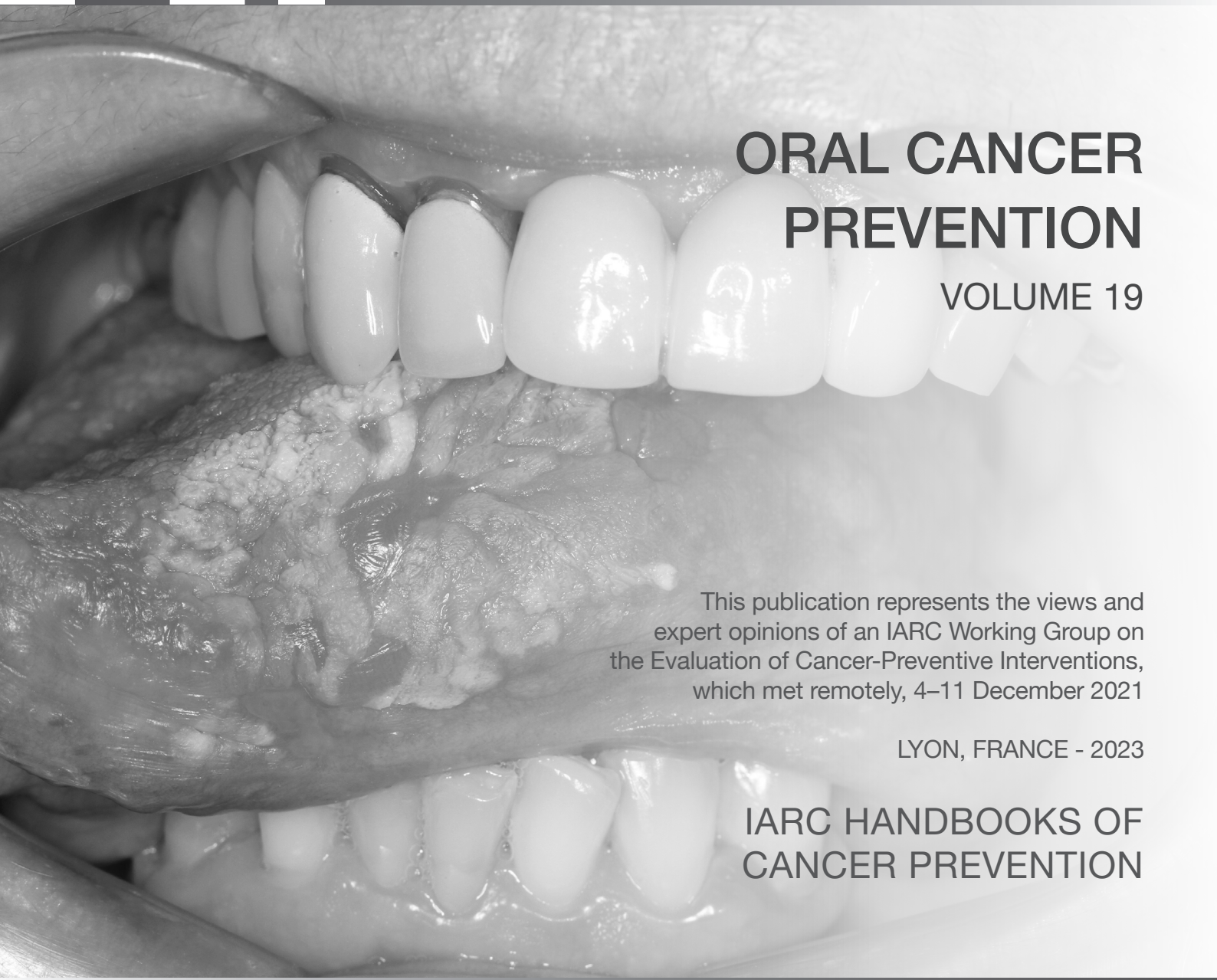
IARC HANDBOOKS



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

LYON, FRANCE - 2023

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

2. REDUCING INCIDENCE OF CANCER OR PRECANCER

2.1 Established risk factors

2.1.1 Tobacco smoking

The carcinogenicity of tobacco smoking was first established by the *IARC Monographs* programme in 1985, including evidence on "the occurrence of malignant tumours of the respiratory tract" (IARC, 1986). Subsequent evaluations have individually listed the oral cavity, oropharynx, and hypopharynx among the multiple affected anatomical sites (IARC, 2004b, 2012b). In most countries, tobacco smoking is the leading cause of oral cancer and oral cancer death (Chang et al., 2015a; Inoue-Choi et al., 2019).

(a) Risk of oral cancer

Observational studies that reported pooled relative risk (RR), meta-RR, or single RR estimates of oral cancer incidence or mortality, whether associated with ever or current cigarette smoking, consistently showed statistically significantly elevated risk estimates (Supplementary Table S2.1, web only; available from https://publications.iarc.fr/617). A meta-analysis of studies published in the 1990s (Gandini et al., 2008), a pooled analysis from the International Head and Neck Cancer Epidemiology (INHANCE) consortium (Wyss et al., 2013), and more recent multi-country (Agudo et al., 2012) and single-country (Maasland et al., 2014) cohort studies in Europe typically reported a 3-fold increase in risk for current smokers or ever-smokers compared with never-smokers (range of RR, 2.11–3.53). Similarly increased risks of oral cancer were reported for smoked tobacco products other than cigarettes (i.e. cigars, pipe, bidi) (Balaram et al., 2002; Wyss et al., 2013).

In non-alcohol users, the INHANCE consortium reported a lower-magnitude pooled risk estimate (odds ratio [OR], 1.35; 95% confidence interval [CI], 0.9–2.01) associated with ever cigarette smoking (Hashibe et al., 2007), whereas a multicentre population-based case–control study in France reported a higher-magnitude risk estimate (OR, 3.2; 95% CI, 1.9–5.3) (Radoï et al., 2015).

The most prevalent tumour histology in the oral cavity is squamous cell carcinoma, and observational studies have reported strong associations with tobacco smoking, whether including all histology subtypes diagnosed (Hashibe et al., 2007; Wyss et al., 2013) or only squamous cell carcinoma (Lee et al., 2009; Maasland et al., 2014).

Reported RRs of oral cancer death in current cigarette smokers (hazard ratio [HR], 5.32; 95% CI, 2.95–9.58) and in daily cigarette smokers (HR, 6.23; 95% CI, 3.42–11.33) were of large magnitude (Inoue-Choi et al., 2019). Significantly increased risks of oral cancer death, with estimates varying between 4.0 and 7.9, were also

reported in primary cigar smokers, including in people who reported no inhalation (Chang et al., 2015a).

RR estimates for oropharyngeal cancer associated with ever or current cigarette smoking have shown larger variations than those for oral cancer, with RR of 3.01 (95% CI, 2.71–3.35) in the INHANCE consortium (Wyss et al., 2013), 5.95 (95% CI, 3.41–10.4) and 8.53 (95% CI, 3.38–21.55) in studies in Europe (Agudo et al., 2012; Maasland et al., 2014), and 1.63 (95% CI, 1.08–2.45) in a study in the USA (Stingone et al., 2013) (Supplementary Table S2.1, web only; available from https://publications.iarc.fr/617).

(i) Smoking intensity, duration, and pack-years

The risk of oral cancer increases with increasing frequency (number of cigarettes smoked per day), duration (in years), and cumulative pack-years of smoking, showing significant dose–response trends (IARC, 2012b; Toporcov et al., 2015) (Supplementary Table S2.2, web only; available from https://publications.iarc.fr/617). Elevated risks of oral cancer associated with current smoking are also evident even at a low daily dose (2 cigarettes) (Polesel et al., 2008). Also, a more pronounced effect for the duration of smoking than for frequency was observed for oral and pharyngeal cancers combined (Di Credico et al., 2019).

The risk of oropharyngeal cancer also increases with increasing frequency, duration, and cumulative pack-years of smoking, showing significant dose–response trends (IARC, 2012b; Toporcov et al., 2015) (Supplementary Table S2.2, web only; available from https://publications.iarc.fr/617).

(ii) Demographic characteristics

Effect estimates from large studies show that the association of smoking with oral cancer is retained when the population is stratified by sex (Agudo et al., 2012) and age at diagnosis (Toporcov et al., 2015) (Supplementary Table S2.1, web only; available from https://publications.iarc.fr/617). A suggested trend of increasing risk of oral cancer with decreasing age at initiation of tobacco smoking appeared to be driven by longer duration of smoking or higher cumulative pack-years of smoking (age at initiation and duration of use are highly correlated), because statistical adjustment for these factors eliminated the originally observed trend (Chang et al., 2019). Geographically, studies in North and South America (Szymańska et al., 2011) and in Europe (Bosetti et al., 2008) have consistently reported positive and significant associations of cigarette smoking with risks of oral cancer and oropharyngeal cancer.

(b) Risk of OPMDs

Tobacco smoking is associated with the occurrence of oral potentially malignant disorders (OPMDs), specifically leukoplakia and erythroplakia, and their malignant transformation, including epithelial dysplasia (Warnakulasuriya et al., 2010; Li et al., 2011; van der Waal, 2014; Mello et al., 2018a). Increased risk of oral submucous fibrosis (OSF) was also reported (Lee et al., 2003) (Supplementary Table S2.1, web only; available from https://publications.iarc.fr/617).

(c) Population attributable fraction

Among studies that reported population attributable fractions (PAFs), there were variations in the anatomical site of the cancer, the definitions of tobacco products, and the geographical span of the populations comprised. Studies reported estimated PAFs of cigarette smoking for oral cancer of 33% (95% CI, 23–48%; Agudo et al., 2012), 21.6% (95% CI, 15.9–25.8%; Anantharaman et al., 2011), and 24.8% (95% CI, 19.6–31.1%; Hashibe et al., 2009), and for oropharyngeal cancer of 49% (95% CI, 36–69%; Agudo et al., 2012) and 29.7% (95% CI, 24.6–33.1%; Anantharaman et al., 2011). Estimates from those studies had at a minimum overlapping

95% CIs; this points to the sizeable proportion of oral and oropharyngeal cancers that are due to tobacco smoking, mainly cigarette smoking. For OPMDs, in particular leukoplakia, the PAF can be even higher (e.g. 56.4% in Taiwan, China; Lee et al., 2003).

(d) Interaction between tobacco smoking and alcohol consumption

Studies assessing the joint effect of tobacco smoking and other established risk factors on the risk of oral cancer are discussed in Section 2.1.7.

2.1.2 Alcohol consumption

(a) Risk of cancer

Consumption of alcoholic beverages has been classified as carcinogenic to humans (Group 1) by the *IARC Monographs* programme, causing cancers of the oral cavity and pharynx, among multiple other sites (IARC, 2010, 2012b). The risks of oral and oropharyngeal cancer associated with alcohol consumption become more apparent in relation to dose–response and in combination with smoking (Supplementary Table S2.3, web only; available from https://publications.iarc.fr/617). Smoking-adjusted estimates for oral and pharyngeal cancer range from a 4-fold to a 9-fold increased risk; in non-smokers, "the majority of the studies found a strong association with alcoholic beverage consumption among non-smokers with a dose–response relationship" (IARC, 2010). Similar risk estimates were reported across types of alcoholic beverages (Purdue et al., 2009; IARC 2012b; Turati et al., 2013) (Supplementary Table S2.4, web only; available from https://publications.iarc.fr/617).

(i) Drinking intensity and duration

In non-tobacco users, there was a clear dose–risk response with increased frequency of alcohol consumption (drinks per day) for oropharyngeal and hypopharyngeal cancers combined (OR for ≥ 5 drinks per day, 5.50; 95% CI, 2.26–13.4); the dose–risk response was less apparent for oral cancer and for duration of drinking (Hashibe et al., 2007) (Supplementary Table S2.3, web only; available from https://publications.iarc.fr/617).

Three systematic reviews and meta-analyses investigated risks of increasing alcohol intake associated with oral and pharyngeal cancers combined (Tramacere et al., 2010; Turati et al., 2013; Bagnardi et al., 2015). When measured in drinks per day, the pooled RR was 1.21 (95% CI, 1.10–1.33) for ≤ 1 drink per day and increased to 5.24 (95% CI, 4.36–6.30) for heavy alcohol consumption (≥ 4 drinks per day); when measured in grams of ethanol per day, the pooled RR ranged from 1.29 (95% CI, 1.25–1.32) for 10 g ethanol per day to 13.02 (95% CI, 9.87–17.18) for 125 g ethanol per day. Bagnardi et al. (2015) reported pooled risks associated with oral and pharyngeal cancer with increasing alcohol consumption, with RRs of 1.13 (95% CI, 1.00–1.26) for light drinking, 1.83 (95% CI, 1.62–2.07) for moderate drinking, and 5.13 (95% CI, 4.31–6.10) for heavy drinking. Risks were broadly similar in men and in women, for heavy drinking versus non-drinking or occasional drinking.

(ii) Total exposure and frequency of exposure

Lubin et al. (2009) assessed the risk of oral cancer by total exposure and by frequency of use. For equal drink-years (a function of the frequency of alcohol use per day and the duration of drinking in years), higher alcohol intake for a shorter duration conferred a greater risk compared with lower alcohol intake for a longer duration [these data are not shown in the table].

(iii) Gene polymorphisms and ethnic differences

Gene polymorphisms of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), two important enzymes in alcohol metabolism, have been well described; individuals with some of these gene polymorphisms are

at increased risk of oral cancer associated with alcohol consumption (IARC, 2012b). Individuals with homozygous *ADH1B*1/*1* and *ADH1C*1/*1* genotypes are at increased risk of oral cancers (Hashibe et al., 2006; Marichalar-Mendia et al., 2010). *ALDH2*1/*2* heterozygotes are also at increased risk of head and neck cancer (HNC) (Boccia et al., 2009). The *ALDH2*2* variant allele is prevalent in up to 30% of East Asian populations (IARC, 2012b). A significantly increased risk of oral cancer in individuals with *ALDH2*1/*2* genotype was shown in the Japanese population (Nomura et al., 2000).

In their systematic review, Turati et al. (2013) reported minimal differences with respect to geographical area both for drinking overall and for heavy drinking (≥ 4 drinks per day); the RR was lowest for Asia (4.75; 95% CI, 3.14–7.17) and highest for Europe (5.63; 95% CI, 4.09–7.77).

Voltzke et al. (2018) investigated ethnic differences in the relationship between alcohol consumption and risk of oral and oropharyngeal cancer in the USA. They reported consistently stronger risk estimates for Blacks than for Whites (Supplementary Table S2.4, web only; available from https://publications.iarc.fr/617).

(b) Risk of OPMDs

A total of 11 case–control studies investigated the association between alcohol consumption and risk of OPMDs (Supplementary Table S2.5, web only; available from https://publications.iarc.fr/617). Estimates of risk of any OPMDs for alcohol consumption ranged from 0.63 (95% CI, 0.33–1.21) (Li et al., 2011) to 1.4 (95% CI, 0.7–2.7) (Thomas et al., 2003) to 2.7 (95% CI, 1.2–6.3) (Amarasinghe et al., 2010b). Estimates of risk of leukoplakia for alcohol consumption ranged from an OR of 0.22 (95% CI, 0.12–0.37) (Petti and Scully, 2006) to 1.8 (95% CI, 1.1–2.8) (Lee et al., 2003) and to 3.00 (95% CI, 10.27–33.50) for frequent alcohol drinkers (Shiu et al., 2000). In the largest case–control study in India, Hashibe et al. (2000a) reported an OR of 1.4 (95% CI, 1.2–1.7) for ever versus never alcohol consumption. A stronger alcohol–risk association was observed for erythroplakia (OR, 3.0; 95% CI, 1.6–5.7) (Hashibe et al., 2000b). The two case–control studies in Taiwan (China) with data on alcohol consumption and OSF had quite different findings: an OR of 0.68 (95% CI, 0.28–1.64) in men (Yang et al., 2010) and an OR of 1.8 (95% CI, 1.1–3.1) (Lee et al., 2003). No systematic reviews or meta-analyses were identified that assessed the risks of alcohol consumption associated with OPMDs.

(c) Interaction of alcohol consumption with other risk factors

Studies assessing the joint effect of alcohol consumption and other established risk factors on the risk of oral cancer are discussed in Section 2.1.7.

2.1.3 Smokeless tobacco use

In this *Handbook*, the term "smokeless tobacco" refers to products containing tobacco but not including areca nut or other non-tobacco components of betel quid. The composition and use of these products are presented in Section 3.1 and in Table 3.1.

(a) Risk of oral cancer

Use of smokeless tobacco has been classified as carcinogenic to humans (Group 1) by the *IARC Monographs* programme (IARC, 2007a, 2012b). Meta-analyses have reported RRs for oral and pharyngeal cancers combined ranging from 1.3 to 1.8 (Weitkunat et al., 2007; Boffetta et al., 2008; Lee and Hamling, 2009; IARC, 2012b). Since then, one meta-analysis (Asthana et al., 2019), one pooled analysis (Wyss et al., 2016), and three hospital-based case–control studies that were not included in either the meta-analysis or the pooled analysis (Nasher et al., 2014; Quadri et al., 2015; Gupta et al., 2017) have confirmed the increased risk (Supplementary Table S2.6,

web only; available from https://publications.iarc.fr/617).

Risk estimates by type of smokeless tobacco products vary greatly. Asthana et al. (2019) reported smoking-adjusted ORs ranging from 0.86 (95% CI, 0.58–1.29) for snus/moist snuff to 1.20 (95% CI, 0.80–1.81) for nasal snuff/dipping and 4.18 (95% CI, 2.37–7.38) for oral snuff. Risk estimates for other smokeless tobacco products were also elevated, such as for *naswar* (OR, 11.8; 95% CI, 8.4–16.4; Khan et al., 2019) and for *shammah* (OR, 20.14; 95% CI, 8.23–49.25; Quadri et al., 2015; and 39; 95% CI, 14–105; Nasher et al., 2014).

Smoking-adjusted summary risk estimates are generally higher in women than in men (Weitkunat et al., 2007; Asthana et al., 2019).

Clear and significant positive dose–response relationships were reported between duration of use (in years), frequency of chewing (times per day), smokeless tobacco retention time in the mouth (in minutes), and risk of oral cancer (see Supplementary Table S2.7, web only; available from https://publications.iarc.fr/617).

There was no clear association of smokeless tobacco use with oropharyngeal cancer, with RRs close to 1 in ever-smokers and in never-smokers (Wyss et al., 2016; Supplementary Table S2.6, web only; available from https://publications.iarc.fr/617).

(b) Risk of OPMDs

Numerous studies have consistently shown an increased risk of OPMDs, particularly leukoplakia, in current users or ever-users of snuff or chewing tobacco compared with never-users (Supplementary Table S2.6, web only; available from https://publications.iarc.fr/617). The direction of the risk association was similar by country and type of product chewed (snuff, *naswar*, *shammah*, chewing tobacco, and other products), and a clear dose–response relationship was demonstrated in terms of frequency of chewing (times per day), duration of use (in months), and retention time of the product in the mouth (see Supplementary Table S2.7, web only; available from https://publications.iarc.fr/617). These results were consistent when smoking was accounted for or when restricted to never-smokers.

(c) Population attributable fractions

Based on the GLOBOCAN 2002 incidence data, the proportion of cases attributable to smokeless tobacco use was estimated to be 68.2% in men and 13.6% in women in the Sudan, 52.5% in men and 51.6% in women in India, 50.6% in men and women in other countries in Asia (including Bangladesh, Bhutan, Indonesia, Myanmar, Nepal, Pakistan, and Sri Lanka), 6.6% in men in the USA, and 1.6% in men in Canada (Boffetta et al., 2008). These estimates are similar to those of a more recent report (NCI and CDC, 2014).

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

Areca nut products (including betel quid) with added tobacco include a variety of products with compositions and names that may differ depending on the geographical area where they are used. For more detailed information on the products, see Section 3.1.

(a) Risk of oral cancer

Chewing areca nut products (including betel quid) with added tobacco is an established risk factor for oral cancer and pharyngeal cancer. With the terminology of "betel quid with added tobacco", these products have been classified as carcinogenic to humans (Group 1) by the *IARC Monographs* programme (IARC, 2004a, 2012b). The RRs for ever-chewers versus never-chewers ranged from 2.1 (95% CI, 2.1–3.4) to 45.9 (95% CI, 25.0–84.1), and the highest RR was reported in women (IARC, 2012b). Since then, one meta-analysis, a large number of case–control studies, and

a few cross-sectional studies, conducted mainly in the Indian subcontinent, have confirmed the clear relationship between areca nut products with added tobacco and increased risk of oral cancer (see Supplementary Table S2.8; web only; available from https://publications.iarc.fr/617).

The risk is higher in women (14.6; 95% CI, 7.6–27.8) than in men (5.4; 95% CI, 3.9–7.4) (Guha et al., 2014). A clear and significant dose–response relationship was reported between the quantity and duration of chewing areca nut with added tobacco and the risk of oral cancer (Madathil et al., 2016; Supplementary Table S2.9, web only; available from https://publications.iarc.fr/617).

(b) Risk of OPMDs

Evidence has accumulated on the association between chewing areca nut products (including betel quid) with added tobacco and the risk of OPMDs (Supplementary Table S2.8, web only; available from https://publications.iarc.fr/617). Risk estimates for chewers versus never-chewers for combinations of OPMDs ranged from 1.4 (95% CI, 0.5–3.7) to 50.5 (95% CI, 21.5–119.5). When OPMDs were considered separately, risk estimates adjusted for tobacco smoking and alcohol consumption ranged from 6.1 (95% CI, 1.8–21.3) to 55.6 (95% CI, 27.4–112.7) for OSF and from 2.5 (95% CI, 1.1–5.6) to 10.0 (95% CI, 8.3–12.0) for leukoplakia. However, when the corresponding estimates were restricted to non-smokers and non-drinkers, the ORs for the different types of OPMDs showed less discrepancy (Jacob et al., 2004).

Significant dose–response relationships were reported between chewing areca nut with added tobacco and the risk of OPMDs, in terms of frequency of chewing (times per day), duration of use (in years), and age at the start of the chewing habit (Supplementary Table S2.9, web only; available from https://publications.iarc.fr/617).

The combined effects of betel quid chewing with other established risk factors are discussed in Section 2.1.7.

(c) Population attributable fractions

In high-prevalence geographical areas, the PAF of chewing betel quid with added tobacco for oral cancer and OPMDs may be very high. In India, the PAF for oral cancer was estimated to be 49.5% for both sexes, and higher in women (63.2%) than in men (44.7%) (Guha et al., 2014). For OPMDs, the PAF was estimated to be 84% in Sri Lanka (Amarasinghe et al., 2010a).

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

Areca nut products (including betel quid) without tobacco include a variety of products with specific compositions and names that may differ depending on the geographical area where they are used. For more detailed information on the products, see Section 3.1.

(a) Risk of oral cancer

Chewing areca nut products (including betel quid) without tobacco is an established risk factor for oral cancer. The *IARC Monographs* programme classified separately "betel quid without added tobacco" (IARC, 2004a, 2012b) and areca nut (IARC, 2012b) as carcinogenic to humans (Group 1). Since then, one meta-analysis, a very large number of case–control studies, and a few cohort studies, mainly in Taiwan (China) and some in India, have confirmed the clear relationship between chewing areca nut products without tobacco and increased risk of oral cancer (Supplementary Table S2.10 (web only; available from https://publications.iarc.fr/617).

Guha et al. (2014) reported meta-RRs for oral cancer of 11.0 (95% CI, 4.9–24.8) for Taiwan (China) and 2.4 (95% CI, 1.8–3.2) for the Indian subcontinent. Meta-RRs were also calculated for cancer at specific subsites of the oral cavity for the Indian subcontinent; the highest estimates were reported for the cancer of the palate: 5.1 (95% CI, 1.1–24.9). Guha et al. (2014) also reported a

meta-RR of 2.6 (95% CI, 1.7–3.9) for oropharyngeal cancer.

Significant dose–response relationships were reported between chewing areca nut products without tobacco and the risk of oral cancer (Yang et al., 2014; Hu et al., 2020) or oral cancer death (Wen et al., 2010) in terms of quantity, frequency of use, and duration of use (Supplementary Table S2.11, web only; available from https://publications.iarc.fr/617).

(b) Risk of OPMDs

Evidence has accumulated on the association between chewing areca nut products (including betel quid) without tobacco and the risk of OPMDs (Supplementary Table S2.10, web only; available from https://publications.iarc.fr/617). Risk estimates for chewers versus non-chewers for a combination of OPMDs grouped together ranged from 8.8 (95% CI, 3.2–24.5) to 25.3 (95% CI, 20.8–30.7). When OPMDs were considered separately, risk estimates adjusted for tobacco smoking and alcohol consumption ranged from 4.5 to 65.9 for OSF and from 3.7 to 22.3 for leukoplakia. In a study where estimates were restricted to non-smokers and non-drinkers, the ORs for men and women combined were 22.2 (95% CI, 11.3–43.7) for leukoplakia, 29.0 (95% CI, 5.6–149.5) for erythroplakia, and 56.2 (95% CI, 21.8–144.8) for OSF (Jacob et al., 2004; Supplementary Table S2.10, web only; available from https://publications.iarc.fr/617).

Significant dose–response relationships were reported between chewing areca nut without tobacco and the risk of OPMDs, in terms of frequency of chewing, duration of use, and age at the start of chewing (see Supplementary Table S2.11, web only; available from https://publications.iarc.fr/617).

(c) Population attributable fractions

In high-prevalence geographical areas, the PAF of chewing betel quid without tobacco for oral cancer and OPMDs may be very high. In Taiwan (China), the PAF for oral cancer was estimated to be 57.3% for both sexes (Guha et al., 2014). For OPMDs, the PAFs were estimated to be 85.4% for OSF and 73.2% for leukoplakia, in the southern part of the main island (Lee et al., 2003).

2.1.6 HPV16 infection

(a) Risk of cancer

The *IARC Monographs* programme (IARC, 2012a) determined that there is *sufficient evidence* in humans for the carcinogenicity of human papillomavirus type 16 (HPV16); the virus causes oral cancer and oropharyngeal cancer (IARC, 2012a). The association of HPV16 infection with risk of cancer is heterogeneous in terms of the anatomical site (oral cavity vs oropharynx) as well as the method of assessment of HPV exposure (oral HPV16 DNA, systemic HPV16 L1 antibodies, and systemic HPV16 E6 antibodies). HPV16 infection is associated with a moderately elevated risk of oral cancers; ORs are generally < 5 for oral HPV16 DNA prevalence and HPV16 L1 or E6 seropositivity (Supplementary Table S2.12, web only; available from https://publications.iarc.fr/617).

HPV16 infection is strongly associated with risk of oropharyngeal cancers; the risk estimates from case–control studies range from 14 to > 100 for oral HPV16 DNA prevalence, from 1.1 to > 100 for HPV16 L1 seropositivity, and from 10 to > 200 for HPV16 E6 seropositivity. Reported risk estimates from prospective cohort studies were > 20 for oral HPV16 DNA prevalence, 2–14 for HPV16 L1 seropositivity, and 98–274 for HPV16 E6 seropositivity (Supplementary Table S2.12, web only; available from https://publications.iarc.fr/617). Importantly, HPV16 E6 seropositivity precedes diagnosis of oropharyngeal cancer by several decades, underscoring the temporality of HPV16 exposure and cancer incidence (Kreimer et al., 2013, 2017, 2019).

(b) Risk of OPMDs

A recent systematic review and meta-analysis reported an HPV16 prevalence of 10.8% in OPMDs, primarily leukoplakia, with a similar prevalence in dysplastic and non-dysplastic lesions (de la Cour et al., 2021). [The reporting studies have generally used only HPV16 DNA detection, which does not indicate either an established or active HPV infection, or HPV causality in cancers.]

(c) Population attributable fractions

Globally, the PAF of HPV is ~2% for oral cancers and ~31% for oropharyngeal cancers, and most of the cancers are caused by HPV16 infection (de Martel et al., 2017). There is a wide geographical heterogeneity in HPV etiological fractions for oropharyngeal cancers, ranging from estimates of 40% to > 50% in North America, Europe, Australia and New Zealand, Japan, and the Republic of Korea to estimates of < 15% in most other parts of the world (Ndiaye et al., 2014; de Martel et al., 2017). This heterogeneity may reflect differences in sexual behaviours that are relevant for acquisition of oral HPV infection (e.g. lifetime and recent oral sex behaviours) as well as the relative contributions of HPV infection compared with tobacco use and alcohol consumption across countries and geographical regions (Heck et al., 2010).

