Table S2.1 Tobacco smoking and risk of oral and oropharyngeal cancers or OPMDs

Risk factor	Level of exposure	OR, RR, or HR (95% CI)	Adjustments	Reference Study design
Oral cancer				
Cigarette smoking in never alcohol drinkers	Ever vs never	OR: 1.35 (0.9–2.01)	Age, sex, race/ethnicity, education level, study centre, years of cigar smoking (continuous), and years of pipe smoking (continuous)	Hashibe et al. (2007) Meta-analysis of 14 case–control studies in the INHANCE consortium, including 717 oral cancer cases and 4051 controls
	Ever vs never	OR: 3.2 (1.9–5.3)	Age, sex, area of residence, education level, family history of head and neck cancer, alcohol consumption, BMI 2 yr before interview, tea consumption, and history of candidiasis	Radoï et al. (2015) Multicentre case–control study (ICARE), conducted in 10 departments in France; 689 oral cancer cases and 3481 controls
Any smoked tobacco product in never alcohol drinkers	Ever vs never	OR: 2.37 (1.74–3.23)	Age, sex, country of residence, and education level	Anantharaman et al. (2011) Multicentre case–control study (ARCAGE), conducted in 14 centres in 10 European countries, not including France in this analysis; 477 oral cancer cases and 1959 controls
Cigarette smoking	Ever vs never	OR: 2.87 (2.60–3.18)	Age, sex, race, education level, frequency of alcohol consumption, duration of pipe smoking (for cigar smoking), and duration of cigar smoking (for pipe smoking)	Wyss et al. (2013) Pooled analysis of cases and controls of the INHANCE consortium; 4110 oral cancer cases and 18 691 controls
	Ever vs never		Age, sex, study, education level, and frequency of alcohol consumption	Toporcov et al. (2015) Pooled analysis of 25 case–control studies in the INHANCE consortium; 5573 oral cancer cases and 25 976 controls
	Age ≤ 45 yr	OR: 1.91 (1.53–2.38)		
	Age > 45 yr	OR: 2.18 (1.99–2.39)		
Cigarette smoking	Current vs never		Age, sex, education level, BMI, alcohol consumption, physical activity, total energy intake, and consumption of fruits and vegetables	Agudo et al. (2012) Multicentre cohort EPIC study in 10 European countries; 350 oral cancers in 441 211 cohort members
	Overall	HR: 3.53 (2.21–5.65)		
	Men	HR: 4.21 (2.17–8.16)		
	Women	HR: 3.17 (1.52–6.61)		
Cigarette smoking	Current vs never	OR: 2.11 (1.23–3.62)	Age, sex, and alcohol consumption	Maasland et al. (2014) Netherlands Cohort study, including 110 oral cancers and 4288 randomly selected non-cancer cohort members
	Current vs never	RR: 3.43 (2.37–4.94)	Fully adjusted estimates included when available	Gandini et al. (2008) Meta-analysis of 11 case–control studies and 1 cohort study
Cigar smoking in never cigarette smokers	Ever vs never	OR: 2.83 (1.91–4.17)	Age, sex, race, education level, frequency of alcohol consumption, duration of pipe	

Table S2.1 Tobacco smoking and risk of oral and oropharyngeal cancers or OPMDs

Risk factor	Level of exposure	OR, RR, or HR (95% CI)	Adjustments	Reference Study design
Pipe smoking in never cigarette smokers	Ever vs never	OR: 2.51 (1.68–3.75)	smoking (for cigar smoking), and duration of cigar smoking (for pipe smoking)	Wyss et al. (2013) Pooled analysis of cases and controls of the INHANCE consortium; 4110 oral cancer cases and 16 152 controls
Cigarette and bidi smoking	Ever vs never		Age, centre, education level, chewing habits, and alcohol consumption	Balaram et al. (2002) Multicentre case–control study in India; 591 oral cancer cases and 582 hospital controls
	Men	OR: 1.77 (1.2–2.7)		
	Women	OR: 3.18 (0.6–17.5)		
Oropharyngeal cancer				
Any smoked tobacco product in never alcohol drinkers	Ever vs never	OR: 3.67 (2.53–5.34)	Age, sex, country of residence, and education level	Anantharaman et al. (2011) Multicentre case–control study (ARCAGE), conducted in 14 centres in 10 European countries, not including France in this analysis; 399 oropharyngeal cancer cases and 1959 controls
Cigarette smoking	Ever vs never	OR: 3.01 (2.71–3.35)	Age, sex, race, education level, frequency of alcohol consumption, duration of pipe smoking, and duration of cigar smoking	Wyss et al. (2013) Pooled analysis of cases and controls of the INHANCE consortium; 3834 oropharyngeal cancer cases and 16 152 controls
Cigarette smoking	Ever vs never		Age, sex, study, education level, and frequency of alcohol consumption	Toporcov et al. (2015) Pooled analysis of 25 case–control studies in the INHANCE consortium; 4373 oropharyngeal cancer cases and 25 976 controls
	Age ≤ 45 yr	OR: 1.86 (1.47–2.37)		
	Age > 45 yr	OR: 2.77 (2.50–3.08)		
Cigarette smoking	Current vs never		Age, sex, education level, BMI, alcohol consumption, physical activity, total energy intake, and consumption of fruits and vegetables	Agudo et al. (2012) Multicentre cohort EPIC study in 10 European countries; 203 oropharyngeal cancers in 441 211 cohort members
	Overall	HR: 5.95 (3.41–10.4)		
	Men	HR: 6.67 (3.05–14.6)		
	Women	HR: 5.03 (2.05–12.3)		
Cigarette smoking	Current vs never	OR: 8.53 (3.38–21.55)	Age, sex, and alcohol consumption	Maasland et al. (2014) Netherlands Cohort study, including 83 oropharyngeal cancers and 4288 randomly selected non-cancer cohort members
Cigar smoking in never cigarette smokers	Ever vs never	OR: 2.31 (1.54–3.45)	Age, sex, race, education level, frequency of alcohol consumption, duration of pipe smoking (for cigar smoking), and duration of cigar smoking (for pipe smoking)	Wyss et al. (2013) Pooled analysis of cases and controls of the INHANCE consortium; 4110 oral cancer cases, 3834 oropharyngeal cancer cases, and 16 152 controls
Pipe smoking in never cigarette smokers	Ever vs never	OR: 1.65 (1.04–2.60)		

Table S2.1 Tobacco smoking and risk of oral and oropharyngeal cancers or OPMDs

Risk factor	Level of exposure	OR, RR, or HR (95% CI)	Adjustments	Reference Study design
Oral cancer and oropharyngeal cancer				
Cigarette smoking	Ever vs never	OR: 5.83 (4.40–7.54)	Age, sex, centre, education level, and frequency and duration of alcohol consumption	Lee et al. (2009) Multicentre case–control study in 14 centres in 10 European countries, not including France in this analysis; 993 cases and 2221 controls
Oropharyngeal and hypopharyngeal cancer				
Cigarette smoking in never-drinkers	Ever vs never	OR: 2.02 (1.34–3.05)	Age, sex, race/ethnicity, education level, study centre, years of cigar smoking (continuous), and years of pipe smoking (continuous)	Hashibe et al. (2007) Meta-analysis of 14 case–control studies in the INHANCE consortium including 717 oral cancer cases and 4051 controls
Leukoplakia				
Tobacco smoking (cigarettes and bidis)	Ever vs never	OR: 3.0 (2.5–3.7)	Age, sex, education level, BMI, chewing habits, and alcohol consumption	Hashibe et al. (2000a) Nested case–control study in a randomized cancer screening study in India; 927 leukoplakia cases and 47 773 controls
Cigarette smoking	1–10 pack-years	OR: 3.3 (1.5–7.2)	Education level, occupation, alcohol consumption, and betel quid chewing	Lee et al. (2003) Population-based case–control study in Taiwan (China); 125 leukoplakia cases and 500 randomly selected age- and sex-matched community controls
OSF				
Cigarette smoking	1–10 pack-years	OR: 1.8 (0.7–5.1)	Education level, occupation, alcohol consumption, and betel quid chewing	Lee et al. (2003) Population-based case–control study in Taiwan (China); 94 OSF cases and 500 controls
Erythroplakia				
Tobacco smoking (cigarettes and bidis)	Ever vs never	OR: 1.6 (0.9–2.9)	Age, sex, education level, BMI, chewing habits, and alcohol consumption	Hashibe et al. (2000b) Nested case–control study in a randomized cancer screening study in India; 100 erythroplakia cases and 47 773 controls

ARCAGE, Alcohol-Related Cancers and Genetic Susceptibility in Europe; BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; ICARE, Investigation of Occupational and Environmental Causes of Respiratory Cancers; INHANCE, International Head and Neck Cancer Epidemiology; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; RR, relative risk; vs, versus; yr, year or years.

Table S2.2 Tobacco smoking and risk of oral and oropharyngeal cancers – dose–response relationship

Risk factor	Level of exposure	OR (95% CI)	Adjustments	Reference Study design
Oral cancer				
Cigarette smoking	Ever vs never:		Age, sex, study, education level, and frequency of alcohol consumption	Toporcov et al. (2015) Pooled analysis of 25 case–control studies in the INHANCE consortium; 5573 oral cancer cases and 25 976 controls
	Pack-years:	Age > 45 yr:		
	Never	1.00 (ref)		
	> 0–10	0.92 (0.79–1.08)		
	10–20	1.39 (1.20–1.61)		
	20–30	2.22 (1.94–2.54)		
	30–40	2.82 (2.47–3.21)		
	40–50	3.25 (2.82–3.74)		
	> 50	3.49 (3.10–3.92)		
		$P < 0.001$		
	Pack-years:	Age ≤ 45 yr:		
	Never	1.00 (ref)		
	> 0–10	1.11 (0.83–1.49)		
	10–20	1.87 (1.39–2.51)		
	20–30	2.80 (2.06–3.81)		
	30–40	4.09 (2.75–6.07)		
	40–50	3.73 (2.28–6.11)		
	> 50	4.99 (3.22–7.73)		
		$P < 0.001$		
Cigarette smoking	vs never:		Age, sex, race, education level, fruit and vegetable consumption, alcohol consumption, and use of other tobacco	Stingone et al. (2013) The Carolina Head and Neck Cancer population-based case–control study of squamous cell carcinoma of the head and neck, recruiting cases and controls from North Carolina; 192 oral cancer cases and 1377 controls
	Intensity:			
	1–19 cig/day	2.21 (1.13–4.31)		
	≥ 20 cig/day	4.95 (2.73–8.96)		
	Duration:			
	1–19 yr	1.36 (0.60–3.05)		
	≥ 20 yr	4.90 (2.74–8.77)		

Table S2.2 Tobacco smoking and risk of oral and oropharyngeal cancers – dose–response relationship

Risk factor	Level of exposure	OR (95% CI)	Adjustments	Reference Study design
Bidi smoking	Current vs never:		Age, centre, education level, alcohol consumption, and chewing	Balaram et al. (2002) 591 oral cancer cases (282 women) and 582 controls (290 women)
	< 20 bidis/day	2.04 (1.10–3.79)		
	≥ 20 bidis/day	2.50 (1.41–4.42)		
Oropharyngeal cancer				
Cigarette smoking	Ever vs never:		Age, sex, study, education level, and frequency of alcohol consumption	Toporcov et al. (2015) Pooled analysis of 25 case–control studies in the INHANCE consortium; 4373 oropharyngeal cancer cases and 25 976 controls
	Pack-years:	Age > 45 yr:		
	> 0–10	1.36 (1.16–1.58)		
	10–20	1.81 (1.56–2.10)		
	20–30	2.56 (2.22–2.95)		
	30–40	3.39 (2.95–3.89)		
	40–50	3.69 (3.17–4.29)		
	> 50	4.96 (4.37–5.62)		
		$P < 0.001$		
	Pack-years:	Age ≤ 45 yr:		
	> 0–10	1.01 (0.73–1.40)		
	10–20	1.81 (1.31–2.50)		
	20–30	2.69 (1.94–3.72)		
	30–40	4.55 (3.02–6.87)		
	40–50	4.09 (2.48–6.73)		
	> 50	3.99 (2.46–6.48)		
		$P < 0.001$		

Table S2.2 Tobacco smoking and risk of oral and oropharyngeal cancers – dose–response relationship

Risk factor	Level of exposure	OR (95% CI)	Adjustments	Reference Study design
Oral and oropharyngeal cancers combined				
Cigarette smoking	Current vs never:		Age, sex, centre, education level, and alcohol consumption	Lee et al. (2009) Multicentre case–control study (ARCAGE), conducted in 14 centres in 10 European countries, not including France in this analysis; 993 cases and 2221 controls
	Intensity:			
	1–2 cig/day	2.44 (1.27–4.69)		
	3–4 cig/day	2.76 (1.51–5.02)		
	5–10 cig/day	1.99 (1.44–2.75)		
	11–20 cig/day	4.24 (3.26–5.52)		
	> 20 cig/day	4.85 (3.64–6.47)		
		$P < 0.01$		
	Duration:			
	1–20 yr	1.31 (0.94–1.83)		
	21–40 yr	3.76 (2.90–4.87)		
	> 40 yr	6.81 (5.06–9.16)		

ARCAGE, Alcohol-Related Cancers and Genetic Susceptibility in Europe; CI, confidence interval; cig, cigarettes; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio; ref, reference; vs, versus; yr, year or years.

Table S2.3 Alcoholic beverage consumption and risk of oral and oropharyngeal cancers

Risk factor	Level of exposure	OR or RR (95% CI)	Adjustments	Reference Study design
Oral cancer				
Alcohol consumption in never-users of tobacco	Ever vs never	OR: 1.17 (0.92–1.48)	Age, sex, race/ethnicity, education level, and study centre	Hashibe et al. (2007) Meta-analysis of 14 case–control studies in the INHANCE consortium, including 383 oral cancer cases, 369 oropharyngeal/hypopharyngeal cancer cases, and 5775 controls
Alcohol consumption frequency in never-smokers	Never-drinkers	1.00 (ref)		
	< 1 drinks/day	OR: 1.14 (0.80–1.63)		
	1–2 drinks/day	OR: 1.64 (1.19–2.25)		
	3–4 drinks/day	OR: 1.11 (0.57–2.15)		
	≥ 5 drinks/day	OR: 1.23 (0.59–2.57)		
		P_{trend} = 0.032		
Alcohol consumption duration	Never-drinkers	1.00 (ref)		
	1–10 yr	OR: 2.36 (1.43–3.88)		
	11–20 yr	OR: 1.09 (0.65–1.85)		
	21–30 yr	OR: 0.81 (0.49–1.33)		
	31–40 yr	OR: 1.29 (0.88–1.90)		
	> 40 yr	OR: 1.15 (0.77–1.73)		
		P_{trend} < 0.001		
Alcohol consumption	Alcohol consumption alone vs never-smokers and never-drinkers	OR: 1.1 (0.4–2.6)	Age, sex, area of residence, education level, family history of head and neck cancer, alcohol consumption, BMI 2 yr before interview, tea consumption, and history of candidiasis	Radoï et al. (2015) Multicentre case–control study (ICARE), conducted in 10 departments in France; 689 cases and 3481 controls
Oropharyngeal and hypopharyngeal cancer				
Alcohol consumption frequency	Never-drinkers	1.00 (ref)	Age, sex, race/ethnicity, education level, and study centre	Hashibe et al. (2007) Meta-analysis of 14 case–control studies in the INHANCE consortium, including 383 oral cancer cases, 369 oropharyngeal/hypopharyngeal cancer cases, and 5775 controls
	< 1 drinks/day	OR: 1.39 (0.99–1.96)		
	1–2 drinks/day	OR: 1.66 (1.18–2.34)		
	3–4 drinks/day	OR: 2.33 (1.37–3.98)		
	≥ 5 drinks/day	OR: 5.50 (2.26–13.4)		
		P_{trend} < 0.001		

Table S2.3 Alcoholic beverage consumption and risk of oral and oropharyngeal cancers

Risk factor	Level of exposure	OR or RR (95% CI)	Adjustments	Reference Study design
Alcohol consumption duration	Never-drinkers	1.00 (ref)		
	1–10 yr	OR: 1.76 (0.99–3.14)		
	11–20 yr	OR: 1.34 (0.81–2.11)		
	21–30 yr	OR: 1.95 (1.37–2.77)		
	31–40 yr	OR: 1.44 (0.78–2.66)		
	> 40 yr	OR: 1.51 (0.68–3.37)		
		P_{trend} = 0.003		
Alcohol consumption in never-users of tobacco	Ever vs never	OR: 1.38 (0.99–1.94)		
Oral and pharyngeal cancers				
Alcohol consumption frequency	≤ 1 drink/day	RR: 1.21 (1.10–1.33)	3 of 19 studies had no adjustment	Tramacere et al. (2010) Meta-analysis of 43 case–control studies and 2 cohort studies
	≥ 4 drinks/day	RR: 5.24 (4.36–6.30)	5 of 29 studies had no adjustment	
Demographics	Heavy drinking vs non-drinkers or occasional drinkers			Turati et al. (2013) Meta-analysis of 49 observational studies
	Men	RR: 5.49 (4.36–6.92)		
	Women	RR: 5.69 (3.74–8.66)		
	Asia	RR: 4.75 (3.14–7.17)		
	North America	RR: 5.36 (4.11–7.00)		
	South America	RR: 5.21 (3.77–7.19)		
	Europe	RR: 5.63 (4.09–7.77)		
	Incidence	RR: 5.51 (4.54–6.69)		
	Mortality	RR: 4.25 (3.03–5.96)		
Alcohol consumption intensity	Light drinking	RR: 1.13 (1.00–1.26)	Adjusted estimates included; adjustment factors not specified	Bagnardi et al. (2015) Meta-analysis of 52 observational studies
	Moderate drinking	RR: 1.83 (1.62–2.07)		
	Heavy drinking	RR: 5.13 (4.31–6.10)		

BMI, body mass index; CI, confidence interval; ICARE, Investigation of Occupational and Environmental Causes of Respiratory Cancers; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio; ref, reference; RR, relative risk; vs, versus; yr, year or years.

