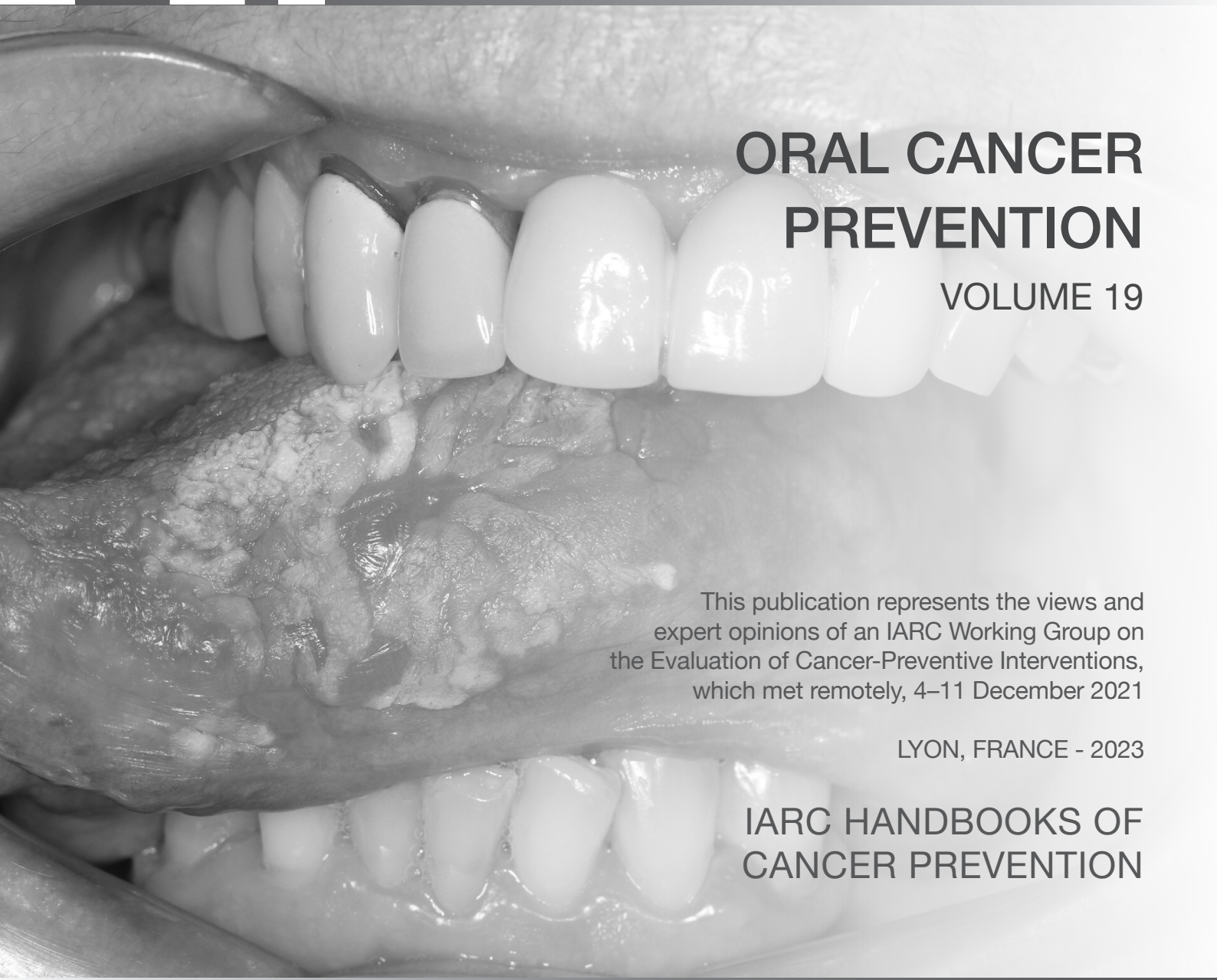
IARC HANDBOOKS



ORAL CANCER PREVENTION

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IARC HANDBOOKS OF CANCER PREVENTION

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6. EVALUATIONS, STATEMENTS, AND CONSIDERATIONS

6.1 Impact of quitting exposure to a risk factor on incidence of or mortality from oral cancer

6.1.1 Tobacco smoking

There is *sufficient evidence* that quitting tobacco smoking reduces the risk of oral cancer.

The risk decreases with increasing time since quitting smoking.

Rationale. *IARC Handbooks* Volume 11, published in 2007, already concluded that the risk of oral cancer decreases with increasing time since quitting smoking. Thus, in updating this evaluation, the Working Group restricted its review to recent studies that reported risk of oral cancer by time since quitting smoking, adjusted for important confounders. Recent evidence also reported a reduction in risk of oral cancer within 10 years of quitting smoking; the relative risk in former smokers reaches the relative risk in never-smokers after ≥ 20 years of cessation. The Working Group also reviewed the available evidence on smoking cessation and risk of leukoplakia, which suggests that the risk of leukoplakia decreases after quitting smoking.