2.1.7 Combined effects of established risk factors

Tobacco smoking, alcohol consumption, smokeless tobacco use, chewing areca nut products with or without tobacco, and HPV16 infection are independent risk factors for OPMDs, oral cancers, and oropharyngeal cancers. Combined exposure to more than one of these carcinogens can confer a risk that is at least the sum of the individual risks for each of these carcinogens (risk additivity) or can confer a risk that exceeds the sum (greater-than-additive) or that exceeds the multiplication product (greater-than-multiplicative) of the individual risk estimates. A summary of statistical interactions across these established risk factors is given in Supplementary Table S2.13 (web only; available from https://publications.iarc.fr/617).

(a) Interactions between tobacco smoking and alcohol consumption

Several studies have reported a greater-than-multiplicative interaction between tobacco smoking and alcohol consumption for the risk of oral cancers and pharyngeal cancers (which included cancers of the oropharynx, hypopharynx, and other pharynx) (Blot et al., 1988; Barón et al., 1993; Hayes et al., 1999; Schlecht et al., 1999; Anantharaman et al., 2011). In a meta-analysis of seven observational studies in India and seven studies in Taiwan (China), Petti et al. (2013) found a 6.3-fold increased risk in oral cancer for tobacco smoking and alcohol consumption combined, showing an at least additive effect.

A pooled analysis of 17 case–control studies in Europe and the USA from the INHANCE consortium (Hashibe et al., 2009) reported a greater-than-multiplicative interaction between tobacco use (smoking and chewing) and alcohol consumption for the risk of oral cancer (multiplicative interaction parameter, 3.09; 95% CI, 1.82–5.23) and the risk of pharyngeal cancers (multiplicative interaction parameter, 1.90; 95% CI, 1.41–2.56). The interaction was also greater-than-multiplicative with high exposure to both smoking (> 20 cigarettes per day) and alcohol consumption (> 3 drinks per day); the ORs for joint exposure were 15.49 (95% CI, 7.24–33.14) for oral cancers and 14.29 (95% CI, 7.26–28.15) for pharyngeal cancers. Tobacco use and alcohol consumption collectively accounted for PAFs of 67.1% for oral cancers (23.5% from the tobacco–alcohol interaction effect) and 74.3% for pharyngeal cancers (24.6% from the tobacco–alcohol interaction effect).

(b) Interactions with smokeless tobacco use

Few studies reported formal statistical evaluations of interaction effects of smokeless tobacco use with tobacco smoking or with alcohol consumption on the risk of OPMDs, oral cancers, or oropharyngeal cancers. The few available studies reported the absence of statistical interaction (i.e. consistency with risk additivity) with tobacco smoking or with alcohol consumption on the risk of oral cancers (Winn et al., 1981).

(c) Interactions with chewing betel quid with or without tobacco

Reports of effect modification of the risk conferred by chewing betel quid with or without tobacco by tobacco smoking and/or alcohol consumption have been inconsistent (IARC, 2012b). Some studies have reported the absence of statistical interaction (i.e. consistency with risk additivity) between ever chewing betel quid and ever smoking or ever alcohol consumption for the risk of oral cancers (Subapriya et al., 2007; Muwonge et al., 2008). Some studies have reported a greater-than-additive interaction between ever chewing betel quid and ever smoking in non-drinkers on the risk of oral cancers (Sankaranarayanan et al., 1989). Some studies have reported a greater-than-multiplicative interaction between ever chewing betel quid without tobacco and ever smoking on the risk of oral and pharyngeal cancers (Znaor et al., 2003). A few studies have also reported a greater-than-additive interaction between ever chewing betel quid without tobacco and ever smoking on the risk of OPMDs, particularly leukoplakia (Lee et al., 2003).

Petti et al. (2013) conducted a meta-analysis that included 14 studies – 7 in India (without separation of chewing betel quid with or without tobacco) and 7 in Taiwan, China (chewing betel quid without tobacco) – to evaluate two-way and three-way additive interactions, as measured by relative excess risk due to interaction (RERI) across betel quid chewing, smoking, and alcohol consumption. A statistically significant greater-than-additive interaction was observed between betel quid chewing and tobacco smoking (RERI, 5.48; 95% CI, 1.06–8.20), and a non-significant additive interaction was observed between betel quid chewing and alcohol consumption (RERI, 1.34; 95% CI, –1.29 to 4.50). Importantly, a statistically significant greater-than-additive three-way interaction was observed across betel quid chewing, smoking, and alcohol consumption (RERI, 28.36; 95% CI, 22.92–33.74). Furthermore, the extent of the three-way greater-than-additive interaction was similar in studies in India (RERI, 38.11; 95% CI, 30.05–41.62) and studies in Taiwan, China (RERI, 36.42; 95% CI, 24.87–53.68). Betel quid chewing, tobacco smoking, and alcohol consumption collectively accounted for 74.9% of oral cancers (68.4% from joint effects of all three exposures).

(d) Interactions with HPV16 infection

Reports are sparse for interactions of HPV16 infection with other risk factors for the risk of OPMDs or oral cancers. Most previous evaluations of the interaction of HPV16 infection (as determined by oral HPV16 DNA or systemic HPV16 L1 or HPV16 E6 antibodies) with smokeless tobacco, chewing betel quid with or without tobacco, smoking, and alcohol consumption have included oropharyngeal cancers and have been conducted in Europe and North and South America. Perhaps because of the geographical clustering of these studies, most of the studies have primarily addressed the interaction of HPV16 infection with tobacco smoking and alcohol consumption. Results for the interaction of HPV16 infection with other risk factors have been very inconsistent in the literature: studies have reported a lack of statistical interaction between HPV16 infection and smoking or alcohol consumption on an additive scale (D'Souza et al., 2007; Anantharaman et al.,

2016) or a multiplicative scale (Herrero et al., 2003; Farsi et al., 2017), the presence of a greater-than-additive interaction between HPV16 L1 antibodies and smoking (Schwartz et al., 1998), greater-than-additive interactions between oral HPV16 DNA and alcohol consumption (Smith et al., 2004), and less-than-multiplicative interactions between HPV16 E6 antibodies and smoking (Ribeiro et al., 2011) and between HPV16 L1 antibodies and smoking and HPV16 L1 antibodies and alcohol consumption (Applebaum et al., 2007). [Despite this inconsistency, smoking and heavy alcohol consumption are associated with increased risk of both HPV16-positive and HPV16-negative oropharyngeal cancers and, at the very least, should be considered to be independent risk factors for oropharyngeal cancers.]

2.2 Additional potential risk factors for oral cancer

A proportion of oral cancers cannot be attributed to the major established risk factors (Sections 2.1.1–2.1.6), particularly oral cancers that occur in women and young people. There is a substantial amount of literature on several other putative risk factors, for some of which there is only little evidence.

2.2.1 Environmental factors

(a) Second-hand smoke

The most recent evaluation by the *IARC Monographs* programme (IARC, 2012b) confirmed that second-hand tobacco smoke (also called environmental tobacco smoke, passive smoking, or involuntary smoking) is carcinogenic to humans (Group 1), although evidence for oral cancer was sparse. A recent meta-analysis of five case–control studies reported a positive association between exposure to second-hand smoke and risk of oral cancer (overall OR, 1.51; 95% CI, 1.20–1.91). A duration of exposure of > 10 or 15 years conferred a higher risk of oral cancer (OR, 2.07; 95% CI, 1.54–2.79) compared with non-exposed people (Mariano et al., 2022).

(b) Indoor air pollution

The *IARC Monographs* programme classified indoor emissions from household combustion of coal as carcinogenic to humans (Group 1), with *sufficient evidence* for lung cancer (IARC, 2012b). More recently, a meta-analysis of 4 studies found a significant risk from household air pollution for the development of oral cancer (OR, 2.44; 95% CI, 1.87–3.19) (Josyula et al., 2015). Notably, a high incidence of oral cancer was reported in chefs engaged in regular cooking (Foppa and Minder, 1992). Indoor air pollution could be a risk factor that increases risk in women more than in men.

(c) Heavy metals in soil

Most of the studies on heavy metals in soil and risk of oral cancer are from Taiwan (China), particularly from Changhua County, which has a higher environmental heavy metal concentration than the other counties. Studies pointed to arsenic and nickel in farm soils as new risk factors for oral cancer (Su et al., 2010). Significant associations between oral cancer and blood levels of nickel and/or chromium have been reported after controlling for potential confounders (Chiang et al., 2011; Yuan et al., 2011). Also, Tsai et al. (2017) reported that 68.8% of leukoplakia with subsequent malignant transformation occurred in people exposed to high levels of nickel in soil.

(d) Occupational exposures

Increased risks due to occupational exposure to heavy metals were reported, for oral cancer due to exposure to metal dust containing chromium and nickel (OR, 3.4; 95% CI, 1.7–7.0) (Tisch et al., 1996) and for risk of tongue cancer due to exposure to chromium(VI) compounds (Tisch

and Maier, 1996). A recent systematic review analysed risk of HNC and occupational exposure to formaldehyde, wood dust, metal, coal particles, and asbestos, but it included only few studies on oral cancer (Awan et al., 2018).

2.2.2 Lifestyle factors

(a) Maté drinking

Maté is a beverage prepared from the leaves of the *Ilex paraguariensis* plant and is usually drunk very hot with a metal straw in Argentina, southern Brazil, Chile, Paraguay, and Uruguay. The *IARC Monographs* programme concluded that drinking very hot beverages – at temperatures above 65 °C – is probably carcinogenic to humans (Group 2A) (IARC, 2018). Two meta-analyses reported a significant association between maté drinking and oral cancer (OR, 2.11; 95% CI, 1.39–3.19) (Dasanayake et al., 2010) and oral and oesophageal cancers (OR, 1.49; 95% CI, 1.08–2.05) (Mello et al., 2018b). The 2018 World Cancer Research Fund (WCRF) reported that the evidence suggesting that greater consumption of maté increases the risk of oral cancer is limited (WCRF, 2018).

(b) Khat chewing

Khat (*Catha edulis* Forsk), also known as qat, is consumed in Yemen and in East Africa, particularly in Somalia and Ethiopia, as well as in the global diaspora from this region. Although khat chewing has detrimental effects on teeth and the periodontium, a systematic review (El-Zaemey et al., 2015) and a narrative review (Al-Maweri et al., 2018) did not demonstrate any significant association between khat use and oral cancer.

(c) Cannabis smoking

Evidence is lacking on the association between smoking of cannabis (also called marijuana) and oral cancer. Cannabis smoking is often combined with heavy tobacco use and alcohol consumption, which makes it difficult to properly adjust for confounding and interactions. One case–control study, in the USA, reported an increased risk of HNC in regular marijuana users (Zhang et al., 1999), whereas an analysis from the INHANCE consortium (Marks et al., 2014) found no such risk.

(d) Opium consumption

The *IARC Monographs* programme recently evaluated the carcinogenicity of opium consumption, smoked or ingested (IARC, 2021). One ecological study, one case–control study, and one large case series (Fahmy et al., 1983; Razmpa et al., 2014; Rashidian et al., 2016) reported that opium use was associated with increased risk of oral cancer; however, these studies had some limitations, and the evidence was considered to be inadequate (Warnakulasuriya et al., 2020).

(e) Mouthwash use

Several case–control studies have examined the risk of mouthwash use for the causation of oral cancer. Several reviews and meta-analyses were performed, which reported conflicting evidence (Lewis and Murray, 2006; McCullough and Farah, 2008; La Vecchia, 2009; Gandini et al., 2012; Currie and Farah, 2014). A risk quantitative meta-analysis (Gandini et al., 2012) and an independent expert group assembled by the United States Food and Drug Administration (FDA, 2003) found no excess risk of oral cancer from use of mouthwash containing or not containing alcohol. However, daily use of mouthwash over a prolonged period (> 35 years) was suggested to cause oral cancer by an international consortium (Boffetta et al., 2016). [It is likely that people with oral cancer may use mouthwashes to mask their halitosis or to control symptoms of the disease. In many of the case–control studies, reverse causation was not considered.]

2.2.3 Demographic factors

Studies conducted in the United Kingdom and in several countries in Europe indicate that most patients with oral cancer have lower socioeconomic status, live in low-resource settings, or have jobs with low occupational social prestige (Woolley et al., 2006; Conway et al., 2008, 2021). Also, patients with oral cancer living in deprived areas had an increased risk of death from oral cancer (RR, 1.28; 95% CI, 1.11–1.47) compared with people living in affluent areas (Edwards and Jones, 1999).

In contrast, a study in Brazil reported no significant risk of oral cancer in people with lower education levels (OR, 1.71; 95% CI, 0.74–3.96) (Andrade et al., 2015). A study in Scotland was also inconclusive regarding the individual components of socioeconomic status and the risk of HNC (Conway et al., 2010).

2.2.4 Orodental factors

(a) Chronic mechanical irritation

Chronic mechanical irritation to the oral mucosa may, over a period of time, lead to OPMDs and oral cancer (Piemonte et al., 2010, 2018). Because of loss of the protective barrier of the mucosa, chronic mechanical irritation arising from dental factors could facilitate the entry of carcinogens or infections into deeper layers of the squamous epithelium (Gilligan et al., 2017).

Poor dentition (faulty restorations, malpositioned teeth, or sharp or broken teeth due to decay or fractures) and ill-fitting prosthesis have been associated with risk of oral cancer in several case–control studies (Lockhart et al., 1998; Velly et al., 1998; Rosenquist, 2005; Vaccarezza et al., 2010; Bektas-Kayhan et al., 2014; Huang et al., 2015; Li et al., 2015; Chen et al., 2018; Piemonte and Lazos, 2018) (Supplementary Table S2.14, web only; available from https://publications.iarc.fr/617). A meta-analysis based on 9 studies (mostly in the USA) also found that ill-fitting dentures substantially increased the risk of oral cancer (OR, 3.90; 95% CI, 2.48–6.13) (Manoharan et al., 2014).

(b) Oral hygiene

Several studies have provided evidence that advanced periodontal disease due to poor oral hygiene may be an independent risk factor for oral cancer and HNC (Guha et al., 2007; Meyer et al., 2008). Bleeding gums (OR, 3.94; 95% CI, 2.49–6.25) and dental check-ups only at the time of pain (OR, 3.84; 95% CI, 2.38–6.20) were both associated with significantly increased risk after adjustment for potential confounders (Gupta et al., 2017). The INHANCE consortium reported a strong association of poor oral health with oral cancer (OR for worst oral health vs best oral health, 3.12; 95% CI, 2.08–4.68) (Hashim et al., 2016). Three meta-analyses reported that periodontal disease (OR, 3.08; 95% CI, 1.60–3.93) (Zeng et al., 2013a), tooth loss (OR, 1.72; 95% CI, 1.26–2.36) (Zeng et al., 2013b), and infrequent tooth brushing (OR, 1.73; 95% CI, 1.36–2.20) (Zeng et al., 2015) were associated with increased risk of oral cancer or head and neck squamous cell carcinoma.

(c) Oral infections

Several reviews have examined the published evidence on the relationship between the oral microbiome and oral squamous cell carcinoma (OSCC) (Whitmore and Lamont, 2014; Gholizadeh et al., 2016; Perera et al., 2016; Chen et al., 2017). In multiple studies, significantly higher levels of *Porphyromonas* spp. and *Fusobacterium* spp. were found in OSCC tissues than in healthy mucosa (Nagy et al., 1998; Katz et al., 2011; Pushalkar et al., 2012). The presence of specific species of bacteria in tumour tissue (Zhang et al., 2020) adds strength to the specificity of these studies.

High lipopolysaccharide levels in cancerous conditions were indicative of Gram-negative

bacteria found in the subgingival microflora, which have lipopolysaccharide in their cell wall, thus causing lipopolysaccharide-induced inflammation (Kavarthapu and Gurumoorthy, 2021). A systematic review of 14 in vitro studies and 3 studies in animal models proposed a role of *Porphyromonas gingivalis* in the development of OSCC through epithelial–mesenchymal transition of malignant cells, neoplastic proliferation, and tumour invasion (Lafuente Ibáñez de Mendoza et al., 2020).

A nested case–control study conducted in prospective studies in two populations in the USA found that abundance of *Corynebacterium* and *Kingella* was associated with a decreased risk of head and neck squamous cell carcinoma, whereas *Parvimonas micra* and *Neisseria sicca* were associated with a decreased risk of oral cancer. However, an unnamed *Actinomyces* was associated with an increased risk of oral cancer (Hayes et al., 2018).

Several studies and meta-analyses have investigated the presence of Epstein–Barr virus in oral carcinoma, with a reported prevalence ranging from 0% to 100% (Acharya et al., 2015; She et al., 2017; de Lima et al., 2019). A meta-analysis of 8 case–control studies reported a significant positive association between Epstein–Barr virus infection and oral lichen planus (OLP) (Ashraf et al., 2020).

Candida is frequently present in oral biopsy samples of moderate and severe dysplasia, and significant dysplastic changes have been noted in the epithelium of candidal leukoplakia harbouring *Candida* species (McCullough et al., 2002; Shukla et al., 2019). A recent systematic review on candidal leukoplakia (Shukla et al., 2019) identified three studies, which reported malignant transformation ratios of 2.5%, 6.5%, and 28.7%.

2.2.5 Systemic factors

(a) Immunosuppression

Immunosuppression has also been shown to be a mechanism that can lead to cancer (Baan et al., 2019). A few case series of secondary oral cancer after allogeneic haematopoietic cell transplantation or after renal transplantation have been published (King et al., 1995; van Leeuwen et al., 2009; Santarone et al., 2021). The studies of Laprise et al. (2019) and van Leeuwen et al. (2009) confirmed that immunosuppressive agents (azathioprine and cyclosporine) used after organ transplantation may increase susceptibility to lip and oral cancer.

Patients with inflammatory bowel disorders (e.g. Crohn disease) who may take long-term immunosuppressive agents (e.g. azathioprine) may be at increased risk of tongue or oral cancer (Li et al., 2003; Katsanos et al., 2016).

In a study conducted during the pandemic of HIV infection before the era of combined antiretroviral therapy (cART), patients diagnosed with HIV disease did not have an increased risk of oral cancer (Hille and Johnson, 2017). However, the rate of HPV-associated HNC is higher in people living with HIV (Beachler and D'Souza, 2013).

(b) Obesity, underweight, and body mass index

Obesity is an established risk factor for many cancer types (Arnold et al., 2016). The 2018 WCRF report, which analysed 25 studies, reported that obesity marked by BMI, waist circumference, and waist-to-hip ratio probably increased the risk of oral and pharyngeal cancers (WCRF, 2018). In contrast, in a pooled data analysis from 15 case–control studies, ORs were increased in underweight (BMI < 18.5 kg/m^2) compared with normal weight (BMI, 18.5–24.9 kg/m^2) and decreased in overweight and obese categories (BMI ≥ 25 kg/m^2) for oral cancer and other HNC; ORs were similar in men and women (Lubin et al., 2011). A more

recent study from the INHANCE consortium also found that low BMI (i.e. < 18.5 kg/m^2) was associated with higher risk of HNC (Gaudet et al., 2015).

A study in Sri Lanka found that low BMI (< 18.5 kg/m^2) was a significant independent risk factor for the development of OPMDs (Amarasinghe et al., 2013).

(c) Metabolic syndrome

In two studies of people with metabolic syndrome (Chang et al., 2015b; Siewchaisakul et al., 2020) the condition was found to be significantly associated with OPMDs. Three components of metabolic syndrome were reported to be significantly associated with OPMDs: central obesity, hypertriglyceridaemia, and hyperglycaemia (Siewchaisakul et al., 2020).

(d) Haematinic and micronutrient deficiency

Haematinic deficiency (e.g. deficiency of iron, folate, or vitamin B12) can cause histopathological changes in the oral mucosa and/or clinically detectable OPMDs, presumably by interfering in epithelial proliferation and/or maturation (Ranasinghe et al., 1983). A recent study reported significantly higher frequencies of haematinic deficiencies and hyperhomocysteinaemia in patients with OPMDs than in healthy controls (Wu et al., 2019).

2.2.6 Familial or genetic predisposition

Sporadic case reports proposed that oral cancer could be familial (Ankathil et al., 1996). A case–control study in Italy and Switzerland reported that a family history of oral cancer, pharyngeal cancer, or laryngeal cancer is a strong determinant of risk of oral and pharyngeal cancer, independent of tobacco use and alcohol consumption (Garavello et al., 2008). The INHANCE consortium reported that a family history of cancer in first-degree relatives increased the risk of oral cancer (OR, 1.53; 95% CI, 1.11–2.11) (Negri et al., 2009).

Of the many familial cancer syndromes, patients with Fanconi anaemia, xeroderma pigmentosum, Li–Fraumeni syndrome, Bloom syndrome, ataxia–telangiectasia, and Cowden syndrome have shown an increased susceptibility to oral cancer due to genetic instability, and those with Fanconi anaemia have the strongest predisposition (Furquim et al., 2018; Amenábar et al., 2019). Dyskeratosis congenita (also called Zinsser–Cole–Engman syndrome) is a rare hereditary condition with predisposition to leukoplakia of the tongue that could transform into cancer in early life (Handley and Ogden, 2006).

A genome-wide association study of oral and pharyngeal cancers with 6034 cases and 6585 controls in Europe, North America, and South America detected 8 loci (regions) contributing to susceptibility to oral and pharyngeal cancers. Oral cancer was associated with two new regions (2p23.3 and 9q34.12) and with known cancer loci (9p21 and 5p15.33). Oral and pharyngeal cancers combined were associated with loci at 6p21.32, 10q26.13, and 11p15.4 (Lesseur et al., 2016).

The TP53 codon 72 polymorphism has been suggested to play a role in cancer susceptibility, and more specifically susceptibility to HPV-associated cancers. An association between p53 gene variants and oral cancer susceptibility was reported in India (Patel et al., 2013). A study in Argentina reported that the frequency of TP53 codon 72 Pro72variant was higher in patients with OSCC and OPMDs than in controls (Zarate et al., 2017), and a study in China (Hou et al., 2015) reported that p53 Arg72Pro polymorphism together with HPV infection may jointly alter an individual's susceptibility to oral cancer. A meta-analysis of 11 studies suggested that in the absence of HPV infection the TP53 codon 72 polymorphism (Arg vs Pro) is not associated with the risk of OSCC (Zeng et al., 2014).

2.3 Impact upon quitting

For the evaluation of studies in humans on the potential reduction in cancer risk due to reduction or cessation of exposure to a risk factor for oral cancer, intervention studies, cohort studies, case–control studies, and cross-sectional studies were eligible for inclusion. The selection was limited to studies of established risk factors, i.e. tobacco smoking, consumption of alcoholic beverages, use of smokeless tobacco, and chewing of areca nut (including betel quid) with added tobacco or without tobacco [hereafter described as the exposure]. Only studies that evaluated separately the effect on cancer of the oral cavity, or of the oral cavity and the pharynx combined (oropharynx and/or hypopharynx) were included. Studies of cancer incidence and cancer mortality were eligible for inclusion. In addition, studies on OPMDs, such as oral leucoplakia or erythroplakia, were included as supporting evidence.

Only those studies that compared former exposure and current exposure with never exposure, and former exposure with current exposure, were included. Studies that compared former exposure versus never exposure but not current exposure versus never exposure were excluded. No studies reported on reduction of exposure and risk of cancer or OPMDs.

For the evaluation of cessation of chewing areca nut with added tobacco and chewing areca nut without tobacco, in addition to the analyses in published studies, Working Group performed primary analyses of unpublished data on the associations with risk of oral cancer or risk of OPMDs. Table 2.15 shows the number of analyses for each exposure, by study design; some studies contributed evidence to more than one group.

2.3.1 Tobacco smoking

(a) Risk of oral cancer and oropharyngeal cancer

Volume 11 of the *IARC Handbooks of Cancer Prevention* evaluated the scientific evidence available until the first trimester of 2006 on the effects of smoking cessation on the risk of cancer (IARC, 2007b). The Working Group concluded that for oral and pharyngeal cancer, the risk "is lower in former smokers than in otherwise similar current smokers", the relative reduction in risk increases with duration of quitting, and the RR after ≥ 2 decades of smoking cessation returns to that in never-smokers (IARC, 2007b).

(i) Overview of studies

The Working Group assessed all the available studies published since 2006. Studies that reported risk estimates in former smokers by time since quitting smoking were considered to be more informative and included individual cohort studies (Freedman et al., 2007; Maasland et al., 2014), a pooled analysis of 17 case–control studies (Marron et al., 2010), a pooled analysis of 2 case–control studies (Bosetti et al., 2008), and 4 individual case–control studies (De Stefani et al., 2007; Lee et al., 2009; Varela-Lema et al., 2010; Radoï et al., 2013a). Two mortality cohort studies that included former smokers but did not report risk estimates by duration of smoking cessation were identified (Ide et al., 2008; Christensen et al., 2018). Most of the studies included male and female participants; two studies included only male participants (De Stefani et al., 2007; Varela-Lema et al., 2010).

The studies varied with respect to the definitions of study population, cancer outcome, and former smoker, the categorization of time since quitting smoking, the reference group used to estimate RRs, and the extent of adjustment for potential confounders. The definition of former smoker, when available, varied from having quit smoking ≥ 6 months before enrolment to having

Table 2.15 Number of studies that assess quitting exposure to the risk factor and reduction in risk of oral cancer or OPMDs

Risk factor	Type of studies	Number of studies	
		Oral cavity or oral cavity and pharynx	OPMDs
Tobacco smoking	Cohort	4	1
	Case–control	4	6
	Cross-sectional	0	1
	Pooled analysis (of case–control studies)	2	0
	Meta-analysis	0	0
Alcoholic beverage consumption	Cohort	3	0
	Case–control	6	7
	Pooled analysis (of case–control studies)	1	0
	Meta-analysis	0	0
Smokeless tobacco use	Cohort	2	4
	Case–control	4	2
	Cross-sectional	0	2
	Pooled analysis	0	0
	Meta-analysis by the Working Group (of cohort studies and case–control studies)	1	1
Chewing areca nut products (including betel quid) with added tobacco	Cohort (published/primary analysis[a])	2/1	1
	Case–control (published/primary analysis[a])	3/1	2
	Pooled analysis	0	0
	Meta-analysis (of cohort studies and case–control studies)	1	0
Chewing areca nut products (including betel quid) without tobacco	Cohort (published/primary analysis[a])	0/3	0/3
	Case–control (published/primary analysis[a])	4/1	3/1
	Cross-sectional	0	2
	Meta-analysis (of case–control studies)	1	0

OPMDs, oral potentially malignant disorders.
[a] Primary analyses of unpublished data performed by the Working Group.

quit > 2 years before enrolment. The duration of smoking cessation was reported in at least two categories, usually using a cut-off point of 10 years; few studies used more categories of duration of smoking cessation. Few studies controlled for cumulative smoking or presented estimates by time since quitting smoking stratifying by quantity smoked or cumulative smoking. Only the pooled analysis and three case–control studies used current smokers as the reference group to assess reductions in RR associated with quitting smoking. Outcomes of oral cancer, oropharyngeal and hypopharyngeal cancer, pharyngeal cancer, and oral and pharyngeal cancer were used to report RRs associated with smoking cessation. No studies reported risk of oropharyngeal cancer alone or risk of oropharyngeal cancer death. In most studies, the smoked tobacco product was cigarettes.

(ii) Cohort studies

See Table 2.16.