Table S2.4 Alcoholic beverage consumption and risk of oral and oropharyngeal cancers – supplementary data

Organ site	Level of exposure	OR (95% CI)	Adjustments	Reference Study design
Type of alcoholic beverage				
Oral cavity	Wine vs never (ref)		Age, sex, race/ethnicity, study centre, education level, pack-years of smoking, years of cigar smoking, and years of pipe smoking	Purdue et al. (2009) Pooled analysis of cases and controls from the INHANCE consortium; 344 oral cancer cases, 330 pharyngeal cancer cases, and 3487 controls
	≤ 15 drinks/week	1.3 (0.7–2.2)		
	> 15 drinks/week	5.9 (2.3–15.4)		
	Beer vs never (ref)			
	≤ 15 drinks/week	2.0 (1.4–2.8)		
	> 15 drinks/week	6.4 (3.9–10.3)		
	Liquor vs never (ref)			
	≤ 15 drinks/week	1.7 (0.9–3.3)		
	> 15 drinks/week	3.2 (1.6–6.4)		
Pharynx	Wine vs never (ref)			
	≤ 15 drinks/week	1.4 (0.9–2.2)		
	> 15 drinks/week	4.4 (2.0–9.6)		
	Beer vs never (ref)			
	≤ 15 drinks/week	2.3 (1.7–3.1)		
	> 15 drinks/week	4.3 (2.7–6.8)		
	Liquor vs never (ref)			
	≤ 15 drinks/week	2.0 (0.9–4.6)		
	> 15 drinks/week	3.6 (2.0–6.3)		

Table S2.4 Alcoholic beverage consumption and risk of oral and oropharyngeal cancers – supplementary data

Organ site	Level of exposure	OR (95% CI)	Adjustments	Reference Study design
Ethnic differences in alcohol risk				
Oral cavity	Never to < 20 yr	1.0 (ref)	Age, sex, study centre, education level, pack-years of smoking, duration of cigar smoking (years), duration of pipe smoking (years), ever snuff use, and ever chew use	Voltzke et al. (2018) Pooled analysis of cases and controls from the INHANCE consortium; 2248 oral cancer cases, 2154 oropharyngeal cancer cases, and 9194 controls
	≥ 20– < 30 yr	White: 1.62 (1.36–1.94)		
		Black: 2.01 (1.07–3.79)		
	≥ 30 yr	White: 1.38 (1.20–1.58)		
		Black: 2.20 (1.38–3.50)		
Oropharyngeal cancer	Never to < 20 yr	1.0 (ref)		
	≥ 20– < 30 yr	White: 1.83 (1.56–2.16)		
		Black: 4.12 (2.33–7.27)		
	≥ 30 yr	White: 1.81 (1.59–2.06)		
		Black: 4.60 (2.79–7.59)		

CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio; ref, reference; vs, versus; yr, year or years.

Table S2.5 Alcoholic beverage consumption and risk of OPMDs

OPMD	Level of exposure	OR (95% CI)	Adjustments	Reference Location, study design
Multiple OPMDs	Ever vs never	0.63 (0.33–1.21)	Age, sex, education level, fruit and vegetable intake, and current smoking	Li et al. (2011) Puerto Rico (USA); case–control study; 95 OPMD cases, 155 benign oral lesion controls
Multiple OPMDs	Current (monthly, weekly, daily)	2.7 (1.2–6.3)	Sex, age, socioeconomic status, β-carotene-containing fruit and vegetable portions, BMI, smoking, betel quid chewing, and alcohol consumption	Amarasinghe et al. (2010b) Sri Lanka; case–control study; 101 OPMD cases, 728 controls
Leukoplakia	Current vs never	Men: 0.76 (0.42–1.38) Women: 1.10 (0.72–1.69)	Age, sex, tobacco smoking, and betel quid chewing	Yang et al. (2010) Taiwan (China); case–control study; 224 leukoplakia cases, 1365 controls
Leukoplakia	Current vs never	1.8 (1.1–2.8)	Education level and occupation	Lee et al. (2003) Taiwan (China); case–control study; 125 leukoplakia cases, 500 controls
Leukoplakia	Ever vs never	1.4 (1.2–1.7)	Age, sex, education level, BMI, smoking, and tobacco chewing	Hashibe et al. (2000a) India; case–control study; 927 cases, 47 773 controls
Leukoplakia	Occasional vs never Frequent vs never	0.28 (0.03–2.56) 3.00 (0.27–33.5)	Tobacco smoking and areca nut chewing	Shiu et al. (2000) Taiwan (China); case–control study; 100 cases, 100 controls
OSF	Current vs never	Men: 0.68 (0.28–1.64) Women: 0.98 (0.53–1.82)	Age, sex, tobacco smoking, and betel quid chewing	Yang et al. (2010) Taiwan (China); case–control study; 89 OSF cases, 1365 controls
OSF	Current vs never	1.8 (1.1–3.1)	Education level and occupation	Lee et al. (2003) Taiwan (China); case–control study; 94 OSF cases, 500 controls
Erythroplakia	Ever vs never	3.0 (1.6–5.7)	Age, sex, education level, BMI, smoking, and tobacco chewing	Hashibe et al. (2000b) India; case–control study; 100 erythroplakia cases, 47 773 controls
Multiple OPMDs	Ever vs never	1.4 (0.7–2.7)	Age, sex, education level, BMI, smoking, tobacco chewing, fruit intake, and vegetable intake	Thomas et al. (2003) India; case–control study; 115 multiple OPMD cases, 47 773 controls

BMI, body mass index; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; vs, versus.

Table S2.6 Smokeless tobacco use and risk of oral or oropharyngeal cancer or OPMDs

Risk factor	RR or OR (95% CI)[a]	Adjustments Comments	Reference Location, study design
Oral cancer			
Several smokeless tobacco products	Overall: 3.53 (2.75–4.51) Oral snuff (*n* = 8): 4.18 (2.37–7.38) Snus/moist snuff (*n* = 3): 0.86 (0.58–1.29) Nasal snuff/dipping (*n* = 6): 1.20 (0.80–1.81)	Overall estimates include products such as *paan* tobacco, *gutka*, and *mainpuri*, which are areca nut products with added tobacco	Asthana et al. (2019) Worldwide Meta-analysis of 37 studies (61 estimates) published until 2016 on oral cancers; excluded studies on oral and pharyngeal cancers combined. Authors restricted to studies of ≥ 200 people where case ascertainment was by histology or cancer registry and which were at least adjusted for smoking
Naswar	Overall: 11.8 (8.4–16.4) Men: 16.4 (10.7–25.1) Women: 18.8 (12.5–28.2)	Estimates adjusted for tobacco smoking and alcohol consumption	Khan et al. (2019) Pakistan Meta-analysis of 6 studies on oral and oropharyngeal cancers combined in the population in Pakistan published until mid-2017. Cases were ascertained by histological/medical records
Snuff	Oral cavity: 3.01 (1.63–5.55) Gum: 12.7 (4.76–33.7) Oropharynx: 1.07 (0.55–2.08)	Data reported for never-smokers	Wyss et al. (2016) USA Pooled analysis of 11 case–control studies in the USA (1981–2006) of oral cancer (2034), oropharyngeal cancer (2373), and 8375 controls in the INHANCE consortium
Chewing tobacco	Oral cavity: 1.81 (1.04–3.17) Gum: 3.07 (1.10–8.59) Oropharynx: 0.98 (0.57–1.68)		
Tobacco chewing[c] and *mishri*	Oral cancer Tobacco chewing[c]: 8.51 (4.90–14.77) *Mishri*: 3.41 (1.90–6.12)	Estimates adjusted for age, sex, education level, income, tobacco smoking, alcohol consumption, and dietary habits	Gupta et al. (2017) Pune, India Hospital-based case–control study in Pune, India, in 2014–2015, which recruited 187 cases of histologically confirmed oral cancer and 240 hospital-based age- and sex-matched controls

Table S2.6 Smokeless tobacco use and risk of oral or oropharyngeal cancer or OPMDs

Risk factor	RR or OR (95% CI)[a]	Adjustments Comments	Reference Location, study design
Shammah	Oral cancer 20.14 (8.23–49.25)	Estimates adjusted for khat chewing, cigarette smoking, and pipe smoking	Quadri et al. (2015) Jazan, Saudi Arabia Hospital-based case–control study on 48 histologically confirmed oral cancer cases and 96 controls. Shammah use, duration, khat chewing, cigarette smoking (number of packs per day), and pipe smoking were recorded via questionnaire
Shammah (snuff)	Oral cancer 39 (14–105)[b]	Estimates adjusted for age, sex, EBV status, and smoking	Nasher et al. (2014) Yemen Hospital-based case–control study in Yemen of 60 oral cancer cases and 120 hospital-based age- and sex-matched controls. Cases were confirmed by histopathology
OPMDs			
Chewing tobacco and snuff	Leukoplakia Chewing: 2.5 (1.3–5.0)[b] Snuff: 18.4 (8.5–39.8)[b]	Estimates adjusted for age, cigarette smoking, and alcohol consumption	Tomar et al. (1997) USA Cohort of 17 027 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 snuff, and 1.5% used chewing tobacco. Oral lesions were classified broadly as “white or whitish oral soft-tissue lesions” (leukoplakia)
Chewing tobacco and snuff	Leukoplakia Chewing: 60 (27.8–129.5)[b] Snuff: 86.9 (39.9–189.5)[b]		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; 42% were current users and 13% were former users as defined at entry. Leukoplakia identified by dentists on entry and biopsy-confirmed
Shammah	Leukoplakia *Shammah* use: 2.17 (0.95–4.96)[b]	Estimates adjusted for age	Scheifele et al. (2007) Yemen Hospital-based case–control study of 54 leukoplakia cases and 58 habit-matched controls

Table S2.6 Smokeless tobacco use and risk of oral or oropharyngeal cancer or OPMDs

Risk factor	RR or OR (95% CI)[a]	Adjustments Comments	Reference Location, study design
Shammah	Leukoplakia-like Former users: 3.65 (1.51–8.82) Current users: 16.70 (8.75–1.87)	Multivariate model adjusted for age and education level	Al-Tayar et al. (2015) Yemen Cross-sectional study in 2014 involving 346 male residents aged ≥ 18 yr. An interview-based questionnaire was used to collect information on sociodemographic characteristics, oral hygiene practices, shammah types, and patterns of use. Diagnosis of leukoplakia-like lesion based on Axell criteria

CI, confidence interval; EBV, Epstein–Barr virus; INHANCE, International Head and Neck Cancer Epidemiology; OPMDs, oral potentially malignant disorders; OR, odds ratio; RR, relative risk; yr, year or years.

[a] RR or OR (95% CI) for ever-users versus never-users or for users versus non-users, unless indicated otherwise.

[b] Current chewers versus non-chewers.

[c] May include areca nut products (including betel quid) with added tobacco.

Table S2.7 Smokeless tobacco use and risk of oral cancer or OPMDs – dose–response relationship

Risk factor	RR or OR (95% CI)	Study design Adjustments Comments	Reference Location
Oral cancer			
Tobacco chewing and *mishri*[a]	Duration of chewing: < 10 yr: 5.22 (1.95–13.90) 11–20 yr: 6.65 (2.96–14.96) 21–30 yr: 8.33 (4.13–16.78) 31–40 yr: 9.25 (4.47–19.16) > 41 yr: 11.17 (5.37–23.24) Frequency of chewing (times/day): 1–5: 2.18 (1.14–4.20) 6–10: 8.73 (4.23–18.02) > 10: 41.87 (19.61–89.40)	Hospital-based case–control study in 2014–2015 that recruited 187 cases of histologically confirmed oral cancer and 240 hospital-based age- and sex-matched controls Estimates adjusted for age, sex, education level, income, tobacco smoking, alcohol consumption, and dietary habits	Gupta et al. (2017) Pune, India
Shammah[a]	Duration of use (% of cases/% of controls): < 10 yr: 4.16/8.33 10–20 yr: 14.58/0.69 $P < 0.001$	Hospital-based case–control study on 48 cases of histologically confirmed oral cancer and 96 controls. *Shammah* use, duration, khat chewing, cigarette smoking (number of packs per day), and pipe smoking were recorded via questionnaire Estimates adjusted for khat chewing, cigarette smoking, and pipe smoking	Quadri et al. (2015) Jazan, Saudi Arabia
Chewing tobacco[a]	Frequency of tobacco chewing (times/day): 1–2: 1.72 (0.56–5.37) 3–5: 2.44 (1.08–5.52) 6–10: 8.19 (3.73–17.99) > 10: 20.02 (8.15–48.98) Duration of tobacco chewing: < 20 yr: 1.78 (0.72–4.42) 20–40 yr: 12.78 (7.04–23.20) > 40 yr: 8.10 (4.02–16.31)	Hospital-based case–control study that recruited 123 cases of histologically confirmed oral and pharyngeal cancers combined and 246 hospital-based age- and sex-matched controls falling into 2 groups: non-cancer controls and other cancer controls. Although *paan* with added tobacco was the most commonly used product (42% of cases), exclusive tobacco use was reported to be prevalent in almost 20% of the cases Estimates adjusted for age, sex, occupation, income, tobacco smoking, and alcohol consumption	Wasnik et al. (1998) Nagpur, India

Table S2.7 Smokeless tobacco use and risk of oral cancer or OPMDs – dose–response relationship

Risk factor	RR or OR (95% CI)	Study design Adjustments Comments	Reference Location
	Retention time of tobacco in the mouth: < 30 minutes: 2.57 (1.17–5.68) 30–60 minutes: 5.01 (2.61–9.59) > 60 minutes: 33.64 (15.32–73.64) Overnight: 35.88 (13.38–95.53)		
OPMDs			
Shammah	Relative risk per 1 incremental unit of use: Frequency (times/day): 1.17 (1.02–1.36) Duration of being a user (in years): 1.07 (0.98–1.17) Duration of retention in the mouth (in minutes): 1.02 (0.95–1.10)	Cross-sectional study in 2014 involving 346 male residents aged ≥ 18 yr. An interview-based questionnaire was used to collect information on sociodemographic characteristics, oral hygiene practices, *shammah* types, and patterns of use. Leukoplakia-like lesion based on Axell criteria was the outcome of interest Multivariate model was adjusted for age and education level	Al-Tayar et al. (2015) Dawan Valley, Yemen
Shammah[b]	Frequency of use (times/day): 1–5: 1 (ref) 5–10: 1.93 (0.55–6.74) > 10: 4.90 (1.99–12.08) Duration of use per serving (minutes): < 1: 1 (ref) 1–5: 2.71 (0.96–7.68) > 5: 6.91 (2.66–17.95) Mouth-rinse after use: No: 1 (ref) Yes: 0.39 (0.18–0.85)	Hospital-based case–control study of 54 leukoplakia cases and 58 habit-matched controls Estimates adjusted for age	Scheifele et al. (2007) Yemen

Table S2.7 Smokeless tobacco use and risk of oral cancer or OPMDs – dose–response relationship

Risk factor	RR or OR (95% CI)	Study design Adjustments Comments	Reference Location
Chewing tobacco[b]	Duration (months): 1–12: 2.0 (0.6–6.1) 13–24: 6.6 (1.7–25.2) > 24: 13.4 (6.1–29.5) Frequency (days/month): 1–14: 2.9 (1.1–7.9) 15–29: 4.8 (1.3–18.2) 30–31: 12.1 (5.5–26.5) Exposure time (minutes): 1–30: 2.8 (1.1–7.1) 31–105: 6.3 (2.7–14.5) > 105: 11.1 (4.3–29.1)	Cross-sectional study of 17 027 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 snuff, and 1.5% used chewing tobacco. Oral lesions were classified broadly as "white or whitish oral soft-tissue lesions" (leukoplakia) Estimates adjusted for age, cigarette smoking, and alcohol consumption	Tomar et al. (1997) USA
Snuff[b]	Duration (months): 1–12: 8.1 (3.8–17.4) 13–24: 23.3 (10.5–51.4) > 24: 58.9 (21.3–162.6) Frequency (days/month): 1–14: 4.2 (1.6–11.4) 15–29: 7.9 (2.9–21.7) 30–31: 51.4 (19.7–133.7) Exposure time (minutes): 1–30: 9.5 (4.3–20.7) 31–105: 14.6 (5.5–39.0) > 105: 26.7 (9.8–72.9)		

CI, confidence interval; OPMDs, oral potentially malignant disorders; OR, odds ratio; ref, reference; RR, relative risk; yr, year or years.

