

ORAL CANCER PREVENTION

VOLUME 19

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met remotely, 4–11 December 2021

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GENERAL REMARKS

In April 2016, an international group of scientific and public health leaders from 21 countries met in Kuala Lumpur, Malaysia, at the International Conference on Betel Quid and Areca Nut, to identify research needs and discuss strategies to reduce the prevalence of use of betel quid and areca nut, and thereby the incidence of oral cancers related to their use ([Mehrtash et al., 2017](#)). Several members of the panel suggested that IARC – in particular, the *IARC Handbooks of Cancer Prevention* – perform a review and an evaluation of the current scientific literature on several aspects of oral cancer prevention, with a specific focus on South-East Asia.

Volume 19 of the *IARC Handbooks of Cancer Prevention* series provides a first-time evaluation of primary and secondary prevention approaches for oral cancer. The expert knowledge summarized in this *Handbook* will play a major role as a resource for policy-makers involved in the regulation of smokeless tobacco and will help fight a major public health problem. In addition, this *Handbook* aligns with the World Health Organization (WHO) mission of tobacco control, including the WHO Framework Convention on Tobacco Control (FCTC), and with IARC's mission of cancer research for cancer prevention with a particular focus on low- and middle-income countries.

History of use of smokeless tobacco and areca nut

Smokeless tobacco was originally used by the Indigenous populations of South America for various purposes, including in spiritual ceremonies, as a poultice with potential therapeutic effects, and as an exchangeable good ([Shafey et al., 2009](#)). In the 15th century, Columbus brought tobacco from his transatlantic expeditions to Europe ([Shafey et al., 2009](#)). By the mid-16th century, adventurers and diplomats such as Nicot began to popularize its use, with the introduction of tobacco in France in 1556, Portugal in 1558, Spain in 1559, and England in 1565 ([CNN.com, 2000](#)). In India, tobacco was introduced by the Portuguese in the 17th century ([Prasad, 2007](#)). Despite changes in consumption patterns with the global spread of tobacco through the centuries (from smokeless tobacco in the 18th century to cigars in the 19th century and cigarettes in the 20th century), tobacco is still currently used in a smokeless form ([Shafey et al., 2009](#)).

The chewing of areca nut is deeply embedded in the sociocultural history of South-East Asia and many parts of the Western Pacific. It is mentioned in the *Mahāvamsa*, a historical chronicle of Sri Lanka written in 504 BCE ([Krenger, 1942](#)), and in ancient writings of Hinduism in about 600 BCE ([Bhishagratna, 1907](#)) and in

writings of mainland China during the Tang dynasty (7th to 9th centuries CE). Cultivation of the *Areca catechu* palm tree has been widespread across South-East Asia and South Asia for millennia, initially in the Philippines and then gradually spreading across the Western Pacific Islands.

Distinguishing between smokeless tobacco products

Oral smokeless tobacco products are traditionally sold in various forms, but they can be broadly categorized as snuff (powdered or ground tobacco) or chewing tobacco (leaf, plug, or twist) ([Stanfill et al., 2011](#)). Smokeless tobacco products may contain different concentrations of tobacco-specific *N'*-nitrosamines, depending on their preparation and processing ([NCI and CDC, 2014](#)). *N'*-nitrosonornicotine (NNN), one of the most abundant tobacco-specific *N'*-nitrosamines, is formed by *N*-nitrosation of tobacco alkaloids, particularly during tobacco curing; NNN is classified by the *IARC Monographs* as carcinogenic to humans (Group 1) ([IARC, 2007](#); [Ammann et al., 2016](#)). The water content of smokeless tobacco products also varies; the water content of chewing tobacco (which ranges between 7% and 21%) is lower than that of moist snuff but higher than that of dry snuff ([IARC, 2007](#)). The variation in water content under the same manufacturing and storage conditions has the potential to influence the level of NNN.

Despite the differences between smokeless tobacco products and the potential differences in toxicant exposure and carcinogenic potential, most epidemiological studies do not distinguish between smokeless tobacco products, and this makes it difficult to evaluate cancer risks by product type. For the same reason, the Working Group's evaluation of smokeless tobacco (without areca nut) does not distinguish

between outcomes by type of smokeless tobacco and includes both oral snuff and chewing tobacco products.