Freedman et al. (2007) reported on the association of smoking status and HNC in men and in women in the prospective United States National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, which enrolled 476 211 participants from October 1995 until the end of 2000. Former smokers were defined as people who had quit smoking > 1 year before the date of completing

Table 2.16 Cessation of tobacco smoking and risk of oral cancer and/or pharyngeal cancer – cohort studies

Reference Location	Study population, number of participants, follow-up period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/number in cohort	RR or HR (95% CI)	Adjustments/comments
Cancer incidence						
Freedman et al. (2007) USA	Prospective NIH-AARP Diet and Health Study, following up 283 691 men and 192 520 women; aged 50–71 yr, in 6 states of the USA, from 1995 until the end of 2000; 759 head and neck cancers, 310 oral cancers, and 139 oropharyngeal/ hypopharyngeal cancers were diagnosed	SCC of the oral cavity (lips, tongue, gums, palate, floor of the mouth, and other parts of the mouth) and oro-hypopharynx (oropharynx, tonsils, hypopharynx, pyriform sinus, and pharynx not otherwise specified)	Cigarette smoking:	Oral cancer:	HR:	Current smokers included regular smokers and people who stopped smoking within the year before enrolment Estimates adjusted for age at entry into cohort, BMI, education level, alcohol consumption, vigorous physical activity, usual activity throughout the day, fruit intake, vegetable intake, and total energy
				Men:		
			Never-smokers	54	1.0 (ref)	
			Current smokers	71	2.99 (2.05–4.38)	
			Former smokers	104	1.00 (0.72–1.40)	
			Duration of cessation (yr):			
			1–4	18	2.49 (1.45–4.28)	
			5–9	17	1.29 (0.74–2.25)	
			≥ 10	69	0.83 (0.58–1.19)	
					$P_{trend} < 0.001$	
				Women:		
			Never-smokers	14	1.0 (ref)	
			Current smokers	42	7.57 (4.02–14.28)	
			Former smokers	25	2.10 (1.08–4.06)	
			Duration of cessation (yr):			
			1–4	8	6.18 (2.57–14.86)	
			5–9	4	1.88 (0.62–5.75)	
			≥ 10	13	1.53 (0.72–3.27)	
					$P_{trend} < 0.001$	
			Cigarette smoking:	Oro/hypopharyngeal cancer:		
				Men:		
			Never-smokers	16	1.0 (ref)	
			Current smokers	41	5.29 (2.88–9.73)	
			Former smokers	49	1.52 (0.86–2.70)	

Table 2.16 (continued)

Reference Location	Study population, number of participants, follow-up period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/number in cohort	RR or HR (95% CI)	Adjustments/comments
Freedman et al. (2007) (cont.)			Duration of cessation (yr):			
			1–4	8	3.42 (1.45–8.07)	
			5–9	13	3.05 (1.45–6.40)	
			≥ 10	28	1.10 (0.59–2.05)	
					P_{trend} < 0.001	
				Women:		
			Never-smokers	3	1.0 (ref)	
			Current smokers	16	11.39 (3.21–40.40)	
			Former smokers	14	5.29 (1.50–18.61)	
			Duration of cessation (yr):			
			1–4	4	12.57 (2.78–56.86)	
			5–9	3	6.11 (1.22–30.60)	
			≥ 10	7	3.81 (0.98–14.89)	
					P_{trend} < 0.001	
Maasland et al. (2014) The Netherlands	The Netherlands Cohort Study, initiated in 1986, enrolled 120 852 men and women aged 55–69 yr from 204 municipal population registers in the Netherlands. In 17.3 yr of follow-up, 110 oral cancers and 83 oropharyngeal/ hypopharyngeal cancers were diagnosed	Microscopically confirmed SCC of the head and neck, including the oral cavity and the oropharynx and hypopharynx	Smoking:	Oral cancer:		Former smoker status not defined, but from categorization of the variable "years since quitting" recorded at baseline, it is evident that people who quit within the year of enrolment or earlier were considered former smokers. Estimates adjusted for age (years), sex, and alcohol consumption (grams of ethanol per day; continuous). Analysis by duration of cessation also adjusted by pack-years of cigarette smoking (continuous)
			Never-smokers	29	1.0 (ref)	
			Current smokers	57	2.03 (1.16–3.56)	
			Former smokers	24	–	
			Duration of cessation (yr):			
			> 0 – < 10	11	0.84 (0.39–1.83)	
			10 – < 20	8	0.78 (0.32–1.86)	
			≥ 20	5	0.63 (0.22–1.81)	
					P_{trend} < 0.004	
			Smoking:	Oro/hypopha-ryngeal cancer:		
			Never-smokers	6	1.0 (ref)	
			Current smokers	55	8.10 (3.14–20.87)	
			Former smokers	22	–	

Table 2.16 (continued)

Reference Location	Study population, number of participants, follow-up period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/number in cohort	RR or HR (95% CI)	Adjustments/comments
Maasland et al. (2014) (cont.)			Duration of cessation (yr)			
			> 0 – < 10	8	2.48 (0.77–7.93)	
			10 – < 20	8	3.29 (1.04–10.39)	
			≥ 20	6	3.35 (0.97–11.55)	
					P_{trend} < 0.001	
Cancer mortality						
Ide et al. (2008) Japan	The Japan Collaborative Cohort Study for Evaluation of Cancer Risk covered 45 geographical areas in the country, enrolling 46 465 men and 64 327 women aged 40–79 yr in 1988–1990, with 12.5 yr of follow-up and identification of 52 oral and pharyngeal cancer deaths (41 in men)	Annual ascertainment of oral and pharyngeal cancer deaths, identified by ICD-10 codes C01–C14, excluding C07–C08 (salivary gland cancer) and C11 (nasopharyngeal cancer)	Smoking status:	Oral and pharyngeal cancer deaths:		Current or former smokers not defined RR of death adjusted for age, alcohol consumption, consumption of green tea, preference for salty foods, and consumption of green and yellow vegetables
				Men:		
			Non-smokers	5	1.0 (ref)	
			Current smokers	29	2.6 (1.0–6.7)	
			Former smokers	7	0.9 (0.3–3.0)	
Christensen et al. (2018) USA	The National Longitudinal Mortality Study included a representative sample of civilian, non-institutionalized men and women aged 35–80 yr (n = 357 420) who completed the Tobacco Use Supplement of the national Current Population Survey starting in 1985, with death ascertainment until the end of 2011	Lip, oral, and pharyngeal cancer deaths (ICD-10 codes C00–C14)	Exclusive cigarette smoking:	Oral and pharyngeal cancer deaths:		Former smokers were defined as people who had ever smoked ≥ 100 cigarettes but were non-smokers at the time of the baseline survey Risk of death (HR) adjusted for age, sex, race/ethnicity, education level, and year of survey Estimates not adjusted for alcohol consumption, and therefore probably confounded
			Never-smokers	31	1.0 (ref)	
			Current smokers	79	9.02 (5.78–14.09)	
			Former smokers	50	2.70 (1.66–4.39)	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; NIH-AARP, United States National Institutes of Health-American Association of Retired Persons; ref, reference; RR, relative risk; SCC, squamous cell carcinoma; yr, year or years.

the baseline questionnaire, which also recorded time since quitting smoking.

The RRs of oral cancer in former smokers decreased progressively with increasing time since quitting smoking in men (from HR for 1–4 years since quitting, 2.49; 95% CI, 1.45–4.28 to HR for > 10 years since quitting, 0.83; 95% CI, 0.58–1.19) and in women (from HR for 1–4 years since quitting, 6.18; 95% CI, 2.57–14.86 to HR for > 10 years since quitting, 1.53; 95% CI, 0.72–3.27); these estimates were lower than the RRs in current male smokers (HR, 2.99; 95% CI, 2.05–4.38) and current female smokers (HR, 7.57; 95% CI, 4.02–14.28). RRs of oral cancer were steadily higher in women than in men, whether in former smokers or in current smokers compared with never-smokers. [A larger proportion of oral cancers in men (23%) than in women (17%) were diagnosed in never-smokers, which may suggest that there are factors increasing the background risk in men more than in women, and this differential appears to lower the magnitude of the RRs compared with never-smokers reported in men with respect to the RRs reported in women.]

The elevated RRs of oropharyngeal and hypopharyngeal cancer in former smokers compared with never-smokers decreased with increasing time since quitting smoking in men (from HR for 1–4 years since quitting, 3.42; 95% CI, 1.45–8.07 to HR for > 10 years since quitting, 1.10; 95% CI, 0.59–2.05) and in women (from HR for 1–4 years since quitting, 12.6; 95% CI, 2.78–56.86 to HR for > 10 years since quitting, 3.81; 95% CI, 0.98–14.89); although these estimates remained elevated, they were of lower magnitude than the RRs in current male smokers (HR, 5.29; 95% CI, 2.88–9.73) and current female smokers (HR, 11.39; 95% CI, 3.21–40.40).

[The Working Group noted that this is one of the very few studies that investigated the association with quitting smoking separately in men and in women, and cautioned about interpreting differences in RR by sex.]

Maasland et al. (2014) reported on the Netherlands Cohort Study, which was initiated in 1986 and enrolled 120 852 men and women aged 55–69 years from 204 Dutch municipal population registers. Follow-up for cancer incidence, extended until 2003, was done through annual record linkage to the Netherlands Cancer Registry and the nationwide network of pathology registries. Former smoker status was not defined. The RR estimates for oral cancer in former smokers by time since quitting smoking were < 1, and the CIs included 1. A tendency of decreasing RR with increasing duration of quitting was observed, from RR for > 0 to < 10 years since quitting, 0.84 (95% CI, 0.39–1.83) to RR for ≥ 20 years since quitting, 0.63 (95% CI, 0.22–1.81); for current smokers, RR was 2.03 (95% CI, 1.16–3.56; P_{trend} < 0.004). A similar tendency of decreasing RR with increasing duration of quitting was observed for oropharyngeal and hypopharyngeal cancer; the magnitude of the RR at any duration of quitting was still elevated in former smokers with respect to never-smokers but was substantially lower than the RR in current smokers.

Two cohort studies reported risk of death in former smokers and current smokers using non-smokers as the reference group (Ide et al., 2008; Christensen et al., 2018). The Japan Collaborative Cohort Study for Evaluation of Cancer Risk, conducted in 45 geographical areas in the country, enrolled 46 465 men and 64 327 women who were followed up for an average of 12.5 years (Ide et al., 2008). In men, the RR of oral and pharyngeal cancer death in former smokers compared with non-smokers was 0.9 (95% CI, 0.3–3.0), and the risk of death in current smokers was more than twice that in non-smokers (RR, 2.6; 95% CI, 1.0–6.7). In women, the risk of oral and pharyngeal cancer death in current smokers compared with non-smokers was substantially higher (RR, 8.2; 95% CI, 2.1–32.1). [The Working Group noted the lack of a definition of former smoker and the absence of deaths in female

former smokers, which precluded the generation of a mortality risk estimate. No estimates by time since quitting were available.]

The National Longitudinal Mortality Study includes a representative sample of the civilian, non-institutionalized population of the USA, including men and women. For the analysis reported by Christensen et al. (2018), cohort members who completed the tobacco use questionnaire included 357 420 participants (excluding exclusive smokeless tobacco users and users of multiple types of tobacco). Former smokers were defined as people who had ever smoked ≥ 100 cigarettes but were non-smokers at the time of the survey. The definition of former smoker did not specify the duration of cessation.

The RR of death from oral and pharyngeal cancer in former smokers was almost 3 times that in never-smokers (RR, 2.70; 95% CI, 1.66–4.39) and was much lower than the RR of death in current smokers (RR, 9.02; 95% CI, 5.78–14.09). [The Working Group noted that, given that study participants were classified as former smokers or current smokers at baseline and cancer mortality was ascertained years later, changes in smoking status during follow-up could have introduced misclassification of exposure in the cohort, which could lead to underestimation or overestimation of the reported risks. Risk estimates may be confounded by lack of adjustment for alcohol consumption.]

(iii) Case–control studies

See Table 2.17.

Marron et al. (2010) reported on a large individual-level data pooled analysis of 17 case–control studies exploring the association of smoking cessation and HNC within the INHANCE consortium, reporting ORs for oral cancer and oro-hypopharyngeal cancer by time since quitting smoking using current smokers as the reference group. The risk of oral cancer decreased with quitting smoking compared with continuing smoking, and the reduction in risk became more pronounced the longer the cessation interval (P_{trend} < 0.01). In recent quitters (from 13 months to 4 years since quitting), the OR was 0.65 (95% CI, 0.52–0.80). With ≥ 20 years since quitting, the RR decreased to 0.19 (95% CI, 0.15–0.24), a RR similar in magnitude and precision to the RR reported for never-smokers (OR, 0.19; 95% CI, 0.14–0.27). Similarly, for oropharyngeal and hypopharyngeal cancers combined, the magnitude of the reduction in risk increased progressively with longer time since quitting (P_{trend} < 0.01). The reduction in risk was already evident in recent quitters (OR for > 1–4 years since quitting, 0.72; 95% CI, 0.52–1.00) and became more pronounced the longer the cessation interval, until the RR reached that in never-smokers after ≥ 20 years of cessation. [The Working Group recognized the large sample size of this pooled study based on harmonized data collected in countries encompassing a wide geographical distribution. Risk estimates were adjusted for alcohol consumption and cumulative smoking for oral cancer and oro-hypopharyngeal cancer by time since quitting smoking. Current smokers were used as the reference group, and reduction in risk was reported in a dose-dependent manner, including cessation intervals of ≥ 20 years.]

In addition to the data included in the pooled analysis (Marron et al., 2010), Bosetti et al. (2008) reported RR estimates of oral and pharyngeal cancers combined in former smokers by age at quitting using current smokers as the reference group and using data from two hospital-based case–control studies in Italy. The risk of oral and pharyngeal cancer decreased with quitting smoking irrespective of the age at quitting, and the magnitude of the reduction in risk decreased progressively with lowering of the age at quitting smoking, from OR for quitting at age 55–64 years of 0.48 (95% CI, 0.34–0.66) to OR for quitting at age < 35 years of 0.14 (95% CI, 0.08–0.26). [The Working Group noted that this is the only study

Table 2.17 Cessation of tobacco smoking and risk of oral cancer and/or pharyngeal cancer – case–control studies

Reference Location	Study population, number of participants, study period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/controls	RR or OR (95% CI)	Adjustments/comments
Marron et al. (2010) Central Europe, France, Italy, Switzerland, Latin America, Puerto Rico, USA	Pooled analysis of the INHANCE consortium of 17 hospital-based and population-based case–control studies (including men and women) accruing a total of 3302 oral cancer cases, 3989 oropharyngeal or hypopharyngeal cancer cases, and 16 377 controls. Most cases were diagnosed with SCC	Invasive tumour of the oral cavity, oropharynx, hypopharynx, or oral cavity or pharynx not otherwise specified		Oral cancer:		Former smokers include people who had quit smoking cigarettes, cigars, or pipe for > 1 year as of date of diagnosis or date of interview Risk estimates adjusted for age, sex, race/ethnicity, study centre, education level, pack-years of tobacco smoking, and frequency of alcohol consumption
			Smoking:		meta-OR:	
			Current smokers	2256/5183	1.0 (ref)	
			Former smokers	583/5009	0.30 (0.26–0.34)	
			Duration of cessation (yr):			
			> 1–4	156/620	0.65 (0.52–0.80)	
			5–9	129/836	0.43 (0.32–0.58)	
			10–19	144/1582	0.25 (0.21–0.31)	
			≥ 20	154/1971	0.19 (0.15–0.24)	
			Never-smokers	463/6186	0.19 (0.14–0.27)	
					$P_{trend} < 0.01$	
				Oro/hypopharyngeal cancer:		
			Current smokers	2565/5183	1.0 (ref)	
			Former smokers	957/5009	0.41 (0.32–0.53)	
			Duration of cessation (yr):			
			> 1–4	260/620	0.72 (0.52–1.00)	
			5–9	198/836	0.51 (0.38–0.67)	
			10–19	272/1582	0.36 (0.27–0.49)	
			≥ 20	281/1971	0.29 (0.19–0.43)	
			Never-smokers	467/6186	0.25 (0.15–0.42)	
					$P_{trend} < 0.01$	

Table 2.17 (continued)

Reference Location	Study population, number of participants, study period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/controls	RR or OR (95% CI)	Adjustments/comments
Radoï et al. (2013a) France	Multicentre population-based case–control study of UADT and lung cancer (ICARE) conducted in 10 departments in France with cancer registration (2002–2007), including men and women. Of 968 oral cancer cases contacted, 792 (82%) completed the questionnaire and 772 cases aged ≤ 75 yr were included. Controls were randomly selected from the population by random-digit dialling; 3555 (80.6%) were included	Incident and histology- or cytology-confirmed SCC of the oral cavity including the floor of the mouth, mobile tongue, base of the tongue, soft palate, gums, hard palate, and other parts of the mouth (ICD-10 codes C01–C06)		Oral cancer:		Former smokers were people who had stopped smoking for ≥ 2 yr before the study interview. Current smokers included people who had stopped recently (within < 2 yr of the date of the interview) Estimates adjusted for age, sex, area of residence, pack-years of smoking, (continuous variable), and alcohol consumption (categories of grams per day)
			Any smoking:			
			Never-smokers	62/1262	1.0 (ref)	
			Current smokers	537/820	9.8 (7.0–16.6)	
			Former smokers	171/1464	–	
			Duration of cessation (yr):			
			2–9	90/318	3.9 (2.7–5.9)	
			10–19	42/384	2.1 (1.3–3.3)	
			20–29	22/413	1.3 (0.7–2.2)	
			≥ 30	15/346	1.6 (0.9–3.0)	
De Stefani et al. (2007) Montevideo (Uruguay)	Hospital-based case–control study enrolling study participants (men only) in 4 hospitals (1988–2000), including 335 oral cancer and 441 pharyngeal cancer cases and 1501 controls with non-neoplastic conditions not related to tobacco use or alcohol consumption	Microscopically confirmed SCC of the mouth and pharynx	Smoking:	Oral cancer:		Current smokers include people who smoked at the time of the interview or had quit smoking ≤ 1 yr before the date of the interview. Smokers who had quit > 1 yr before the interview were considered former smokers Estimates adjusted for age, residence, urban/rural status, hospital, year at diagnosis, education level, family history of cancer among first-degree relatives, occupation, total consumption of vegetables and fruits, maté intake, and alcohol consumption. No adjustment for intensity or duration of smoking
			Current smokers	261/639	1.0 (ref)	
			Former smokers, duration of cessation (yr):			
			≤ 9	47/182	0.65 (0.44–0.94)	
			10–19	10/146	0.16 (0.08–0.32)	
			≥ 20	9/160	0.15 (0.07–0.31)	
			Never-smokers	8/374	0.08 (0.04–0.16)	
					$P_{trend} < 0.0001$	
				Pharyngeal cancer:		
			Current smokers	340/639	1.0 (ref)	
			Former smokers, duration of cessation (yr):			
			≤ 9	63/182	0.64 (0.45–0.91)	
			10–19	18/146	0.22 (0.13–0.39)	
			≥ 20	15/160	0.22 (0.12–0.40)	
			Never-smokers	5/374	0.04 (0.01–0.10)	
					$P_{trend} < 0.0001$	

Table 2.17 (continued)

Reference Location	Study population, number of participants, study period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/controls	RR or OR (95% CI)	Adjustments/comments
Lee et al. (2009) Czech Republic, Croatia, France, Germany, Greece, Ireland, Italy, Norway, Spain, and the United Kingdom	Multicentre hospital-based case–control study (ARCAGE) of aerodigestive tract cancer, including men and women, enrolling 993 cases of oral or oropharyngeal cancer and 2221 controls (1987–1992; 2002–2005) with conditions not related to tobacco use or alcohol consumption. In this analysis, 974 cases and 2168 controls were included	Histology- or cytology-confirmed SCC of the oral cavity or the pharynx (excluding the nasopharynx)		Oral and pharyngeal cancer:		Former smokers included people who had stopped smoking ≥ 12 months before enrolment Estimates adjusted for age, sex, education level, centre, and alcohol consumption frequency (continuous) and duration (continuous)
			Any smoking:			
			Never-smokers	109/712	1.0 (ref)	
			Current smokers	660/715	5.83 (4.50–7.54)	
			Former smokers	205/741	1.80 (1.37–2.37)	
			Duration of cessation (yr):			
			< 20 yr, > 0–20 pack-years	40/132	2.13 (1.40–3.25)	
			< 20 yr, > 20 pack-years	106/247	3.05 (2.19–4.25)	
			≥ 20 yr, > 0–20 pack-years	40/263	1.09 (0.73–1.64)	
			≥ 20 yr, > 20 pack-years	19/95	1.49 (0.84–2.63)	
			Current smokers:			
			> 0–20 pack-years	102/219	3.42 (2.45–4.78)	
			21–40 pack-years	257/258	6.65 (4.95–8.93)	
			> 40 pack-years	298/244	8.46 (6.22–11.5)	
					$P_{trend} < 0.001$	
Varela-Lema et al. (2010) Galicia (Spain)	Hospital-based case–control study enrolling men aged > 20 yr with newly diagnosed oral or pharyngeal cancer and controls from consecutive patients to undergo surgery not related to tobacco use or alcohol consumption at the same hospital (1996–2000), including 92 cancer cases and 230 controls	Incident histopathology-confirmed primary oral or pharyngeal cancer (ICD-10 codes C00–C14), excluding the lip		Oral and pharyngeal cancer:		Former smokers defined as people who had quit > 6 months before the date of the study interview Estimates adjusted for age, lifetime tobacco consumption, alcohol consumption in grams per week, high-risk occupation, and education level
			Smoking:			
			Current smokers	73/67	1.0 (ref)	
			Former smokers, duration of cessation (yr):			
			1–10	10/31	0.6 (0.2–1.5)	
			> 10	7/50	0.3 (0.1–0.9)	

Table 2.17 (continued)

Reference Location	Study population, number of participants, study period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/controls	RR or OR (95% CI)	Adjustments/comments
Bosetti et al. (2008) Milan, Pordenone, Rome (Italy)	Data from 2 multicentre hospital-based case–control studies on UADT cancer conducted in 1984–1997 in northern and central Italy. Analysis shown restricted to enrolled men aged < 75 yr. 961 cases of oral and pharyngeal cancer and 2824 controls included. This study population is included in the INHANCE consortium data set, but analysis by age at quitting is not reported in Marron et al. (2010)	Incident histologically confirmed oral and pharyngeal cancer		Oral and pharyngeal cancer:		Former smokers defined as people who had stopped smoking ≥ 12 months before enrolment and at age < 65 yr Reference group included current smokers and former smokers who had quit at age ≥ 65 yr Estimates adjusted for age, centre, education level, and alcohol consumption
			Smoking:			
			Current smokers	712/1176	1.0 (ref)	
			Former smokers, age at quitting:			
			55–64 yr	75/203	0.48 (0.34–0.66)	
			45–54 yr	90/301	0.36 (0.27–0.48)	
			35–44 yr	45/279	0.20 (0.14–0.29)	
			< 35 yr	13/162	0.14 (0.08–0.26)	

ARCAGE, Alcohol-Related Cancers and Genetic Susceptibility in Europe; CI, confidence interval; ICARE, Investigation of Occupational and Environmental Causes of Respiratory Cancers; ICD, International Classification of Diseases; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio; ref, reference; RR, relative risk; SCC, squamous cell carcinoma; UADT, upper aerodigestive tract; yr, year or years.

identified that documents the impact of age at quitting on the RR reduction.]

Radoï et al. (2013a) reported on a multicentre population-based case–control study (the Investigation of Occupational and Environmental Causes of Respiratory Cancers [ICARE] study) of upper aerodigestive tract cancer, including oral cancer, conducted in 2002–2007 in 10 departments in France with cancer registration, including male and female participants. The ICARE study documented time since quitting smoking in former smokers and used never-smokers as the reference group. The RR of oral cancer in former smokers decreased in magnitude with increasing time since quitting smoking but remained significantly elevated with up to 19 years since quitting (OR for 2–9 years of quitting, 3.9; 95% CI, 2.7–5.9; OR for 10–19 years of quitting, 2.1; 95% CI, 1.3–3.3; OR for 20–29 years of quitting, 1.3; 95% CI, 0.7–2.2; OR for ≥ 30 years of quitting, 1.6; 95% CI, 0.9–3.0) [no trend reported]. The estimates were markedly lower than the RR in current smokers (OR, 9.8; 95% CI, 7.0–16.6). [The Working Group acknowledged the moderate sample size of this study, which used robust definitions of former smoker and current smoker and enrolled participants from a wide geographical distribution in France, and also generated risk estimates adjusted for alcohol consumption and cumulative smoking by time since quitting smoking but used never-smokers as the reference group.]

De Stefani et al. (2007) conducted a male-only hospital-based case–control study assessing the effects of tobacco smoking and alcohol consumption on the occurrence of oral and pharyngeal cancers in Montevideo, Uruguay, in 1988–2000. The risk of oral cancer in former smokers was lower than that in current smokers within 9 years of quitting smoking (OR, 0.65; 95% CI, 0.44–0.94) and decreased markedly with longer time since quitting (OR for 10–19 years of smoking cessation, 0.16; 95% CI, 0.08–0.32; OR for ≥ 20 years of smoking cessation, 0.15, 95% CI, 0.07–0.31). Similarly, the risk of pharyngeal cancer in former smokers was lower than that in current smokers within 9 years of quitting smoking (OR, 0.64; 95% CI, 0.45–0.91) and continued to decrease with longer time since quitting (OR for ≥ 20 years of cessation, 0.22; 95% CI, 0.12–0.40). [The Working Group noted the high participation rates of eligible cases and controls, the generation of fully adjusted risk estimates, including by alcohol consumption, and the use of a definition of former smoker that classified smokers quitting within 1 year of the date of cancer diagnosis or interview as current smokers rather than former smokers, which reduced the possible distortion of risk estimates by exposure misclassification. The Working Group also observed that the ORs for former smokers by time since quitting smoking were not adjusted for intensity, duration, or cumulative past smoking.]

Lee et al. (2009) reported on a multicentre international hospital-based case–control study of aerodigestive tract cancer (the Alcohol-Related Cancers and Genetic Susceptibility in Europe [ARCAGE] study), which collected information on smoking and smoking cessation interval in former smokers. The study enrolled male and female cases and controls in 10 countries (the Czech Republic, Croatia, France, Germany, Greece, Ireland, Italy, Norway, Spain, and the United Kingdom) in 2002–2005 (with the exception of cases and controls in France, recruited earlier). The RR of oral and pharyngeal cancer in former smokers decreased with longer duration of cessation in people with equivalent cumulative pack-years of smoking, and the RR in current smokers with similar smoking history was markedly higher ($P < 0.001$). For instance, for former smokers with > 0 to 20 pack-years of smoking, the ORs were 2.13 (95% CI, 1.40–3.25) for < 20 years of quitting and 1.09 (95% CI, 0.73–1.64) for ≥ 20 years of quitting, compared with an OR of 3.42 (95% CI, 2.45–4.78) in current smokers. The reduction in risk with increasing

time since quitting was observed for both categories of cumulative smoking (0–20 pack-years and > 20 pack-years), but the magnitude of the risk estimates was higher in former smokers with higher cumulative smoking. [The Working Group acknowledged the large size of this multicentre study based on European populations, and the calculation of risk estimates by time since quitting, using two categories of cumulative smoking; however, the study reported RR estimates for oral and pharyngeal cancers combined, precluding the identification of risk of oral cancer alone.]

Varela-Lema et al. (2010) reported on a hospital-based case–control study in Santiago de Compostela, Galicia, Spain, in 1996–2000 investigating the association between tobacco smoking and oral cancer and/or pharyngeal cancer in men. A total of 92 cases and 230 controls were included in the analysis, which combined cases of oral and pharyngeal cancer and considered two categories for time since quitting smoking: 1–10 years and > 10 years. Using current smokers as the reference group, the risk of oral and pharyngeal cancer decreased in former smokers with > 10 years of quitting (OR, 0.3; 95% CI, 0.1–0.9). This study also provided ORs using never-smokers as the reference group, generating very high ORs in former smokers (OR, 4.8; 95% CI, 2.9–73.5) and in current smokers (OR, 34.5; 95% CI, 7.5–157.8), which included light and heavy consumers of alcohol; heavy alcohol consumers were over-represented in current smokers. [Adjustment by alcohol consumption may not have entirely controlled for the risk-potentiating effect of dual exposure to these two risk factors, particularly in current consumers. The Working Group acknowledged the reporting of cancer risk estimates by time since quitting smoking in this small study. However, this study did not include any description of matching of controls to cases, and participation rates in cases and controls were not mentioned. The definition of former smoker included people who had quit smoking for only ≥ 6 months by the time of enrolment, and risk estimates were combined for oral and pharyngeal cancers.]

(b) Risk of OPMDs

See Table 2.18.

(i) Overview of studies

A group of studies, limited in sample size, addressing cessation of tobacco smoking and incidence of OPMDs was available to the Working Group. These included one cohort study (Gupta et al., 1995), six case–control studies (Macigo et al., 1996; Hashibe et al., 2000a, b; Shiu et al., 2000; Fisher et al., 2005; Amarasinghe et al., 2010a; Li et al., 2011), and one cross-sectional study (Pivovar et al., 2017). Most of these studies included male and female participants; two studies were based only on men (Gupta et al., 1995; Pivovar et al., 2017). Most of these studies reported the RR of OPMDs or a specific OPMD (i.e. leukoplakia or erythroplakia) in former smokers using never-smokers as the reference group, and one study described effect estimates by time since quitting smoking (Macigo et al., 1996).