[a] RR or OR (95% CI) for ever versus never.

[b] RR or OR (95% CI) for current versus never.

Table S2.8 Chewing of areca nut (including betel quid) with added tobacco and risk of oral cancer or OPMDs

Risk factors	RR or OR (95% CI)[a]	Reference Location Study design/comments
Betel quid + tobacco	Oral and oropharyngeal cancer: Overall meta-RR: 9.6 (5.9–15.6) Men meta-RR: 5.4 (3.9–7.4) Women meta-RR: 14.6 (7.6–27.8) Oral cancer: Meta-RR: 8.5 (6.5–11.1) Buccal mucosa, cheek cancer: Meta-RR: 13.6 (6.9–26.9) Tongue cancer: Meta-RR: 4.1 (2.6–6.5) Palate cancer: Meta-RR: 2.1 (1.0–4.1) Oropharyngeal cancer: Meta-RR: 4.4 (2.2–8.5)	Guha et al. (2014) Indian subcontinent Meta-analysis of 50 reports published in 1933–2013. Estimates reported for betel quid + tobacco use only; estimates adjusted for both tobacco use and alcohol consumption
Gutka, *mawa*, *mainpuri*	Oral cancer: OR: 1.2 (1.1–1.3)	Azhar et al. (2018) Pakistan Hospital-based case–control study in 2015–2016; 62 oral cancer cases and 62 controls In the study, gutka, mawa, and mainpuri, 3 areca nut products with added tobacco, were categorized as "smokeless tobacco". Estimates are given of this group of products. No adjustments were reported
Chewing betel quid with added tobacco	Oral and pharyngeal cancers combined: OR: 1.56 (0.65–3.73)	Gunasekera et al. (2015) Sri Lanka Case–control study; 78 cases of oral and pharyngeal cancer and 51 controls. Estimates adjusted for alcohol consumption, tobacco smoking, and HPV16/18 status
Gutka	Oral cancer: OR: 5.1 (2.0–10.3)	Mahapatra et al. (2015) Manipal, India Hospital-based case–control study in 2003; 134 oral cancer cases and 268 controls. Estimates adjusted for other tobacco and oral dip products, alcohol consumption, diet, education level, social class, age, and sex

Table S2.8 Chewing of areca nut (including betel quid) with added tobacco and risk of oral cancer or OPMDs

Risk factors	RR or OR (95% CI)[a]	Reference Location Study design/comments
Betel leaf, areca nut, lime, tobacco	Oral cancer: OR: 4.7 (1.1–19.9)	Amtha et al. (2014) Jakarta, Indonesia Hospital-based case–control study in 2005 and 2006; 81 oral cancer cases and 162 controls. Estimates adjusted for alcohol consumption, tobacco smoking, and diet
Chewing betel quid with added tobacco	Oral cancer: OR: 2.2 (1.3–3.7)	Mondal et al. (2013) India Hospital-based case–control study in 2010–2012; 124 oral cancer cases and 140 controls. Adjustments were not given
Gutka	Oral cancer:[e] OR: 12.8 (7.0–23.7)	Madani et al. (2012) Pune, India Hospital-based case–control study in 2005–2006; 350 oral cancer cases and 350 controls. Estimates adjusted for other tobacco and oral dip products, alcohol consumption, non-vegetarian dietary habits, education level, occupation, age, and sex
Gutka	Leukoplakia: OR: 2.5 (1.1–5.6) OSF: OR: 17.7 (4.8–64.6) Oral cancer: OR: 1.6 (0.5–4.5)	Khan et al. (2020) Mangaluru, India Retrospective cohort study from hospital records in 2013–2017 of 1007 people. Estimates adjusted for alcohol consumption and tobacco smoking
Gutka chewing	Oral cancer: OR: 3.0 (1.3–7.4)	Anwar et al. (2020) Pakistan Cross-sectional study; 186 cases of OSCC diagnosed in 2007. Estimates adjusted for other tobacco and other types of chewing substances, occupation, marital status, age, and sex
Areca nut + betel leaf + lime + catechu + tobacco	Oral cancer and OPMDs: OR: 10.97 (7.93–15.17)	Rimal et al. (2019) Nepal Cross-sectional study in 2012–2014; 60 oral cancer cases and 468 OPMD cases. No information given about the adjustment Among the OPMDs, a high prevalence of tobacco pouch keratosis and of OSF was noted

Table S2.8 Chewing of areca nut (including betel quid) with added tobacco and risk of oral cancer or OPMDs

Risk factors	RR or OR (95% CI)[a]	Reference Location Study design/comments
Smokeless tobacco + betel quid chewing	OPMDs:[b] OR: 4.65 (2.79–7.76)	Worakhajit et al. (2021) Thailand Community-based case–control study in 2019–2021; 562 OPMD cases and 886 controls. Estimates calculated by multivariate logistic regression analysis
Chewing betel quid with added tobacco	OPMDs: OR: 2.5 (1.2–5.5)	Kadashetti et al. (2015) India Hospital-based case–control study; 100 OPMD cases and 100 controls. Estimates calculated by multivariate logistic regression analysis
Tobacco *paan masala* (*gutka*)/Tobacco *paan*	OSF: *Gutka* OR: 10.77 (8.18–14.18) Tobacco *paan* OR: 7.89 (4.02–15.47)	Mehrotra et al. (2013) India Population-based case–control study; 448 OSF cases and 2688 controls. Estimates were adjusted for the effect of other factors (not further defined)
Areca nut category (included mostly *gutka*)	Leukoplakia: Male OR: 0.77 (0.22–2.92) Female OR: 3.63 (1.10–13.26) OSF: Male OR: 15.05 (2.19–298.01) Female OR: 18.17 (2.53–369.12)	Ray et al. (2013) Kolkata, India Case–control study in 2010–2011; 698 OPMD cases and 948 controls The areca nut category included gutka and betel quid (not stated whether with or without tobacco); however, gutka was the most used product. Estimates were unadjusted
Betel quid composed of betel leaf, areca nut, lime and tobacco or betel leaf, lime and tobacco	OPMDs: OR: 14.9 (4.5–49.3)	Amarasinghe et al. (2010a) Sri Lanka Nested case–control study; 102 OPMD cases detected in the cohort of 1029 participants. Estimates adjusted for tobacco smoking, alcohol consumption, occupation, education level, diet, age, and sex
Betel leaves, areca, lime, tobacco	OSF: OR: 16.2 (5.9–44.9)	Ariyawardana et al. (2006) Sri Lanka Hospital-based case–control study; 74 OSF cases and 74 age- and sex-matched controls

Table S2.8 Chewing of areca nut (including betel quid) with added tobacco and risk of oral cancer or OPMDs

Risk factors	RR or OR (95% CI)[a]	Reference Location Study design/comments
Betel quid with added tobacco	*OR adjusted for tobacco smoking and alcohol consumption:* Multiple OPMDs: Overall: 50.7 (21.5–119.5) Women: 61.5 (21.3–177.3) Men: 37.6 (8.65–163.8) Leukoplakia (*n* = 577): Overall: 10.0 (8.3–12.0) Women: 197.0 (22.6–∞) Men: 4.1 (3.3–5.1) OSF (*n* = 124): Overall: 55.6 (27.4–112.7) Women: 59.0 (27.7–125.7) Men: 48.7 (6.3–374.7) Erythroplakia (*n* = 76): Overall: 28.6 (13.3–61.4) Women: 50.5 (14.8–172.7) Men: 15.8 (5.9–42.0) *OR restricting to non-smokers and non-drinkers:* Multiple OPMDs (*n* = 67): 71.0 (24.8–202.8) Leukoplakia (*n* = 339): 72.2 (44.1–118.1) OSF (*n* = 110): 73.0 (32.9–162.2) Erythroplakia (*n* = 41): 63.7 (18.7–217.2)	Jacob et al. (2004) Kerala, India Case–control study design with cross-sectional data from a trial; 927 leukoplakia cases, 170 OSF cases, 100 erythroplakia cases, 115 multiple OPMD cases, and 47 773 controls

Table S2.8 Chewing of areca nut (including betel quid) with added tobacco and risk of oral cancer or OPMDs

Risk factors	RR or OR (95% CI)[a]	Reference Location Study design/comments
Areca nut or *paan masala* + chewed tobacco	OSF: OR: 6.1 (1.8–21.3)	Ranganathan et al. (2004) Chennai, India Hospital-based case–control study in 2000–2003; 185 OSF cases and 185 controls. Adjustments not reported
Chewing *paan* with added tobacco	Any oral mucosal lesions OR: 1.4 (0.5–3.7) Leukoplakia: OR: 5.2 (1.3–21.4)	Pearson et al. (2001) Multicentre cross-sectional study in Bangladeshi adults aged ≥ 40 yr in the United Kingdom; 137 study participants. Estimates calculated by multivariate logistic regression analysis

CI, confidence interval; HPV16/18, human papillomavirus type 16/18; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSCC, oral squamous cell carcinoma; OSF, oral submucous fibrosis; RR, relative risk; yr, year or years.

[a] RR or OR (95% CI) for chewers versus non-chewers or for users versus non-users, unless indicated otherwise.

[b] Current and former chewers versus non-chewers.

Table S2.9 Chewing of areca nut (including betel quid) with added tobacco and risk of oral cancer or OPMDs – dose–response relationship

Risk factors	OR (95% CI)	Reference Location Study design/adjustments/comments
Chewing betel quid (containing areca nut, tobacco, or both)	Oral cancer: Cumulative use (chew-years[a]) vs no use: Overall: 12.4 (9.6–16.1) < 86: 5.3 (2.9–9.7) 86–170: 9.6 (6.0–15.4) 171–289: 16.1 (9.4–27.6) 290–404: 22.5 (11.9–42.7) > 404: 22.7 (11.1–46.6) Dose–response: quantity and duration vs none: 1 quid/day for 1 yr: 3.9 (1.9–8.2) to ≥ 10 quids/day for > 10 yr: 8.1 (5.0–13.2)	Madathil et al. (2016) India Hospital-based case–control study; 331 oral cancer cases and 355 controls. Estimates adjusted for bidi and cigarette smoking, alcohol consumption, missing teeth, and diet Note from the authors: In India, tobacco is usually included in the betel quid
Chewing betel quid composed of betel leaf, areca nut, lime, and tobacco or betel leaf, lime, and tobacco	OPMDs: Daily use (quids/day) vs no chewing: 1–3: 2.6 (0.6–11.4) 4–5: 10.2 (2.8–37.0) 6–10: 17.7 (5.1–61.3) > 10: 75.5 (17.6–324.7) Age started chewing (yr) vs no chewing: ≤ 18: 15.2 (4.2–54.2) > 18: 9.4 (3.0–29.4) Duration (yr) vs no chewing: ≤ 10: 8.1 (2.3–28.5) 10–20: 8.2 (2.2–30.3) > 20: 18.6 (4.9–69.6)	Amarasinghe et al. (2010a) Sri Lanka Community-based nested case–control study in 2006–2007; 102 OPMD cases detected in the cohort of 1029 participants. Estimates adjusted for age, sex, tobacco smoking, alcohol consumption, education level, occupation, BMI, and diet The estimates reported here included both betel quid with and without tobacco

BMI, body mass index; CI, confidence interval; OPMDs, oral potentially malignant disorders; OR, odds ratio; vs, versus; yr, year or years.

[a] 1 "chew-year" was defined as the equivalent of chewing 1 quid every day for 1 year.

Table S2.10 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs

Risk factor[a]	OR (95% CI)[b]	Reference Location Study design/adjustments/comments
Oral cancer		
Betel quid without tobacco	Oral cancer (meta-RR): Indian subcontinent: 2.4 (1.8–3.2) Taiwan (China): 11.0 (4.9–24.8) Buccal mucosa, cheek cancer: Indian subcontinent: 2.1 (1.0–4.1) Tongue cancer: Indian subcontinent: 1.6 (1.1–2.3) Palate cancer: Indian subcontinent: 5.1 (1.1–24.9) Oropharyngeal cancer: Indian subcontinent: 2.6 (1.7–3.9) Oral and oropharyngeal cancer (meta-RR): Indian subcontinent overall: 2.9 (2.2–3.9) Men: 2.1 (1.5–3.1) Women: 3.0 (1.8–5.1) Taiwan (China) overall: 11.5 (4.6–29.0) Men: 8.6 (4.1–17.9)	Guha et al. (2014) Indian subcontinent; Taiwan (China) Meta-analysis of 50 reports published in 1933–2013. Estimates adjusted for both tobacco use and alcohol consumption
Betel quid chewing	Oral cancer: 9.2 (2.8–30.7)	Chang et al. (2011) Taiwan (China) Cohort study in 2005–2010; 282 oral cancer cases and 13 321 controls. Estimates reported here are for non-smokers and non-drinkers. Multivariate logistic regression model
Betel quid	Oral cancer: 12.0 (3.5–40.3)	Lin et al. (2011) Taiwan (China) Cohort study in 2005–2008; 10 657 study participants. Estimates reported for non-smokers and non-drinkers. Multivariate logistic regression

Table S2.10 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs

Risk factor[a]	OR (95% CI)[b]	Reference Location Study design/adjustments/comments
Betel quid without tobacco or *paan*	Oral cancer death: HR: 12.5 (5.5–28.8)	Wen et al. (2010) Taiwan (China) Cohort study of adults; 177 271 study participants. Estimates adjusted for age and alcohol consumption represent total risk for chewers compared with non-smoking non-chewers
Dried fibre shell of processed betel quid	Oral cancer: 5.4 (3.3–8.8)	Hu et al. (2020) Hunan Province, China Case–control study in 2014–2015; 304 cases and 304 controls. Estimates adjusted for smoking, alcohol consumption, age, sex, education level, occupation, and marital status
Betel quid chewing	Oral cancer: 13.5 (9.7–18.6) Oral and pharyngeal cancer (SCC): 14.0 (8.7–22.5)	Yang et al. (2014) Taiwan (China) Case–control study in 2004–2011; 463 oral cancer cases, 129 oropharyngeal and hypopharyngeal cancer cases, and 623 controls. Estimates are crude estimates
Betel quid chewing	Oral cancer: 9.0 (3.8–21.2)	Loyha et al. (2012) Thailand Case–control study in 2010–2011; 104 oral cancer cases and 104 controls. Estimates adjusted for occupation, tobacco smoking, betel quid chewing, and interaction term of sex and alcohol consumption
Supari	Oral cancer: 6.6 (3.0–14.8)	Madani et al. (2012) India Hospital-based case–control study in 2005–2006; 350 oral cancer cases and 350 controls. Estimates adjusted for other tobacco and oral dip products, alcohol consumption, non-vegetarian dietary habits, education level, occupation, age, and sex
Betel quid chewing	Oral cancer: 17.3 (9.0–33.2)	Chen et al. (2011) Taiwan (China) Case–control study; 247 oral cancer cases and 338 controls. Adjusted for age, education level, employment status, religion, and covariates (use of alcohol, betel quid, and cigarettes)
Tobacco-free betel quid: unripe areca nut, slaked lime, and a piece of betel leaf or inflorescence or stem of *Piper betle* Linn.	Oral cancer: HR: 1.6 (1.3–2.0)	Lee et al. (2011) Taiwan (China) Case–control study in 2001–2007; 1522 study participants. Estimates adjusted for sex, ethnicity, education level, diet, cigarette smoking, and alcohol consumption
Areca quid chewing	Oral cancer: 19.9 (11.5–34.3)	Zavras et al. (2011) Taiwan (China) Case–control study in 2007–2009; 240 oral cancer cases and 347 controls. Adjusted for age, sex, tobacco, alcohol, and areca nut use

Table S2.10 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs

Risk factor[a]	OR (95% CI)[b]	Reference Location Study design/adjustments/comments
Betel quid chewing	Oral cancer: 20.1 (12.6–32.0)	Chen et al. (2009) Taiwan (China) Case–control study in 2007–2009; 174 oral cancer cases and 347 controls. Multiple logistic regression models after controlling for age, sex, alcohol consumption, tobacco use, and areca nut chewing
Betel quid chewing	Oral cancer: 45.4 (21.1–97.5)	Chung et al. (2009) Taiwan (China) Case–control study in 1999–2001; 160 oral cancer cases and 218 controls. Multiple logistic regression model after adjustment for age, cigarette smoking, and betel quid chewing
OPMDs		
Areca nut chewing	OPMDs: 25.3 (20.8–30.7)	Yen et al. (2011) Taiwan (China) Cohort study in 2003–2008; 79 940 study participants. Estimates adjusted for education level, tobacco smoking, and alcohol consumption
Chewing betel quid without tobacco	OPMDs: 5.5 (1.6–19.2)	Amarasinghe et al. (2010a) Sri Lanka Case–control study; 1029 study participants. Adjusted for sex, age, education level, occupation, BMI, diet, tobacco smoking, and alcohol consumption
Chewing areca/betel quid	OSF: Overall: 4.5 (1.2–16.9) Men: 2.9 (0.3–29.3) Women: 5.6 (1.1–28.0)	Yang et al. (2005) Taiwan (China) Case–control study; 62 OSF cases, 62 oral mucosal lesion cases, and 62 controls. Estimates were for chewers who were not smoking vs non-chewers
Chewing betel quid without tobacco	*OR adjusted for tobacco smoking and alcohol consumption:* Leukoplakia: Overall: 4.0 (2.7–6.1) Women: 16.8 (8.9–31.8) Men: 2.2 (1.1–4.5) OSF: Overall: 47.2 (20.2–110.4) Women: 42.8 (17.0–107.7) Men: 108.1 (11.0–∞)	Jacob et al. (2004) Kerala, India Case–control study; 927 leukoplakia cases, 170 OSF cases, 100 erythroplakia cases, 115 multiple oral precancer cases, and 47 773 controls. Estimates adjusted for age, sex, education level, BMI, tobacco smoking, and alcohol consumption