Additional considerations. Quitting smoking has additional benefits; it reduces the risk of other chronic diseases, such as vascular diseases (coronary heart disease, cerebrovascular disease, aortic aneurysm, and peripheral arterial disease), non-malignant lung disease, other cancer types, and oral health problems.

Given that the joint effect of tobacco smoking and alcohol consumption is greater than multiplicative, quitting smoking reduces the large risk of oral cancer in individuals who continue to drink alcohol; this is an indisputable additional benefit of quitting smoking. Large reductions in risk would also be expected after smoking cessation in dual users of other agents known to be associated with oral cancer and correlated with tobacco smoking for which greater-than-additive or greater-than-multiplicative interactions have been established (i.e. smokeless tobacco, areca nut).

6.1.2 Alcohol consumption

There is *sufficient evidence* that cessation of alcohol consumption reduces the risk of oral cancer.

The risk decreases with increasing time since cessation of alcohol consumption.

Rationale. In reaching this evaluation, the Working Group gave more weight to studies that reported risk estimates by time since cessation of alcohol consumption; supporting evidence was provided by studies that reported risk estimates in former drinkers or current drinkers relative to never-drinkers. Studies that adjusted for

multiple potential confounders were also given more weight in the evaluation.

The evidence comes mainly from one large pooled analysis of data from 13 case–control studies, conducted in Asia, Europe, and North and South America. Although the original case–control studies have limitations in terms of recall bias and selection bias and there is significant heterogeneity in the pooled analysis, robust methodologies were used for data harmonization and statistical analyses, and consistent patterns of reduced risk after cessation of alcohol consumption were observed.

Additional considerations. The reduction in risk of oral cancer becomes more apparent after 10 years of cessation of alcohol consumption. There is some evidence that the reduction in risk of oral cancer is greater in former heavy drinkers (≥ 3 drinks per day).

Increased reductions in risk would also be expected after cessation of alcohol consumption in dual users of other agents known to be associated with oral cancer and correlated with alcohol consumption for which greater-than-additive or greater-than-multiplicative interactions have been established (i.e. smoked tobacco, smokeless tobacco, areca nut).

6.1.3 Smokeless tobacco use

There is *inadequate evidence* that quitting use of smokeless tobacco reduces the risk of oral cancer.

Rationale. In evaluating the body of evidence on risk of oral cancer upon quitting exposure to different risk factors, the Working Group gave the most weight to cohort studies and case–control studies that reported risk of oral cancer by time since cessation. In the case of smokeless tobacco, no studies were available based on this criterion.

The body of evidence supporting the evaluation consisted of two cohort studies and four case–control studies, conducted predominantly in Sweden and thus not providing data from other world regions where use of smokeless tobacco is highly prevalent.

The available studies had major limitations, including the absence of a clear period of abstinence in the definition of former users of smokeless tobacco, sparse numerical representation, and lack of sufficient adjustment for potential confounding factors.

Data from eight studies on the association between former use of smokeless tobacco and risk of oral potentially malignant disorders (OPMDs) were inconsistent.

Additional considerations. The Working Group noted the minimal geographical diversity in the studies, particularly the absence of studies from countries in South Asia, the world region that has the highest prevalence of use of smokeless tobacco. The Working Group also noted the absence of studies for smokeless tobacco products other than moist snuff, except for one small study on *shammah* use in Yemen.

6.1.4 Chewing areca nut products (including betel quid) with or without tobacco

There is *sufficient evidence* that cessation of use of areca nut products (including betel quid) with or without tobacco reduces the risk of oral cancer.

Cessation of use of areca nut products (including betel quid) with or without tobacco also reduces the risk of OPMDs.

Rationale. The Working Group elected to conduct a combined evaluation for chewing areca nut products without tobacco and chewing areca nut products with added tobacco, in view of several considerations. First, chewing behaviours and use of areca nut products are very heterogeneous between geographical regions and subregions. Second, the available literature does not enable a separate evaluation for each product.

The Working Group based the evaluation on data from published studies and from primary

analyses, using principally evidence on time since cessation, supported by the comparison of former users versus current users, and age at quitting. Particular attention was given to adjustment for important confounders and to the precision of the risk estimates. Three cohort studies had large sample sizes and long follow-up periods, which strengthened the temporal relationship between time since cessation and risk of oral cancer.