(ii) Intervention study

Gupta et al. (1995) reported on a very large cohort study in Ernakulam District in Kerala, India, with a 10-year follow-up (Table 2.18). Men accrued 77 681 person-years of observation, and women accrued 32 544 person-years of observation. The prevailing risk factors in the study population were bidi smoking and betel quid chewing, along with commercial cigarette smoking. The study calculated age-adjusted incidence rates separately for each type of OPMD, and the ratio of leukoplakia incidence was estimated between former smokers and current smokers. In men, who reported smoking more frequently than women, the age-adjusted incidence of leukoplakia was 24 per 100 000 (1 incident case) in former bidi smokers and 155 per 100 000 (80

Table 2.18 Cessation of tobacco smoking and risk of OPMDs

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Gupta et al. (1995) Kerala, Trivandrum (India) Intervention study	Cohort of 12 212 male and female tobacco users aged ≥ 15 yr identified in a baseline house-to-house survey (1977–1978) and recontacted annually for tobacco control education. Incidence of OPMDs at the 10-yr follow-up visit is reported by tobacco cessation Men accrued 77 681 person-years, and women accrued 32 544 person-years	Leukoplakia	Bidi smoking: Stopped Continued	Men (cases/ age-adjusted incidence): 1/24 per 100 000 80/155 per 100 000	Incidence ratio: 0.15 (N/A) –	Stopping smoking defined as quitting bidi or cigarette smoking for > 6 months at the time of the 10-year survey. Duration of cessation not reported Incidence rates age-adjusted Large sample size of men and women at high risk of developing OPMDs. The proportion of person-years accrued of tobacco cessation was higher in women (14.4%, mainly chewing) than in men (6.5%, mainly bidi smoking). Risk estimates reported without a measure of precision

Table 2.18 (continued)

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Macigo et al. (1995, 1996) Meru District (Kenya)	Community-based case–control study of cases of leukoplakia, including men and women aged 21–75 yr residing for ≥ 5 yr in the Githongo sublocation of Meru District (n = 85), and age-, sex-, and sampling cluster-matched controls (n = 141), including administration of structured questionnaire and oral examination	Clinically diagnosed cases of leukoplakia	Industrial cigarette smoking:	Cases/controls:	Leukoplakia:	Definition of former smoker not provided RRs not adjusted for potential confounders (i.e. alcohol consumption) Well-defined clinical diagnostic criteria and histological confirmation
			Never-smokers	18/78	1.0 (ref)	
			Former smokers	5/31	0.7 (0.2–2.3)	
			Current smokers	62/32	8.4 (4.1–17.4)	
			Kiraiku hand-rolled cigarette smoking:			
			Never-smokers	42/120	1.0 (ref)	
			Former smokers	29/17	4.9 (2.3–10.4)	
			Current smokers	14/4	10.0 (2.9–43.4)	
			Time smoking before quitting (yr):			
			≤ 10	24/15	4.6 (2.1–10.2)	
			> 10	5/2	7.1 (1.1–76.6)	
			Duration of cessation (yr):			
			≤ 4	6/2	8.6 (1.4–88.7)	
			5–9	12/7	4.9 (1.7–14.9)	
			≥ 10	11/8	3.9 (1.4–11.6)	

Table 2.18 (continued)

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Hashibe et al. (2000a, b) Kerala (India)	Community-based case–control study nested in an intervention trial screening male and female residents aged ≥ 35 yr and identifying 49 174 eligible study participants examined at home. 3585 people with suspicious OPMDs or cancer lesions referred to the dentist or the oncologist. The study included 927 cases of leukoplakia, 100 cases of erythroplakia, and 47 773 controls	Leukoplakia or erythroplakia diagnosed by a dentist	Tobacco smoking: Never-smokers Former smokers Occasional smokers Current smokers Never-smokers Former smokers Current smokers, 1–20×/day Current smokers, 21–40×/day	Cases/controls: 428/35 591 46/1815 19/764 434/9602 428/35 591 NR NR NR	Leukoplakia: 1.0 (ref) 1.7 (1.0–2.7) 2.0 (1.4–2.8) 3.4 (2.8–4.1) Erythroplakia: 1.0 (ref) 1.6 (0.8–2.9) 1.2 (0.6–2.4) 2.3 (1.1–5.1)	Former smoker not defined, and duration of smoking cessation not reported Former smoking-associated leukoplakia and erythroplakia effect estimates adjusted for age, sex, education level, BMI, years of chewing, and years of alcohol consumption Large sample size, leukoplakia lesions confirmed by a dentist, and effect estimates fully adjusted for important confounders
Shiu et al. (2000) Taiwan (China)	Hospital-based case–control study of 100 randomly selected cases of leukoplakia out of a cohort of 580 patients with leukoplakia diagnosed at a single institution in 1988–1998, and 100 age-, sex-, and date of diagnosis-matched controls randomly selected from patients diagnosed with periodontal disease at the same hospital	Cohort of leukoplakia cases clinically diagnosed according to WHO definition	Cigarette smoking: Never-smokers Former smokers Current smokers	Cases/controls: NR NR NR	Leukoplakia: 1.0 (ref) 1.04 (0.24–4.59) 3.22 (1.06–9.78)	Former smoker not defined, and duration of smoking cessation not reported ORs adjusted for alcohol consumption and areca nut chewing Effect estimates are adjusted for important confounders. Incomplete reporting, and estimates with low precision

Table 2.18 (continued)

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Fisher et al. (2005) West Virginia (USA)	Community-based case–control study of cases (n = 90) identified at a leukoplakia tissue registry and controls (n = 78) at the surgical biopsy service supporting the tissue registry but with a diagnosis of periapical cyst (ICD-9 code 522.8) and no diagnosis of leukoplakia	Leukoplakia histologically confirmed as ICD-9 code 528.6 with hyperkeratosis with or without epithelial atypia or dysplasia	Tobacco smoking: Never-smokers Former smokers Current smokers	Cases/controls: 38/25 30/29 22/24	Leukoplakia:* 1.0 (ref) 0.71 (0.27–1.86) 0.48 (0.17–1.33)	Former smoker not defined, and duration of smoking cessation not reported. Leukoplakia ORs adjusted for age, sex, smokeless tobacco use, daily alcohol consumption, and dental prostheses use. [*Results shown correspond to model assessing smokeless tobacco use] Cases with histological confirmation, and effect estimates fully adjusted, but small sample size
Amarasinghe et al. (2010a) Sabaragamuwa Province (Sri Lanka)	Community-based case–control study built on a randomly selected multistage cross-sectional sample (n = 1029) of people aged > 30 yr drawn to assess the prevalence of OPMDs in a rural setting. People with suspected OPMDs on oral examination were considered cases (n = 102), and screenees free of oral mucosa abnormalities were considered controls	Suspected cases of leukoplakia identified during screening referred to the hospital for histopathological confirmation	Tobacco smoking: Never-smokers Former smokers Occasional smokers Current smokers	Cases/controls: 43/NR 6/NR 6/NR 15/NR	Leukoplakia: 1.0 (ref) 0.5 (0.2–1.6) 0.8 (0.3–2.5) 0.7 (0.3–1.6)	Former smokers included ever-smokers who had quit > 1 calendar year before the date of diagnosis or interview Smoking-related effect estimates adjusted for sex, age, education level, BMI, occupation, β-carotene-containing total fruit and vegetable portions, betel quid chewing, and alcohol consumption Cases with histological confirmation, and risk estimates fully adjusted, but incomplete exposure reporting and small number of exposed cases. Study in a population where chewing is common

Table 2.18 (continued)

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Li et al. (2011) Puerto Rico (USA)	Case–control study identifying men and women aged ≥ 30 yr with an oral cavity examination histopathology report generated in 2003–2007 at pathology laboratories in Puerto Rico. People with benign oral lesions (n = 155) were considered controls, and those with OPMDs (n = 86) were considered cases	Histopathological diagnosis of oral hyperkeratosis, epithelial hyperplasia, and epithelial dysplasia in people with no prior history of oral lesions	Tobacco smoking: Never-smokers Former smokers Current smokers	Cases/controls with benign lesions: 38/99 17/30 31/26	OPMD, OR: 1.0 (ref) 1.47 (0.67–3.21) 4.32 (1.99–9.38)	Former smoker defined as a person who was an ever-smoker and quit smoking for > 1 calendar year before the year of diagnosis. No information on duration of cessation was reported Estimates adjusted for age, sex, education level, fruit and vegetable intake, and alcohol consumption (4 levels) Cases histologically confirmed, and interviewer blinded on case–control status of responders. Original specific OPMDs in cases not reported
Pivovar et al. (2017) Curitiba, Paraná (Brazil)	Cross-sectional study to screen for oral cancer in high-risk men (former or current smokers) aged 50–65 yr registered in a primary health-care programme; 233 were ever-smokers, and 202 completed the oral examination at the dentist	OPMDs and oral cancer first diagnosed by a dentist on clinical grounds and suspected lesions with histological analysis.	Tobacco smoking: Former smokers Current smokers Leukoplakia: Former smokers Current smokers	Screened OPMD-positive/ negative: 13/76 44/69 6/83 34/79	Prevalence ratio: 1.0 (ref) 2.66 (NR) 1.0 (ref) 4.31 (1.76–10.57)	Former smokers included ever-smokers with a smoking history of ≥ 20 yr and who had quit < 5 yr before the interview. Model generating leukoplakia prevalence ratios in current smokers to former smokers adjusted for family income and history of compliance with clinical examinations Histological confirmation. No adjustment for alcohol consumption

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; N/A, not available; NR, not reported; OPMDs, oral potentially malignant disorders; OR, odds ratio; ref, reference; RR, relative risk; WHO, World Health Organization; yr, year or years.

incident cases) in current bidi smokers, generating an incidence ratio of 0.15. [The Working Group noted that although the incidence ratio was reported without an estimate of precision and without taking alcohol consumption into account, such a large decrease in the incidence of leukoplakia after quitting bidi smoking, in a population known to have low or no alcohol consumption, is probably not due to chance or confounding.]

(iii) Case–control studies

One hospital-based case–control study (Shiu et al., 2000) and five community-based case–control studies (Macigo et al., 1996; Hashibe et al., 2000a, b; Fisher et al., 2005; Amarasinghe et al., 2010a; Li et al., 2011) were identified, including participants from India, Kenya, Puerto Rico, Sri Lanka, Taiwan (China), and the USA (Table 2.18).

In a community-based case–control study in Meru District in north-eastern Kenya, 85 leukoplakia cases and 141 controls were identified in a house-to-house survey of eligible residents (Macigo et al., 1995, 1996). The RR of leukoplakia in former smokers of commercial cigarettes compared with never-smokers was < 1 (OR, 0.7; 95% CI, 0.2–2.3); this estimate is substantially lower than that in current smokers (OR, 8.4; 95% CI, 4.1–17.4). In contrast, the RR of leukoplakia in former smokers of *kiraiku* hand-rolled cigarettes compared with never-smokers was markedly elevated (OR, 4.9; 95% CI, 2.3–10.4) but was lower than the RR in current smokers of *kiraiku* cigarettes (OR, 10.0; 95% CI, 2.9–43.4). The risk of leukoplakia remained elevated in former smokers with > 10 years of *kiraiku* smoking cessation (OR, 3.9; 95% CI, 1.4–11.6). [The Working Group noted the omission of definitions of former smoker and current smoker. Furthermore, effect estimates associated with smoking were not adjusted for important confounders, including alcohol consumption, a behaviour that is socially accepted in Kenya.]

Hashibe et al. (2000a) reported on a large community-based case–control study embedded in a randomized intervention trial in Kerala, India, screening for oral cancer in male and female residents. The study included 927 cases of leukoplakia confirmed by a dentist and 47 773 screened people free of oral diseases (controls). The RR of leukoplakia in former smokers compared with never-smokers (OR, 1.7; 95% CI, 1.0–2.7) was lower than that in current smokers (OR, 3.4; 95% CI, 2.8–4.2); the effect estimates were controlled for important confounders. In a related publication from the same population (Hashibe et al., 2000b), the association between cigarette smoking and erythroplakia was investigated (100 cases). The RR of erythroplakia in former cigarette smokers compared with never-smokers (OR, 1.6; 95% CI, 0.8–2.9) was lower than the RR in current smokers who reported smoking 21–40 times per day (OR, 2.3; 95% CI, 1.1–5.1) but not lower than the RR in current smokers who reported smoking 1–20 times per day (OR, 1.2; 95% CI, 0.6–2.4). [The Working Group noted that the studies did not provide definitions of former smoker or current smoker and did not present leukoplakia or erythroplakia effect estimates by number of years since quitting smoking.]

Shiu et al. (2000) randomly selected 100 cases of leukoplakia in a cohort of 435 cases diagnosed in 1988–1998 at a medical institution in Taiwan (China) and 100 matched controls. Leukoplakia risk estimates were calculated using never-smokers as the reference group. Multivariate analysis adjusting for alcohol intake and betel quid chewing generated RR estimates in former smokers (OR, 1.04; 95% CI, 0.24–4.59) of lower magnitude than the RR estimates in current smokers (OR, 3.22; 95% CI, 1.06–9.78). [The Working Group noted that the study did not provide definitions of former smoker and current smoker and did not present effect estimates by number of years since quitting smoking.]

Fisher et al. (2005) reported on a case–control study in West Virginia (USA) including cases

of leukoplakia (n = 90; response rate of eligible people, 55%) and controls with a periapical cyst (n = 78; response rate of eligible people, 50%) identified at the same tissue registry in 2001–2002. The fully adjusted RRs of leukoplakia in former smokers (OR, 0.71; 95% CI, 0.27–1.86) and in current smokers (OR, 0.48; 95% CI, 0.17–1.33) were < 1. [The Working Group noted the very modest response rate in cases and in controls, which raises concerns of selection bias. Furthermore, the Working Group acknowledged the omission of a definition of former smoker and the use of a control group with a pathology condition that was not described in any detail; this control group was probably not appropriate. Also, cases and controls differed by socioeconomic status or by education level, factors that were not taken into account and that may influence the level of smoking. Finally, the restriction of controls to people with a periapical cyst may have indirectly selected for controls with prevalent smoking.]

The very small study by Amarasinghe et al. (2010a) included few cases, and all ORs were < 1; it was considered uninformative.

The community-based case–control study of Li et al. (2011) identified men and women aged ≥ 30 years with an oral cavity examination histopathology report generated in 2003–2007 at pathology laboratories in Puerto Rico and lacking a previous history of oral diseases. People with benign oral conditions (n = 155) were considered controls, and those with OPMDs (n = 86), defined as oral epithelial dysplasia, oral hyperkeratosis, or epithelial hyperplasia without epithelial dysplasia, were considered cases. The effect estimate for OPMDs in former smokers compared with never-smokers (OR, 1.47; 95% CI, 0.67–3.21) was lower than that for current smokers compared with never-smokers (OR, 4.32; 95% CI, 1.99–9.38). [The Working Group noted that this case–control study, which clearly defined former smoker, was the only study that defined OPMDs by histopathology features, rather than by clinical entity or diagnosis, so that the dysplasia observed microscopically may have emerged from leukoplakia or from erythroplakia originally detected in the mouth.]

(iv) Cross-sectional studies

Pivovar et al. (2017) reported on a cross-sectional study within the framework of oral cancer screening in primary health care in the city of Curitiba in the state of Paraná in southern Brazil. The prevalence of OPMDs and leukoplakia in former smokers and current smokers was adjusted for family income and history of compliance with clinical examinations. The prevalence of leukoplakia was markedly higher in current smokers than in former smokers (prevalence ratio, 4.31; 95% CI, 1.76–10.57) (Table 2.18). [The Working Group noted that this study compared former smokers with current smokers but calculated the leukoplakia prevalence ratio using former smokers rather than current smokers as the reference group.]

2.3.2 Alcohol consumption

This section summarizes the findings from observational case–control studies, cohort studies, and a pooled analysis that investigated the effect of cessation of alcohol consumption and duration of alcohol cessation on the risks of oral cancer and OPMDs. These included the pooled analysis from the INHANCE consortium with data from 13 case–control studies (Marron et al., 2010), three cohort studies (Ide et al., 2008; Cancela et al., 2009; Im et al., 2021), and two individual case–control studies, one published before the INHANCE analysis (Takezaki et al., 1996) and one published since the INHANCE analysis (Andrade et al., 2015).

(a) Risk of oral cancer

See Table 2.19.

The INHANCE Consortium investigated the effects of quitting alcohol consumption on the

Table 2.19 Cessation of alcoholic beverage consumption and risk of oral cancer and/or pharyngeal cancer

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Pooled analysis of case–control studies						
Marron et al. (2010) International (multiple studies in (France, Italy Switzerland, Latin/Central America, USA)	INHANCE consortium pooled analysis of case–control studies, including men and women; 2615 oral cancer cases, 3989 oropharyngeal or hypopharyngeal cancer cases, and 12 359 and 12 593 controls, respectively (~1990s to early 2000s)	Invasive tumour of the oral cavity, oropharynx, hypopharynx, or oral cavity or pharynx not otherwise specified		Oral cancer:		Former drinkers were defined as people who had quit drinking the following alcoholic beverages: wine, beer, liquor, and aperitifs. People who had stopped drinking for > 1 yr were classified as former drinkers. The number of years that former drinkers had quit drinking was determined from age at reference date (interview or diagnosis date) and age at which they had stopped drinking Analysis adjusted for age, sex, race/ethnicity, study centre, education level, and pack-years of tobacco smoking
			Current drinkers	1131/5715	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	132/504	0.81 (0.61–1.07)	
			5–9	149/576	0.77 (0.52–1.15)	
			10–19	174/801	0.66 (0.47–0.92)	
			≥ 20	155/763	0.45 (0.26–0.78)	
			Never-drinkers	737/3674	0.65 (0.36–1.16)	
					P_{trend} = 0.05	
			< 1 drink/day:			
			Current drinkers	256/2250	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	30/144	1.51 (0.80–2.87)	
			5–9	22/204	1.06 (0.39–2.88)	
			10–19	40/307	0.80 (0.37–1.75)	
			≥ 20	57/338	0.98 (0.54–1.77)	
			Never-drinkers	727/3238	0.86 (0.39–1.89)	
			1–2 drinks/day:			
			Current drinkers	234/1539	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	24/149	0.67 (0.33–1.35)	
			5–9	36/154	1.22 (0.43–3.43)	
			10–19	30/205	0.34 (0.15–0.80)	
			≥ 20	29/186	0.59 (0.22–1.57)	
			Never-drinkers	717/3144	0.58 (0.26–1.28)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Marron et al. (2010) (cont.)			≥ 3 drinks/day:			
			Current drinkers	589/1554	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	77/206	0.79 (0.54–1.14)	
			5–9	90/207	0.85 (0.51–1.41)	
			10–19	102/279	0.82 (0.50–1.34)	
			≥ 20	69/232	0.43 (0.28–0.67)	
			Never-drinkers	727/3580	0.19 (0.09–0.39)	
					P_{trend} = 0.06	
				Oro/hypopharyngeal cancer:		
			Alcohol cessation:			
			Current drinkers	1703/5915	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	213/505	1.04 (0.73–1.48)	
			5–9	240/576	0.95 (0.61–1.49)	
			10–19	340/802	1.15 (0.92–1.43)	
			≥ 20	221/763	0.74 (0.50–1.09)	
			Never-drinkers	406/3693	0.65 (0.42–1.02)	
					P_{trend} = 0.18	
			< 1 drink/day:			
			Current drinkers	338/2444	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	29/144	2.02 (1.07–3.80)	
			5–9	28/205	1.44 (0.65–3.16)	
			10–19	67/309	1.49 (0.96–2.34)	
			≥ 20	60/338	1.16 (0.65–2.05)	
			Never-drinkers	406/3693	0.97 (0.59–1.58)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Marron et al. (2010) (cont.)			1–2 drinks/day:			
			Current drinkers	335/1808	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	38/152	1.09 (0.65–1.82)	
			5–9	33/156	1.09 (0.55–2.16)	
			10–19	55/205	1.06 (0.67–1.68)	
			≥ 20	45/186	0.80 (0.47–1.37)	
			Never-drinkers	400/3599	0.49 (0.30–0.81)	
			≥ 3 drinks/day:			
			Current drinkers	926/1554	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	141/206	1.05 (0.69–1.59)	
			5–9	174/207	1.12 (0.60–2.08)	
			10–19	213/279	1.15 (0.73–1.81)	
			≥ 20	115/232	0.77 (0.45–1.30)	
			Never-drinkers	397/3580	0.19 (0.10–0.37)	
					$P_{trend} < 0.01$	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Case–control studies						
Huang et al. (2017) Taiwan (China)	Hospital-based case–control study, including men and women; 509 oral cancer cases, 118 oropharynx cases, and 89 hypopharynx cases (2010–2016)	ICD-classified primary pathologically confirmed squamous cell carcinoma of the oral cavity		Oral cancer:		Age, sex, education, cigarette smoking (pack-year categories), and betel quid chewing (pack-year categories) Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol use No adjustment for past amount of alcohol consumed or duration of smoking cessation
			Non-drinkers (never + occasional)	195/517	1.0 (ref)	
			Former drinkers	61/109	0.77 (0.51–1.17)	
			Current drinkers	253/314	1.29 (0.97–1.73)	
				Oropharyngeal cancer:		
			Non-drinkers (never + occasional)	29/517	1.0 (ref)	
			Former drinkers	20/109	2.83 (1.39–5.76)	
			Current drinkers	69/314	4.23 (2.38–7.52)	
				Hypopharyngeal cancer:		
			Non-drinkers (never + occasional)	4/517	1.0 (ref)	
			Former drinkers	19/109	14.02 (4.38–44.85)	
			Current drinkers	66/314	21.55 (7.36–63.15)	
Andrade et al. (2015) Brazil	Hospital-based case–control study, with data abstracted from medical records, including men and women; 127 oral cancer cases and 381 controls (2002–2012)	Histopathologically confirmed oral squamous cell carcinoma		Oral cancer:		Moderate-sized case–control study Alcohol consumption categories not defined Crude ORs, no adjustment
			Non-drinkers	27/113	1.0 (ref)	
			Former drinkers	56/57	2.73 (1.73–4.31)	
			Current drinkers	44/84	1.07 (0.69–1.68)	
			Duration of cessation (yr):			
			≥ 10	20/41	1.0 (ref)	
			< 10	36/16	4.61 (2.08–10.22)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
De Stefani et al. (2007) Uruguay	Hospital-based case–control study, including men only; 335 oral cancer cases and 441 pharyngeal cancer cases (1998–2000)	Microscopically confirmed squamous cell carcinoma of the mouth or pharynx		Oral cancer:		Adjusted for age, residence, urban/rural status, hospital, diagnosis year, education, first-degree family history of cancer, total vegetable and fruit, and maté intake, occupation, smoking status, years since quitting smoking and current cigarettes/day Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol use No adjustment for past amount of alcohol consumed
			Non-drinkers	34/527	1.0 (ref)	
			Former drinkers	91/317	3.0 (1.9-4.7)	
			Current drinkers	210/657	3.4 (2.3-5.2)	
				Pharyngeal cancer:		
			Non-drinkers	33/527	1.0 (ref)	
			Former drinkers	116/317	3.9 (2.5-6.1)	
			Current drinkers	292/657	4.5 (3.0-6.8)	
Zheng et al. (1997) China	Hospital-based case–control study, including men and women; 111 tongue cancer and 111 sex- and age-matched controls (1988–1989)	Histologically confirmed tongue cancer		Tongue cancer:		Adjusted for tobacco, years of education and matching factors Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol use No adjustment for past amount of alcohol consumed or duration of smoking cessation
			Non-drinkers	64/72	1.0 (Ref.)	
			Former drinkers	7/6	1.20 (0.58–2.50)	
			Current drinkers	40/33	0.94 (0.28–3.22)	
Takezaki et al. (1996) Japan	Hospital-based case–control study, including men and women; 203 oral cancer cases, 35 oropharyngeal cancer cases, and 28 hypopharyngeal cancer cases	Histologically confirmed, ICD-classified primary oral cancer, oropharyngeal cancer, and hypopharyngeal cancer		Oral, oropharyngeal, and hypopharyngeal cancer:		Alcohol consumption defined and standardized Crude ORs, no adjustment Not clear what reference group is – possibly never-drinkers
			Duration of cessation (yr):			
			0 (never quit)	138/13 811	1.2 (0.9–1.6)	
			0–4	9/320	2.4 (1.1–5.1)	
			5–14	4/180	1.7 (0.6–4.8)	
			≥ 15	4/62	3.4 (1.2–9.9)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Ko et al. (1995) Taiwan (China)	Hospital-based case–control study, including men and women; 107 oral cancer cases and 200 controls (1992–1993)	Histologically confirmed, ICD-classified oral cancer,		Oral cancer:		Adjusted for education, occupation, cigarette smoking and betel chewing status No details on selection of hospital-based controls provided No adjustment for past amount of alcohol consumed or duration of smoking cessation
			Non-drinkers	25/89	1.0 (ref)	
			Former drinkers	14/37	1.0 (0.3–3.3)	
			Current drinkers	68/74	2.2 (1.0–4.9)	
Cohort studies						
Im et al. (2021) China	Cohort study. 209 237 men, aged 30–79 years, with no previous history of cancer; follow-up time from 2004 until January 2017 (median 10 years); incident cancer cases ascertained by linkage with cancer registries and the National Health insurance databases	Cancer of mouth or throat by ICD-10 codes (C00-C14, C32)		Mouth or throat cancer incidence:		Analysis adjusted for age, study area, education, income, smoking, physical activity, fruit intake, BMI, and family history of cancer Floating standard errors were used to estimate the confidence intervals Abstention is the reference category No adjustment for past amount of alcohol consumed or duration of smoking cessation No data on alcohol and oral cancer risk among women provided
			Abstention	23/42 479	1.00 (0.65–1.53)	
			Ex-regular drinkers	12/18 061	1.06 (0.60–1.87)	
			Occasional drinkers	39/78 963	1.33 (0.96–1.86)	
			Current regular drinkers	66/69 734	1.89 (1.46–2.45)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Cancela et al. (2009) India	Cohort study. Trivandrum Oral Cancer Screening Study RCT, with cancer registry follow-up of incidence and mortality, including men and women aged 35–100 yr; 32 347 participants recruited in 1996. In 10 yr of follow-up (1996–2006), 134 oral cancer cases were diagnosed, and 91 oral cancer deaths were registered	Oral cancer was defined by ICD-10 codes C02 (other and unspecified parts of the tongue), C03 (gum), C04 (floor of the mouth), C05 (palate), and C06 (other and unspecified parts of the mouth)		Oral cancer:		Small numbers of cases and deaths, and consequently wide CIs Individuals who had never consumed alcohol during their lifetime were categorized as never, those who were currently consuming alcohol or those who had stopped drinking alcohol for < 6 months were categorized as current, and those who had quit drinking ≥ 6 months before the time of the interview were categorized as former Analyses adjusted for age, education level, religion, occupation, standard of living, betel quid chewing habits, smoking habits, intake of vegetables, and intake of fruits
				Incidence (person-years):	HR:	
			Never-drinkers	61/178 932	1.00 (ref)	
			Current drinkers	52/85 022	1.49 (1.01–2.21)	
			Former drinkers	21/19 127	1.90 (1.13–3.18)	
				Mortality (person-years):		
			Never-drinkers	43/179 134	1.00 (ref)	
			Current drinkers	34/85 158	1.76 (1.08–2.86)	
			Former drinkers	14/19 212	2.04 (1.08–3.86)	
Ide et al. (2008) Japan	Cohort study. 110 792 participants, including men (46 465) and women (64 327) aged 40–79 yr, recruited in 1988–1990. In 12.5 yr of follow-up, 52 deaths: 25 from oral cancer and 27 from pharyngeal cancer	Oral and pharyngeal cancer deaths were identified by ICD-10 codes C01–C14, excluding C07–C08 (salivary gland cancer) and C11 (nasopharyngeal cancer)	Men:	Oral and pharyngeal cancer mortality:		Non-drinker and former drinker were not defined Small numbers and wide CIs Adjusted for age (continuous), smoking status (never, former, current), consumption of green tea (≥ 1 cups per day, < 1 cup per day, unknown), preference for salty foods (like, normal or dislike, unknown), and consumption of green and yellow vegetables (daily or not)
			Non-drinkers	5/77 513	1.0 (ref)	
			Former drinkers	2/23 423	1.2 (0.2–6.0)	
			Current drinkers	34/319 502	2.0 (0.8–5.1)	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio; RCT, randomized controlled trial; ref, reference; yr, year or years.

risks of oral cancer (based on 12 studies) and oropharyngeal and hypopharyngeal cancers (based on 13 studies) by performing a robust pooled analysis with comprehensive adjustment for confounding factors (Marron et al., 2010). Cessation of alcohol consumption was associated with a reduced risk of oral cancer (OR, 0.60; 95% CI, 0.43–0.84). The reduction in risk after alcohol cessation increases with duration of cessation, with the risk decreasing by > 50% by 20 years of quitting for oral cancer (OR, 0.45; 95% CI, 0.26–0.78) and by about 25% by 20 years of quitting for oropharyngeal and hypopharyngeal cancers combined (OR, 0.74; 95% CI, 0.50–1.09). Further subgroup analyses showed that the effects of quitting on the risk of oral cancer were more pronounced in former heavy drinkers (≥ 3 drinks per day) and the RR reduction became significant after ≥ 20 years of quitting (OR, 0.43; 95% CI, 0.28–0.67); there was no relationship with duration of consumption. For oropharyngeal and hypopharyngeal cancers, the relationship with previous frequency of alcohol consumption and duration of quitting was less clear.