Table S2.10 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs

Risk factor[a]	OR (95% CI)[b]	Reference Location Study design/adjustments/comments
	Erythroplakia: Overall: 12.5 (3.7–42.4) Women: 22.7 (4.4–116.7) Men: 6.6 (0.8–57.0) *OR restricting to non-smokers and non-drinkers:* Leukoplakia: Overall: 22.2 (11.3–43.7) OSF: Overall: 56.2 (21.8–144.8) Erythroplakia: Overall: 29.0 (5.6–149.5)	
3 types: areca nut with a piece of inflorescence of *Piper betle* Linn., areca nut with a piece of betel leaf, and both mixed	Leukoplakia: 22.3 (11.3–43.8) OSF: 40.7 (16.0–103.7)	Lee et al. (2003) Taiwan (China) Case–control study in 1994–1995; 219 leukoplakia or OSF cases and 876 controls. Estimates were for current chewers, adjusted for education level, occupation, cigarette smoking, and alcohol consumption
Areca nut chewing	OPMDs: 8.8 (3.2–24.5)	Juntanong et al. (2016) Thailand Cross-sectional study in 2014; 2300 study participants. Estimates adjusted for tobacco smoking and alcohol consumption
Chewing betel quid without tobacco	Leukoplakia: Men: 6.6 (3.5–12.3) Women: 15.6 (8.3–29.4) OSF: Men: 22.9 (7.3–71.7) Women: 13.0 (5.2–32.6)	Yang et al. (2010) Taiwan (China) Cross-sectional study in October–December 2005; 2 cancer cases, 313 precancers, 340 OPMD cases, and 1365 healthy people. Adjusted ORs computed by multiple logistic regressions with sex, age, smoking, and alcohol consumption as covariates

Table S2.10 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs

Risk factor[a]	**OR (95% CI)**[b]	**Reference** **Location** **Study design/adjustments/comments**
Betel quid chewing	Leukoplakia: 8.6 (0.8–88.2) OSF: 65.9 (3.9–∞)	Chung et al. (2005) Taiwan (China) Cross-sectional study in 1998–1999; 1075 study participants. Estimates for chewers who were not smoking or drinking
Paan without tobacco (a mixture of betel leaf, areca nut, and lime)	Leukoplakia: 3.7 (0.9–15.1)	Pearson et al. (2001) Bangladesh Multicentre cross-sectional study on Bangladeshi adults aged ≥ 40 yr in the United Kingdom; 137 study participants

BMI, body mass index; CI, confidence interval; HR, hazard ratio; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; RR, relative risk; SCC, squamous cell carcinoma; vs, versus; yr, year or years.

[a] As reported in the publication.

[b] OR (95% CI) for chewers versus non-chewers, unless indicated otherwise.

Table S2.11 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs – dose–response relationship

Risk factor[a]	OR (95% CI)[b]	Reference Location Study design/adjustments/comments
Dried fibre shell of processed betel quid	Oral cancer: Frequency of use (times/day): 1–10: 4.7 (2.7–78.0) 11–19: 8.8 (2.3–34.8) > 20: 8.0 (3.3–20.1) Duration of use (yr): < 10: 5.3 (2.9–9.9) 10–19: 4.8 (2.4–9.6) > 20–29: 8.4 (2.4–29.0) Age at start of chewing (yr): < 30: 15.3 (3.4–68.3) ≥ 30: 4.7 (2.8–7.8)	Hu et al. (2020) Hunan Province, China Case–control study in 2014–2015; 304 cases and 304 controls. Estimates adjusted for smoking, alcohol consumption, age, sex, education level, occupation, and marital status
Betel quid chewing	OPMDs: Intensity of chewing, HR: High: 4.5 (2.7–7.6) Low: 2.4 (1.6–3.6)	Yen et al. (2019) Taiwan (China) Cohort study based on both nationwide oral and colorectal cancer screening programmes implemented in 2004–2009; 235 234 study participants; OPMD, n = 33 082. Intensity corresponds to duration × quantity; low intensity (< median) and high intensity (> median). Estimates were for chewing only compared with smoking only. Adjusted by multivariate analysis
Betel quid chewing	Oral cancer: Quantity (packs of 20 quids/yr): 0.21–11.50: 5.3 (3.7–7.5) > 11.50: 13.5 (9.7–18.7)	Yang et al. (2014) Taiwan (China) Case–control study in 2004–2011; 463 oral cancer cases and 623 controls. Estimates adjusted for age, ethnicity, education level, tobacco smoking, and alcohol consumption

Table S2.11 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs – dose–response relationship

Risk factor[a]	OR (95% CI)[b]	Reference Location Study design/adjustments/comments
Betel quid chewing	Oral cancer: Age at start of chewing (yr): 1–20: 9.4 (4.3–20.3) > 20: 15.0 (7.2–31.0) Duration of chewing (yr): 1–20: 20.0 (8.8–45.6) > 20: 9.0 (4.4–18.6)	Chen et al. (2011) Taiwan (China) Case–control study; 247 oral cancer cases and 338 controls. Adjusted for age, education level, employment status, religion, and covariates (use of alcohol, betel quid, and cigarettes)
Tobacco-free betel quid: unripe areca nut, slaked lime, and a piece of betel leaf or inflorescence or stem of *Piper betle* Linn.	Oral cancer: Age at start of chewing (yr), HR: < 20: 2.5 (1.9–3.4) ≥ 20: 1.5 (1.2–1.8) Daily use (quids/day), HR: 1–19: 1.6 (1.3–2.0) ≥ 20: 1.6 (1.3–2.0)	Lee et al. (2011) Taiwan (China) Hospital-based case–control study in 2001–2007; 1522 study participants. Estimates adjusted for sex, ethnicity, education level, diet, cigarette smoking, and alcohol consumption
Chewing betel quid without tobacco	OPMDs: Quantity chewed (quids/day): 1–3: 2.6 (0.6–11.4) 4–5: 10.2 (2.8–37.0) 6–10: 17.7 (5.1–61.3) > 10: 75.5 (17.6–324.7) Age at start of chewing (yr): ≤ 18: 15.2 (4.2–54.2) > 18: 9.4 (3.0–29.4) Duration of chewing (yr): ≤ 10: 8.1 (2.3–28.5) 10–20: 8.2 (2.2–30.3) > 20: 18.6 (4.9–69.6)	Amarasinghe et al. (2010a) Sri Lanka Case–control study; 1029 study participants Adjusted for sex, age, education level, occupation, BMI, diet, tobacco smoking, and alcohol consumption

Table S2.11 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs – dose–response relationship

Risk factor[a]	OR (95% CI)[b]	Reference Location Study design/adjustments/comments
Betel quid without tobacco	Oral cancer death: Quantity (pieces/day), HR: 1–5: 5.3 (2.1–13.7) 6–9: 12.1 (4.3–33.6) ≥ 10: 25.6 (10.0–65.6)	Wen et al. (2010) Taiwan (China) Cohort study of adults; 177 271 study participants. Estimates adjusted for age and alcohol consumption represent total risk for chewers compared with non-smoking non-chewers
Betel quid chewing	Dose–response by quid chewed (pieces/day): Leukoplakia: 1–10: 2.1 (1.6–2.8) 11–20: 3.0 (2.1–4.3) ≥ 20: 5.4 (3.8–7.5) Erythroplakia: 1–10: 3.7 (1.6–8.8) 11–20: 13.8 (5.8–33.0) ≥ 20: 36.6 (15.9–84.2) OSF: 1–10: 1.3 (0.9–1.7) 11–20: 3.9 (2.8–5.6) ≥ 20: 6.9 (5.0–9.6)	Yen et al. (2007) Taiwan (China) Cohort study in 1998–1999; 8360 study participants. Estimates vs occasional use of non-smoking, non-drinking chewers. Adjusted for age, education level, occupational level, and quantity of the 3 risk factors (betel quid, cigarette, and alcohol use)
Betel quid without tobacco	Leukoplakia: Duration of chewing (yr): 1–10: 16.3 (7.5–35.7) > 11: 12.6 (4.2–38.0) Frequency of chewing (times/day): 1–10: 12.4 (5.7–27.2) > 11: 57.6 (17.5–189.3)	Jacob et al. (2004) Kerala, India Case–control study; 927 leukoplakia cases, 170 OSF cases, 100 erythroplakia cases, 115 multiple oral precancer cases, and 47 773 controls. Estimates adjusted for age, sex, education level, and BMI, in non-smokers and non-drinkers

Table S2.11 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs – dose–response relationship

Risk factor[a]	OR (95% CI)[b]	Reference Location Study design/adjustments/comments
	OSF:	
	Duration of chewing (yr):	
	1–10: 39.1 (13.8–110.9)	
	> 11: 15.2 (2.68–86.3)	
	Frequency of chewing (times/day):	
	1–10: 28.9 (9.9–597.6)	
	> 11: 133.0 (29.6–597.6)	
	Erythroplakia:	
	Duration of chewing (yr):	
	1–10: 14.09 (2.2–91.8)	
	> 11: 28.0 (2.0–386.9)	
	Frequency of chewing (times/day):	
	1–10: 11.6 (1.7–78.3)	
	> 11: 68.9 (6.0–787.0)	
3 types: areca nut with a piece of inflorescence of *Piper betle* Linn., areca nut with a piece of betel leaf, and both mixed	Leukoplakia:	Lee et al. (2003) Taiwan (China)
	Duration of chewing (yr):	Case–control study in 1994–1995; 219 leukoplakia or OSF cases and 876 controls. Estimates adjusted for education level, occupation, cigarette smoking, and alcohol consumption
	1–10: 15.9 (7.1–35.6)	
	11–20: 20.7 (8.9–48.2)	
	> 21: 24.0 (10.8–53.4)	
	Dose–response: 3.0 (2.3–3.9)	
	Quantity of chewing (pieces/day):	
	1–10: 16.6 (8.2–33.8)	
	11–20: 21.0 (8.8–49.7)	
	> 21: 38.5 (14.1–105.1)	
	Dose–response: 3.8 (2.8–5.1)	

Table S2.11 Chewing of areca nut (including betel quid) without tobacco and risk of oral cancer or OPMDs – dose–response relationship

Risk factor[a]	OR (95% CI)[b]	Reference Location Study design/adjustments/comments
	OSF:	
	Duration of chewing (yr):	
	1–10: 30.9 (11.3–84.7)	
	11–20: 41.9 (14.1–124.9)	
	> 21: 39.3 (11.7–131.7)	
	Dose–response: 4.2 (2.9–5.8)	
	Quantity of chewing (pieces/day):	
	1–10: 31.4 (11.9–82.5)	
	11–20: 37.4 (12.6–110.4)	
	> 21: 53.5 (16.4–174.8)	
	Dose–response: 4.1 (2.9–5.8)	
Areca nut chewing	Leukoplakia:	Shiu et al. (2000) Taiwan (China)
	Intensity of chewing:	
	Low: 9.1 (1.0–81.6)	Case–cohort study in 1988–1998; 435 leukoplakia cases. Adjusted for alcohol consumption and cigarette smoking
	High: 22.5 (1.4–351.0)	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; vs, versus; yr, year or years.

[a] As reported in the publication.

[b] OR (95% CI) for chewers versus non-chewers, unless indicated otherwise.

Table S2.12 HPV16 positivity and risk of oral and oropharyngeal cancers

Risk factor	Level of exposure	Range of RR or OR (95% CI)[a]	References
Oral cancer			
Oral/oropharyngeal HPV16 DNA	Positive vs negative	Case–control studies: ORs ranging from 1.0 to 3.4 Cohort studies: RR of 4.5	Pintos et al. (2008); Gillison et al. (2012); Agalliu et al. (2016)
HPV16 L1 serum antibodies	Seropositive vs seronegative	Case–control studies: ORs ranging from 1.2 to 5.5 Cohort studies: RRs ranging from 1.2 to 3.6	Herrero et al. (2003); Gillison et al. (2012); Anantharaman et al. (2013); Kreimer et al. (2013)
HPV16 E6 serum antibodies	Seropositive vs seronegative	Case–control studies: ORs ranging from 0.9 to 4.9 Cohort studies: RR of 1.3	Herrero et al. (2003); Gillison et al. (2012); Anantharaman et al. (2013); Kreimer et al. (2013)
Oropharyngeal cancer			
Oral/oropharyngeal HPV16 DNA	Positive vs negative	Case–control studies: ORs ranging from 14.6 to 131.0 Cohort studies: RR of 22.4	D'Souza et al. (2007); Gillison et al. (2008, 2012); Agalliu et al. (2016); Tota et al. (2019)
HPV16 L1 serum antibodies	Seropositive vs seronegative	Case–control studies: ORs ranging from 1.1 to 182 Cohort studies: RRs ranging from 2.3 to 14.4	Mork et al. (2001); Pintos et al. (2008); Gillison et al. (2012); Anantharaman et al. (2013); Kreimer et al. (2013)
HPV16 E6 serum antibodies	Seropositive vs seronegative	Case–control studies: ORs ranging from 9.2 to 231 Cohort studies: RRs ranging from 98 to 274	Pintos et al. (2008); Gillison et al. (2012); Anantharaman et al. (2013); Kreimer et al. (2013)

CI, confidence interval; HPV, human papillomavirus; OR, odds ratio; RR, relative risk; vs, versus.

[a] Estimates across studies are adjusted for age, sex, smoking, and alcohol consumption.

Prepared by the Working Group.

Table S2.13 Combined effects of established risk factors

Reference Study type and location	Outcome	Specific exposure	Individual effects, OR or RR, (95% CI)	Joint effects and interaction tests, OR or RR (95% CI)	Interpretation
Tobacco smoking × alcohol consumption					
Anantharaman et al. (2011) Multicentre case–control study in Europe	Oral cancer	Smoking	Ever smoking: 2.4 (1.7–3.2) Ever alcohol consumption: 1.0 (0.5–2.2)	Smoking + alcohol consumption: 7.1 (5.0–10.0) Multiplicative interaction parameter: 2.8 (1.3–6.1)	Greater-than-multiplicative interaction
	Oropharyngeal cancer	Smoking	Ever smoking: 3.7 (2.5–5.3) Ever alcohol consumption: 1.2 (0.5–2.8)	Smoking + alcohol consumption: 9.9 (6.7–14.8) Multiplicative interaction parameter: 2.2 (0.9–5.2)	Greater-than-multiplicative interaction
Hashibe et al. (2009) Pooled analysis of 17 case–control studies in Europe and the USA	Oral cancer	Tobacco use (chewing + smoking)	Ever smoking: 1.7 (1.1–2.8) Ever alcohol consumption: 0.7 (0.6–1.0)	Smoking + alcohol consumption: 4.8 (2.6–8.8) Multiplicative interaction parameter: 3.1 (1.8–5.2)	Greater-than-multiplicative interaction
	Pharyngeal cancer	Tobacco use (chewing + smoking)	Ever smoking: 1.9 (1.4–2.6) Ever alcohol consumption: 1.3 (0.9–1.8)	Smoking + alcohol consumption: 5.4 (3.2–9.2) Multiplicative interaction parameter: 1.9 (1.4–2.6)	Greater-than-multiplicative interaction
Petti et al. (2013) Meta-analysis of 14 studies, 7 in India and 7 in Taiwan (China)	Oral cancer	Smoking	Smoking: 3.6 (1.9–7.0) Alcohol consumption: 2.2 (1.6–3.0)	Smoking + alcohol consumption: 6.3 (5.4–7.3) RERI estimates: 1.5 (−2.1 to 3.4)	Consistent with risk additivity
Chewing betel quid with or without tobacco × other risk factors					
Petti et al. (2013) Meta-analysis of 14 studies, 7 in India and 7 in Taiwan (China)	Oral cancer	Chewing betel quid with or without tobacco	Ever chewing: 7.9 (6.7–9.3) Ever smoking: 3.6 (1.9–7.0) Ever alcohol consumption: 2.2 (1.6–2.9)	Chewing + smoking: 16.0 (13.7–18.8) Chewing + alcohol consumption: 10.4 (8.0–13.6) Chewing + smoking + alcohol consumption: 40.0 (35.1–45.8) RERI estimates: Chewing + smoking: 5.5 (1.1–8.2) Chewing + alcohol consumption: 1.3 (−1.3 to 4.5) Chewing + smoking + alcohol consumption: 28.4 (22.9–33.7)	Greater-than-additive interaction with smoking and alcohol consumption
Muwonge et al. (2008) Nested case–control in Trivandrum, India	Oral cancer	Chewing *paan* with or without tobacco	Ever chewing: 4.8 (2.2–10.5) Ever smoking: 1.3 (0.6–2.6) Ever alcohol consumption: 1.2 (0.3–6.0)	Chewing + smoking: 5.5 (2.6–11.4) Chewing + alcohol consumption: 6.4 (2.8–14.6) Chewing + smoking + alcohol consumption: 4.8 (2.5–9.3)	Consistent with risk additivity