Distinguishing between products that contain smokeless tobacco or areca nut or both

Smokeless tobacco and areca nut may be used either on their own or in combination. Thus, the resultant products may be categorized as containing only smokeless tobacco, only areca nut, or both smokeless tobacco and areca nut. However, a lack of clarity in reporting ([Theilmann et al., 2022](#)) the product categories has been observed in many studies, possibly leading to inappropriate interpretation and evaluation of the evidence. For example, in many studies, products that contain both smokeless tobacco and areca nut are reported as smokeless tobacco (or chewing tobacco). In other instances, the presence or absence of tobacco in the betel quid – a preparation that always contains areca nut – is not specified. In both cases, identification of the specific product(s) relies heavily on knowledge of the practices in the region(s) where the study was conducted ([Gupta and Warnakulasuriya, 2002](#)). Hence, it is essential that either the correct **product category** (as mentioned above) is specified or the **specific products** are clearly listed in the study details.

Differences in cessation interventions among youth and adults

The impact of an intervention to quit use of smokeless tobacco or areca nut on adults and youth differs because of age, perception of health risks associated with tobacco use, and the impact of tobacco advertising. Initiation of use is mainly at ages 13–14 years, and most of the initiation

happens before age 18 years. There is a paucity of data in the literature on the efficacy of interventions in preventing initiation of use. Also, young people generally do not perceive that tobacco kills or causes serious diseases. Hence, interventions based on communicating long-term health risks may not be salient to adolescents. However, attitudes and behaviours regarding tobacco use among youth are influenced by advertising in any form. Although performing such an evaluation was outside the scope of this *Handbook*, mass media anti-tobacco advertisements in the form of audiovisual spots, radio spots, print media, and educational awareness campaigns can be effective in promoting cessation.

Framework of evaluation of primary prevention interventions

The impact of preventive interventions on risk behaviours may take more than a decade to produce any significant beneficial effect on the future incidence of cancer. For this reason, it is necessary to monitor intermediate outcomes to assess the benefits of quitting risk habits. For this *Handbook*, IARC used the new Preamble, developed in 2019 ([IARC, 2019](#)), with a two-step evaluation: step 1 to assess whether a community programme or an intervention directed at an individual leads to cessation of use of smokeless tobacco and/or areca nut, and step 2 to evaluate whether quitting an exposure leads to a reduction in oral cancer incidence or mortality. However, as mentioned above, the lack of consistency in the terminology that has been used in the literature to describe the products prevented the Working Group from making a full evaluation, from intervention to cancer outcome, for any product category or specific product.

Research gaps in oral cancer prevention

Globally, research efforts for oral cancer trail behind those for most other common cancer types. A comprehensive, well-funded research strategy is needed to assess changes in the patterns of oral potentially malignant disorders (OPMDs) and cancer, especially in parts of the world where the burden of oral cancer is increasing. The reasons for the geographical variations in the incidence of oral cancer must be better understood, with a focus on disparities in the socioeconomic status of the global population and lifestyle habits related to use of tobacco, use of areca nut, and alcohol consumption. Research on the association between use of smokeless tobacco or areca nut and oral cancers in lower-middle-income countries is lacking. In addition, new prevention and cessation intervention models need to be developed and tested at the population and individual levels.

The Working Group also identified the following in high-risk populations: a lack of knowledge of signs, symptoms, and risk factors for oral cancer; inconsistencies in the assessment of risk behaviours; and gaps in the technical practice of clinical oral examination. With respect to screening, research gaps include the following: identifying approaches in the population to encourage and sustain participation among the hard-to-reach, high-risk population; assessing the cost-effectiveness of standard clinical oral examination as a screening approach for oral cancer compared with the addition of new point-of-care diagnostics; and improving the overall 5-year survival rate, which remains about 50%. Finally, an increase in research efforts to control the use of smokeless tobacco products, and strict implementation of the WHO FCTC recommendations, are desirable goals to reduce the global burden of oral cancer.

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