Three cohort studies analysed the risk associated with former alcohol consumption [none of them reported duration of alcohol cessation]. In a cohort in India, former drinkers had a higher risk of oral cancer incidence and death than current drinkers relative to never-drinkers (Cancela et al., 2009). [This study had small numbers of cases and deaths, well-defined categories of alcohol consumption, and robust analyses.] In a cohort in Japan, the RR of oral and pharyngeal cancer death associated with former drinking relative to non-drinking in men was lower than the RR in current drinkers (Ide et al., 2008). [This study had small numbers of deaths. No categories of alcohol consumption were defined, but the analyses were adjusted for potential confounders.] In a recent cohort study of men in China, former drinkers relative to never-drinkers had a lower RR for lip and oral cavity cancer than current drinkers relative to never-drinkers (Im et al., 2021). [This relatively small cohort study did not adjust for past alcohol consumption or smoking in the analysis.]

The individual case–control study published before the INHANCE analysis (Takezaki et al., 1996) showed an increase in risk associated with long duration of quitting (OR for > 15 years of quitting, 3.4; 95% CI, 1.2–9.9). [The numbers of participants in each category were very small, and the estimates were not adjusted for potential confounders, including smoking.] More recently, a small hospital-based case–control study in Brazil (Andrade et al., 2015) reported that cessation of alcohol consumption for < 10 years compared with cessation for ≥ 10 years conferred a large increased risk (OR, 4.61; 95% CI, 2.08–10.22). [The categories of alcohol consumption were not defined, and the crude estimates were not adjusted for any potential confounding factors.]

In addition, four other hospital-based case–control studies (Ko et al., 1995; Zheng et al., 1997; De Stefani et al., 2007; Huang et al., 2017) reported only risks associated with former drinking relative to never drinking. In all four studies, the risk associations for former drinking relative to never drinking were lower than those for current drinking relative to never drinking; ORs ranged from 0.77 to 3.0 for former drinking and from 1.2 to 3.4 for current drinking (relative to never drinking).

(b) Risk of OPMDs

See Table 2.20.

No studies were identified that showed the effect of duration of alcohol cessation on the risk of OPMDs. Seven case–control studies reported risk estimates for former drinkers relative to never-drinkers alongside estimates for current drinkers relative to never-drinkers. [The studies generally had small sample sizes and were of varying quality.] Two studies reported OPMD outcomes combined, one reported multiple

Table 2.20 Cessation of alcoholic beverage consumption and risk of OPMDs

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/ comments
Case–control studies						
Li et al. (2011) Puerto Rico (USA)	Case–control study, including men and women aged ≥ 30 yr. People with benign oral lesions (n = 155) were considered controls, and those with OPMDs (n = 86) were considered cases (2003–2007)	Histopathological diagnosis of oral hyperkeratosis, epithelial hyperplasia, and epithelial dysplasia in people with no prior history of oral lesions		OPMDs:		Never-drinker and former drinker not defined. Small numbers and wide CIs Adjusted for age (4 levels), sex, education level (3 levels), fruit and vegetable intake (4 levels), and current smoking
			Never-drinkers	41/73	1.0 (ref)	
			Ever-drinkers	45/82	0.63 (0.33–1.21)	
			Former drinkers	14/22	0.63 (0.25–1.57)	
			Current drinkers	31/60	0.63 (0.32–1.26)	
Amarasinghe et al. (2010a) Sri Lanka	Community-based case–control study. Randomly selected multistage cross-sectional sample (n = 1029) including men and women aged > 30 yr. People with suspected OPMDs on oral examination were considered cases (n = 102), and screenees free of oral mucosa abnormalities were considered controls	Suspected cases of leukoplakia identified during screening referred to the hospital for histopathological confirmation		OPMDs:		Former drinkers also include current occasional drinkers Adjusted for sex, age, socioeconomic status, β-carotene-containing fruits and vegetables portion, BMI, smoking, betel quid chewing, and alcohol consumption
			Non-drinkers	39/551	1.0 (ref)	
			Monthly, weekly, and daily drinkers	27/114	2.7 (1.2–6.3)	
			Former, occasional drinkers	35/63	1.1 (0.5–2.6)	
Lee et al. (2003) Taiwan (China)	Community-based case–control study, including men and women aged ≥ 15 yr. Cases of leukoplakia or OSF (1994 and 1995). 219 OPMD cases and 876 age- and sex-matched controls were enrolled	Leukoplakia or OSF. Histologically confirmed and diagnosed according to WHO definitions		Leukoplakia:		Adjusted for education level and occupation
			Never-drinkers	72/349	1.0 (ref)	
			Former drinkers	9/40	1.1 (0.5–2.4)	
			Current drinkers	44/111	1.8 (1.1–2.8)	
				OSF:		
			Never-drinkers	55/266	1.0 (ref)	
			Former drinkers	7/27	1.4 (0.6–3.4)	
			Current drinkers	32/83	1.8 (1.1–3.1)	

Table 2.20 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/ comments
Thomas et al. (2003) India	Community-based case–control study nested in an intervention trial screening men and women aged ≥ 35 yr and identifying 49 174 eligible study participants examined at home. 3585 people with suspicious OPMDs or cancer lesions referred to the dentist or the oncologist. The study included 927 cases of leukoplakia, 100 cases of erythroplakia, 115 people with multiple OPMDs, and 47 773 controls	Multiple OPMDs diagnosed by a dentist		Multiple OPMDs:		Large sample size. Confirmed diagnosis by dentist Adjusted for age, sex, education level, BMI, smoking (continuous, pack-years), tobacco chewing (continuous, duration in years), fruit intake (low or high), and vegetable intake (low or high)
			Non-drinkers	91/40 801	1.0 (ref)	
			Occasional drinkers	4/2743	1.1 (0.4–3.2)	
			Current drinkers	13/2754	1.3 (0.6–3.0)	
			Former drinkers	7/1475	1.8 (0.7–4.5)	
Hashibe et al. (2000a) India	Community-based case–control study described above in Thomas et al. (2003)	Leukoplakia diagnosed by a dentist		Leukoplakia:		Large sample size. Confirmed diagnosis by dentist Adjusted for age, sex, education level, BMI, smoking, and tobacco chewing
			Non-drinkers	619/40 801	1.0 (ref)	
			Occasional drinkers	65/2743	1.2 (0.9–1.6)	
			Current drinkers	165/2754	1.6 (1.2–2.0)	
			Former drinkers	78/1475	1.4 (1.1–1.9)	
Hashibe et al. (2000b) India	Community-based case–control study described above in Thomas et al. (2003)	Erythroplakia diagnosed by a dentist		Erythroplakia:		Large sample size. Confirmed diagnosis by dentist Adjusted for age, sex, education level, BMI, smoking (continuous, pack-years), and chewing tobacco (continuous, duration in years)
			Non-drinkers	62/40 801	1.0 (ref)	
			Occasional drinkers	3/2743	0.9 (0.3–3.1)	
			Current drinkers	21/2754	5.8 (2.7–12.5)	
			Former drinkers	14/1475	4.8 (2.4–9.7)	

Table 2.20 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/ comments
Macigo et al. (1996) Kenya	Community-based case–control study of cases of leukoplakia, including men and women aged 21–75 yr residing for ≥ 5 yr in the Githongo sublocation of Meru District (n = 85), and age-, sex-, and sampling cluster-matched controls (n = 141), including administration of structured questionnaire and oral examination	Clinically diagnosed cases of leukoplakia (147 lesions in 85 cases). Only 5 cases had non-homogeneous lesions. Biopsies obtained in 49 cases, and histopathology examination revealed no cancer and 11 cases of moderate to severe dysplasia		Leukoplakia:		Alcohol consumption not defined RRs not adjusted for potential confounders (i.e. alcohol consumption) Crude estimates, not adjusted for potential confounders
			Never-drinkers	26/62	1.0 (ref)	
			Current drinkers	39/47	2.0 (1.0–3.9)	
			Former drinkers	36/49	1.5 (0.7–3.3)	

BMI, body mass index; CI, confidence interval; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; ref, reference; RR, relative risk; WHO, World Health Organization; yr, year or years.

OPMDs, three reported leukoplakia, one reported erythroplakia, and one reported OSF. Relative to never-drinkers, the RR estimates for OPMDs were generally (in 4 of 7 studies) lower in former drinkers than in current drinkers, for former drinkers ranging from 1.1 to 1.8 and for current drinkers ranging from 1.3 to 2.7. In the three studies that reported leukoplakia outcomes, the risk estimates in former drinkers compared with never-drinkers ranged from 1.1 to 1.5 and those in current drinkers compared with never-drinkers ranged from 1.6 to 2.0; however, the CIs were wide and overlapping.

2.3.3 Smokeless tobacco use

(a) Risk of oral cancer

Six informative observational studies that reported on the association between former use of smokeless tobacco and risk of oral cancer, including two cohort studies and four case–control studies, were identified by the Working Group. In most of these studies, the former use category was defined at study entry, and often no information was provided with respect to duration of cessation. Studies were well powered with sufficient sample size to estimate overall effects but tended to have small numbers of former users. There were no studies that provided risk estimates for former users compared with current users, and none that provided risk estimates by time since quitting smokeless tobacco use. Detailed information on the six identified observational studies is presented in Table 2.21 and Table 2.22.

Two cohort studies, one in Sweden (Luo et al., 2007) and one in Norway (Boffetta et al., 2005), examined the association between oral snuff use and risk of oral cancer. Data on snuff use were collected using questionnaires, and cancer outcome data were obtained through linkage to cancer registries. The follow-up period between exposure and outcome was 12–35 years. Both analyses accounted for potential confounding due to smoking. Neither study found an association between snuff use (former or current) and risk of oral cancer; they reported risk estimates for former users of 0.7 (95% CI, 0.1–5.0) (Luo et al., 2007) and 1.0 (95% CI, 0.3–3.5) (Boffetta et al., 2005). [The Working Group noted the small number of incident oral cancers in former snuff users in both studies: 1 event in the study in Sweden (Luo et al., 2007) and 3 events in the study in Norway (Boffetta et al., 2005). The Working Group noted the absence of repeat assessment of status of snuff use as an important limitation in these studies, particularly given the long follow-up period. In addition, neither of the studies adjusted for alcohol consumption.]

Four case–control studies examined the risk of oral cancer in former users of smokeless tobacco. Of these, three were conducted in Sweden (Lewin et al., 1998; Schildt et al., 1998; Rosenquist, 2005) and examined oral snuff use. Exposure data were collected using questionnaires, and cancer outcome data were obtained through linkage to hospital or cancer registries. Controls from population-based registries were matched to cases. All three studies accounted for potential confounding due to smoking either by statistical adjustment or by providing stratified estimates in never-smokers. Two studies found 1.5–1.8-fold non-statistically significant increased risk of oral cancer in former oral snuff users compared with never-users, whereas no association was observed in current users (OR, 0.7 and 1.0). In the third study (Rosenquist, 2005), using never-users as the reference group, former users had a lower risk of oral cancer (OR, 0.3; 95% CI, 0.1–0.9) compared with current users (OR, 1.1; 95% CI, 0.5–2.5). [All three studies were conducted in Sweden, where reported associations between current snuff use and risk of oral cancer are weak. A role for reverse causation in the observed elevated estimates cannot be ruled out.]

The fourth case–control study, conducted in Yemen, found a significantly elevated risk of oral

Table 2.21 Cessation of smokeless tobacco use and risk of oral cancer – cohort studies

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure categories (number of cases)	Number of cases	RR (95% CI)	Comments
Luo et al. (2007) Sweden	Cohort study of 279 897 male construction workers in the Swedish building industry in 1978–1992 Detailed information on smoking and snus use collected through personal interview Oral cancer incidence data collected thorough complete linkage to population and health registries 12-yr follow-up (until 2004)	Oral cancer (ICD-7 codes 140, 141, 143, and 144 not including cancers of the salivary glands, pharynx, or larynx)	Snus use: Never-users of any tobacco Former users Current users	 50 1 9	 1.0 (ref) 0.7 (0.1–5.0) 0.9 (0.4–1.8)	Association between snus use and oral cancer was adjusted for age and BMI Former snus user was defined on entry into study; changes in habit were not accounted for Very small number of exposed cases
Boffetta et al. (2005) Norway	Cohort study in Norwegian general population that included a probability sample of the general adult population from the 1960 census who were alive on 1 January 1966 Questionnaires were mailed for collection of data on smokeless tobacco use 35-yr follow-up completed through cancer registry linkage until 2001 Study included only men (n = 10 136)	Oral and pharyngeal cancer (ICD-7 codes 141–148)	Snus use: Never-users Former users Current users	 25 3 6	 1.00 (ref) 1.04 (0.31–3.50) 1.13 (0.45–2.83)	Adjusted for age and smoking Former users were defined at entry into study, with no repeat assessment No clear definition of former users

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; N/A, not available; ref, reference; RR, relative risk; yr, year or years.

Table 2.22 Cessation of smokeless tobacco use and risk of oral cancer – case–control studies

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of cases/ controls	OR (95% CI)	Comments
Lewin et al. (1998) Stockholm (Sweden)	Registry-based case–control study Included men registered in hospital-based or population-based registries in 2 geographical regions, aged 40–79 yr in 1988–1990 128 oral cancer cases, 756 randomly selected controls matched on age, sex, region, and vital status Exposure data collected through personal interview	Oral cancer	Oral moist snuff: Never-users Former users Current users Ever-users	 103/550 15/41 10/50 25/91	 1.0 (ref) 1.8 (0.9–3.7) 1.0 (0.5–2.2) 1.4 (0.8–2.4)	Estimates adjusted for age, region, smoking, and alcohol consumption
Schildt et al. (1998) Sweden	Population-based case–control study Oral cancer cases confirmed by histopathology and registered in 4 northern regions of Sweden in 1980–1989 Controls from population registries matched on age, sex, county, and vital status and year of death where applicable Questionnaires mailed to collect information on tobacco use (smoking and moist snuff)	Oral cancer (ICD-7 codes 140, 141, 143–145).	Oral moist snuff: Never-users Former users Current users In never-smokers: Never-users Former users Current users	 287/282 28/18 23/54 124/144 9/4 19/23	 1.0 (ref) 1.5 (0.8–2.9) 0.7 (0.4–1.1) 1.0 (ref) 1.8 (0.9–3.5) 0.7 (0.4–1.2)	Estimates adjusted for age, sex, and county of residence. Smoking was not adjusted for, but stratified estimates were provided A former smoker or former snuff user was defined as a person who had quit smoking or snuff use ≥ 1 yr before the diagnosis
Rosenquist (2005) Sweden	Hospital-based case–control study in Sweden in 2000–2004 132 oral cancer cases (91 men) identified from 2 hospitals reflecting 80% participation rate of cases in the region. 320 controls (215 men) matched on age, sex, and county from the population registry. Data were collected by interview; oral examination and HPV testing were completed	Oral cancer	Oral snuff: Never-users Former users Current users	 112/255 7/34 13/31	 1.0 (ref) 0.3 (0.1–0.9) 1.1 (0.5–2.5)	ORs adjusted for smoking and total alcohol consumption. Further adjustment for HPV status had minor effects A former snuff user was defined as a person who had quit the habit ≥ 6 months before the interview

Table 2.22 (continued)

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of cases/ controls	OR (95% CI)	Comments
Nasher et al. (2014) Yemen	Hospital-based case–control study. Cases were confirmed by histopathology Oral cancer cases and age- and sex-matched controls	Oral cancer in users of *shammah* dipping	*Shammah*: Never-users Former users Current users	 11/98 7/8 42/14	 1.0 (ref) 12.6 (3.3–48.2) 39 (14–105)	Estimates were adjusted for age, sex, EBV status, and tobacco smoking

CI, confidence interval; EBV, Epstein–Barr virus; HPV, human papillomavirus; ICD, International Classification of Diseases; ref, reference; RR, relative risk; yr, year or years.

cancer in former *shammah* users compared with non-users (OR, 12.6; 95% CI, 3.3–48.2), which was significantly lower than that in current users (OR, 39; 95% CI, 14–105) (Nasher et al., 2014). [The Working Group noted that the estimates were based on a small number of former chewers; no definition was provided with respect to duration of cessation, and the estimates were not adjusted for alcohol consumption.]

(b) Risk of OPMDs

Four cohort studies, two case–control studies, and two cross-sectional studies have examined the association between former use of smokeless tobacco and risk of OPMDs. [Most of these studies were well powered with sufficient sample size to estimate overall effects, but they tended to have small numbers of former users.] Many of these studies reported risk estimates using never-users as the reference group, and some studies reported only the prevalence of lesions across exposed groups (Table 2.23).

The four cohort studies were all conducted in the USA: two were in baseball players, and two were large population-based cohorts. Three of the four studies diagnosed leukoplakia as the outcome of interest at baseline entry into the study, whereas Shulman et al. (2004) diagnosed oral mucosal lesions. Histopathological confirmation was indicated in only one study (Ernster et al., 1990). All four studies examined use of oral snuff and chewing tobacco; Sinusas et al. (1992) also examined use of moist snuff. In these studies, former users were categorized at study entry as past users, with no further definition with regard to duration of cessation, except in the study of Ernster et al. (1990), in which former users were defined as past users who had used smokeless tobacco more than once per month in the past and who had quit use ≥ 1 month ago. Three studies found no increased risk in former users of smokeless tobacco compared with never-users and found increased risk estimates for current users (Ernster et al., 1990; Tomar et al., 1997; Shulman et al., 2004). Sinusas et al. (1992) found a prevalence of leukoplakia in former users equivalent to that in never-users (6%). Current users had a much higher prevalence of lesions (37%), corresponding to a > 9-fold increase compared with former smokeless tobacco users and non-users (Sinusas et al., 1992). [In two studies (Ernster et al., 1990; Sinusas et al., 1992), chewing tobacco use and snuff use were combined to generate risk estimates; it is likely that snuff and chewing tobacco may reflect differential risks towards oral cancer. In the other two studies (Tomar et al., 1997; Shulman et al., 2004), multiple OPMDs were grouped together; because some of these may not be etiologically related to smokeless tobacco use, these results should be interpreted with caution.]

Two case–control studies were identified, one in the USA and one in Uzbekistan. In the study in Uzbekistan, risk estimates for former users of *naswar* (*nass*) were slightly lower than those for current users when compared with never-users (Evstifeeva and Zaridze, 1992). The study in the USA (Fisher et al., 2005) reported risks of leukoplakia for smokeless tobacco use and snuff use separately. For both products, higher risk estimates were found for current users than for former users compared with never-users. [Both studies accounted for smoking and other potential confounding factors, but neither of the studies defined former use with respect to the duration of cessation. In addition, the criteria for identification of leukoplakia and pre-leukoplakia were not defined in the study in Uzbekistan.]

One cross-sectional study, conducted in Uzbekistan, reported percentages of leukoplakia and pre-leukoplakia that were similar for former and current *naswar* use: 11.5% for former use and 12% for current use, compared with 2.2% in never-users (Zaridze et al., 1986). [No definition was provided for former users.] The other cross-sectional study, conducted in Yemen, included 346 people diagnosed with leukoplakia-like lesions based on the Axell criteria. Khat

Table 2.23 Cessation of smokeless tobacco use and risk of OPMDs

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of participants/ cases/controls (% with OPMDs)	RR (95% CI)	Comments
Cohort studies						
Ernster et al. (1990) USA	Cohort of 1109 baseball players who underwent training in 1988 (median age, 18 yr), of whom 75% used snuff and 21% chewed tobacco Leukoplakia was identified by dentists on entry and was biopsy-confirmed	Leukoplakia (as per the Greer and Poulson criteria)	Smokeless tobacco: Never-users Former users Current chewing tobacco users Current snuff users	 493 (1.4%) 138 (1.4%) 88(17.2%) 304 (55.6%)	 1.0 (ref) 1.0 (0.2–5.0) 14.5 (5.7–36.7) 86.9 (39.9–189.5)	Analysis adjusted for age, race, smoking, alcohol consumption, and dental hygiene Smokeless tobacco use defined at entry Snuff users had a significantly increased prevalence of leukoplakia compared with chewing tobacco users, OR: 4.4 (2.4–9.3) Former users were those who had used smokeless tobacco more than once a month in the past but had not used it within the previous month
Sinusas et al. (1992) Florida (USA)	Cohort of 206 professionals in baseball organization, of whom 42.7% were current users and 16.5% were former users of smokeless tobacco (moist snuff and chewing tobacco)	Leukoplakia (Greer and Poulson and Axell criteria)	Moist snuff and chewing tobacco: Non-users Former users Current seasonal users Current year-round users	[Crude estimates based on reported numbers] 79 (6.0%) 32 (5.9%) 24 (7.6%) 39 (37.1%)	 1.0 (ref) [0.99 (0.18–5.35)] [1.32 (0.24–7.22)] [9.32 (3.29–26.37)]	No definition was given for former users No adjustment was made for smoking, but only 7 of the 206 participants were smokers (3.4%); 4 also used smokeless tobacco
Tomar et al. (1997) USA	Cohort of 17 206 children aged 12–17 yr who participated in the 1986–1987 National Survey of Oral Health in schoolchildren in the USA, of whom 3.1% used any smokeless tobacco, 2.0% used any snuff, and 1.5% used any chewing tobacco	Oral mucosal lesions classified using Greer and Poulson and Axell criteria as "white or whitish oral soft-tissue lesions"	Chewing tobacco: Never-users Former users Current users Snuff: Never-users Former users Current users	 5195 (3.0%) 527 (6.0%) 273 (19.6%) 5359 (1.9%) 329 (5.6%) 307 (34.9%)	 1.0 (ref) 1.3 (0.7–2.2) 2.5 (1.3–5.0) 1.0 (ref) 2.4 (1.0–6.1) 18.4 (8.5–39.8)	RRs adjusted for age, smoking, and alcohol consumption Former users of snuff or chewing tobacco were defined as those who reported that they had ever used these products but were not using them at the time of the survey

Table 2.23 (continued)

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of participants/ cases/controls (% with OPMDs)	RR (95% CI)	Comments
Shulman et al. (2004) USA	A sample of 17 235 people aged ≥ 17 yr from the Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III) who underwent oral examination by dentists for identification of oral lesions Lifestyle data were collected by interview	48 different oral mucosal lesion types classified based on the WHO *Guide to epidemiology and diagnosis of oral mucosal diseases and conditions*	Smokeless tobacco: Never-users Former users Current users	 8143 (23.8%) 183 (12.8%) 371 (60.3%)	 1.00 (ref) 0.53 (0.25–1.13) 3.90 (2.75–5.55)	Analyses adjusted for age, sex, denture status, race, and smoking Specific type of smokeless tobacco used was not indicated Definition of former users is unclear Oral lesions considered included denture-related (8.4%) and tobacco-related lesions (smokeless tobacco-related and nicotine stomatitis) (4.7%)
Cross-sectional studies						
Zaridze et al. (1986) Uzbekistan	Cross-sectional study in Uzbekistan 1569 people from a population-based cohort of men invited for medical examination by local authority; 42% used *nass* Oral lesions clinically diagnosed, and exposure assessed by interview	Leukoplakia and pre-leukoplakia	*Nass*: Never-users Former users Current users	 625 (2.2%) 26 (11.5%) 525 (12%)	 1.0 (ref) NR 5.6 (3.4–9.5)	Estimates are provided for never-smokers It is unclear whether these estimates were adjusted for potential confounding factors Definition of former users is unclear
Al-Tayar et al. (2015) Yemen	Cross-sectional study in 2014 in Dawan Valley, Yemen, involving 346 male residents aged ≥ 18 yr. An interview-based questionnaire was used to collect demographic, oral hygiene, and *shammah* use information Smokers and khat users were excluded	Leukoplakia-like lesions (Axell criteria) 80 leukoplakias were diagnosed at grade 1–4 and 266 at grade 0	*Shammah*: Never-users Former users Current users	 248 (NR) 30 (NR) 68 (NR)	 1.00 (ref) 3.65 (1.40–9.50) 12.99 (6.34–26.59)	Analyses were adjusted for age, education level, and frequency of *shammah* use Former *shammah* users were those individuals who had previously consumed *shammah* but stopped their consumption for ≥ 1 yr

Table 2.23 (continued)

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of participants/ cases/controls (% with OPMDs)	RR (95% CI)	Comments
Case–control studies						
Evstifeeva and Zaridze (1992) Uzbekistan	Case–control study in a region of Uzbekistan with high incidence of oral and oesophageal cancer 191 men with leukoplakia and 466 controls Data on use of *nass* quid, cigarette smoking, and alcohol consumption were collected by interview from 1569 men	Leukoplakia and pre-leukoplakia	*Nass*: Never-users Former users Current users	 66/282 7/13 118/171	 1.00 (ref) 3.00 (1.08–8.32) 3.86 (2.60–5.72)	Analyses adjusted for age, smoking, and alcohol consumption
Fisher et al. (2005) West Virginia (USA)	Hospital-based case–control study in the USA 90 cases (54 men) aged ≥ 18 yr with leukoplakia with histopathological confirmation of hyperkeratosis were compared with 78 (37 men) controls with periapical cysts from the same surgical pathology unit Smokeless tobacco and related data collected by postal questionnaires	Leukoplakia (ICD-9 classification)	Smokeless tobacco: Never-users Former users Current users Snuff: Never-users Former users Current users	 55/64 19/9 16/5 64/71 8/5 15/2	 1.00 (ref) 2.73 (0.69–10.84) 9.21 (1.49–57.00) 1.00 (ref) 0.98 (0.17–5.61) 30.08 (2.67–338.48)	ORs adjusted for age, sex, smoking, alcohol consumption, and denture status

CI, confidence interval; ICD, International Classification of Diseases; NHANES, National Health and Nutrition Examination Survey; NR, not reported; OPMDs, oral potentially malignant disorders; OR, odds ratio; ref, reference; RR, relative risk; WHO, World Health Organization.

users and smokers were excluded. Past history of *shammah* use was reported to increase the risk of oral cancer by > 3-fold (3.65; 95% CI, 1.40–9.50). Current *shammah* use further increased the risk of oral cancer in this population (Al-Tayar et al., 2015). [The study appears to be of limited power because of a small number of former users. Also, duration of cessation was not defined.]

Although the body of evidence appeared inconsistent with regard to the direction and the magnitude of risk of OPMDs, the RR estimates for former users of smokeless tobacco were generally lower than those for current users when compared with never-users as the reference group within each study. To clarify whether the distribution of covariance within individual studies could explain or potentially reveal underlying risk trends, the Working Group undertook additional analysis (Table 2.24). First, the RR in former users compared with current users was estimated for each study based on the Dirichlet–multinomial distribution method (Gelman et al., 1995). Next, the recalculated risk estimates and 95% CIs were used to derive the variance and covariance matrices of case and control populations based on the tri-gamma distribution of the corresponding variables, which were then approximated. [The meta-estimate reflected nearly 70% reduction in RR for former users compared with current users of smokeless tobacco (OR, 0.30; 95% CI, 0.14–0.46).]

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

Two prospective cohort studies (Jayalekshmi et al., 2009, 2011), one nested case–control study (Muwonge et al., 2008), two case–control studies (Balaram et al., 2002; Znaor et al., 2003), and a recent meta-analysis (Gupta et al., 2022) assessed the effect of cessation of chewing areca nut with added tobacco on the incidence of oral cancer (Table 2.25). To complement the evidence available from the published literature, the Working Group undertook primary data analyses from unpublished data from one cohort study and one case–control study, both conducted in India and providing information on incidence of oral cancer in relation to time since chewing cessation (Table 2.26).