Table S2.13 Combined effects of established risk factors

Reference Study type and location	Outcome	Specific exposure	Individual effects, OR or RR, (95% CI)	Joint effects and interaction tests, OR or RR (95% CI)	Interpretation
Subapriya et al. (2007) Case–control study in Chidambaram, India	Oral cancer	Chewing *paan* with or without tobacco	Ever chewing: 4.1 Ever smoking: 7.45 Ever alcohol consumption: 3.88	Chewing + smoking: 3.94 Chewing + alcohol consumption: 4.21 Chewing + smoking + alcohol consumption: 11.34	Consistent with risk additivity
Znaor et al. (2003) Case–control study in India	Oral cancer	Chewing betel quid without tobacco	Ever chewing: 3.4 (2.0–5.7) Ever smoking: 2.4 (1.9–3.1) Ever alcohol consumption: 2.6 (1.4–4.6)	Chewing + smoking: 4.8 (2.8–8.3) Chewing + alcohol consumption: 4.4 (1.5–12.3) Chewing + smoking + alcohol consumption: 8.1 (4.7–14.0)	Greater-than-multiplicative interaction with smoking
		Chewing betel quid with added tobacco	Ever chewing: 9.3 (6.8–12.7)	Chewing + smoking: 8.5 (6.1–11.9) Chewing + alcohol consumption: 24.3 (14.9–39.6) Chewing + smoking + alcohol consumption: 16.3 (12.1–22.0)	Consistent with risk additivity
Znaor et al. (2003) Case–control study in India	Pharyngeal cancer	Chewing betel quid without tobacco	Ever chewing: 1.6 (0.6–4.2) Ever smoking: 3.5 (2.5–4.9) Ever alcohol consumption: NR	Chewing + smoking: 4.9 (2.3–10.4) Chewing + alcohol consumption: NR Chewing + smoking + alcohol consumption: 10.7 (5.5–20.9)	Greater-than-multiplicative interaction with smoking
		Chewing betel quid with added tobacco	Ever chewing: 3.7 (2.2–6.3)	Chewing + smoking: 4.5 (2.7–7.6) Chewing + alcohol consumption: 4.3 (1.7–10.6) Chewing + smoking + alcohol consumption: 13.4 (8.9–20.3)	Greater-than-multiplicative interaction with smoking
Sankaranarayanan et al. (1989) Case–control study in Kerala, India	Gingival cancer	Chewing *paan* with or without tobacco	Ever chewing: 8.8 (3.6–21.5) Ever smoking (bidi): 3.8 (1.2–11.7) Ever alcohol consumption: NR	Chewing + smoking: 16.3 (6.5–40.9) Chewing + alcohol consumption: 21.3 (7.7–58.8) Chewing + smoking + alcohol consumption: 21.4 (6.8–67.2)	Greater-than-additive interaction with smoking and alcohol consumption
Lee et al. (2003) Case–control study in Taiwan (China)	Leukoplakia	Chewing betel quid without tobacco	Ever chewing: 10.0 (3.1–32.7) Ever smoking: 2.4 (1.0–5.5) Ever alcohol consumption: 1.0 (0.4–2.6)	Chewing + smoking: 40.2 (16.3–99.2) Chewing + alcohol consumption: 16.8 (7.2–39.5) Synergy index estimates: Chewing + smoking: 3.8 (1.4–10.5) Chewing + alcohol consumption: 1.1 (0.6–2.1)	Greater-than-additive interaction with smoking

Table S2.13 Combined effects of established risk factors

Reference Study type and location	Outcome	Specific exposure	Individual effects, OR or RR, (95% CI)	Joint effects and interaction tests, OR or RR (95% CI)	Interpretation
Lee et al. (2003) Case–control study in Taiwan (China)	Oral submucous fibrosis	Chewing betel quid without tobacco	Ever chewing: 39.3 (7.5–206.9) Ever smoking: 2.3 (0.6–9.1) Ever alcohol consumption: 0.7 (0.1–3.4)	Chewing + smoking: 57.9 (16.0–209.6) Chewing + alcohol consumption: 31.7 (10.1–99.3) Synergy index estimates: Chewing + smoking: 1.4 (0.4–4.7) Chewing + alcohol consumption: 1.2 (0.6–2.5)	Consistent with risk additivity
Hashibe et al. (2000b) Case–control study in Kerala, India	Erythroplakia	Chewing *paan* with or without tobacco	Ever chewing: 43.3 (13.3–141.1) Ever smoking: 5.8 (1.3–25.3) Ever alcohol consumption: 3.7 (0.9–16.1)	Chewing + smoking: 50.1 (14.1–178.4) Chewing + alcohol consumption: 43.1 (16.1–115.3)	Consistent with risk additivity
HPV16 infection × other risk factors					
Anantharaman et al. (2016) Joint analysis of a multicentre case–control study and nested case–control study in Europe	Oropharyngeal cancer	HPV16 L1 serology	HPV16: 5.8 (4.0–8.4) Ever smoking: 6.7 (4.0–11.2)	HPV16 + smoking: 9.1 (5.9–14.1) Synergy index: 0.7 (0.5–1.1)	Consistent with risk additivity
		HPV16 E6 serology	HPV16: 235.7 (99.9–555.7) Ever smoking: 6.8 (4.5–10.3)	HPV16 + smoking: 355.8 (177.0–715.3) Synergy index: 1.3 (0.5–3.4)	Consistent with risk additivity
D'Souza et al. (2007) Case–control study in Maryland, USA	Oropharyngeal cancer	HPV16 L1 serology	HPV16: 37.1 (15.6–88.4) Smoking (> 20 pack-years): 2.8 (1.2–6.4) Alcohol consumption (> 15 drink-years): 2.5 (1.1–5.5)	HPV16 + smoking: 27.8 (6.7–114.6) HPV16 + alcohol consumption: 29.1 (7.4–115.3) HPV16 + smoking + alcohol consumption: 19.4 (3.3–113.9)	Consistent with risk additivity
		Oral HPV16 DNA	HPV16: 17.2 (6.4–46.3) Smoking (> 20 pack-years): 2.4 (1.2–4.7) Alcohol consumption (> 15 drink-years): 2.2 (1.1–4.3)	HPV16 + smoking: 13.2 (2.4–65.8) HPV16 + alcohol consumption: 16.6 (3.6–81.9) HPV16 + smoking + alcohol consumption: 11.0 (1.0–120.6)	Consistent with risk additivity
Smith et al. (2004) Case–control study in Iowa, USA	Oral and oropharyngeal cancers	Oral hrHPV DNA	hrHPV: 1.4 (0.5–3.6) Smoking (> 30 pack-years): 1.6 (0.9–2.8) Alcohol consumption (> 21 drinks/week): 2.6 (1.4–4.8)	hrHPV + smoking: 5.5 (2.1–14.1) hrHPV + alcohol consumption: 18.8 (5.1–69.5) Synergy indices: hrHPV + smoking: 4.5 (0.7–27.4) hrHPV + alcohol consumption: 7.4 (1.7–33.4)	Consistent with risk additivity for smoking. Greater-than-additive interaction with alcohol consumption

Table S2.13 Combined effects of established risk factors

Reference Study type and location	Outcome	Specific exposure	Individual effects, OR or RR, (95% CI)	Joint effects and interaction tests, OR or RR (95% CI)	Interpretation
Schwartz et al. (1998) Case–control study in Washington State, USA	Oral and oropharyngeal cancer	HPV16 L1 serology	HPV16: 1.7 (1.1–2.6) Current smoking: 3.2 (2.0–5.2) Alcohol consumption (> 15 drinks/week): 2.0 (1.1–3.6)	HPV16 + smoking: 8.5 (5.1–14.4) HPV16 + alcohol consumption: 4.4 (2.5–7.6) Synergy indices: HPV16 + smoking: 2.6 (1.3–5.0) HPV16 + alcohol consumption: 1.5 (0.6–3.4)	Greater-than-additive interaction with smoking. Consistent with risk additivity for alcohol consumption

CI, confidence interval; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; NR, not reported; OR, odds ratio; RERI, relative excess risk due to interaction; RR, relative risk.

Table S2.14 Studies of chronic mechanical irritation and oral cancer

Reference	Study type	Description of chronic mechanical irritation	OR (95% CI)
Velly et al. (1998)	Case–control	Oral sore from ill-fitting dentures	2.3 (1.2–4.6)
		Broken teeth	1.13 (0.75–1.69)
Lockhart et al. (1998)	Case–control	Dental and prosthetic factors	No significant differences
Rosenquist (2005)	Case–control	> 5 defective teeth	3.1 (1.2–8.2)
		Poorly fitting or defective complete dentures	3.8 (1.3–11.4)
Vaccarezza et al. (2010)	Case–control	Recurrent sores from ill-fitting denture	4.58 (1.52–13.76)
Piemonte et al. (2010)	Cross-sectional	Chronic mechanical irritation	$P < 0.0001$
Bektas-Kayhan et al. (2014)	Case–control	Chronic trauma	$P = 0.0001$
Manoharan et al. (2014)	Meta-analysis	Denture	1.42 (1.01–1.99)
		Ill-fitting denture	3.90 (2.48–6.13)
Huang et al. (2015)	Case–control	Bad prosthesis	2.33 (1.79–3.04)
		Recurrent oral ulcerations	3.96 (2.11–7.44)
		Recurrent oral ulcerations in non-smokers	5.21 (2.42–11.18)
		Recurrent oral ulcerations in non-drinkers	4.71 (2.37–9.36)
Li et al. (2015)	Case–control	Repetitive dental ulcers	5.12 (3.17–8.28)
Singhvi et al. (2017)	Meta-analysis	Denture	1.45 (1.28–1.64)
		Ill-fitting denture	2.62 (2.1–3.25)
Piemonte and Lazos (2018)	Case–control	Chronic mechanical irritation	4.84 (2.12–11.08)
Chen et al. (2018)	Case–control	Repetitive dental ulcer (women)	6.00 (3.67–9.80)
		Repetitive dental ulcer (men)	4.76 (2.75–8.21)

CI, confidence interval; OR, odds ratio.

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
Coffee consumption							
He et al. (2020) Meta-analysis of 14 case–control studies and 5 cohort studies	6456 patients with oral cancer Percentage male ranged from 44.5% to 100% among the studies Exposure assessment method: FFQ	Oral cavity	Highest vs lowest category of coffee consumption:			Each study had its own covariates for which the estimates were adjusted	Recall bias of case–control studies. The significant associations may be affected by study design, year of publication, country where the study took place, and lifestyle habits. The mean age of participants and the prevalence of oral cavity cancer in different age groups was lacking from most studies. The current analysis is based on pooled data, and detailed subgroup analyses were not conducted
			Case–control	4 studies	0.79 (0.40–1.58) P = 0.512 I^2 = 81.2% $P_{heterogeneity}$ = 0.001		
			Cohort	0 studies	–		
			Intermediate vs low coffee consumption:				
			Case–control	3 studies	0.76 (0.54–1.06) P = 0.108 I^2 = 47.8% $P_{heterogeneity}$ = 0.147		
			Cohort	0 studies	–		
Miranda et al. (2017) Meta-analysis of 13 case–control studies and4 cohort studies	5151 patients Exposure assessment method: FFQ	Oral cavity and pharynx	Highest vs lowest category of coffee consumption:			Each study had its own covariates for which the estimates were adjusted	The exact location of the cancers was taken into account, highlighting that the inverse association was clearer when cases of pharyngeal or pharyngeal cancers were taken into account together with oral cancer cases High-quality studies without publication bias observed Little information was provided on the coffee beans (Arabica or Robusta), the brewing procedure, the concentration of caffeine, or the size of the cups used Also, different categories of coffee consumption in the studies do not allow quantification of the association
			Overall	17 studies	0.69 (0.57–0.84) P = 0.009		
			Case–control	13 studies	0.67 (0.53–0.84) P = 0.033		
			Cohort	4 studies	0.86 (0.69–1.08) P = 0.085		
			Americas	5 studies	0.80 (0.52–1.13) P = 0.049		
			Asia	4 studies	0.65 (0.44–0.97) P = 0.128		
			Europe	8 studies	0.64 (0.48–0.85) P = 0.072		
			> 300 cases	7 studies	0.73 (0.60–0.90) P = 0.159		

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
			< 300 cases	10 studies	0.64 (0.45–0.91) P = 0.006		The temperature of the coffee was not controlled
		Oral cavity	Overall	6 studies	0.82 (0.58–1.16) P = 0.056		Tobacco and alcohol consumption may differ across the selected articles
		Pharynx	Overall	4 studies	0.72 (0.54–0.95) P = 0.188		
Galeone et al. (2010) Pooled analysis of 9 case–control studies of INHANCE cohort (Europe, North America, Central America)	1191 oral cavity, 2112 oropharynx/hypopharynx, 612 oral cavity/pharynx NOS, 1224 laryngeal cancer cases, and 9028 controls 76% male for cancer of total oral cavity/pharynx (70.3% controls), and 90.3% male for laryngeal cancer (70.4% controls) Exposure assessment method: FFQ	Oral cavity	Consumption of caffeinated coffee (cups/day):			Age, sex, race/ethnicity, education level, study, cigarette smoking (pack-years), duration of cigar smoking, duration of pipe smoking, alcohol intake, weight, and vegetable and fruit intake	Large number of oral cancer cases included Lack of information on HPV infection. Lack of information on the duration of coffee drinking. Lack of information on the type of beans (Arabica or Robusta). Some of the case–control studies may overlap with case–control studies included in the other meta-analysis studies, because references to the studies correspond to currently unpublished data
			Non-drinkers	177	1 (ref)		
			Drinkers	953	0.62 (0.40–0.99)		
			> 0 to < 3	538	0.65 (0.42–1.02)		
			3 to 4	259	0.52 (0.27–0.98)		
			> 4	156	0.46 (0.30–0.71)		
			Increment of 1 cup/day		0.96 (0.92–0.99)		
			P_{trend} < 0.01				
			$P_{heterogeneity}$ < 0.01				
		Oral cavity	Consumption of decaffeinated coffee (cups/day):				
			Non-drinkers	512	1 (ref)		
			Drinkers	89	1.17 (0.81–1.69)		
			> 0 to < 1	37	1.18 (0.67–2.08)		
			≥ 1	52	1.51 (0.97–2.35)		
			Increment of 1 cup/day		1.04 (0.87–1.23)		
			P_{trend} = 0.17				
			$P_{heterogeneity}$ = 0.67				

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
Tea consumption							
Ren et al. (2010) USA Enrolment 1995–1996; follow-up to 2003 Cohort	481 563 participants; 286 402 men and 195 161 women aged 50–71 yr in NIH-AARP Study Exposure assessment method: FFQ	Oral cavity	Hot tea consumption:		HR:	Age, sex, tobacco smoking, alcohol consumption, BMI, education level, ethnicity, usual physical activity throughout the day, vigorous physical activity, daily intake of fruit, daily intake of vegetables, daily intake of red meat, daily intake of white meat, and daily intake of calories	Large prospective analysis with exposure information collected before cancer diagnosis. Lag analysis was done to examine whether reverse causation affected the results Small number of incident oral cancers (391). Lack of information on the drinking temperature of hot tea and the type of tea consumed (green, black, or herbal). Only 16% of participants drank ≥ 1 cup/day of hot tea, which is lower intake than in most populations in Asia
			None	153	1 (ref)		
			< 1 cup/mo	80	0.96 (0.73–1.26)		
			1–3 cups/mo	57	0.84 (0.61–1.14)		
			1–6 cups/wk	57	0.88 (0.65–1.21)		
			≥ 1 cup/day	44	0.75 (0.53–1.06)		
			P_{trend} = 0.083				
			Iced tea consumption:				
			None	79	1 (ref)		
			≤ 3 cups/mo	85	0.98 (0.72–1.34)		
			1–6 cups/wk	114	0.96 (0.72–1.29)		
			≥ 1 cup/day	114	0.89 (0.67–1.19)		
			P_{trend} = 0.42				
Zhou et al. (2018) Meta-analysis of 14 case–control studies: Asia (7 China, 1 India); Americas (2 Brazil); Europe (1 Denmark, 1 France, 1 Italy); Africa (1 Egypt)	5920 patients and 10 553 controls Exposure assessment method: FFQ	Oral cavity	Tea consumption:			The maximally adjusted ratio was selected as the only evaluation index for preventing possible confounders when studies reported multivariable adjusted-effect estimates	The risk of oral cancer decreased by 6.2% with each increase of 1 cup/day in the range 0–8.75 cups/day Detailed subgroup analysis was performed. First dose–response meta-analysis Only case–control studies are included, which may lead to publication bias and selection bias. Pooled data were used for the meta-analysis, lacking individual data In the dose–response analysis, 120 mL/day was transformed to 1 cup/day
			Overall	14 studies	0.700 (0.609–0.805)		
			Asia	8 studies	0.661 (0.560–0.780)		
			Americas	2 studies	1.250 (0.797–1.967)		
			Europe	3 studies	0.714 (0.573–0.891)		
			Green tea	6 studies	0.656 (0.533–0.808)		
			Black tea	3 studies	0.940 (0.786–1.125)		
			Oolong tea	4 studies	0.567 (0.420–0.766)		
			Drinking vs no drinking	8 studies	0.647 (0.580–0.723)		
			Highest vs lowest consumption	6 studies	0.836 (0.736–0.950)		