Key observations that guided the Working Group in making this evaluation include:

- Three large cohort studies and two case–control studies consistently showed a statistically significant association and statistically significant trend of reduced risk of oral cancer with increasing time since cessation of chewing areca nut products without tobacco.
- For cessation of chewing areca nut products with added tobacco, although the evidence was inconsistent across published studies, one large cohort study showed reduced risk of oral cancer with increasing time since cessation in former chewers.
- Risk reductions were also observed for OPMDs with increasing time since cessation of chewing areca nut products without tobacco, and for leukoplakia after cessation of chewing areca nut products with added tobacco.

Additional considerations. Cessation of chewing areca nut products with or without tobacco would be broadly beneficial for a reduced global burden of oral cancer. In addition to oral cancer and OPMDs, quitting chewing could prevent other cancer types (e.g. cancers of the pharynx and of the oesophagus) and other chronic diseases.

6.1.5 HPV16 infection

There are no studies to date on vaccination-related reductions in oral infection with human papillomavirus type 16 (HPV16) resulting in reduction in the incidence of HPV-associated oral cancer or oropharyngeal cancer. HPV vaccination has been shown to result in reduction in the prevalence of oral HPV16 infection in vaccinated individuals and in populations with high vaccination coverage. HPV vaccination has also been shown to result in reduction in the incidence, prevalence, and persistence of vaccine-type HPV infections, reduction in the incidence of associated precancers at the cervix, vagina, vulva, penis, and anus, and reduction in the incidence of cervical cancer in vaccinated individuals and in populations with high vaccination coverage.

There is a strong rationale and analogy, based on observations at other anatomical sites, that HPV vaccination would result in reduction in the incidence of HPV-associated oral cancer and oropharyngeal cancer in vaccinated individuals and in the populations at large, depending on vaccination coverage.

6.2 Interventions for cessation of smokeless tobacco or areca nut use

6.2.1 Behavioural interventions in adults

There is *sufficient evidence* that behavioural interventions in adults are effective in inducing quitting use of smokeless tobacco.

Rationale. Nine studies (seven randomized controlled trials and two cohort studies), including several high-quality studies, were available for evaluation. A positive effect of the intervention on the quit rates was observed consistently in the body of evidence, and chance, bias, and confounding as causes of this association were ruled out with reasonable confidence. Despite some limitations, all the studies showed a positive association, and six of the studies showed statistically significant effects.

6.2.2 Behavioural interventions in youth

There is *limited evidence* that behavioural interventions in young people are effective in inducing quitting use of smokeless tobacco.

Rationale. Five studies (four randomized controlled trials and one cohort study) were available for evaluation. The body of evidence provided apparently inconsistent results: one study showed significant effects, three studies showed non-significant positive effects, and one study showed a non-significant negative effect. However, this could be explained as follows:

- In the study that showed significant effects on the quit rates, the control arm had no intervention.
- Three of the four studies that showed non-significant effects, two positive and one negative, had some form of intervention in the control arm, thus pulling the estimates towards the null.

In addition, one study reported a significant positive effect of the intervention on the prevention of initiation of smokeless tobacco use.

6.2.3 Pharmacological interventions

There is *limited evidence* that pharmacological interventions with nicotine replacement therapy or antidepressants (escitalopram and moclobemide) are effective in inducing quitting use of smokeless tobacco and areca nut with tobacco.

Rationale. Three randomized controlled trials were available for evaluation. Two studies assessed the effectiveness of nicotine replacement therapy (one with gum and one with lozenges), and one study assessed the effectiveness of antidepressants (escitalopram and moclobemide). All three studies followed a good methodology, had adequate controls, and used proper outcome measurements. However, the studies had several limitations, including short follow-up periods (< 12 months) and confounding by the presence of some dual users (tobacco smoking and smokeless tobacco use).

Two studies showed an effect of the intervention in inducing quitting; one was statistically significant, and one was non-significant. The third study showed no effect. However, in the latter two studies, the control groups were provided with behavioural intervention instead of placebo, thus reducing the potential effect size.

6.2.4 Combined pharmacological and behavioural interventions

There is *limited evidence* that combined pharmacological and behavioural interventions are effective in inducing quitting use of smokeless tobacco.

Rationale. A large number of randomized controlled trials (16) were available for evaluation. A positive effect of the intervention on the quit rates was observed in some studies, but chance, bias, or confounding could not be ruled out with reasonable confidence, for several reasons:

- A positive effect of the intervention was reported in most studies (13 of 16). However, in most of these studies (11 of 13), the association was not statistically significant.
- Eight of the studies had large study populations (≥ 100 participants in each arm) and long follow-up periods. However, only two of these eight studies showed significant effects.
- Most studies had the same behavioural intervention in the control arm, thus pulling the estimates towards the null.

6.2.5 Policies

Few data are available on the effect of the individual World Health Organization Framework Convention on Tobacco Control policies on smokeless tobacco control. The strongest effect, despite limited evidence, was shown for taxation in reducing the prevalence of smokeless tobacco use. One study in India showed a positive effect of school-based tobacco control policies. A combination of policies was shown to be more effective than a single policy.