One intervention study and three follow-up studies focusing on assessing the relationship between cessation of chewing areca nut with added tobacco and the incidence of leukoplakia and OSF at the 5-year and 10-year follow-ups (Gupta et al., 1986; Murti et al., 1990; Gupta et al., 1992, 1995) were available to the Working Group (Table 2.27). Two additional case–control studies focused on the incidence of OPMDs as the outcome (Amarasinghe et al., 2010a; Worakhajit et al., 2021) (Table 2.28).

(a) Studies of oral cancer

(i) Evidence from the published literature

See Table 2.25.

The two reports of Jayalekshmi et al. (2009, 2011) were based on a large cohort established as a part of the cancer registry in Karunagappally in Kerala, India. The cohort included 66 277 men and 78 140 women; by 2005, 160 cases of oral cancer in men and 92 in women were identified from the cancer registry. The association between chewing areca nut with added tobacco and risk of oral cancer was examined overall for both men and women, as well as in men who were never and current bidi smokers. In men, the risk of oral cancer in former chewers (OR, 2.1; 95% CI, 1.3–3.6) was comparable to that in current chewers (OR, 2.4; 95% CI, 1.7–3.3). Among never bidi smokers, the RR estimate in former chewers (OR, 3.2; 95% CI, 1.1–9.6) was lower than that in current chewers (OR, 5.4; 95% CI, 3.0–9.0); in current bidi smokers, the risk estimate for former chewers was not significantly elevated compared with never-chewers (OR, 1.3; 95% CI, 0.6–2.9). In women, a 9-fold increased risk of oral cancer was reported in former chewers (OR, 9.2; 95% CI,

Table 2.24 Cessation of smokeless tobacco use and risk of OPMDs – recalculation of the relative risk for former chewers versus current chewers, and meta-analysis of results

Reference	Study design	Effect size for chewing habit (versus never-chewers)		Effect size for chewing habit with consideration of covariance
		Former chewers Estimate (95% CI)	Current chewers Estimate (95% CI)	Former chewers versus current chewers Estimate (95% CI)
Ernster et al. (1990)	Cohort	1.0 (0.2–5.0)	14.5 (5.7–36.7)	0.07 (0.01–0.44)
Sinusas et al. (1992)	Cohort	0.99 (0.18–5.35)	9.32 (3.29–26.37)	0.11 (0.02–0.48)
Tomar et al. (1997)	Cohort	1.3 (0.7–2.2)	2.5 (1.3–5.0)	0.52 (0.31–0.87)
Shulman et al. (2004)	Cohort	0.5 (0.3–1.1)	3.9 (2.8–5.6)	0.14 (0.06–0.30)
Al-Tayar et al. (2015)	Cross-sectional	3.7 (1.4–9.5)	13.0 (6.3–26.6)	0.28 (0.11–0.73)
Evstifeeva and Zaridze (1992)	Case–control	3.0 (1.1–8.3)	3.9 (2.6–5.5)	0.77 (0.28–2.14)
Fisher et al. (2005)	Case–control	2.7 (0.7–10.8)	9.2 (1.5–57.0)	0.30 (0.05–1.69)
Results of meta-analysis				
Random-effect model				0.30 (0.14–0.46)
Fixed-effect model				0.34 (0.22–0.45)

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

4.6–18.1), whereas a nearly 5-fold increased risk was reported in current chewers (OR, 5.5; 95% CI, 3.3–9.0) compared with never-chewers. This study also examined risk of oral cancer by time since quitting chewing areca nut with added tobacco. In men, ≥ 10 years of quitting appeared to reduce risks to levels comparable to those in never-chewers, with differences in estimates that were not statistically significant. No such reduction was noted in women (Jayalekshmi et al., 2009, 2011). [The higher risk in former chewers compared with current chewers in women is difficult to understand and cannot be attributed to reverse causation, because the risk of oral cancer in those with ≥ 10 years of quitting was still higher than that in current chewers. Estimates were not adjusted for tobacco smoking and alcohol consumption, although these behaviours were reported to be rare in women in this population.]

Muwonge et al. (2008) enrolled 282 incident oral cancer cases and 1410 matched controls in a case–control study nested in the cohort of a randomized controlled study in Trivandrum, India (Sankaranarayanan et al., 2000). In this study, the RR of chewing areca nut with added tobacco for the incidence of oral cancer was 4.3 (95% CI, 3.1–6.1) in current chewers and 11.9 (95% CI, 7.0–20.4) in former chewers compared with never-chewers. [The Working Group noted that the higher risk reported for former chewers could result from reverse causation.]

A matched case–control study enrolled 591 cases of oral cancer and 582 controls who were frequency-matched (on age, sex, and centre) in three centres in Bangalore, Madras, and Trivandrum in southern India (Balaram et al., 2002). In men, the risk of oral cancer in former chewers decreased progressively with increasing time since chewing cessation compared with current chewers, reaching a reduction of 25% (RR, 0.75; 95% CI, 0.23–2.52) ≥ 10 years after cessation. In women, on contrast, the risk of oral cancer was higher for ≥ 10 years of cessation than

Table 2.25 Cessation of chewing of areca nut products (including betel quid) with added tobacco and risk of oral cancer – observational studies

Reference Location	Study population, sample selection, response rate	Study design, number of participants, study period, follow-up time	Exposure category Number of exposed cases/controls	RR (95% CI)	Comments
Cohort studies					
Jayalekshmi et al. (2009) India	Women aged 30–84 yr in Karunagappally, Kerala, were enrolled with house-to-house surveys to have baseline information The response rate was 93%	Prospective cohort study designed to link 78 140 enrolled women participating in the baseline survey with the cancer registry. Baseline information was collected on lifestyle, including tobacco chewing, and sociodemographic factors in 1990–1997. By the end of 2005, 92 oral cancer cases were identified	Women: Never-chewers: 25 Former chewers: 14 Current chewers: 53 Duration of cessation (yr): Current chewers: 53 < 10: 7 ≥ 10: 4 Never-chewers: 25	 1.0 (ref) 9.2 (4.6–18.1) 5.5 (3.3–9.0) 1.0 (ref) 1.7 (0.8–3.7) 2.6 (0.9–7.2) 0.2 (0.1–0.3)	Poisson regression model was used to calculate relevant estimates Adjusted for age and family income Estimates not adjusted for tobacco smoking and alcohol consumption; however, according to the authors these habits are rare in women in this population
Jayalekshmi et al. (2011) India	Men aged 30–84 yr in Karunagappally, Kerala, were enrolled with house-to-house surveys to have baseline information The response rate was 93%	The same prospective cohort study was designed as above, but the target participants were 66 277 men. By the end of 2005, 160 oral cancer cases were identified	Men (cases/person-yr): Overall: Never-chewers: 64 Former chewers: 19 Current chewers: 75 In never bidi smokers: Never-chewers: 18 Former chewers: 4 Current chewers: 37 In current bidi smokers: Never-chewers: 38 Former chewers: 7 Current chewers: 27 Duration of cessation (yr): Current chewers: 75 < 10: 12 ≥ 10: 2 Never-chewers: 64	 1.0 (ref) 2.1 (1.3–3.6) 2.4 (1.7–3.3) 1.0 (ref) 3.2 (1.1–9.6) 5.4 (3.0–9.0) 1.0 (ref) 1.3 (0.6–2.9) 1.3 (0.8–2.1) 1.0 (ref) 1.1 (0.6–2.0) 0.3 (0.1–1.2) 0.4 (0.3–0.6)	Poisson regression model was used to calculate relevant estimates Adjusted for age and family income. Estimates not adjusted for alcohol consumption

Table 2.25 (continued)

Reference Location	Study population, sample selection, response rate	Study design, number of participants, study period, follow-up time	Exposure category Number of exposed cases/controls	RR (95% CI)	Comments
Case–control studies					
Balaram et al. (2002) India	Patients with incident oral cancer and their hospital-based matched controls in Bangalore, Madras, and Trivandrum centres	Matched case–control study conducted in 1996–1999 Case group: 591 incident cases of oral cancer Control group: 582 hospital controls, frequency-matched to cases on age and sex and on centre (relatives and friends of patients admitted to hospitals because of diseases other than oral cancer in Bangalore and Madras, and outpatients in Trivandrum) Confounding factors adjusted for in the logistic regression model were age, location, education level, and only for men: tobacco smoking (never/ever) and alcohol consumption (never/ever)	Men: Duration of cessation (yr): Current chewers: 120/37 < 10: 45/14 ≥ 10: 14/6 Women: Duration of cessation (yr): Current chewers: 203/29 < 10: 31/6 ≥ 10: 17/3	 1.0 (ref) 1.02 (0.45–2.29) 0.75 (0.23–2.52) 1.0 (ref) 0.72 (0.23–2.21) 0.97 (0.23–4.11)	The sex-related differences in the results may be attributed to selection bias for women, who may be less likely to go to hospitals, because the proportion of ever-chewers in women in such hospital-based controls was lower than that in women in the general population
Znaor et al. (2003) India	Male patients with oral cancer as cases in Chennai (Tamil Nadu) and Trivandrum (Kerala)	Case–control study conducted in 1993–1999 Case group: 1563 oral cancer cases Control group: 1711 male patient controls from both centres and 1927 male healthy hospital visitors in Chennai Confounding factors adjusted for in the logistic regression model were age, location, education level, tobacco smoking, and alcohol consumption (never/ever)	Duration of cessation (yr): Current chewers: 640/460 2–4: 93/41 5–9: 59/20 10–14: 30/19 ≥ 15: 30/19	 1.0 (ref) 1.15 (0.75–1.77) 1.60 (0.92–2.81) 0.71 (0.37–1.35) 0.67 (0.36–1.26)	

Table 2.25 (continued)

Reference Location	Study population, sample selection, response rate	Study design, number of participants, study period, follow-up time	Exposure category Number of exposed cases/controls	RR (95% CI)	Comments
Muwonge et al. (2008) India	People aged ≥ 35 yr in Trivandrum District	Nested case–control design based on data from a randomized control trial for oral cancer screening conducted in 1996–2004 in Trivandrum (Kerala) Case group: 282 incident oral cancer cases Control group: 1410 controls matched on sex, age (± 1 yr), area of residence, and screening participation	Overall: Never-chewers: 80/915 Current chewers: 160/445 Former chewers: 42/50 Men: Never-chewers: 64/561 Current chewers: 78/222 Former chewers: 21/32 Women: Never-chewers: 16/354 Current chewers: 82/223 Former chewers: 21/18	 1.0 (ref) 4.3 (3.1–6.1) 11.9 (7.0–20.4) 1.0 (ref) 2.7 (1.8–4.2) 5.9 (3.0–11.7) 1.0 (ref) 9.5 (5.0–18.0) 39.0 (15.0–101.8)	The high risk in former chewers compared with current chewers was observed in both sexes in this study. It may be the result of reverse causation (i.e. the more severe cases are more likely to quit chewing)
Meta-analysis					
Gupta et al. (2022)	2 cohort and 4 case–control studies and one case–control study nested in a randomized trial		Never-chewers Former chewers Current chewers Duration of cessation (yr): < 10 > 10	1.0 (ref) 6.87 (4.10–11.52) 6.29 (3.83–10.33) 1.21 (0.90–1.63) 0.72 (0.48–1.07)	6 of the 7 studies were restricted to men or provided sex-specific results; 4 studies did not provide a clear definition of former users; 2 case–control studies provided relative risks of oral cancer by duration of cessation

CI, confidence interval; ref, reference; RR, relative risk; yr, year or years.

for < 10 years of cessation. [A selection bias may explain the results in women – who may be less likely to go to hospitals – because the proportion of ever-chewers in women in such hospital-based controls was lower than that in women in the general population.]

Another case–control study, conducted in 1993–1999 at the cancer institute in Chennai (Tamil Nadu) and the Regional Cancer Centre in Trivandrum (Kerala), India, enrolled 1563 male oral cancer cases and 3638 male hospital controls (Znaor et al., 2003). The risk estimate of oral cancer compared with current chewers decreased by 29% (RR, 0.71; 95% CI, 0.37–1.35) for 10–14 years of cessation and by 33% (RR, 0.67; 95% CI, 0.36–1.26) for ≥ 15 years of cessation. [The selection of the control group was different: the hospital control from both centres and an additional healthy control from only one of the two centres. In addition, compared with cases of oral cancer, the control group was younger and educated. Although these demographic characteristics were considered in the multivariate analysis, residual confounding may still exist.]

In the last days of the Working Group meeting, a meta-analysis was made available to the Working Group that combined seven reports to assess the potential benefit of long-term cessation of chewing areca nut with added tobacco (Gupta et al., 2022). [The meta-analysis includes all the cohort and case–control studies reported above (Balaram et al., 2002; Znaor et al., 2003; Muwonge et al., 2008; Jayalekshmi et al., 2009, 2011).] The meta-RR of oral cancer for former chewers with < 10 years of cessation compared with current chewers was increased (1.21; 95% CI, 0.90–1.63) and for former chewers with > 10 years of cessation was decreased (0.72; 95% CI, 0.48–1.07). [The increased risk after < 10 years of cessation could be due to reverse causation. The sample size was still insufficient to reach statistical significance in the reversal of risk of oral cancer after long-term cessation.]

(ii) Evidence from primary data analyses

See Table 2.26.

Data collected at two sites in India were used for primary analysis by the Working Group to assess the impact of quitting chewing betel quid with added tobacco on the risk of oral cancer.

The first primary analysis used data derived from the cluster-randomized controlled trial in Trivandrum, India (Sankaranarayanan et al., 2000). The data were from a cohort of 191 870 participants aged ≥ 35 years enrolled in 1996–2006. Incident oral cancer was ascertained until 31 December 2009; the average follow-up period was 7 years. The main exposure of interest included the chewing status (current, former, and never) and duration of cessation. The major confounders were adjusted for in the Cox proportional hazards regression model. Per year of quitting chewing betel quid with added tobacco, the risk of oral cancer decreased significantly (HR, 0.97; 95%, 0.96–0.99). However, for participants with > 15 years of cessation, the risk of oral cancer remained high (HR, 2.5; 95% CI, 1.6–3.7) compared with current chewers. Compared with people with < 2 years of cessation, those with > 10 years of cessation had a lower risk of oral cancer (HR for 10–15 years, 0.8; 95% CI, 0.3–2.0; HR for > 15 years, 0.7; 95% CI, 0.4–1.4), although this was not statistically significant. [Duration of cessation was imputed using current age and duration of chewing, which may explain the wide 95% CIs. There are issues with identifiability and collinearity of time since quitting with duration and age. The median age was different between current and former chewers: 52 years for current chewers and 62–65 years for the several categories of former chewers.]

The second primary analysis used data derived from cancer hospitals in India. A case–control study design was applied. Cases were patients with oral cavity cancer diagnosed in the cancer hospital from three cities: Mumbai, Varanasi, and Guwahati. Controls

Table 2.26 Cessation of chewing of areca nut products (including betel quid) with added tobacco and risk of oral cancer – primary data analyses performed by the Working Group

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/controls	OR (95% CI)	Comments
Kerala oral cancer screening trial (several previous publications)	Kerala, India	Cluster-randomized trial of 191 870 participants aged ≥ 35 yr who were recruited in 1996–2006 and followed up until 31 December 2009. Data on exposures collected at baseline was used for analysis The analysis was Cox proportional hazards regression The key exposure was duration of cessation of chewing of betel quid (primarily with added tobacco). This metric was derived using simple, single-value imputation of age at initiation of chewing (10-year birth cohort and sex-specific, estimated from GATS India 2009–2010), duration of chewing, and age at study participation. Individuals with negative duration of cessation were excluded from analyses Analyses were adjusted for age, sex, education level, chewing duration and intensity, smoking duration and intensity, and alcohol consumption duration and intensity (days per week of alcohol consumption) Two sets of analyses were conducted: (1) analyses restricted to ever-chewers (n = 40 860), and (2) analyses restricted to former chewers (n = 3441)	Oral cancer incidence during 7 yr of follow-up	202 cases in ever-chewers, 65 cases in former chewers		Difference between categories of duration of cessation was not statistically significant Duration of cessation was imputed using current age and duration of chewing. There are issues with identifiability and collinearity of duration of cessation with duration of use and age There is age confounding between current and former chewers (the median age is 52 yr for current chewers, and 62, 62, 62, 59, and 65 yr for former chewers with < 2, 2–5, 5–10, 10–15, and > 15 yr of cessation, respectively)
					Compared with current chewers:	
				Current chewers:		
				202/37 419	1.0 (ref)	
				Duration of cessation (yr):		
				< 2: 13/567	3.7 (2.1–6.5)	
				2–5: 6/195	5.1 (2.2–11.8)	
				5–10: 12/390	5.1 (2.8–9.4)	
				10–15: 7/435	3.1 (1.4–6.5)	
				> 15: 27/1854	2.5 (1.6–3.7)	
					Compared with quitting < 2 yr:	
				Duration of cessation (yr):		
				< 2	1.0 (ref)	
				2–5	1.4 (0.5–3.8)	
				5–10	1.4 (0.6–3.1)	
				10–15	0.8 (0.3–2.0)	
				> 15 yr	0.7 (0.4–1.4)	
				Per year of cessation	0.97 (0.96–0.99)	

Table 2.26 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/controls	OR (95% CI)	Comments
Unpublished, Tata Memorial Centre, Mumbai. Study is part of a GWAS of buccal cancers	Mumbai, Varanasi, and Guwahati, India	Hospital-based case–control study of patients with buccal mucosa cancer and controls, matched on 5-year age, sex, and site The main exposure was duration of cessation of chewing Logistic regression analyses were adjusted for age, sex, study site, alcohol consumption intensity, smoking duration and intensity, and chewing duration and intensity	Buccal mucosa cancers	391 cancers in current chewers, 99 cancers in former chewers, 1367 controls		Inverse relationship between the categories of duration of cessation and the risk of buccal mucosa cancer
					Compared with current chewers:	
				Current chewers:		
				391/969	1.0 (ref)	
				Duration of cessation (yr):		
				< 1: 15/146	3.1 (1.4–7.1)	
				2–5: 25/136	1.5 (0.8–2.8)	
				5–10: 14/41	1.1 (0.4–2.5)	
				≥ 10: 45/75	0.7 (0.3–1.5)	
				Per year of cessation	0.98 (0.95–1.02)	

CI, confidence interval; GATS, Global Adult Tobacco Survey; GWAS, genome-wide association study; OR, odds ratio; ref, reference; yr, year or years.

matched on age (5-year band), sex, and site were selected from the hospital. The main exposures of interest were the status of chewing betel quid with added tobacco and duration of cessation. The confounding factors were adjusted for in the logistic regression analysis. There were 391 cancers in current chewers, 99 cancers in former chewers, and 1367 matched controls. A 2% reduction in risk of oral cavity cancer was calculated per year of cessation (OR, 0.98; 95% CI, 0.95–1.02). The risk of oral cavity cancer was lower in former chewers with > 10 years of cessation (OR, 0.7; 95% CI, 0.3–1.5) compared with current chewers. [Neither estimate was statistically significant.]

(b) Studies of OPMDs

(i) Intervention study

See Table 2.27.

The intervention study (Gupta et al., 1986) enrolled tobacco chewers and smokers older than 15 years in three districts in India in 1966: Ernakulam District in Kerala, Srikakulam District in Andhra Pradesh, and Bhavnagar District in Gujarat. This is currently the only study worldwide that was designed to evaluate the effectiveness of an education programme for tobacco users in reducing incidence of OPMDs. The intervention arm received primary prevention in the form of an education programme with professional advice provided by dentists and trained social scientists, as well as radio broadcasts and newspaper articles. Ernakulam District was the only one of the three districts in which chewing betel quid with added tobacco was the main habit in the population; therefore, only results from that district were relevant here. After the 5-year follow-up, the proportion of individuals who had stopped chewing betel quid with added tobacco was higher in the intervention cohort than in the control cohort (9% vs 3%), and the proportion of individuals who reduced the intensity of chewing betel quid with added tobacco was also higher in the intervention cohort than in the control cohort (28% vs 9%). The education programme showed significant effectiveness in reducing the risk of leukoplakia: reported rate ratios were 0.51 [95% CI, 0.28–0.93] in men and 0.19 [95% CI, 0.11–0.30] in women for chewers, and 0.20 [95% CI, 0.13–0.30] in men and 0.19 [95% CI, 0.02–2.12] in women for chewers who also smoked. [Because this study was not randomized, the effectiveness may be affected by unadjusted confounding factors, such as demographic characteristics. Age was not adjusted for, and only stratification by sex was provided. A second unadjusted confounding factor was baseline socioeconomic status, which may have differed between the intervention cohort and the control cohort (recruited 10 years earlier than the intervention cohort). Also, cases in the intervention cohort included individuals who had reduced the intensity of chewing, who had stopped chewing, and those who had continued chewing.]

Murti et al. (1990) reported on the cohorts in Ernakulam District, focusing on the incidence of OSF, with a follow-up period of 10 years. The education programme resulted in a RR reduction of OSF incidence of 62% (RR, 0.38; [95% CI, 0.06–2.24]) in men and 37% (RR, 0.63; [95% CI, 0.25–1.65]) in women for chewers. [The major limitation of this study is the small number of OSF events in chewers.]

Gupta et al. (1992) also reported on a 10-year follow-up of the cohorts, focusing on leukoplakia. The incidence of leukoplakia was reduced significantly, by 37% (RR, 0.63; [95% CI, 0.37–1.06]) in men and by 55% (RR, 0.45; [95% CI, [0.32–0.63]) in women for chewers, and by 63% (RR, 0.37; [95% CI, 0.25–0.54]) in men for chewers who also smoked. In a later report, Gupta et al. (1995) also reported on a 10-year follow-up by comparing the incidence of leukoplakia and of OLP between the "stopped" category (former chewers who stopped chewing ≥ 6 months ago) and "all others" (other categories combined) using the intervention

Table 2.27 Cessation of chewing of areca nut products (including betel quid) with added tobacco and risk of OPMDs – intervention study

Reference Location	Study population, sample selection, response rate	Study design, number of participants, intervention, study period, follow-up time	OPMD end-point	Exposure category Number of cases, intervention/ control	RR 95% CI)	Comments
Gupta et al. (1986, 1992, 1995); Murti et al. (1990) Kerala, India	Tobacco users (chewers and smokers) aged ≥ 15 yr in 3 districts in India Two distinct cohorts were selected in each district through house-to-house surveys to have an interview and a clinical mouth examination at baseline and regular follow-up ≥ 97% follow-up rate for the intervention cohort, and 84–95% follow-up rate for the control cohort	Prospective study with intervention cohort and control cohort Intervention cohort (n = 12 212) and control cohort (n = 6075) in Ernakulam District Recruitment in 1976–1985 for intervention cohort, and in 1966–1977 for control cohort 10-yr follow-up Intervention was an education programme through professional advice (dentist and social scientist) and social media Higher stoppage of chewing (15.1% vs 2.3% for men; 18.4% vs 7.8% for women) and of mixed chewing and smoking (3.8% vs 2.0% for men;13.2% vs 3.8% for women)	Incidence of leukoplakia	Chewing only: Men: [32/25] Women: [60/72] Mixed chewing and smoking: Men: [44/68] Women:	 0.63 [(0.37–1.06)] 0.45 [(0.32–0.63)] 0.37 [(0.25–0.54)] 0.52 [(0.01–29.85)]	10 yr of follow-up of the main study focusing on Ernakulam District in Kerala conducted by Gupta et al. (1986) Chewing betel quid with added tobacco was the main habit in the population in Ernakulam District in Kerala Results are crude incidence stratified by sex, not adjusted for age. Only 5-year age-adjusted incidence was reported for total tobacco use (rather than different categories) Baseline socioeconomic status may have differed between the intervention cohort and the control cohort (10 yr earlier than the intervention cohort)
	81–93% follow-up rate for the intervention cohort, and 71–75% follow-up rate for the control cohort	Intervention cohort (n = 6341 chewers) and control cohort (n = 3809 chewers)	Incidence of OSF	Men: 2/3 Women: 9/8	0.38 (0.06–2.24) 0.63 (0.25–1.65)	Murti et al. (1990). Analysis restricted to chewers only. Events of OSF are too rare to have sufficient statistical power

Table 2.27 (continued)

Reference Location	Study population, sample selection, response rate	Study design, number of participants, intervention, study period, follow-up time	OPMD end-point	Exposure category Number of cases, intervention/ control	RR 95% CI)	Comments
Gupta et al. (1986, 1992, 1995); Murti et al. (1990) (cont.)			Incidence of OLP	"stopped"/"all others":		Gupta et al. (1995). Part of the main study focusing on Ernakulam District in Kerala conducted by Gupta et al. (1986) with 10 yr of follow-up Only chewers in the intervention cohort were considered. The "stopped" category included former chewers who stopped chewing ≥ 6 months ago
				Men: 1/30	0.02 [(0.00–0.13)]	
				Women: 18/90	1.29 [(0.78–2.14)]	
			Incidence of leukoplakia	"stopped"/"all others":		
				Men: 4/33	0.81 [(0.29–2.28])]	
				Women: 5/52	0.30 [(0.12–0.75)]	

CI, confidence interval; OLP, oral lichen planus; OPMDs, oral potentially malignant disorders; OSF, oral submucous fibrosis; RR, relative risk; vs, versus.

cohort only. Cessation of chewing betel quid with added tobacco significantly reduced the incidence of leukoplakia, by 19% (RR, 0.81; 95% CI, 0.29–2.28) in men and 70% (RR, 0.30; 95% CI, 25–88%) in women for former chewers, whereas there was no effect of chewing cessation in reducing the incidence of OLP. [There was a lack of statistical power for OLP incidence because of too few OLP events.]

(ii) Observational studies

See Table 2.28.

In a case–control study in Sri Lanka, chewers of betel quid were categorized as daily, occasional, and former chewers (Amarasinghe et al., 2010a). Two thirds of the chewers used betel quid with added tobacco: 82% among the cases and 32% among the controls. The incidence of leukoplakia, OSF, and OLP were used as outcomes. For daily chewers, the risk of OPMDs increased 10-fold (OR, 10.6; 95% CI, 3.6–31.0) compared with never-chewers. For former chewers, the incidence of OPMDs increased 2-fold (OR, 2.4; 95% CI, 0.4–14.5), similarly to occasional chewers (OR, 2.0; 95% CI, 0.4–9.4). The Working Group calculated a lower, non-significant RR of OPMDs for former chewers compared with current chewers [OR, 0.23; 95% CI, 0.03–1.79]. [The Working Group noted two major limitations of this study: (i) the results were for a mixture of chewers of betel quid with and without tobacco, and (ii) no information on the time since quitting was available.]

A case–control study in northern Thailand (Worakhajit et al., 2021) was conducted in 2019–2021 to investigate the relationship between betel quid chewing and risk of OPMDs. This study enrolled 562 cases (people with identified OPMD) and 886 controls (people without OPMD). Using those with < 5 years of quitting as the reference group, those with ≥5 years of quitting had a slightly lower, but not statistically significantly so, RR of OPMDs (OR, 0.94; 95% CI, 0.22–3.92). [Not enough information on the number of cases by duration of quitting chewing was available to judge the strength of the results.]

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

Published evidence on the impact of quitting chewing areca nut products without tobacco on the risk of oral cancer consisted of four case–control studies with data in former chewers and current chewers compared with never-chewers (Table 2.29). In addition, a recent meta-analysis of 14 case–control studies provided estimates of oral cancer incidence after cessation of chewing areca nut without tobacco (Gupta et al., 2022). To complement the evidence available from the published literature, the Working Group undertook primary analyses from unpublished data from three large cohort studies and one case–control study providing information on incidence of oral cancer (Table 2.30) in relation to time since chewing cessation and age at quitting.

Published evidence on the impact of quitting chewing areca nut products without tobacco on the risk of OPMDs consisted of three case–control studies and two cross-sectional studies (Table 2.31). Similarly, the Working Group undertook primary analyses from unpublished data from three large cohort studies and one case–control study providing information on incidence of OPMDs in relation to time since chewing cessation and age at quitting (Table 2.32).

(a) Studies on oral cancer

(i) Evidence from the published literature

See Table 2.29.