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
			Male	3 studies	0.838 (0.723–0.971)		The dose–response analysis suggested that high dietary dose, long-term and high concentration of tea intake may be associated with a reduced risk of oral cancer
			Female	4 studies	0.692 (0.514–0.931)		
			≤ 60 yr	3 studies	0.686 (0.520–0.852)		
			> 60 yr	3 studies	0.547 (0.384–0.709)		
Filippini et al. (2020) China (Asia) Meta-analysis of 1 cohort study and 4 case–control studies	2343 cases and 53634 controls	Oral cavity	Green tea consumption: Highest vs lowest exposure	5 studies	0.71 (0.62–0.82)	Age, smoking	
Galeone et al. (2010) Pooled analysis of 9 case–control studies of INHANCE cohort (Europe, North America, Central America)	1191 oral cavity, 2112 oropharynx/hypopharynx, 612 oral cavity/pharynx NOS, 1224 laryngeal cancer cases, and 9028 controls 76% male for cancer of total oral cavity/pharynx (70.3% controls), and 90.3% male for laryngeal cancer (70.4% controls) Exposure assessment method: FFQ	Oral cavity	Tea consumption (cups/day): Non-drinkers Drinkers ≤ 1 > 1 Increment of 1 cup/day P_{trend} = 0.90 $P_{heterogeneity}$ = 0.45	 604 523 433 90	 1.00 (ref) 1.06 (0.88–1.27) 1.10 (0.92–1.33) 0.94 (0.68–1.29) 0.98 (0.91–1.06)	Age, sex, race/ethnicity, education level, study, cigarette smoking (pack-years), duration of cigar smoking, duration of pipe smoking, alcohol intake, weight, and vegetable and fruit intake	A large number of oral cancer cases from different countries A pooled estimate based on case–control studies with inherent limitations of that study design. Lack of information on the duration of tea drinking. Lack of information on the type of tea consumed. Some of the case–control studies may overlap with case–control studies included in the other meta-analysis studies

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
Consumption of fruits and vegetables							
Chuang et al. (2012) Pooled analysis of 22 case–control studies of INHANCE cohort	14 520 cases and 22 737 controls (mixed hospital and non-hospitalized) 26.6% oral cavity, 32.7% pharynx, 10.4% oral/pharynx NOS, 28.1% larynx, 2.2% HNC NOS 78.8% male cases All ages Exposure assessment method: questionnaire-based standardized interview	Oral cavity	Consumption of vegetables: Quartile 4 vs quartile 1 Consumption of fruits: Quartile 4 vs quartile 1	 3342/20 011 3183/19 759	 0.69 (0.61–0.79) 0.46 (0.38–0.56)	All studies: matched on age and sex Adjustments for the subgroups not clear	A large number of people from different geographical areas Non-standardized questionnaires but population-based. No quantitative information on food consumption. Total energy intake is not known for all studies. Heterogeneity across studies was detected for almost all food items
Pavia et al (2006) North America, South America, Europe, Asia Meta-analysis of 15 case–control studies and 1 cohort study	65802 cases and 60951 controls	Oral cavity	Per portion of fruits Per portion of vegetables	12 studies 11 studies	0.49 (0.39–0.63) 0.43 (0.31–0.59)	Age, sex, cigarette smoking, and alcohol consumption	
Galvão De Podestá et al. (2019) Brazil July 2011–July 2017 Case–control	847 cases (398 oral cavity cancer cases, 249 oropharyngeal cancer cases), 893 matched hospital controls 77.3% male among oral cancer cases and controls Ages 18–80 yr Exposure assessment method:	Oral cavity	Consumption of apples or pears: Never or < 1/mo 1–3/mo 1–2/we On most days but not every day Every day	 103/87 74/150 109/292 42/147 20/92	 1 (ref) 0.58 (0.35–0.98) 0.51 (0.31–0.82) 0.41 (0.22–0.76) 0.34 (0.17–0.66)	Matched on age and sex Adjusted for consumption of vegetables (except potatoes), natural fruit juice, carrots, raw greens and vegetables, rice and beans, and alcohol	A large, multicentre study including 3 Brazilian states. Subtypes were examined separately Limitations are recall bias and the modification of the diets of the participants during the pre-diagnosis phase of the disease

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
	self-reported food-frequency questionnaires						
			Consumption of citrus fruits (oranges, lemons, tangerines):				
			Never or < 1/mo	78/48	1 (ref)		
			1–3/mo	77/87	0.84 (0.44–1.59)		
			1–2/we	117/243	0.52 (0.29–0.93)		
			On most days but not every day	52/182	0.35 (0.18–0.67)		
			Every day	51/208	0.34 (0.17–0.66)		
			Consumption of fresh tomatoes:				
			Never or < 1/mo	62/35	1 (ref)		
			1–3/mo	39/43	0.65 (0.29–1.45)		
			1–2/we	105/193	0.43 (0.22–0.83)		
			On most days but not every day	94/234	0.32 (0.16–0.62)		
			Every day	75/263	0.28 (0.14–0.56)		
Maasland et al. (2015) The Netherlands Enrolment in September 1986; follow-up for 20.3 yr Cohort	120 852 participants; 415 HNC cases (131 oral cavity cancer, 88 oro/hypopharyngeal cancer, 3 oral cavity/pharynx unspecified or overlapping, and 193 laryngeal cancer); 57.3% male among 131 oral cavity cancer cases	Oral cavity	Total consumption of vegetables and fruits:			Adjusted for age (years), sex, cigarette smoking [status (never/former/current), frequency (number of cigarettes per day; continuous, centred), duration (number of years; continuous, centred)], and alcohol consumption (grams of ethanol per day; continuous)	Strengths are the prospective nature, the completeness and duration of follow-up, and subtype analysis Limitations are that dietary habits may have changed through the years, and that HPV status, pharmaceutical drugs, and oral hygiene were not taken into account Quartiles: Total vegetables (median, 175 g/day; P25–P75, 126–233 g/day for all 415 HNC cases) Total fruits (median, 113 g/day; P25–P75, 56–203 g/day for all 415 HNC cases)
			Quartile 1	47	1 (ref)		
			Quartile 2	33	0.75 (0.47–1.19)		
			Quartile 3	29	0.63 (0.38–1.04)		
			Quartile 4	22	0.46 (0.27–0.81)		
			P_{trend} = 0.005				
			Continuous, per 25 g/day increment	131	0.95 (0.92–0.99)		
			Total consumption of vegetables:				
			Quartile 1	39	1 (ref)		
			Quartile 2	27	0.68 (0.41–1.13)		

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
	Ages 55–69 yr Exposure assessment method: 150-item FFQ (self-administered), validated against a 9-day diet record and by annual repeated measurements in a subgroup		Quartile 3	33	0.86 (0.52–1.41)		Composition: Total vegetables (cooked plus raw vegetables) Total fruits (apples/pears, bananas, grapefruits and fresh grapefruit juice, grapes, mandarins, oranges and fresh orange juice, raisins/other dried fruit, strawberries, and other fruits originating from an open-ended question on frequently consumed items not listed in the questionnaire) Citrus fruits (fresh lemon juice, grapefruits and fresh grapefruit juice, mandarins, and oranges and fresh orange juice)
			Quartile 4	32	0.71 (0.41–1.24)		
			P_{trend} = 0.36				
			Continuous, per 25 g/day increment	131	0.95 (0.89–1.02)		
			Total consumption of fruits:			Additionally adjusted for total vegetable intake (g/day; continuous)	
			Quartile 1	52	1 (ref)		
			Quartile 2	28	0.63 (0.39–1.03)		
			Quartile 3	30	0.79 (0.48–1.31)		
			Quartile 4	21	0.56 (0.33–0.97)		
			P_{trend} = 0.07				
			Continuous, per 25 g/day increment	131	0.95 (0.91–1.01)		
			Consumption of citrus fruits:			Additionally adjusted for total vegetable and fruit intake (g/day; continuous)	
			Quartile 1	45	1 (ref)		
			Quartile 2	31	0.73 (0.44–1.21)		
			Quartile 3	28	0.67 (0.39–1.15)		
			Quartile 4	27	0.94 (0.52–1.71)		
			P_{trend} = 0.95				
			Continuous, per 25 g/day increment	131	1.02 (0.92–1.13)		

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
Freedman et al. (2008) USA (states) 1995–1996; follow-up to 2000 Cohort	490 802 participants of NIH-AARP Diet and Health cohort; 787 HNC cases 77.3% male in the 787 cases Ages 50–71 yr Exposure assessment method: questionnaires by mail	Oral cavity	Total consumption of fruits and vegetables:			Adjusted for age at entry into cohort, alcohol intake, BMI, cigarette-smoke dose, education level, sex, total energy intake, usual activity throughout the day, and vigorous physical activity Quintile 5 additionally adjusted for continuous fruit intake	Questionnaire data were collected before diagnoses, minimizing possibility of recall bias Lack of information on smoking initiation, marijuana use, and past alcohol consumption Fruit and vegetable constituents: Total fruit and vegetables (no potatoes): total fruits and vegetables Total vegetables (no potatoes): spinach, turnip, collard greens, mustard, kale, coleslaw, cabbage, sauerkraut, carrots, dried beans, string beans, peas, corn, broccoli, cauliflower, Brussels sprouts, mixed vegetables, tomatoes, sweet peppers, lettuce salad, sweet potatoes, yams, tomato juice, tomato sauce, chili and salsa Total fruits: whole fruits + 1 fruit juice Whole fruits: apples, apple sauce, pears, bananas, dried fruit excluding apricots, peaches, nectarines, plums, cantaloupe, other melons, strawberries, oranges, tangerines, tangelos, grapefruit, and grapes Fruit juice: orange and grapefruit juice and other fruit juices and drinks
			Per serving per 1000 calories		HR: 0.93 (0.86–1.00)		
			Quintile 1	104	1 (ref)		
			Quintile 2	64	0.81 (0.59–1.11)		
			Quintile 3	57	0.81 (0.58–1.14)		
			Quintile 4	58	0.90 (0.64–1.28)		
			Quintile 5	36	0.61 (0.41–0.93)		
			P_{trend} = 0.052				
			Consumption of vegetables:				
			Per serving per 1000 calories		HR: 0.84 (0.73–0.95)		
			Quintile 1	100	1 (ref)		
			Quintile 2	60	0.72 (0.52–1.00)		
			Quintile 3	64	0.84 (0.61–1.15)		
			Quintile 4	59	0.83 (0.59–1.16)		
			Quintile 5	36	0.56 (0.37–0.84)		
			P_{trend} = 0.017				
			Total consumption of fruits:				
			Per serving per 1000 calories		HR: 1.00 (0.90–1.12)	Additionally adjusted for continuous vegetable intake	
			Quintile 1	99	1 (ref)		
			Quintile 2	64	0.86 (0.63–1.19)		
			Quintile 3	53	0.83 (0.58–1.17)		
			Quintile 4	59	1.02 (0.72–1.45)		
			Quintile 5	44	0.84 (0.57–1.25)		
			P_{trend} = 0.632				

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
			Consumption of whole fruits:				
			Per serving per 1000 calories		HR: 0.96 (0.82–1.12)	Additionally adjusted for continuous vegetable intake and continuous fruit juice intake	
			Quintile 1	98	1 (ref)		
			Quintile 2	72	0.98 (0.71–1.33)		
			Quintile 3	58	0.90 (0.64–1.27)		
			Quintile 4	50	0.87 (0.60–1.27)		
			Quintile 5	41	0.81 (0.54–1.22)		
			P_{trend} = 0.268				
			Consumption of fruit juice:				
			Per serving per 1000 calories		HR: 1.06 (0.90–1.25)	Additionally adjusted for continuous vegetable intake and continuous fruit juice intake	
			Quintile 1	81	1 (ref)		
			Quintile 2	62	0.90 (0.64–1.25)		
			Quintile 3	62	0.91 (0.65–1.27)		
			Quintile 4	49	0.78 (0.54–1.12)		
			Quintile 5	65	1.10 (0.78–1.53)		
					P_{trend} = 0.556		
Rajkumar et al. (2003) Southern India (Bangalore, Madras (Chennai) and Trivandrum) 1996–1999 Case–control	591 cases, 582 matched (hospital) controls* 52.3% male cases Men aged 22–85 yr, women aged 18–87 yr Exposure assessment method: questionnaire-based standardized	Oral cavity (ICD-9 143–145)	Consumption of raw green vegetables:			Matched on centre, quinquennium of age, and sex Adjusted for education level, chewing, smoking, and alcohol consumption *In Bangalore and Madras, controls were relatives or friends of patients with cancer other than oral cancer. In Trivandrum, controls were outpatients	
			< 1/wk		1 (ref)		
			1/wk–2/wk		0.60 (0.41–0.90)		
			≥ 3/wk		0.47 (0.31–0.73)		
			P_{trend} < 0.001				
			Consumption of citrus fruits:				
			< 1/wk		1 (ref)		
			≥ 1/wk		0.27 (0.18–0.41)		

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
	interview by social workers		Consumption of apples and pears:			attending the clinics who were free of malignant diseases	
			0/wk		1 (ref)		
			< 1/wk		0.41 (0.26–0.66)		
			≥ 1/wk		0.04 (0.02–0.08)		
			P_{trend} < 0.001				
Franco et al. (1989) Brazil February 1986–June 1988 Case–control	232 cases, 464 matched controls 45.7% ICD-9 141 (tongue), 9.9% ICD-9 143 (gum), 18.1% ICD-9 144 (floor of the mouth), 26.3% ICD-9 145 (other specified parts of oral cavity) 86.6% male All ages Exposure assessment method: questionnaire-based standardized interview	Oral cavity (ICD-9 141 and 143–145)	Consumption of carotene-rich food group (carrots, pumpkins, papaya):			Matched on age, sex, study site, and admission period Adjusted for smoking and alcohol consumption	Regionally specific lifestyle and behavioural characteristics may interfere with the rate of cancer cases The 3 levels of average past consumption refer to regular-sized servings in each category Consumption of green vegetables was protective in the crude model, but not after controlling for smoking and alcohol consumption
			< 1/mo	62/101	1 (ref)		
			1/mo–3/wk	154/310	0.8 (0.5–1.4)		
			≥ 4/wk	16/53	0.4 (0.2–1.0)		
			P_{trend} = 0.0639				
			Consumption of citrus fruits food group:				
			< 1/mo	77/92	1 (ref)		
			1/mo–3/wk	98/233	0.5 (0.3–0.8)		
			≥ 4/wk	57/137	0.5 (0.3–0.9)		
			P_{trend} = 0.0303				
			Consumption of green vegetables food group:				
			< 1/mo	41/58	1 (ref)		
			1/mo–3/wk	144/299	0.8 (0.5–1.4)		
			≥ 4/wk	47/104	0.7 (0.4–1.4)		
Dietary fibre consumption							
Kawakita et al (2017) Asia, Europe, North America Meta-analysis of 10 case–control studies	559 cases and 12 248 controls	Oral cavity	Quintile 1	331	1 (ref)	Age, sex, race, study centre, education, cigarette smoking status, cigarette smoking intensity (number of cigarettes per day), cigarette smoking duration, cigar smoking status, pipe smoking status, alcohol	
			Quintile 2	267	0.70 (0.58–0.85)		
			Quintile 3	230	0.61 (0.50–0.74)		
			Quintile 4	216	0.51 (0.42–0.63)		
			Quintile 5	190	0.39 (0.29–0.52)		
			P_{trend} < 0.001				