There is a shortage of data with regard to the effect of control policies for areca nut products, because these policies are new and have been implemented recently. The limited but positive results from Taiwan (China) suggest that adoption of a comprehensive set of policies to control areca nut use may lead to reductions in the prevalence of areca nut use.

6.3 Screening for oral cancer and OPMDs

6.3.1 Effectiveness of screening by clinical oral examination

Screening of individuals at high risk by clinical oral examination *may reduce mortality from cancer of the oral cavity* (Group B).

Individuals at high risk are defined as those with tobacco use, areca nut use, alcohol consumption, or a combination of these, in any form.

Rationale. In reaching this evaluation, the Working Group noted the following:

- The randomized controlled trials and cohort studies showed a statistically significant positive effect of oral screening on the incidence of advanced oral cancer and on oral cancer mortality in individuals at high risk (based on tobacco use, areca nut use, alcohol consumption, or a combination of these, in any form).
- The impact of oral screening on oral cancer mortality in the general population cannot be established on the basis of the current evidence.
- The limited number of studies of different designs (one randomized controlled trial, two cohort studies, and one case–control study) in a few settings restricts generalization of the outcomes.
- The limitations of the included studies were likely to pull the effect of screening towards the null:
  - In the randomized controlled trial, there was low compliance of screen-positive cases with further assessment.
  - In the cohort studies, there was selection bias for screening, and possible contamination of the control group.
  - In the case–control study, there was lack of power, possible overestimation of exposure to the intervention (defined as "any visit to a community dentist"), and a low coverage of the programme.
- The included studies did not report whether there were any primary prevention interventions within the studied population, which could have an impact on the estimates.
- The included studies had other limitations with an unclear effect on outcome:
  - The randomized controlled trial used a small number of randomized units.
  - In the retrospective cohort study, the proportion of individuals at high risk in the control group was unclear, possibly leading to information bias.

Regimen to which the evaluation applies. The screening interval used in the included studies was either 2 years or 3 years. The optimal age range could not be established.

6.3.2 Additional considerations

(a) Adjunctive techniques to oral examination

Very few studies have evaluated adjunctive techniques in population screening studies. Most of the adjunctive techniques have been evaluated as diagnostic adjuncts in either prospective accuracy studies or retrospective cohort or case–control studies. All of the available studies report accuracy measures of test results against histopathology as the reference standard. Given the unknown natural history of OPMDs in an individual patient, it is challenging to extrapolate accuracy data to important end-points such as mortality or survival. The added value of adjunctive techniques to clinical oral examination remains unknown. There is a potential for using adjunctive techniques and biomarkers in saliva for the diagnosis of OPMDs and oral cancer. However, there is a lack of clinical validation linked to important end-points as a standalone method in oral cancer screening settings.

(b) Harms of screening

A clear understanding of the harms linked to false-positive screening test results and, more importantly, false-positive diagnostic findings leading to potential overtreatment is hampered by a poor understanding of the natural history of OPMDs. There is currently little evidence that adjunctive techniques can reduce the proportion of false-positive results when screening by clinical oral examination. Adjunctive techniques or biomarkers that are predictive for cancer progression in OPMDs are being investigated. Quality assurance of programme implementation is important to improve the performance of screening programmes and reduce the harms of screening. This issue has not been addressed in the primary studies reviewed by the Working Group.

(c) Risk-based model for screening

Assessment of risk, for example by questionnaire, has the potential to increase programme efficiency and reduce the harms of overscreening, overdiagnosis, and overtreatment. However, implementation of screening programmes using risk-based models for selection of participants is a challenge from a programmatic perspective.

(d) Monitoring and evaluation of screening programmes

Assessment of determinants of partici-pation at all steps of the screening pathway has been demonstrated to be critical for the optimization of cancer screening at other sites (e.g. cervix, breast, and colon). The existing oral cancer screening programmes lack proper monitoring and evaluation mechanisms, preventing evidence-based evaluation of their efficacy and health impact.

It remains unclear whether the known risk factors for oral cancer, as well as age and sex, are positive or negative determinants of participation in oral cancer screening. Identifying and describing the predictors of participation in oral cancer screening, provider training, compliance with referral, the quality of available data, and the interventions to improve these is critical to increase the effectiveness of oral cancer screening programmes. Filling this gap may enable policy-makers and stakeholders to efficiently allocate human and financial resources to obtain higher benefits and reduce inequalities.

The screening trials have not provided a clear understanding of the natural history of OPMDs. The impact of detection, treatment, and surveillance of patients with OPMDs on oral cancer incidence and mortality has not been determined. Among the studies that assessed cancer incidence, most did not observe an impact of oral cancer screening on oral cancer incidence.

The Working Group considers primary prevention to be an integral part of a screening programme.