Ko et al. (1995) reported on a hospital-based matched case–control study that assessed the independent effects of use of betel quid without tobacco, cigarette smoking, and alcohol consumption on oral cancer, as well as the synergistic effect of these behaviours. [Information on time since chewing cessation was lacking.] Current chewers were defined as those chewing ≥ 1 quid daily for

Table 2.28 Cessation of chewing of areca nut products (including betel quid) with added tobacco and risk of OPMDs – observational studies

Reference Location	Study population, sample selection, response rate	Study design, number of participants, study period, follow-up time	OPMDs end-point	Exposure category Cases/controls	OR (95% CI)	Interpretation/comments
Amarasinghe et al. (2010a) Sri Lanka	People aged ≥ 30 yr in Sabaragamuwa Province	Two-phase designed study Phase 1: Cross-sectional community survey with a house-to-house method to screen for OPMDs for 1029 people randomly selected by a multistage, stratified, clustered sampling technique Phase 2: Nested case–control study with a case group (n = 101) who were identified as having OPMDs (i.e. leukoplakia, erythroplakia, OSF, OLP) and a control group (n = 728) without OPMDs from Phase 1 Adjusted for sex, age, education level, occupation, BMI, tobacco smoking, and alcohol consumption	Leukoplakia, OSF, and OLP combined	Non-chewers: 4/277 Former chewers: 2/36 Occasional chewers: 3/83 Daily chewers: 92/332	Compared with non-chewers: 1.0 (ref) 2.4 (0.4–14.5) 2.0 (0.4–9.4) 10.6 (3.6–31.0)	Study based on a screening programme for OPMDs. Results were for a mixture of chewers with and without combined use of tobacco
Worakhajit et al. (2021) Thailand	People aged ≥ 40 yr in north-eastern Thailand	Case–control study design, conducted in 2019–2021 Community-based screening at the village level for 392 396 people with an oral cancer risk screening questionnaire administered by health-care volunteers 1448 people aged ≥ 40 yr were enrolled, including 562 with identified OPMD as the case group and 886 without OPMD as the control group	OPMDs	Duration of cessation (yr): < 5 ≥ 5	 1.00 (ref) 0.94 (0.22–3.92)	

BMI, body mass index; CI, confidence interval; OLP, oral lichen planus; OPMDs, oral potentially malignant disorders; OSF, oral submucous fibrosis; ref, reference; yr, year or years.

Table 2.29 Cessation of chewing of areca nut products (including betel quid) without tobacco and risk of oral cancer – case–control studies

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Ko et al. (1995) Taiwan (China)	Patients at a medical centre in Kaohsiung, southern Taiwan (China)	Hospital-based matched case–control study in 1992–1993 Case group: 107 patients with oral cancer with diagnosis confirmed by histopathology Control group: 200 age- and sex-matched controls consisting of non-carcinoma patients treated during the same period Chewers chewing ≥ 1 quid daily for ≥ 1 yr were defined as current chewers Confounding factors adjusted for in the multivariate analysis included education level, occupation, alcohol consumption, cigarette smoking, residence, marriage status, religion, ethnicity, and dietary habits	Oral cancer	Non-chewers: 31/153 Current chewers: 71/42 Former chewers: 5/5	1.0 (ref) 6.9 (3.1–15.2) 4.7 (0.9–22.7)	Information on duration of cessation was lacking Insufficient statistical power because of too few former chewers
Thomas et al. (2007) Papua New Guinea	Cases were patients with oral cancer hospitalized in 6 hospitals, and controls were those related to someone admitted to the same hospitals	Case–control study in 1985–1987 Case group: 143 patients with first diagnosis of clinically apparent oral squamous cell carcinoma Control group: 477 controls were those admitted or related to someone admitted to the same hospital Frequency-matching was performed on age, sex, and geographical location Confounding factors in the multivariate analysis included age, sex, province, residence, income, education level, and frequency of smoking	Oral cancer	Non-chewers: 2/9 Current daily chewers: 124/375 Current occasional chewers: 8/37 Former chewers: 9/56 Ever-chewers: 141/468	1.0 (ref) 1.29 (0.25–6.51) 0.98 (0.17–5.74) 0.57 (0.10–3.28) 1.10 (0.22–5.51)	This study had an extremely high prevalence of ever betel quid chewing

Table 2.29 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Lee et al. (2012) Taiwan (China)	Patients with carcinoma on the upper aerodigestive tract to gastrointestinal tract at 2 medical centres in Kaohsiung, southern Taiwan (China)	Multicentre case–control study in 2001–2007 Case group: Of the enrolled patients with cancer, 810 with oral cancer and 231 with pharyngeal cancer Control group: 2250 age- and sex-matched controls selected from the same hospital during the same period. Confounding factors in the multivariate analysis included sex, age, ethnicity, education level, drink-years of alcohol consumption, pack-years of cigarette smoking, and consumption of vegetables and fruits	Oral cancer and pharyngeal cancer	Oral cancer: Non-chewers: 136/2002 Current chewers: 450/160 Former chewers: 224/88 Pharyngeal cancer: Non-chewers: 55/2002 Current chewers: 147/160 Former chewers: 29/88	 1.0 (ref) 16.7 (12.1–23.0) 15.3 (10.6–22.0) 1.0 (ref) 9.3 (6.1–14.2) 3.5 (2.0–6.1)	Information on duration of cessation was lacking The possibility of reverse causation is a concern The pharyngeal cancer group included oropharyngeal and hypopharyngeal cancers

Table 2.29 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Wu et al. (2016) Taiwan (China)	Male patients at one medical centre in Tainan City	Hospital-based case–control study in 2010–2014 Case group: 487 male patients aged ≥ 20 yr with a new diagnosis of head and neck cancer. Of them, 313 had oral cancer and 119 had oro-hypopharyngeal cancer Control group: 617 male controls matched to the cases on age and from the same department as the cases but undergoing surgery for non-cancerous disease not related to alcohol consumption, betel quid use, or smoking, and without history of cancer diagnosis Confounding factors in the multivariate analysis included age, education level, cigarette smoking (pack-year categories), and alcohol consumption (frequency)	Oral cancer and pharyngeal cancer	Oral cancer: Non-chewers: 67/446 Current chewers: 113/66 Former chewers: 133/105 Duration of cessation (yr): Current chewers: 113/66 0.0–9.9: 67/59 10.0–19.9: 48/23 ≥ 20: 15/25 Per year of cessation Oro- and hypo-pharyngeal cancer: Non-chewers: 31/446 Current chewers: 45/66 Former chewers: 43/105 Duration of cessation (yr): Current chewers: 45/66 0.0–9.9: 28/56 10.0–19.9: 9/23 ≥ 20: 6/25 Per year of cessation	 1.0 (ref) 8.05 (5.10–12.71) 6.43 (4.25–9.73) 1.0 (ref) 0.72 (0.44–1.17) 1.42 (0.77–2.61) 0.34 (0.16–0.73) 0.976 (0.952–1.001) 1.0 (ref) 4.80 (2.57–8.99) 2.87 (1.61–5.13) 1.0 (ref) 0.74 (0.39–1.42) 0.63 (0.24–1.61) 0.26 (0.09–0.78) 0.967 (0.933–1.001)	Control group selected from the otolaryngology and stomatology departments may not be representative of the general population in their risk of oro- and hypopharyngeal cancer

Table 2.29 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Meta-analysis						
Gupta et al. (2022)	4 case–control studies	Tobacco smoking was adjusted for in all the studies, and alcohol consumption was adjusted for in all studies except one	Oral cancer	Non-chewers Former chewers Current chewers	1.0 (ref) 5.61 (2.24–14.04) 7.89 (3.90–15.98)	Most studies included only or predominantly male participants. The duration of cessation for defining former chewers was > 1 yr in one study and > 6 months in one study; two studies did not mention this aspect

CI, confidence interval; OR, odds ratio; ref, reference; yr, year or years.

≥ 1 year. Compared with never-chewers, the OR for the risk of oral cancer in former chewers was lower (4.7; 95% CI, 0.9–22.7) than that in current chewers (6.9; 95% CI, 3.1–15.2). [The Working Group calculated that the OR for oral cancer in former chewers versus current chewers was 0.68 (95% CI, 0.12–3.79). The Working Group noted three limitations: (i) selecting controls from the ophthalmology and physical check-up departments may have a tendency to enrol few chewers, and this selection bias may lead to overestimation of the risk of oral cancer for current chewers and former chewers; (ii) many confounders may have required adjustment; and (iii) few former chewers led to insufficient statistical power.]

In a hospital-based case–control study in Papua New Guinea (Thomas et al., 2007), daily chewing of betel quid resulted in the highest RR of oral cancer (OR, 1.29; 95% CI, 0.25–6.51) compared with occasional chewing (OR, 0.98; 95% CI, 0.17–5.74) and with former chewing (OR, 0.57; 95% CI, 0.10–3.28). [The Working Group calculated an OR for oral cancer in former chewers compared with current chewers of 0.44 (95% CI, 0.04–4.73). There were very few never-chewers (the reference group): 1.4% (2 of 143) in the case group and 1.9% (9 of 477) in the control group. In addition, because controls were selected from patients who had a diagnosis unrelated to oral cancer but potentially related to other betel quid-related diseases, this may lead to underestimation of the risk of oral cancer.]

A multicentre case–control study was conducted in Taiwan (China) to assess the effect of consumption of betel quid without tobacco on the risk of aerodigestive tract cancers at different anatomical sites, with adjustment for age, ethnicity and education level (Lee et al., 2012). Compared with never-chewers, the OR for the risk of oral cancer in former chewers was 15.3 (95% CI, 10.6–22.0) and in current chewers was 16.7 (95% CI, 12.1–23.0). For pharyngeal cancer (including oropharyngeal and hypopharyngeal cancers), the estimated ORs were 3.5 (95% CI, 2.0–6.1) for former chewers and 9.3 (95% CI, 6.1–14.2) for current chewers, compared with never-chewers. [The Working Group calculated that the OR for former chewers versus current chewers was 0.92 (95% CI, 0.61–1.39) for oral cancer and 0.38 (95% CI, 0.20–0.70) for pharyngeal cancer. Because this is a hospital-based case–control study with study participants recruited from patients, the possibility that patients quit chewing after knowing the diagnosis of oral cancer cannot be ruled out.]

In another hospital-based case–control study to investigate the association between betel quid chewing and the risk of HNC at different sites (Wu et al., 2016), 487 male cancer patients and 617 age- and sex-matched controls were enrolled in 2010–2014. Information obtained by questionnaire included data for the three categories of betel quid chewers – current, former (stopped > 6 months ago), and never. Time since cessation for the former chewers was expressed as a continuous variable in years or an ordinal variable in 10-year categories (0–9.9 years, 10–19.9 years, and ≥ 20 years). For oral cancer, the OR for former chewers (6.43; 95% CI, 4.25–9.73) was lower than that for current chewers (8.05; 95% CI, 5.10–12.71) compared with never-chewers. [This resulted in a 20% reduction in RR of oral cancer (OR, 0.80; 95% CI, 0.51–1.24), calculated by the Working Group.] A significant trend with duration of cessation was noted, with a RR reduction that was significant for ≥ 20 years of betel quid cessation for oral cancer (OR, 0.34; 95% CI, 0.16–0.73) and for pharyngeal cancer (including oropharyngeal and hypopharyngeal cancers) (OR, 0.26; 95% CI, 0.09–0.78), but the risk was still greater than that in never-chewers. Each year of cessation of betel quid chewing was associated with a 2.4% RR reduction (OR, 0.976; 95% CI, 0.952–1.001) for oral cancer and a 3.3% RR reduction (OR, 0.967; 95% CI, 0.933–1.001) for pharyngeal cancer. [The strength of this study is to address a non-linear dose–response relationship between the amount and the duration

of chewing and duration of cessation associated with HNC including oral cancer and pharyngeal cancer by using a spline regression method. The study has three main limitations. First, because the control group was selected from the otolaryngology and stomatology departments, the source population for the control group may be different from that for the case group; thus, selection bias cannot be ruled out. Second, recall bias in the retrieval of information on chewing behaviour cannot be avoided. Third, the findings may have been affected by other unadjusted confounding factors, such as occupation, although age, education level, alcohol consumption, and smoking had been controlled for.]

The recently published meta-analysis (Gupta et al., 2022) combined data on chewing areca nut without tobacco from the four case–control studies described above. The risk estimate for oral cancer in former chewers (meta-RR, 5.61; 95% CI, 2.24–14.04) was lower than that in current chewers (7.89; 95% CI, 3.90–15.98) compared with never-chewers. [The analysis could not report on duration of cessation, because information on duration of cessation is lacking for most of the published studies.]

(ii) Evidence from primary data analyses

See Table 2.30.

Data on duration of cessation and age at quitting from three prospective cohort studies and one case–control study were available for primary analysis by the Working Group. The three cohort studies were derived from three community-based integrated screening programmes for common cancer types (including oral cancer) in three cities in Taiwan (China): Keelung, Changhua, and Tainan, representing the northern, central, and southern parts of the country, where areca nut is consumed unripe and without tobacco. Information on demographic characteristics, education level, duration and frequency of smoking, alcohol consumption, age at quitting, and duration of cessation was collected at entry. The study design and implementation were very similar across studies. The three cohorts were followed up over time to ascertain OPMDs and oral cancers. The case–control study was derived from one of the studies in Taiwan (China) on OPMDs and oral cancer in collaboration with the United States National Cancer Institute.

Results from three cohort studies showed statistically significant trends of reduced risk of oral cancer with an increase in time since quitting ($P_{trend} < 0.01$). The most significant reduction was noted for ≥ 20 years of quitting in Keelung and Tainan and for ≥ 10 years of quitting in Changhua. The RR reductions per year of cessation were all statistically significant: 6.7% (95% CI, 1.9–11.2%) in Keelung, 2.6% (95% CI, 0.8–4.4%) in Changhua, and 2.3% (95% CI, 0.1–4.5%) in Tainan. With respect to age at quitting, the younger the age at quitting, the lower the risk of oral cancer, as shown by the significant increasing trends per year of advancing age at quitting, 13% in Keelung and 3% in Changhua, and a non-significant 1% in Tainan. Notably, the results from the two cohort studies in the areas where the prevalence of areca nut chewing is high – Tainan (in the southern part) and Changhua (in the central part) – showed that quitting areca nut chewing before age 40 years led to a significant reduction in the risk of oral cancer. [For each cohort, a time-dependent Cox regression model was used to consider dynamic change of duration of quitting during follow-up. Relevant confounding factors have been well controlled to avoid recall bias.]

For the case–control study, analyses restricted to ever-chewers resulted in a statistically significant relative reduction in risk per year of cessation, estimated as 7% (95% CI, 5–9%).

[The Working Group also performed a meta-analysis that combined the information on the three user categories from the observational studies presented in Table 2.29 and Table 2.30. Former chewers had a statistically significantly

Table 2.30 Cessation of chewing of areca nut products (including betel quid) without tobacco and risk of oral cancer – primary data analyses performed by the Working Group

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Keelung, Taiwan (China)	Community-based integrated screening study for residents aged 30 yr in Keelung, northern Taiwan (China) (KCIS programme) 121 714 people were enrolled, and 372 oral cancers were ascertained during follow-up	Prospective cohort study People attending the KCIS programme in 1999–2018. This cohort was followed up to ascertain incident oral cancer by linking with the national cancer registry in Taiwan (China) until 31 December 2018 A time-dependent Cox regression model was used to consider dynamic change of duration of cessation during follow-up Confounding factors adjusted for were age, sex, education level, smoking (never, < 10, 10–19.9, 20–29.9, and ≥ 30 pack-years), and alcohol consumption (never, ever, current)	Oral cancer	Never-chewers: 245/110 555	1.00 (ref)	This is a large-scale community-based screening programme with long-term follow-up for the outcome of incident oral cancer and information on betel quid chewing in Keelung, where the prevalence of betel quid chewing is lower than in other parts of Taiwan (China)
				Former chewers: 57/4757	2.40 (1.68–3.42)	
				Current chewers: 64/4034	3.02 (2.16–4.22)	
				Per year of cessation of betel quid chewing	0.933 (0.888–0.981)	
				Duration of cessation (yr):		
				Current chewers	1.00 (ref)	
				< 10: 39/2410	1.78 (1.09–2.90)	
				10–20: 5/973	0.75 (0.43–1.31)	
				≥ 20: 1/465	0.16 (0.04–0.67)	
				Never-chewers	0.32 (0.23–0.45)	
					P_{trend} < 0.0001	
				Per year of age at quitting	1.13 (1.05–1.22)	
				Age at quitting (yr):		
				Current chewers	1.00 (ref)	
				< 40: 18/2364	0.72 (0.42–1.22)	
				40–49: 14/986	0.82 (0.43–1.75)	
				≥ 50: 13/497	1.48 (0.80–2.76)	
				Never-chewers	0.34 (0.24–0.47)	

Table 2.30 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Changhua, Taiwan (China)	Community-based integrated screening study for residents aged 30 yr in Changhua, central Taiwan (China) (CHCIS programme) 92 246 people were enrolled in the CHCIS cohort, and 311 oral cancers were ascertained during follow-up	Prospective cohort study People enrolled in 2005–2014 were used to assess the impact of cessation of betel quid chewing on risk of oral cancer. This cohort was followed up to ascertain incident oral cancer by linking with the national cancer registry until 31 December 2018 Exposures include current chewers, former chewers, and never-chewers; time in years since cessation measured in continuous years Confounding factors adjusted for in the Cox regression model included age, sex, education level, smoking (never, < 10, 10–19.9, 20–29.9, and ≥ 30 pack-years), and alcohol consumption (never, seldom, 1–2 per wk, 3–5 per wk, and daily drinkers) A time-dependent Cox regression model was used to consider dynamic change of duration of cessation during follow-up	Oral cancer	Never-chewers: 109/83 537 Former chewers: 119/5149 Current chewers: 82/2921 Per year of cessation of betel quid chewing Duration of cessation (yr): Current chewers < 10: 61/1992 10–20: 28/1617 ≥ 20: 17/1119 Never-chewers Per year of age at quitting Age at quitting (yr): Current chewers < 40: 25/1793 40–49: 37/1590 ≥ 50: 53/1673 Never-chewers 	1.00 (ref) 3.86 (2.73–5.46) 4.77 (3.31–6.89) 0.974 (0.956–0.992) 1.00 (ref) 1.09 (0.75–1.59) 0.65 (0.44–0.97) 0.59 (0.37–0.93) 0.22 (0.15–0.31) P_{trend} = 0.0142 1.03 (1.00–1.05) 1.00 (ref) 0.64 (0.40–1.00) 0.87 (0.58–1.29) 0.84 (0.58–1.21) 0.21 (0.14–0.30) P_{trend} = 0.3255	This is a large-scale community-based screening programme, in an area with a high prevalence of betel quid chewing

Table 2.30 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Tainan, Taiwan (China)	Community-based integrated screening study for residents aged 40 yr in southern Taiwan (China) (CIS programme) 125 977 people were enrolled in the CIS cohort, and 417 oral cancers were ascertained during follow-up	Prospective cohort study People enrolled in 2004–2009 were used to assess the impact of cessation of betel quid chewing on risk of oral cancer. This cohort was followed up to ascertain incident oral cancer by linking with the national cancer registry until 31 December 2018 Exposures include current chewers, former chewers, and never-chewers; time in years since cessation measured in continuous years Confounding factors adjusted for in the Cox regression model included age, sex, education level, smoking (never, < 10, 10–19.9, 20–29.9, and ≥ 30 pack-years), and alcohol consumption (never, seldom, 1–2 per wk, 3–5 per wk, and daily drinkers)	Oral cancer	Never-chewers: 232/116 869	1.00 (ref)	This is a large-scale community-based screening programme in an area with a higher prevalence of betel quid chewing
				Former chewers: 85/4838	3.20 (2.40–4.29)	
				Current chewers: 99/3806	4.34 (3.27–5.77)	
				Per year of cessation of betel quid chewing	0.977 (0.955–0.999)	
				Duration of cessation (yr):		
				Current chewers:	1.00 (ref)	
				< 10: 48/2263	0.88 (0.58–1.36)	
				10–20: 23/1316	0.83 (0.57–1.12)	
				≥ 20: 6/797	0.40 (0.22–0.75)	
				Never-chewers	0.22 (0.17–0.30)	
					P_{trend} = 0.0068	
				Per year of age at quitting	1.01 (0.99–1.04)	
				Age at quitting (yr):		
				Current chewers:	1.00 (ref)	
				< 40: 17/1598	0.51 (0.30–0.86)	
				40–59: 55/2741	0.80 (0.58–1.12)	
				≥ 60: 12/474	0.91 (0.49–1.69)	
				Never-chewers	0.22 (0.18–0.31)	
					P_{trend} = 0.2362	

Table 2.30 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; US NCI Taiwan (China) OPMD and oral cancer study	Study conducted in 4 hospitals in Taiwan (China): NTUH Taipei, CMUH Taichung, CGMH-Linkou, and CGMH-Kaohsiung	Hospital-based case–control study, with recruitment of controls, patients with oral cancer or OPMDs (primarily leukoplakia and some OSF) Controls were frequency-matched to case group (OPMDs and cancer) on age (5-year groups), sex, study site, ever-smoking, and ever-chewing Participants recruited in 2013–2021; recruitment of controls and OPMD cases is continuing This analysis (conducted in November 2021) included 388 controls and 549 cancer cases. Analyses were restricted to ever-chewers. Multinomial logistic regression models (cancer vs control) were adjusted for age, sex, education level (≤ vs > high school), smoking duration and intensity, alcohol consumption (drinks per week), and chewing duration and intensity. Primary analyses based on duration of cessation (as a continuous, linear variable and a categorical variable: quit ≤ 2 yr, 2–5 yr, 5–10 yr, 10–15 yr, and ≥ 15 yr)	Oral cancer	Per year of cessation of betel quid chewing Duration of cessation (yr): Current chewers: 241/158 < 2: 43/12 2–5: 63/32 5–10: 86/64 10–15: 45/35 ≥ 15: 72/87	0.93 (0.91–0.95) P_{trend} < 0.001 1.00 (ref) 2.08 (1.06–4.09) 1.09 (0.67–1.76) 0.67 (0.44–1.01) 0.49 (0.28–0.84) 0.21 (0.12–0.37) P_{trend} < 0.001	

CGMH, Chang Gung Memorial Hospital; CHCIS, Changhua Community-Based Integrated Screening; CI, confidence interval; CIS, Community-Based Integrated Screening; CMUH, China Medical University Hospital; KCIS, Keelung Community-Based Integrated Screening; NTUH, National Taiwan University Hospital; OPMDs, oral potentially malignant disorders; OSF, oral submucous fibrosis; ref, reference; US NCI, United States National Cancer Institute; vs, versus; wk, week; yr, years or years.

lower risk of oral cancer (OR, 0.79; 95% CI, 0.68–0.94) compared with current chewers.]

(b) Studies on OPMDs

(i) Evidence from the published literature

See Table 2.31.

Shiu et al. (2000) established a leukoplakia cohort, which consisted of 435 patients diagnosed at one medical centre in Taiwan (China) in 1988–1998. To assess the role of betel quid chewing, tobacco smoking, and alcohol consumption on the risk of leukoplakia, the case group consisted of 100 patients with leukoplakia randomly selected from the cohort, and the control group consisted of 100 patients with periodontal disease diagnosed in the same period and at the same medical centre, matched on age, sex, and date of diagnosis. After adjustment for smoking and alcohol consumption, with never-chewers as the reference group, the OR for leukoplakia in former chewers (2.38; 95% CI, 0.34–16.75) was much lower than that in current chewers (17.43; 95% CI, 1.94–156.27). [The Working Group noted the extremely wide CIs. The Working Group estimated the OR for former chewers as 0.14 (95% CI, 0.007–2.73) compared with current chewers. This study enrolled the control group from the same medical centre in the same period as the case group to ensure that both groups were from the same catchment area. Information was collected via telephone survey for both groups, instead of using medical chart review; this can avoid differential misclassification bias because in the medical charts, information on betel quid chewing, tobacco smoking, and alcohol consumption was more likely to be queried at diagnosis of leukoplakia than at diagnosis of periodontal disease. However, the use of a control group derived from patients diagnosed with periodontal disease may be a concern.]

Lee et al. (2003) reported on a hospital-based case–control study on OPMDs, including leukoplakia and OSF, conducted in 1994–1995 in Taiwan (China). Information on betel quid chewing, smoking, and alcohol consumption was collected via a structured questionnaire through in-person interview. A total of 219 cases (leukoplakia or OSF) and 876 controls were included. The OR for leukoplakia in former chewers compared with never-chewers (7.1; 95% CI, 2.3–21.5) was significantly lower than that in current chewers (22.3; 95% CI, 11.3–43.8). Similar findings were reported for OSF. [The Working Group calculated the ORs for former chewers compared with current chewers as 0.32 (95% CI, 0.09–1.10) for leukoplakia and 0.30 (95% CI, 0.06–1.58) for OSF. The fact that oral examination was not performed in the control group may have introduced bias. It is not clear whether the estimates were adjusted for tobacco smoking and alcohol consumption.]

A case–control study in Papua New Guinea (Thomas et al., 2008) reported an OR for former chewers that was lower than that for occasional chewers and daily chewers compared with never-chewers. [The Working Group noted that a limitation of this study was the extremely high prevalence of ever betel quid chewing; the proportion of never-chewers was only 0.5% (1 of 197) in the case group and 6.9% (89 of 1282) in the control group.]

A cross-sectional community screening study for oral cancer conducted in four Indigenous communities in Taiwan (China) in people aged ≥ 35 years in 2005 reported on the association between betel quid chewing and leukoplakia and OSF (Yang et al., 2010). The ORs for former chewers were lower than those for current chewers for leukoplakia in women (OR, 7.8; 95% CI, 3.8–16.0 vs 15.6; 95% CI, 8.3–29.4), for OSF in men (OR, 13.5; 95% CI, 3.8–48.7 vs 22.9; 95% CI, 7.3–71.7), and for OSF in women (OR, 9.3; 95% CI, 3.3–26.0 vs 13.0; 95% CI, 5.2–32.6). In contrast, for leukoplakia in men, ORs for former chewers were similar to those for current chewers (OR, 6.7; 95% CI, 3.2–13.9 vs 6.6; 95% CI, 3.5–12.3). [The ORs calculated for former chewers compared with current chewers were 0.50 (95% CI, 0.20–1.22) for leukoplakia in women, 0.59 (95% CI, 0.12–2.96)

Table 2.31 Cessation of chewing of areca nut products (including betel quid) without tobacco and risk of OPMDs – observational studies

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	OPMDs end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Case–control studies						
Shiu et al. (2000) Taiwan (China)	Patients with leukoplakia in a medical centre in Taipei and their matched controls from patients with periodontal disease	Case–control study Case group: 100 cases randomly selected from a cohort of 435 patients with leukoplakia diagnosed in 1988–1998 Control group: 100 controls with periodontal disease diagnosed in the same period and medical centre, matched to cases on age at diagnosis (± 3 yr), sex, and date of diagnosis Confounding factors in the multivariate analysis included cigarette smoking and alcohol consumption	Leukoplakia	Leukoplakia: Never-chewers Current chewers Former chewers	 1.0 (ref) 17.43 (1.94–156.27) 2.38 (0.34–16.75)	All cases and controls were interviewed via telephone survey, to avoid information bias between the 2 groups
Lee et al. (2003) Taiwan (China)	Patients at a medical centre in Kaohsiung and their sex- and age-matched controls from residents in the Greater Kaohsiung area	Matched case–control study conducted in 1994–1995 Case group: 219 patients with leukoplakia (n = 125) or OSF (n = 94) newly diagnosed and histologically confirmed Control group: 876 sex- and age-matched controls from 1864 household units Confounding factors in the multivariate analysis included education level and occupation	Leukoplakia and OSF	Leukoplakia: Never-chewers: 28/390 Current chewers: 91/88 Former chewers: 6/22 OSF: Never-chewers: 11/302 Current chewers: 78/62 Former chewers: 5/12	 1.0 (ref) 22.3 (11.3–43.8) 7.1 (2.3–21.5) 1.0 (ref) 40.7 (16.0–103.7) 12.1 (2.8–51.9)	People in the control group did not receive an oral inspection. This might result in a biased estimate Data on duration of cessation for former chewers were not available Not clear whether adjusted for tobacco smoking and alcohol consumption

Table 2.31 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	OPMDs end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Thomas et al. (2008) Papua New Guinea	People aged ≥ 18 yr from 2 census divisions (East Coast Kara Nalik and South Lavongai) of New Ireland Province	A case–control study nested in a cross-sectional study in 1992 Case group: 197 patients with identified leukoplakia Control group: 1282 controls ascertained in the cross-sectional study with no evidence of oral squamous cell carcinoma, leukoplakia, leukoedema, erythroplakia, or commissural ulceration Confounding factors in the multivariate analysis included age, sex, census division, and smoking	Leukoplakia	Never-chewers: 1/89 Former chewers: 7/149 Occasional chewers: 26/256 Daily chewers: 163/788	1.0 (ref) 1.4 (0.2–13.0) 6.1 (0.8–48.7) 5.0 (0.6–39.1)	Extremely high prevalence of ever betel quid chewing. The proportion of never-chewers was 0.5% (1 of 197) in the case group and 6.9% (89 of 1282) in the control group
Cross-sectional studies						
Yang et al. (2010) Taiwan (China)	Community oral cancer screening programme in 4 Indigenous communities and 1 remote island in Pingtung County	Cross-sectional study in 2005 Participants aged ≥ 35 yr, including 494 Indigenous men and 892 Indigenous women The proportion of ever-chewers was 11.0%, and the proportion of current chewers was 24.4%. The corresponding proportions were 13.4% and 29.4% for men and 14.6% and 35.2% for women Confounding factors in the multivariate analysis included sex, age, tobacco smoking, and alcohol consumption	Leukoplakia and OSF	Leukoplakia: 224 Men: Non-chewers Current chewers Former chewers Women: Non-chewers Current chewers Former chewers OSF: 89 Men: Non-chewers Current chewers Former chewers Women: Non-chewers Current chewers Former chewers	 1.0 (ref) 6.57 (3.51–12.28) 6.70 (3.21–13.99) 1.0 (ref) 15.63 (8.31–29.39) 7.78 (3.77–16.04) 1.0 (ref) 22.86 (7.28–71.73) 13.53 (3.76–48.65) 1.0 (ref) 13.03 (5.21–32.62) 9.32 (3.34–26.00)	Information on duration of cessation was lacking

Table 2.31 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	OPMDs end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Yen et al. (2011) Taiwan (China)	Community-based integrated screening programme in Keelung City	Cross-sectional study in 2003–2008 79 940 participants aged ≥ 20 yr; 502 OPMDs Confounding factors in the multivariate analysis included metabolic syndrome, age, sex, education level, tobacco smoking, and alcohol consumption	OPMDs	OPMD cases (% lesion):		Estimates provided in the publication were crude ORs
				Non-chewers: 256 (3.4%)	1.0 (ref)	
				Current chewers: 180 (80%)	25.25 (20.77–30.69)	
				Former chewers: 64 (25%)	7.43 (5.64–9.80)	
				Adjusted		
				Non-chewers	1.0 (ref)	
				Current chewers	[9.2 (7.2–11.8)]	
				Former chewers	[2.8 (2.0–3.8)]	
				Former vs current	[0.30 (0.22–0.43)]	

CHCIS, Changhua Community-Based Integrated Screening; CI, confidence interval; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; ref, reference; vs, versus; yr, year or years.

for OSF in men, and 0.72 (95% CI, 0.20–2.58) for OSF in women. This cross-sectional study did not provide information on duration of cessation, and there is a possibility of reverse causation, which may explain the results obtained in men.]