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
		Oro/hypo pharynx	Quintile 1	560	1 (ref)	consumption intensity (number of drinks per day), and the product (interaction) term for cigarette smoking intensity and alcohol consumption	
			Quintile 2	380	0.67 (0.55–0.81)		
			Quintile 3	379	0.65 (0.55–0.77)		
			Quintile 4	354	0.57 (0.47–0.71)		
			Quintile 5	351	0.54 (0.45–0.64)		
			$P_{trend} < 0.001$				
Lam et al (2011) North America NIH-AARP Diet and Health Study Cohort	494 991 participants	Oral cavity	Men:		HR (95% CI):	Age at entry, BMI, education, physical activity, alcohol intake, cigarette smoke dose, red meat intake, total energy intake, total grains	
			Quintile 1	153	1 (ref)		
			Quintile 2	123	1.07 (0.83–1.40)		
			Quintile 3	112	1.06 (0.82–1.38)		
			Quintile 4	82	0.81 (0.60–1.08)		
			Quintile 5	102	0.99 (0.75–1.32)		
			$P_{trend} = 0.576$				
			Women:				
			Quintile 1	76	1 (ref)		
			Quintile 2	39	0.74 (0.49–1.11)		
			Quintile 3	38	0.82 (0.54–1.25)		
			Quintile 4	29	0.67 (0.42–1.07)		
			Quintile 5	25	0.62 (0.37–1.03)		
			$P_{trend} = 0.055$				
Kawakita et al (2019) North America Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial Cohort	101 700 participants	Oral cavity and pharynx	Total fibre (g/day):		HR (95% CI):	Age, sex, BMI, education, race/ethnicity, pipe smoking status, cigar smoking status, cigarette smoking status, pack-year cigarette smoking, alcohol consumption status, alcohol consumption intensity,	
			Quintile 1	42	1 (ref)		
			Quintile 2	41	0.80 (0.49–1.28)		
			Quintile 3	26	0.34 (0.16–0.71)		
			$P_{trend} = 0.007$				

Table S2.33 Studies on potentially preventive dietary agents for the development of oral cancer

Reference Location Enrolment/follow-up period Study design	Population size, description Exposure assessment method	Organ site	Exposure category or level	Exposed cases/controls	Risk estimate (95% CI)	Adjustments	Comments
			Insoluble fibre (g/day):			marital status, non-alcohol total energy, and total vegetable and fruit intake	
			Quintile 1	48	1 (ref)		
			Quintile 2	34	0.57 (0.36–0.93)		
			Quintile 3	27	0.31 (0.15–0.62)		
			P_{trend} = 0.001				
			Soluble fibre (g/day):				
			Quintile 1	42	1 (ref)		
			Quintile 2	41	0.75 (0.47–1.22)		
			Quintile 3	26	0.29 (0.14–0.62)		
			P_{trend} = 0.003				

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; HNC, head and neck cancer; HPV, human papillomavirus; HR, hazard ratio; ICARE, Investigation of Occupational and Environmental Causes of Respiratory Cancers; ICD, International Classification of Diseases; INHANCE, International Head and Neck Cancer Epidemiology; mo, month or months; NOS, not otherwise specified; OC, oral cancer; OR, odds ratio; P25–P75, 25th to 75th percentile; ref, reference; RR, relative risk; SCC, squamous cell carcinoma; vs, versus; wk, week or weeks; yr, year or years.

Table S2.34 Observational studies of potentially preventive dietary agents for the development of OPMDs

Reference Location	Study population	Exposure assessment method	OPMD	Exposure level	RR or OR (95% CI)	Adjustments/comments
Gupta et al. (1998) India	318 men clinically diagnosed with leukoplakia or OSF 318 matched controls Age > 15 yr Only tobacco users and measure of exposure to tobacco products	Home interviews blinded to disease status; FFQ diet and nutrients (92 food items representing > 95% of total energy, fat, fibre, iron, copper, zinc, calcium, ascorbic acid, β-carotene, and B vitamins)	OSF	Dietary fibre (on a continuous scale, g/d)	0.89 (0.81–0.99)	Matched on age (± 5 yr), sex, residence, and tobacco use
			Leukoplakia		0.87 (0.79–0.97)	Adjusted for socioeconomic status, tobacco exposure, and total dietary energy
			Leukoplakia	Ascorbic acid (10 mg/d):	0.95 (0.89–1.01)	Lesions suspicious for oral cancer were confirmed histologically and excluded
				Quartile 2	0.82 (0.45–1.49)	
				Quartile 3	0.48 (0.25–0.95)	
				Quartile 4	0.45 (0.21–1.00)	
					$P_{trend} < 0.01$	
			Leukoplakia	Tomato	0.32 (0.12–0.87)	
				Quartile 2	0.95 (0.53–1.69)	
				Quartile 3	0.66 (0.35–1.23)	
				Quartile 4	0.42 (0.22–0.81)	
					$P_{trend} < 0.01$	
Gupta et al. (1999) India (Kerala)	226 individuals (44 women and 182 men) 226 controls matched on age (± 5 yr), sex, ward of residence, and tobacco use Age > 15 yr All participants were tobacco users (chewers, smokers, or both)	Home interviews blinded to disease status; FFQ diet and nutrients (81 food items representing 95% of total energy, fat, fibre, iron, copper, zinc, calcium, ascorbic acid, β-carotene, and B vitamins)	OPMD	Total fruit as continuous variables (log fruit consumption)	0.82 (0.72–0.95) After inclusion of economic and tobacco-related covariates: 0.89 (0.76–1.03)	Adjusted for mixed smoking and chewing of tobacco, total energy consumption (kcal/d), and economic status Univariate Lesions suspicious for oral cancer were confirmed histologically and excluded Nutrient exposures calculated from the Nutritive Value of Indian Foods
			OPMD	Iron (mg/d):		
				Quartile 2 (6.95–9.57)	0.47 (0.26–0.85)	
				Quartile 3 (9.57–13.91)	0.56 (0.28–1.12)	
				Quartile 4 (> 13.91)	0.65 (0.26–1.60)	
				Quartile 1 vs quartiles 2–4	2.07 (1.18–3.63)	
				Females only	3.45 (0.99–12.07)	
			OPMD	Ascorbic acid (mg/d):		
				Quartile 2 (25.9–43.6)	0.65 (0.37–1.13)	
				Quartile 3 (43.6–69.9)	0.74 (0.41–1.35)	
				Quartile 4 (> 69.9)	0.84 (0.40–1.75)	
				Quartile 1 vs quartiles 2–4	1.44 (0.87–2.39)	

Table S2.34 Observational studies of potentially preventive dietary agents for the development of OPMDs

Reference Location	Study population	Exposure assessment method	OPMD	Exposure level	RR or OR (95% CI)	Adjustments/comments
Hebert et al. (2002) India (19 rural villages in Srikakulam District, Andhra Pradesh)	485 cases (79% women) 487 controls Age > 15 yr All participants were users of tobacco in some form (81.9% reverse smokers in cases, 73.5% in controls)	Home interviews blinded to disease status; FFQ diet and nutrients (80 food items representing > 95% of total energy, fat, fibre, iron, copper, zinc, calcium, ascorbic acid, β-carotene, and B vitamins)	OPMD (mostly keratosis of the palate in reverse smokers)	Iron (10 mg/d, fitted as a continuous variable)	0.82 (0.68–0.99) OR×nutrient$_{75}$ − OR×nutrient$_{25}$ = 16.6%[a] (25% = 18.5 mg/d, 75% = 27.7 mg/d)	Matched on age (± 5 yr), sex, and residence Adjusted for type of tobacco and total energy consumption (kcal/d) A minority of individuals smoked bidis (2.6%), cigarettes (1.7%), and chutta in the conventional manner (14.3%), or chewed tobacco (2.2%) 93% of the population was illiterate, so it was not possible to use education as a covariate The incidence of OPMDs diagnosed after 1 year (39 cases, 39 controls) was similar to that of the main study
				Zinc (mg/d, fitted as a continuous variable)	0.91 (0.85–0.98) OR×nutrient$_{75}$ − OR×nutrient$_{25}$ = 70.2%[a] (25% = 14.7 mg/d, 75% = 22.5 mg/d)	
				Calcium (100 mg/d, fitted as a continuous variable)	0.95 (0.92–0.98) OR×nutrient$_{75}$ − OR×nutrient$_{25}$ = 33.6%[a] (25% = 583 mg/d, 75% = 1255 mg/d)	
				Riboflavin (mg/d, fitted as a continuous variable)	0.51 (0.28–0.93) OR×nutrient$_{75}$ − OR×nutrient$_{25}$ = 22.1%[a] (25% = 1.11 mg/d, 75% = 1.56 mg/d)	
				Fibre (g/d, fitted as a continuous variable)	0.96 (0.94–0.99) OR×nutrient$_{75}$ − OR×nutrient$_{25}$ = 29.6%[a] (25% = 8.5 g/d, 75% = 15.9 g/d)	

Table S2.34 Observational studies of potentially preventive dietary agents for the development of OPMDs

Reference Location	Study population	Exposure assessment method	OPMD	Exposure level	RR or OR (95% CI)	Adjustments/comments
Amarasinghe et al. (2013) Sri Lanka (Sabaragamuwa Province)	Cases 101, clinically diagnosed with OPMDs Leukoplakia: 71 OSF: 25 OLP: 6 Matched controls: 728 Age > 30 yr	Home interviews: a 3-day diet diary for 2 days in the week and 1 day on the weekend, before the oral examinations	OPMD	> 2 portions/d of β-carotene-containing vegetables and fruits (78.9% of cases and 66.1% of controls < 2 portions/d)	Crude OR: 0.5 (0.3–0.8) Adjusted OR: 0.8 (0.4–1.4)	Adjusted for sex, age, occupation, education level, BMI, smoking, betel quid chewing, and alcohol consumption Chewer's mucosa, quid-induced lichenoid reactions, smoker's keratosis of palate, denture-induced stomatitis, angular cheilitis, pallor, and depapillation of the tongue were considered as "other" oral mucosal abnormalities and excluded from analysis All green leafy vegetables, carrots, pumpkin, tomatoes, beans, lady's fingers, snake gourd etc. were considered as β-carotene-containing vegetables
			Leukoplakia	> 2 portions/d of β-carotene-containing vegetables and fruits (78.8% of cases and 66.1% of controls < 2 portions/d)	Crude OR: 0.5 (0.3–0.9) Adjusted OR: 0.8 (0.4–1.7)	
Cianfriglia et al. (1998) Rome, Italy	53 leukoplakia cases Matched controls with other pathological conditions attending hospital	Hospital; dietary questionnaire	Leukoplakia	Dietary retinol-equivalent index	Estimated mean retinol intake (IU/kg per person per day): Leukoplakia group: 68 Controls: 93 $t = 4.8$; $P < 0.001$	Adjusted for sex, age, alcohol consumption, and tobacco use No adjustment

BMI, body mass index; CI, confidence interval; d, day or days; FFQ, food frequency questionnaire; OLP, oral lichen planus; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; RR, relative risk; vs, versus; yr, year or years.

[a] For each nutrient fitted as a continuous variable, the effect was standardized by computing the difference between its effect at the 75th percentile value ($OR \times nutrient_{75}$) and its effect at the 25th percentile value ($OR \times nutrient_{25}$). The value shown represents the percentage reduction across the interquartile range.

Table S2.35 Biochemical studies of potentially preventive dietary agents for the development of OPMDs

Reference Location Study type	Study population	Analyte	Exposure (preventive agent)	Outcome measure	Exposure levels	RR or OR (95% CI) or *P* value	Comments
Ramaswamy et al. (1996) Bangalore, India Case–control	50 leukoplakia cases and 50 controls	Serum samples in a field survey	Vitamins A, β-carotene, C, E, B12, and folate	Leukoplakia	Folate levels (nmol/L): Cases: 8.4 ± 0.86 Controls: Chewers: 13.4 ± 0.91 Non-chewers: 30.4 ± 0.90 Vitamin B12 (pmol/L): Cases: 125.8 ± 12.4 Controls: Chewers: 162.0 ± 21.9 Non-chewers: 306.4 ± 58.3	 *P* < 0.01 *P* < 0.001 *P* < 0.01 *P* < 0.001	Based on univariate analysis No adjustment Based on univariate analysis
Nagao et al. (2000) Tokoname city, Japan Case–control	48 leukoplakia cases (38 males, 10 females) and 192 controls	Clinic serum samples	Fasting serum levels of retinol, α-tocopherol, zeaxanthin and lutein, cryptoxanthin, lycopene, and carotenoids (α-carotene and β-carotene)	Leukoplakia	Men: Mean lycopene (mmol/L): Cases: 0.175 ± 0.202 Controls: 0.257 ± 0.252 β-carotene (mmol/L): Cases: 0.357 ± 0.295 Controls: 0.555 ± 0.408	 *P* < 0.05 *P* < 0.005	No significant differences in any of the serum nutrients estimated in female participants
Nagao et al. (2001) Tokoname city, Japan Case–control	62 OLP cases and 248 controls	Clinic serum samples	Retinol, α-tocopherol, zeaxanthin and lutein, cryptoxanthin, lycopene, α-carotene, and β-carotene	OLP	Lycopene levels: Atrophic/erosive cases (*n* = 4): 0.076 ± 0.04 mmol/L Controls: 0.316 ± 0.205 mmol/L	*P* < 0.05	
Rezazadeh and Haghighat (2021) Islamic Republic of Iran Case–control	34 OLP cases and 43 healthy controls	Clinic serum samples	Vitamins A, C, D3, E, and B12	OLP		*P* > 0.1	
Basu and Guhan (2015) Mumbai, India Case–control	60 cases (leukoplakia and OSF) and 10 controls	Clinic blood samples	β-carotene, retinol, vitamin C, and α-tocopherol	OPMD (OSF, 30; leukoplakia, 30)	Moderate to low plasma levels of β-carotene, retinol, vitamin C, and α-tocopherol in both the leukoplakia and OSF groups compared with the controls		

Table S2.35 Biochemical studies of potentially preventive dietary agents for the development of OPMDs

Reference Location Study type	Study population	Analyte	Exposure (preventive agent)	Outcome measure	Exposure levels	RR or OR (95% CI) or *P* value	Comments
Param et al. (2018) Maharashtra, India Case–control	22 cases of leukoplakia, 20 cases of OSF, and [21] controls (63 is the total)	Plasma	Vitamin C	OPMD (leukoplakia or OSF)	Vitamin C (mg/dL): Leukoplakia: 1.51 ± 0.47 OSF: 2.09 ± 0.55 Controls: 3.14 ± 0.395	$P < 0.05$	
Gupta et al. (2004) Wardha, India Case–control	34 OSF cases and 34 controls	Plasma	β-carotene and vitamin E	OSF	β-carotene (mg/100 mL): OSF: 81.7 ± 14.3 Healthy controls: 110 ± 20.8 Vitamin E (mg/L): OSF: 9.3 ± 0.3 Healthy controls: 10.1 ± 1.2		
Tuovinen et al. (1992) Eastern Finland Case–control	106 people with low plasma AA levels (≤ 25 μmol/L) 103 people with normal AA levels (≥ 50 μmol/L)	Plasma	Ascorbic acid	Leukoplakia	Prevalence of leukoplakia was higher in AA deficiency	$P < 0.01$	
Bose et al (2012) Madhya Pradesh, India Cross-sectional	23 leukoplakia cases and 23 controls	Plasma	Vitamins A, C, E, zinc, glutathione, and total antioxidant status	Leukoplakia	Beta-carotene (μg/L): Cases: 430.47 ± 74 Controls: 634.97 ± 45 Vitamin C (mg/dL): Cases: 0.57 ± 0.16 Controls: 1.08 ± 0.16 Vitamin E (mg/L): Cases: 5.99 ± 0.82 Controls: 10.54 ± 1.1 Reduced glutathione (mg/L): Cases: 6.09 ± 0.67 Controls: 10.09 ± 0.89		

Table S2.35 Biochemical studies of potentially preventive dietary agents for the development of OPMDs

Reference Location Study type	Study population	Analyte	Exposure (preventive agent)	Outcome measure	Exposure levels	RR or OR (95% CI) or *P* value	Comments
					Total antioxidant status (mol/L): Cases: 1.23 ± 0.45 Controls: 2.47 ± 0.43 Zinc (μg/dL): Cases: 59.9 ± 6.91 Controls: 91.2 ± 11.8		

AA, ascorbic acid; CI, confidence interval; OLP, oral lichen planus; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; RR, relative risk.

