highest accuracy among all diagnostic adjuncts compared with histopathological end-points, with a sensitivity of 90% (95% CI, 82–94%) and a specificity of 94% (95% CI, 88–97%).

Liquid biopsy is a minimally invasive diagnostic method that analyses biomarkers in samples of circulating fluids, such as blood or saliva ("salivaomics"). The use of saliva samples in the diagnosis of oral cancer and OPMDs has been extensively explored. Potential salivary biomarkers include minerals, peptides, proteins, DNA, messenger RNA, microRNA, long coding RNA, oxidative stress-related molecules, glucocorticoids, glycosylation-related molecules, telomerase activity, and the microbiome. However, the diagnostic applications of salivaomics have been explored only recently.

(e) Emerging technologies

Artificial intelligence is used in medical diagnostics, and its use has been proposed to improve the detection and diagnosis of OPMDs and to distinguish the oral mucosa at highest risk of malignant transformation from the normal mucosa.

Optical coherence tomography is an optical diagnostic technique used for in vivo imaging of OPMDs. Also, in vivo microscopy can be adapted for the same purpose to provide a cross-sectional image of the oral mucosa: techniques such as reflectance microscopy and fluorescence microscopy provide the possibility of detailed mucosal diagnostics, sometimes with the aid of an optical contrast agent (topical or intravenous). When spectroscopy is used, contrast agents are not needed; instead, the light reflected at the same wavelength (elastic scattering) or different wavelengths (Raman spectroscopy) is measured.

Finally, molecularly targeted optical imaging agents have been developed to delineate the margins of oral cancer; however, it is unclear how they could be used in a screening setting.

5.4.2 Organized and opportunistic oral cancer screening

Worldwide, there are very few large-scale population-based organized or non-organized oral cancer screening programmes, or sporadic screening activities. A large-scale population-based annual oral cancer screening programme has been under way in Cuba since 1982, first targeting individuals aged ≥ 15 years and later those aged ≥ 35 years. A nationwide population-based biennial oral cancer screening programme has been running in Taiwan (China) since 2004, targeting cigarette smokers and/or betel quid chewers aged ≥ 30 years and Indigenous people aged ≥ 18 years; more than 4.6 million people have participated in this screening programme.

In India and Sri Lanka, the governments have issued guidelines for oral cancer screening, but these have yet to be implemented systematically on a large scale. 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 clinical oral examination for the population aged ≥ 60 years in São Paulo State, Brazil. No population-based oral cancer screening programmes have been reported in Europe, North America, or Oceania.

5.4.3 Determinants of participation in screening for oral cancer

Few studies have reported determinants of participation in oral cancer screening, with different outcome measurements for participation in screening (screening participation, compliance with referral, and adherence to follow-up visits or screening rounds). Determinants of participation can be identified mainly at three distinct levels: the individual, the health-care provider, and the health-care system. Factors that are positively associated with screening participation and compliance with referral include the presence of symptoms, a family history of cancer, higher education levels, and exposure to risk factors such as tobacco smoking, alcohol consumption, and betel quid chewing. In addition, training of primary health-care workers for oral cancer screening and adequate referral of patients are positively linked to acceptance of oral cancer screening from a health-care provider and a health-care system perspective, respectively.

5.4.4 Effectiveness of screening

(a) Preventive effects of screening

One RCT (in India) and three observational studies – two based on the same screened cohort in Taiwan (China) and one in Cuba – have assessed the effect of screening individuals at high risk (defined in the studies as users of tobacco, alcohol, and/or betel quid) with clinical oral examination on incidence of advanced oral cancer and on mortality from oral cancer. In the RCT, after 15 years of follow-up, in users of tobacco and/or alcohol the relative risk of incidence of advanced oral cancer was 0.79 (95% CI, 0.65–0.95) and the relative risk of oral cancer mortality was 0.76 (95% CI, 0.60–0.97). The relative risks in the observational studies were very similar to those observed in the RCT, with reductions of 21–22% for incidence of advanced oral cancer and 24–26% for oral cancer mortality, and the findings were statistically significant in the cohort studies.

The studies were heterogeneous in the design of the screening intervention. The observational studies were based on evaluations of the performance of the national screening programmes, which included mainly male participants. Most

of the studies did not identify an impact of oral cancer screening on incidence of oral cancer overall.

(b) Harms of screening

Screening programmes may be associated with some harms, and it is important to consider the balance of benefits and harms for any screening activity. The potential harms of screening are associated with false-positive tests, false-negative tests, overdiagnosis, and overtreatment. Information about the harms of oral cancer screening is lacking.

5.4.5 Risk-based model for screening

Cancer screening has historically been based on age, without any assessment of exposure to known risk factors. Selectively screening only individuals at high risk may improve the efficiency and effectiveness of screening while minimizing the harms. A reanalysis of the findings of the RCT in India showed that a tailored approach based on alcohol consumption and use of any tobacco by the individuals increased the efficiency of oral cancer screening. A risk-based model for screening has been considered to be an appropriate approach for resource-limited countries with a high incidence of oral cancer.