The cross-sectional study of Yen et al. (2011) reported data on the risk of OPMDs in the Keelung Community-Based Integrated Screening (KCIS) programme in Taiwan (China) in 2003–2008 in former and current chewers of betel quid aged ≥ 20 years. [The Working Group recalculated adjusted ORs: the estimate for former chewers versus never-chewers (2.8; 95% CI, 2.0–3.8) was lower than that for current chewers versus never-chewers (9.2; 95% CI, 7.2–11.8), giving an OR for former chewers versus current chewers of 0.30 (95% CI, 0.22–0.43). When former chewers were stratified by duration of quitting, an inverse dose–response relationship was noted between time since quitting and the risk of OPMDs, with ORs of 0.39 (95% CI, 0.27–0.56) for < 10 years of quitting, 0.22 (95% CI, 0.10–0.44) for 10–19 years of quitting, and 0.19 (95% CI, 0.06–0.60) for ≥ 20 years of quitting. This large-scale community-based screening programme provided stable estimates. This was an integrated screening programme that targeted multiple neoplasms and chronic diseases, for which information on general health was queried, instead of focusing on oral health; therefore, participants were less likely to avoid answering questions about smoking and betel quid chewing. In addition, all disease status data were measured or collected upon screening activity. Information bias on both independent covariates and disease outcomes could be ruled out.]

(ii) Evidence from primary data analyses

See Table 2.32.

Data on duration of cessation and age at quitting from three prospective cohort studies and one case–control study were available for primary analysis by the Working Group. The same three cohorts (in Keelung, Changhua, and Tainan) and the case–control study in Taiwan (China) are described above for oral cancer (see Section 2.3.5(a)(ii)).

The three cohort studies reported statistically significant trends of reduced RR of OPMDs with increasing time since quitting ($P_{trend} < 0.001$). The most significant reduction was noted for ≥ 5 years of abstinence in Keelung and Changhua and for ≥ 2 years of abstinence in Tainan. All the risk reductions per year of cessation were statistically significant: 3.5% (95% CI, 2.3–4.6%) in Keelung, 3.2% (95% CI, 2.2–4.2%) in Changhua, and 0.8% (95% CI, 0.5–1.1%) in Tainan. With respect to age at quitting, the younger the age at quitting the lower the risk of OPMDs, with significant RR reductions per year of younger age at quitting of 2% in Keelung, 1.4% in Changhua, and 2% in Tainan. When comparing former versus current chewers, cessation of chewing areca nut products without tobacco led to a significant reduction in the risk of OPMDs in all three cohorts.

In the case–control study in southern Taiwan (China), analyses restricted to ever-chewers resulted in a statistically significant 5% reduction in RR per year of cessation (OR, 0.95; 95% CI, 0.93–0.98).

The Working Group performed a meta-analysis combining information on the three user categories (current chewers, former chewers, and never-chewers) from the observational studies presented in Table 2.31 and Table 2.32. Former chewers had a statistically significantly lower risk of OPMDs (OR, 0.55; 95% CI, 0.39–0.72) compared with current chewers.]

2.3.6 HPV16 infection

Three types of HPV vaccines are currently available: a bivalent vaccine, a quadrivalent vaccine, and a nonavalent vaccine (Schiller and Lowy, 2012; Arbyn and Xu, 2018). All three target HPV16, the type that causes most HPV-associated oral and oropharyngeal cancers. HPV vaccines are prophylactic (i.e.

Table 2.32 Cessation of chewing of areca nut products (including betel quid) without tobacco and risk of OPMDs – primary data analyses performed by the Working Group

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Keelung, Taiwan (China)	Community-based integrated screening study for residents aged 30 yr in Keelung, northern Taiwan (China) (KCIS) 124 353 people were enrolled in the CHCIS cohort, and 3630 OPMDs were ascertained during follow-up	Prospective cohort study People attending the KCIS programme in 1999–2020 were used to assess the impact of quitting betel quid chewing on risk of OPMDs. This cohort was followed up to ascertain incident OPMDs by linking with the national cancer screening registry until 31 December 2020 Patients with oral cancer and people with a diagnosis of OPMD before the prevalent screen in KCIS were excluded Exposures included current chewers, former chewers, and never-chewers; age at cessation and time in years since cessation measured in continuous years Further details on this study are given in Table 2.30. Confounding factors adjusted for in the Cox regression model included age, sex, education level, smoking (never, < 10, 10–19.9, 20–29.9, and ≥ 30 pack-years), and alcohol consumption (never, ever, current) A time-dependent Cox regression model was used to consider dynamic change of duration of cessation during follow-up	OPMD (leukoplakia, erythroleukoplakia, erythroplakia, OSF, oral verrucous hyperplasia)	Never-chewers: 2124/111 486 Former chewers: 611/4273 Current chewers: 844/3229 Per year of cessation of betel quid chewing Current chewers Duration of cessation (yr): < 2: 116/503 2–5: 132/797 5–10: 97/800 10–15: 70/656 ≥ 15: 78/718 Never-chewers Per year of age at quitting Current chewers Age at quitting (yr): < 40: 275/2174 40–49: 149/850 ≥ 50: 69/444 Never-chewers	1.00 (ref) 2.22 (2.00–2.46) 3.43 (3.11–3.78) 0.965 (0.954–0.977) 1.00 (ref) 0.83 (0.57–1.19) 0.83 (0.65–1.07) 0.75 (0.61–0.91) 0.66 (0.55–0.81) 0.50 (0.42–0.60) 0.29 (0.26–0.32) P_{trend} < 0.0001 1.02 (1.01–1.04) 1.00 (ref) 0.58 (0.50–0.67) 0.77 (0.64–0.92) 0.77 (0.60–0.99) 0.30 (0.27–0.33) P_{trend} = 0.0073	This is a large-scale community-based screening programme, in an area where the prevalence of betel quid chewing is lower than in other parts of Taiwan (China) Because of the repeated attendance to screening, both prevalent and incident OPMDs were included in the analysis

Table 2.32 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Changhua, Taiwan (China)	Community-based integrated screening study for residents aged 30 yr in Changhua, central Taiwan (China) (CHCIS programme) 37 327 people were enrolled in the CHCIS cohort, and 1548 OPMDs were ascertained during follow-up	Prospective cohort study People enrolled in 2005–2014 were used to assess the impact of cessation of betel quid chewing on risk of oral cancer and OPMDs. This cohort was followed up to ascertain incident oral cancer by linking with the national cancer until 31 December 2018 Further details on this study are given in Table 2.30	OPMD (leukoplakia, erythroleukoplakia, erythroplakia, OSF, oral verrucous hyperplasia)	Never-chewers: 646/28 997	1.00 (ref)	Large-scale community-based screening programme in an area where the prevalence of betel quid chewing is higher than in other parts of Taiwan (China)
				Former chewers: 440/4429	1.55 (1.35–1.78)	
				Current chewers: 460/2315	2.57 (2.24–2.95)	
				Per year of cessation of betel quid chewing	0.968 (0.958–0.978)	
				Current chewers	1.00 (ref)	
				Duration of cessation (yr):		
				< 2: 55/314	0.84 (0.43–1.64)	
				2–5: 79/613	0.90 (0.65–1.25)	
				5–10: 85/739	0.64 (0.50–0.80)	
				10–15: 82/960	0.65 (0.52–0.80)	
				≥ 15: 111/1434	0.53 (0.44–0.64)	
				Never-chewers	0.39 (0.34–0.45)	
					$P_{trend} < 0.0001$	
				Per year of age at quitting	1.014 (1.002–1.026)	
				Current chewers:	1.00 (ref)	
				Age at quitting (yr):		
				< 40: 134/1564	0.55 (0.45–0.67)	
				40–49: 154/1348	0.67 (0.55–0.80)	
				≥ 50: 144/1439	0.61 (0.50–0.74)	
				Never-chewers	0.39 (0.34–0.45)	
					$P_{trend} = 0.4313$	

Table 2.32 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Tainan, Taiwan (China)	Community-based integrated screening study for residents aged 40 yr in Tainan, southern Taiwan (China) (CIS programme) 125 977 people were enrolled in the Tainan cohort, and 1584 OPMDs were ascertained during follow-up	Prospective cohort study People attending the CIS programme in 2004–2009 were used to assess the impact of cessation of betel quid chewing on risk of oral cancer and OPMDs. This cohort was followed up for incident oral cancer by the using national cancer registry until 31 December 2018 Patients with oral cancer were excluded Exposures included current chewers, former chewers, and never-chewer; time in years since cessation measured in continuous years Adjustments for confounding factors in this study are given in Table 2.29	OPMD (leukoplakia, erythroleukoplakia, erythroplakia, OSF, oral verrucous hyperplasia)	Never-chewers: 745/95 516	1.00 (ref)	Large-scale community-based screening programme in an area where the prevalence of betel quid chewing is the highest in Taiwan (China)
				Former chewers: 363/4761	1.94 (1.69–2.23)	
				Current chewers: 471/3767	2.95 (2.39–3.37)	
				Per year of cessation of betel quid chewing	0.992 (0.989–0.995)	
				Current chewers	1.00 (ref)	
				Duration of cessation (yr):		
				< 2: 63/464	1.06 (0.81–1.37)	
				2–5: 73/801	0.76 (0.59–0.97)	
				5–10: 66/912	0.62 (0.48–0.79)	
				10–15: 57/941	0.57 (0.43–0.75)	
				≥ 15: 60/1117	0.61 (0.47–0.80)	
				Never-chewers	0.34 (0.30–0.38)	
					P_{trend} < 0.0001	
				Per year of age at quitting	1.02 (1.00–1.03)	
				Current chewers:	1.00 (ref)	
				Age at quitting (yr):		
				< 40: 105/1566	0.54 (0.44–0.67)	
				40–49: 156/1693	0.76 (0.64–0.92)	
				≥ 50: 83/1392	0.75 (0.59–0.95)	
				Never-chewers	0.33 (0.29–0.38)	
					P_{trend} = 0.0002	

Table 2.32 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; US NCI Taiwan (China) OPMD and oral cancer study	Study conducted in 4 hospitals in Taiwan (China): NTUH Taipei, CMUH Taichung, CGMH-Linkou, and CGMH-Kaohsiung	Hospital-based case–control study, with recruitment of controls, patients with oral cancer or OPMDs (primarily leukoplakia and some OSF) This analysis (conducted in November 2021) included 388 controls and 1468 OPMDs Further details on this study are given in Table 2.29 on oral cancer	OPMD	Per year of cessation of betel quid chewing	0.95 (0.93–0.97) $P_{trend} < 0.001$	
				Current chewers: 743/158	1.00 (ref)	
				Duration of cessation (yr):		
				< 2: 106/12	1.78 (0.95–3.34)	
				2–5: 142/32	0.87 (0.57–1.34)	
				5–10: 167/64	0.48 (0.34–0.69)	
				10–15: 11/35	0.49 (0.31–0.79)	
				≥ 15: 199/87	0.30 (0.19–0.47) $P_{trend} < 0.001$	

CGMH, Chang Gung Memorial Hospital; CHCIS, Changhua Community-Based Integrated Screening; CI, confidence interval; KCIS, Keelung Community-Based Integrated Screening; NTUH, National Taiwan University Hospital; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; ref, reference; US NCI, United States National Cancer Institute; yr, year or years.

vaccination prevents future acquisition of infection) and not therapeutic (i.e. vaccination does not enable clearance of prevalent infection) (Schiller and Lowy, 2012; Arbyn and Xu, 2018). The key effector mechanism of vaccine efficacy is through the generation of systemic immunoglobulin G (IgG) antibody responses against the HPV L1 protein (Schiller and Lowy, 2012; Arbyn and Xu, 2018).

The HPV vaccines have been shown to be safe, highly efficacious, and highly effective in preventing infection with vaccine-targeted HPV types (at the cervix, vagina, vulva, anus, penis, and oral cavity), anogenital warts, and HPV-associated precancer end-points (at the cervix, vagina, vulva, anus, and penis), and to result in population-level reductions in the incidence of cervical cancer (Drolet et al., 2019; Lei et al., 2020; Kjaer et al., 2021).

There is currently no empirical evidence that prophylactic HPV vaccination results in a reduction in the incidence of oral or oropharyngeal cancer or in the incidence of OPMDs. This lack of evidence arises from the recency of the introduction of HPV vaccines (in 2006 for women and 2011 for men in most countries) as well as the current recommendations to vaccinate young people (the routine recommendation is for vaccination before sexual debut until age 12–14 years and for catch-up vaccination until age mid-20s in some countries) (WHO, 2019). Because the latency interval between the acquisition of oral or oropharyngeal HPV16 infection and the development of HPV-associated oral or oropharyngeal cancer spans several decades, many more years of observation would be needed for prophylactic HPV vaccination of both sexes to result in a reduction in incidence of oral cancer or oropharyngeal cancer (Gillison et al., 2015).

However, there is a compelling scientific rationale that HPV vaccination would reduce the incidence of HPV-associated oral or oropharyngeal cancer in the future. First, several observational studies have shown that the prevalence of oral or oropharyngeal infection with vaccine-targeted HPV types (including HPV16) is 83–93% lower in vaccinated individuals than in unvaccinated individuals (Herrero et al., 2013; Chaturvedi et al., 2018; Schlecht et al., 2019). Second, emerging evidence indicates herd protection from HPV vaccination in the population with reduced prevalence of oral or oropharyngeal HPV infection in unvaccinated individuals (Chaturvedi et al., 2019; Mehanna et al., 2019). Third, there is a strong analogy from other anatomical sites with respect to vaccine efficacy and effectiveness; analogous decreases in HPV infections, HPV-associated precancers, and cancers at other anatomical sites (cervix, vagina, vulva, anus, and penis) have been consistently reported in vaccinated individuals and populations.

Future reductions in the incidence of HPV-associated oral cancer and oropharyngeal cancer will depend on the extent of female and male vaccination coverage in men and women, as well as achieved levels of herd immunity in a country or region. In regions with high levels of female and/or gender-neutral vaccination coverage, it would be expected that over the next 10–15 years HPV vaccination will result in population-level reductions in the incidence of HPV-associated oral cancer and oropharyngeal cancer.

2.4 Preventive dietary agents

This section presents the available evidence on dietary agents that may have a protective effect on the development of oral cancer and OPMDs.

2.4.1 Preventive dietary agents for the development of oral cancer

(a) Coffee

The 2018 WCRF report (WCRF/AICR, 2018) concluded that there is "limited suggestive evidence" that consumption of coffee may decrease the risk of oral cancer.

Studies on the association between coffee drinking and the incidence of oral cancer has been reviewed in two meta-analyses (Miranda et al., 2017; He et al., 2020) and one pooled analysis (Galeone et al., 2010) (Supplementary Table S2.33, web only; available from https://publications.iarc.fr/617). Miranda et al. (2017) calculated a meta-OR for the association between oral cancer and coffee drinking of 0.82 (95% CI, 0.58–1.16) using data from one cohort study (Ren et al., 2010) and five case–control studies (Franco et al., 1989; Franceschi et al., 1992; Pintos et al., 1994; Bundgaard et al., 1995; Radoï et al., 2013b). He et al. (2020) included all the studies that were part of the meta-analysis by Miranda et al. (2017), alongside with one additional case–control study and one cohort study. They calculated a meta-OR for oral cancer (OR, 0.79; 95% CI, 0.40–1.58) for coffee drinkers using data from four case–control studies (Franco et al., 1989; Franceschi et al., 1992; Bundgaard et al., 1995; Radoï et al., 2013b). Galeone et al. (2010) provided a pooled analysis of nine case–control studies of the INHANCE cohort. They found a significant 54% reduction in RR for drinking > 4 cups per day versus none (OR, 0.46; 95% CI, 0.30–0.71).

(b) Tea

The evidence for the association between tea drinking and cancers of the mouth, pharynx, and larynx was considered limited by the WCRF reports, and no conclusion could be reached as to a protective or harmful effect (WCRF, 2016; WCRF/AICR, 2018).

Current evidence comes from a pooled analysis of cases and controls from 9 studies in the INHANCE consortium (Galeone et al., 2010), a meta-analysis of 14 case–control studies (Zhou et al., 2018), a meta-analysis of one cohort study and four case–control studies (Filippini et al., 2020), and one individual cohort study (Ren et al., 2010) (Supplementary Table S2.33, web only; available from https://publications.iarc.fr/617). These studies reported risk estimates for oral cancer associated with self-reported tea consumption taking into account major risk factors, including tobacco smoking and alcohol consumption.

The pooled analysis, which included study participants from France, Italy, Puerto Rico, Switzerland, and the USA, generated a non-statistically significant adjusted pooled estimate of risk of oral cancer associated with tea drinking of 1.06 (95% CI, 0.88–1.27); the estimate was slightly reduced when based on people drinking > 1 cup of tea per day (OR, 0.94; 95% CI, 0.68–1.29) (Galeone et al., 2010). In a meta-analysis of studies conducted in Brazil, China, Denmark, Egypt, France, India, and Italy that reported adjusted risk estimates for oral cancer, Zhou et al. (2018) generated an overall meta-estimate of risk of oral cancer associated with tea consumption (OR, 0.70; 95% CI, 0.61–0.81). In a dose–response analysis including 8 of the 14 case–control studies, the risk of oral cancer decreased by 6.2% per 1 cup increase per day (OR, 0.938; 95% CI, 0.922–0.955). [This study presented additional pooled risk estimates according to type of tea, geographical region, sex, and age group.]

In their more recent systematic review of green tea drinking and cancer, Filippini et al. (2020) reported a significant inverse association, with a meta-estimate of risk of oral cancer associated with consumption of green tea comparing the highest versus the lowest intake (meta-RR, 0.71; 95% CI, 0.62–0.82).

One cohort study in the USA (Ren et al., 2010) reported non-statistically significant inverse associations, after adjustment for important confounders, in the category of the largest number of cups of tea consumed (HR for ≥ 1 cup of hot tea per day, 0.75; 95% CI, 0.53–1.06; HR for ≥ 1 cup of iced tea per day, 0.89; 95% CI, 0.67–1.19; and HR for ≥ 5 cups of green tea per day, 0.44; 95% CI, 0.19–1.04).

(c) Fruits and vegetables

The preventive role of consumption of fruits and vegetables on risk of oral cancer has been investigated in a large pooled analysis of 22 case–control studies (Chuang et al., 2012), a meta-analysis of 15 case–control studies and one cohort study (Pavia et al., 2006), two cohort studies (Freedman et al., 2008; Maasland et al., 2015), and three additional case–control studies (Supplementary Table S2.33, web only; available from https://publications.iarc.fr/617).

The 2018 WCRF systematic review (WCRF/AICR, 2018) reported a limited–suggestive decrease in risk of oral cancer associated with "healthy dietary patterns" and with "greater intake of non-starchy vegetables".

In the pooled analysis, in which intake of fruits and of vegetables were standardized into frequency quartiles, the highest relative to the lowest consumption level conferred reduced risks of oral cancer for fruits (OR, 0.46; 95% CI, 0.38–0.56) and for vegetables (OR, 0.69; 95% CI, 0.61–0.79) (Chuang et al., 2012). Similarly, the meta-analysis found that each portion consumed per day of fruit (OR, 0.49; 95% CI, 0.39, 0.63) and of vegetables (OR, 0.43; 95% CI, 0.31, 0.59) showed significant reduction in the overall risk of oral cancer (Pavia et al., 2006).

The two cohort studies examined total consumption of fruits and vegetables. The cohort study in the USA, conducted in the late 1990s (Freedman et al., 2008), reported reduced risk of oral cancer with increasing total consumption of fruits and vegetables (HR per serving per 1000 calories, 0.93; 95% CI, 0.86–1.00). The cohort study in the Netherlands (Maasland et al., 2015), in which participants were enrolled in 1986 and followed up for 20 years, reported a reduction in RR with increasing frequency of total consumption of fruits and vegetables (RR per 2.5 g per day, 0.95; 95% CI, 0.92–0.99; $P_{trend} = 0.005$).

A significant reduction in RR associated with increasing consumption of specific fruits or vegetables was observed for raw green vegetables, citrus fruits, apples and pears, fresh tomatoes, and carotene-rich foods in one or several of three case–control studies conducted in Brazil (Franco et al., 1989; Galvão De Podestá et al., 2019) and India (Rajkumar et al., 2003). For non-starchy vegetables, the reduction in RR was modest (RR per 25 g per day, 0.95; 95% CI, 0.89–1.02 to RR per serving per 1000 calories, 0.84; 95% CI, 0.73–0.95) (WCRF, 2018).

(d) Dietary fibre

Evidence on the association between consumption of dietary fibre and oral cancer is available from one large pooled analysis of case–control studies and two individual cohort studies (Supplementary Table S2.33, web only; available from https://publications.iarc.fr/617).

The pooled analysis of 10 case–control studies in the INHANCE consortium (Kawakita et al., 2017), with 559 cases and 12 248 controls enrolled in Asia, Europe, and North America, reported reduced RR with consumption of dietary fibre; the pooled OR for the highest versus the lowest quintile category was 0.39 (95% CI, 0.29–0.52) for oral cancer and 0.54 (95% CI, 0.45–0.64) for oropharyngeal and hypopharyngeal cancers

combined. A cohort study from the NIH-AARP Diet and Health Study with 494 991 participants found a borderline association between dietary fibre intake and risk of oral cancer in women ($P_{trend} = 0.055$) but not in men ($P_{trend} = 0.576$) (Lam et al., 2011). A more recent cohort study from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial in the USA, with 101 700 participants enrolled in 1992–2001, reported a significant risk reduction for oral cavity and pharyngeal cancer with a dose–response relationship for total fibre intake, insoluble fibre intake, and soluble fibre intake (Kawakita et al., 2019).

(e) Mediterranean diet

People who adhere to the Mediterranean diet, which is based on consumption of olive oil in addition to frequent intake of fish and seafood, vegetables, fruits, and cereals, have been shown to have a strong inverse association between adherence to such a diet and risk of oral cancer (Trichopoulou and Lagiou, 1997; Petridou et al., 2002; Filomeno et al., 2014).

2.4.2 Preventive dietary agents for the development or progression of OPMDs

(a) Observational studies

In the mid-1990s, the Tata Institute of Fundamental Research (in Bombay, India) conducted several population-based case–control studies in three regions of India – Gujarat, Kerala, and Andhra Pradesh – to examine the role of food and nutrition on the progression of OPMDs (Gupta et al., 1998, 1999; Hebert et al., 2002; Supplementary Table S2.34, web only; available from https://publications.iarc.fr/617). A food frequency questionnaire was used that was specific to this population and was developed and validated for collecting dietary information needed to estimate exposure to 92 food items; the data included the frequency and quantity of consumption. All people interviewed were tobacco users, and most of the cases and controls had lower socioeconomic status. In Gujarat and Kerala, most of the cases were clinically diagnosed with leukoplakia or OSF, and in Andhra Pradesh most were diagnosed with palatal lesions due to reverse smoking. The study in Andhra Pradesh reported an OR for fibre intake (grams per day) of 0.96 (95% CI, 0.94–0.99; $P = 0.007$) (Hebert et al., 2002).

A case–control study in Sri Lanka (Amarasinghe et al., 2013), with cases of leukoplakia mainly, found a protective effect of consumption of > 2 portions per day of β-carotene-containing vegetables and fruits on development of OPMDs (Supplementary Table S2.34, web only; available from https://publications.iarc.fr/617). [The authors pointed to prevailing undernutrition in OPMD cases in this rural population with very low daily consumption of fruits and vegetables (< 2 portions per day).]

In a hospital-based case–control study in Rome, Italy (Cianfriglia et al., 1998), participants were interviewed about dietary habits, and the survey included questions on foods that are major sources of vitamin A and carotenoids. The consumption of foods rich in vitamin A – butter, eggs, liver, spinach, and carrots – in the control group was > 40% higher than that in the cases ($P < 0.001$). Specifically, the estimated mean retinol intake in the control group was significantly higher than that in the leukoplakia group (Supplementary Table S2.34, web only; available from https://publications.iarc.fr/617). Consumption of foods and nutrients rich in vitamins A, C, E, and B12, β-carotene, lycopene, folate, retinol, α-tocopherol, and antioxidant mineral zinc have been found to be protective against the development of OPMDs.

(b) Biochemical studies

Several biochemical investigations have studied the role of nutrients in blood (serum or plasma) in the development of OPMDs. All but one (cross-sectional) studies were of case–control

design; five were in India, two in Japan, one in Finland, and one in the Islamic Republic of Iran (Supplementary Table S2.35, web only; available from https://publications.iarc.fr/617).

In the studies in India, serum levels of vitamins A, C, E, and B12, β-carotene, folate, retinol, α-tocopherol, and antioxidant mineral zinc were lower in leukoplakia or OSF cases than in controls (Ramaswamy et al., 1996; Gupta et al., 2004; Bose et al., 2012; Basu and Guhan, 2015; Param et al., 2018). In men in Japan, serum levels of lycopene and β-carotene were significantly lower in leukoplakia cases than in healthy controls (Nagao et al., 2000). In the study in Finland, the prevalence of leukoplakia cases was significantly higher in a group with low plasma levels of ascorbic acid (≤ 25 µmol/L) (Tuovinen et al., 1992).

Two case–control studies reported on serum retinol and carotenoid levels in OLP cases (Nagao et al., 2001; Rezazadeh and Haghighat, 2021; Supplementary Table S2.35, web only; available from https://publications.iarc.fr/617). In the study in the Islamic Republic of Iran (Rezazadeh and Haghighat, 2021), neither parameter was found to be a risk factor for the development of OPMDs. In the study in Japan (Nagao et al., 2001), serum retinol levels were elevated in OLP cases. [The authors remarked that this could be due to changes in dietary habits by cases after the development of oral symptoms. In a subgroup analysis, serum lycopene levels were low in 4 cases with erosive lesions.]

Serum analysis of leukoplakia cases in several of the included studies showed that significantly low antioxidant vitamin status and low serum zinc levels could promote the development of OPMDs.

[The Working Group noted that 7-day food dairies recorded after the detection of an OPMD may be biased by the avoidance of certain foods because of new oral symptoms, especially in patients with OSF.]

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