References

Agalliu I, Gapstur S, Chen Z, Wang T, Anderson RL, Teras L, et al. (2016). Associations of oral α-, β-, and γ-human papillomavirus types with risk of incident head and neck cancer. JAMA Oncol. 2(5):599–606. https://doi.org/10.1001/jamaoncol.2015.5504 PMID:26794505

Agudo A, Bonet C, Travier N, González CA, Vineis P, Bueno-de-Mesquita HB, et al. (2012). Impact of cigarette smoking on cancer risk in the European Prospective Investigation into Cancer and Nutrition study. J Clin Oncol. 30(36):4550–7. https://doi.org/10.1200/JCO.2011.41.0183 PMID:23169508

Al-Tayar BA, Tin-Oo MM, Sinor MZ, Alakhali MS (2015). Association between shammah use and oral leukoplakia-like lesions among adult males in Dawan Valley, Yemen. Asian Pac J Cancer Prev. 16(18):8365–70. https://doi.org/10.7314/APJCP.2015.16.18.8365 PMID:26745086

Amarasinghe HK, Johnson NW, Lalloo R, Kumaraarachchi M, Warnakulasuriya S (2010b). Derivation and validation of a risk-factor model for detection of oral potentially malignant disorders in populations with high prevalence. Br J Cancer. 103(3):303–9. https://doi.org/10.1038/sj.bjc.6605778 PMID:20628386

Amarasinghe HK, Usgodaarachchi U, Kumaraarachchi M, Johnson NW, Warnakulasuriya S (2013). Diet and risk of oral potentially malignant disorders in rural Sri Lanka. J Oral Pathol Med. 42(9):656–62. https://doi.org/10.1111/jop.12067 PMID:23601045

Amarasinghe HK, Usgodaarachchi US, Johnson NW, Lalloo R, Warnakulasuriya S (2010a). Betel-quid chewing with or without tobacco is a major risk factor for oral potentially malignant disorders in Sri Lanka: a case-control study. Oral Oncol. 46(4):297–301. https://doi.org/10.1016/j.oraloncology.2010.01.017 PMID:20189448

Amtha R, Razak IA, Basuki B, Roeslan BO, Gautama W, Puwanto DJ, et al. (2014). Tobacco (kretek) smoking, betel quid chewing and risk of oral cancer in a selected Jakarta population. Asian Pac J Cancer Prev. 15(20):8673–8. https://doi.org/10.7314/APJCP.2014.15.20.8673 PMID:25374188

Anantharaman D, Gheit T, Waterboer T, Abedi-Ardekani B, Carreira C, McKay-Chopin S, et al. (2013). Human papillomavirus infections and upper aero-digestive tract cancers: the ARCAGE study. J Natl Cancer Inst. 105(8):536–45. https://doi.org/10.1093/jnci/djt053 PMID:23503618

Anantharaman D, Marron M, Lagiou P, Samoli E, Ahrens W, Pohlabeln H, et al. (2011). Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer. Oral Oncol. 47(8):725–31. https://doi.org/10.1016/j.oraloncology.2011.05.004 PMID:21684805

Anantharaman D, Muller DC, Lagiou P, Ahrens W, Holcátová I, Merletti F, et al. (2016). Combined effects of smoking and HPV16 in oropharyngeal cancer. Int J Epidemiol. 45(3):752–61. https://doi.org/10.1093/ije/dyw069 PMID:27197530

Anwar N, Pervez S, Chundriger Q, Awan S, Moatter T, Ali TS (2020). Oral cancer: clinicopathological features and associated risk factors in a high risk population presenting to a major tertiary care center in Pakistan. PLoS One. 15(8):e0236359. https://doi.org/10.1371/journal.pone.0236359 PMID:32760151

Ariyawardana A, Athukorala AD, Arulanandam A (2006). Effect of betel chewing, tobacco smoking and alcohol consumption on oral submucous fibrosis: a case-control study in Sri Lanka. J Oral Pathol Med. 35(4):197–201. https://doi.org/10.1111/j.1600-0714.2006.00400.x PMID:16519765

Asthana S, Labani S, Kailash U, Sinha DN, Mehrotra R (2019). Association of smokeless tobacco use and oral cancer: a systematic global review and meta-analysis. Nicotine Tob Res. 21(9):1162–71. https://doi.org/10.1093/ntr/nty074 PMID:29790998

Azhar N, Sohail M, Ahmad F, Fareeha S, Jamil S, Mughal N, et al. (2018). Risk factors of oral cancer – a hospital based case control study. J Clin Exp Dent. 10(4):e396–401. https://doi.org/10.4317/jced.54618 PMID:29750103

Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 112(3):580–93. https://doi.org/10.1038/bjc.2014.579 PMID:25422909

Balaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, et al. (2002). Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. Int J Cancer. 98(3):440–5. https://doi.org/10.1002/ijc.10200 PMID:11920597

Basu S, Guhan VN (2015). Antioxidant changes in precancerous and cancerous lesions of oral cavity. Int J Life Sci Res. 3(1):23–8.

Bektas-Kayhan K, Karagoz G, Kesimli MC, Karadeniz AN, Meral R, Altun M, et al. (2014). Carcinoma of the tongue: a case-control study on etiologic factors and dental trauma. Asian Pac J Cancer Prev. 15(5):2225–9. https://doi.org/10.7314/APJCP.2014.15.5.2225 PMID:24716961

Bose SC, Singh M, Vyas P, Singh M (2012). Plasma zinc antioxidant vitamins, glutathione levels and total antioxidant activity in oral leukoplakia. Dent Res J (Isfahan). 9(2):158–61. https://doi.org/10.4103/1735-3327.95229 PMID:22623931

Chang IH, Jiang RS, Wong YK, Wu SH, Chen FJ, Liu SA (2011). Visual screening of oral cavity cancer in a male population: experience from a medical center. J Chin Med Assoc. 74(12):561–6. https://doi.org/10.1016/j.jcma.2011.09.014 PMID:22196472

Chen F, Lin L, Yan L, Liu F, Qiu Y, Wang J, et al. (2018). Nomograms and risk scores for predicting the risk of oral cancer in different sexes: a large-scale case-control study. J Cancer. 9(14):2543–8. https://doi.org/10.7150/jca.24431 PMID:30026853

Chen MK, Chiou HL, Su SC, Chung TT, Tseng HC, Tsai HT, et al. (2009). The association between hypoxia inducible factor-1α gene polymorphisms and increased susceptibility to oral cancer. Oral Oncol. 45(12):e222–6. https://doi.org/10.1016/j.oraloncology.2009.07.015 PMID:19717330

Chen PH, Lee KW, Chen CH, Shieh TY, Ho PS, Wang SJ, et al. (2011). CYP26B1 is a novel candidate gene for betel quid-related oral squamous cell carcinoma. Oral Oncol. 47(7):594–600. https://doi.org/10.1016/j.oraloncology.2011.04.024 PMID:21641851

Chuang SC, Jenab M, Heck JE, Bosetti C, Talamini R, Matsuo K, et al. (2012). Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. Cancer Causes Control. 23(1):69–88. https://doi.org/10.1007/s10552-011-9857-x PMID:22037906

Chung CH, Yang YH, Wang TY, Shieh TY, Warnakulasuriya S (2005). Oral precancerous disorders associated with areca quid chewing, smoking, and alcohol drinking in southern Taiwan. J Oral Pathol Med. 34(8):460–6. https://doi.org/10.1111/j.1600-0714.2005.00332.x PMID:16091112

Chung YT, Hsieh LL, Chen IH, Liao CT, Liou SH, Chi CW, et al. (2009). Sulfotransferase 1A1 haplotypes associated with oral squamous cell carcinoma susceptibility in male Taiwanese. Carcinogenesis. 30(2):286–94. https://doi.org/10.1093/carcin/bgn283 PMID:19126640

Cianfriglia F, Manieri A, Di Gregorio DA, Di Iorio AM (1998). Retinol dietary intake and oral leukoplakia development. J Exp Clin Cancer Res. 17(3):331–6. PMID:9894771

D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. (2007). Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 356(19):1944–56. https://doi.org/10.1056/NEJMoa065497 PMID:17494927

Ernster VL, Grady DG, Greene JC, Walsh M, Robertson P, Daniels TE, et al. (1990). Smokeless tobacco use and health effects among baseball players. JAMA. 264(2):218–24. https://doi.org/10.1001/jama.1990.03450020070029 PMID:2355443

Filippini T, Malavolti M, Borrelli F, Izzo AA, Fairweather-Tait SJ, Horneber M, et al. (2020). Green tea (Camellia sinensis) for the prevention of cancer. Cochrane Database Syst Rev. 3(3):CD005004. https://doi.org/10.1002/14651858.CD005004.pub3 PMID:32118296

Franco EL, Kowalski LP, Oliveira BV, Curado MP, Pereira RN, Silva ME, et al. (1989). Risk factors for oral cancer in Brazil: a case-control study. Int J Cancer. 43(6):992–1000. https://doi.org/10.1002/ijc.2910430607 PMID:2732011

Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, et al. (2008). Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. Int J Cancer. 122(10):2330–6. https://doi.org/10.1002/ijc.23319 PMID:18092323

Galeone C, Tavani A, Pelucchi C, Turati F, Winn DM, Levi F, et al. (2010). Coffee and tea intake and risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology consortium. Cancer Epidemiol Biomarkers Prev. 19(7):1723–36. https://doi.org/10.1158/1055-9965.EPI-10-0191 PMID:20570908

Galvão De Podestá OP, Peres SV, Salaroli LB, Cattafesta M, De Podestá JRV, von Zeidler SLV, et al. (2019). Consumption of minimally processed foods as protective factors in the genesis of squamous cell carcinoma of the head and neck in Brazil. PLoS One. 14(7):e0220067. https://doi.org/10.1371/journal.pone.0220067 PMID:31344089

Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. (2008). Tobacco smoking and cancer: a meta-analysis. Int J Cancer. 122(1):155–64. https://doi.org/10.1002/ijc.23033 PMID:17893872

Gillison ML, Alemany L, Snijders PJ, Chaturvedi A, Steinberg BM, Schwartz S, et al. (2012). Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine. 30(Suppl 5):F34–54. https://doi.org/10.1016/j.vaccine.2012.05.070 PMID:23199965

Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al. (2008). Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 100(6):407–20. https://doi.org/10.1093/jnci/djn025 PMID:18334711

Guha N, Warnakulasuriya S, Vlaanderen J, Straif K (2014). Betel quid chewing and the risk of oral and oropharyngeal cancers: a meta-analysis with implications for cancer control. Int J Cancer. 135(6):1433–43. https://doi.org/10.1002/ijc.28643 PMID:24302487

Gunasekera SK, Perera KA, Fernando C, Udagama PV (2015). A shifting paradigm in the aetiology of oral and pharyngeal cancer in Sri Lanka: a case-control study providing serologic evidence for the role of oncogenic HPV types 16 and 18. Infect Agent Cancer. 10(1):12. https://doi.org/10.1186/s13027-015-0007-z PMID:25908938

Gupta B, Bray F, Kumar N, Johnson NW (2017). Associations between oral hygiene habits, diet, tobacco and alcohol and risk of oral cancer: a case-control study from India. Cancer Epidemiol. 51:7–14. https://doi.org/10.1016/j.canep.2017.09.003 PMID:28968558

Gupta PC, Hebert JR, Bhonsle RB, Murti PR, Mehta H, Mehta FS (1999). Influence of dietary factors on oral precancerous lesions in a population-based case-control study in Kerala, India. Cancer. 85(9):1885–93. PMID:10223226

Gupta PC, Hebert JR, Bhonsle RB, Sinor PN, Mehta H, Mehta FS (1998). Dietary factors in oral leukoplakia and submucous fibrosis in a population-based case control study in Gujarat, India. Oral Dis. 4(3):200–6. https://doi.org/10.1111/j.1601-0825.1998.tb00279.x PMID:9972171

Gupta S, Reddy MV, Harinath BC (2004). Role of oxidative stress and antioxidants in aetiopathogenesis and management of oral submucous fibrosis. Indian J Clin Biochem. 19(1):138–41. https://doi.org/10.1007/BF02872409 PMID:23105446

Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, et al. (2007). Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst. 99(10):777–89. https://doi.org/10.1093/jnci/djk179 PMID:17505073

Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. (2009). Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 18(2):541–50. https://doi.org/10.1158/1055-9965.EPI-08-0347 PMID:19190158

Hashibe M, Mathew B, Kuruvilla B, Thomas G, Sankaranarayanan R, Parkin DM, et al. (2000b). Chewing tobacco, alcohol, and the risk of erythroplakia. Cancer Epidemiol Biomarkers Prev. 9(7):639–45. PMID:10919731

Hashibe M, Sankaranarayanan R, Thomas G, Kuruvilla B, Mathew B, Somanathan T, et al. (2000a). Alcohol drinking, body mass index and the risk of oral leukoplakia in an Indian population. Int J Cancer. 88(1):129–34. https://doi.org/10.1002/1097-0215(20001001)88:1<129::AID-IJC20>3.0.CO;2-U PMID:10962450

He T, Guo X, Li X, Liao C, Yin W (2020). Association between coffee intake and the risk of oral cavity cancer: a meta-analysis of observational studies. Eur J Cancer Prev. 29(1):80–8. https://doi.org/10.1097/CEJ.0000000000000515 PMID:31021885

Hebert JR, Gupta PC, Bhonsle RB, Mehta H, Zheng W, Sanderson M, et al. (2002). Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India. Public Health Nutr. 5(2):303–12. https://doi.org/10.1079/PHN2002249 PMID:12020382

Herrero R, Castellsagué X, Pawlita M, Lissowska J, Kee F, Balaram P, et al.; IARC Multicenter Oral Cancer Study Group (2003). Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst. 95(23):1772–83. https://doi.org/10.1093/jnci/djg107 PMID:14652239

Hu Y, Zhong R, Li H, Zou Y (2020). Effects of betel quid, smoking and alcohol on oral cancer risk: a case-control study in Hunan Province, China. Subst Use Misuse. 55(9):1501–8. https://doi.org/10.1080/10826084.2020.1750031 PMID:32569534

Huang J, He B, Chen F, Liu F, Yan L, Hu Z, et al. (2015). Association between oral hygiene, chronic diseases, and oral squamous cell carcinoma. [in Chinese] Zhonghua Yu Fang Yi Xue Za Zhi. 49(8):688–92. PMID:26733026

Jacob BJ, Straif K, Thomas G, Ramadas K, Mathew B, Zhang ZF, et al. (2004). Betel quid without tobacco as a risk factor for oral precancers. Oral Oncol. 40(7):697–704. https://doi.org/10.1016/j.oraloncology.2004.01.005 PMID:15172639

Juntanong N, Siewchaisakul P, Bradshaw P, Vatanasapt P, Chen SL, Yen AM, et al. (2016). Prevalence and factors associated with oral pre-malignant lesions in northeast Thailand. Asian Pac J Cancer Prev. 17(8):4175–9. PMID:27644680

Kadashetti V, Chaudhary M, Patil S, Gawande M, Shivakumar KM, Patil S, et al. (2015). Analysis of various risk factors affecting potentially malignant disorders and oral cancer patients of Central India. J Cancer Res Ther. 11(2):280–6. https://doi.org/10.4103/0973-1482.151417 PMID:26148585

Kawakita D, Lee YA, Gren LH, Buys SS, La Vecchia C, Hashibe M (2019). Fiber intake and the risk of head and neck cancer in the Prostate, Lung, Colorectal and Ovarian (PLCO) cohort. Int J Cancer. 145(9):2342–8. https://doi.org/10.1002/ijc.32162 PMID:30693489

Kawakita D, Lee YA, Turati F, Parpinel M, Decarli A, Serraino D, et al. (2017). Dietary fiber intake and head and neck cancer risk: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium. Int J Cancer. 141(9):1811–21. https://doi.org/10.1002/ijc.30886 PMID:28710831

Khan A, Ongole R, Baptist J, Srikant N, Lukmani F (2020). Patterns of tobacco use and its relation to oral precancers and cancers among individuals visiting a tertiary hospital in south India. J Contemp Dent Pract. 21(3):304–9. https://doi.org/10.5005/jp-journals-10024-2791 PMID:32434979

Khan Z, Suliankatchi RA, Heise TL, Dreger S (2019). Naswar (smokeless tobacco) use and the risk of oral cancer in Pakistan: a systematic review with meta-analysis. Nicotine Tob Res. 21(1):32–40. https://doi.org/10.1093/ntr/ntx281 PMID:29294113

Kreimer AR, Johansson M, Waterboer T, Kaaks R, Chang-Claude J, Drogen D, et al. (2013). Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. J Clin Oncol. 31(21):2708–15. https://doi.org/10.1200/JCO.2012.47.2738 PMID:23775966

Lam TK, Cross AJ, Freedman N, Park Y, Hollenbeck AR, Schatzkin A, et al. (2011). Dietary fiber and grain consumption in relation to head and neck cancer in the NIH-AARP Diet and Health Study. Cancer Causes Control. 22(10):1405–14. https://doi.org/10.1007/s10552-011-9813-9 PMID:21785948

Lee CH, Ko YC, Huang HL, Chao YY, Tsai CC, Shieh TY, et al. (2003). The precancer risk of betel quid chewing, tobacco use and alcohol consumption in oral leukoplakia and oral submucous fibrosis in southern Taiwan. Br J Cancer. 88(3):366–72. https://doi.org/10.1038/sj.bjc.6600727 PMID:12569378

Lee CH, Lee KW, Fang FM, Wu DC, Shieh TY, Huang HL, et al. (2011). The use of tobacco-free betel-quid in conjunction with alcohol/tobacco impacts early-onset age and carcinoma distribution for upper aerodigestive tract cancer. J Oral Pathol Med. 40(9):684–92. https://doi.org/10.1111/j.1600-0714.2011.01022.x PMID:21385213

Lee YC, Marron M, Benhamou S, Bouchardy C, Ahrens W, Pohlabeln H, et al. (2009). Active and involuntary tobacco smoking and upper aerodigestive tract cancer risks in a multicenter case-control study. Cancer Epidemiol Biomarkers Prev. 18(12):3353–61. https://doi.org/10.1158/1055-9965.EPI-09-0910 PMID:19959682

Li L, Psoter WJ, Buxó CJ, Elias A, Cuadrado L, Morse DE (2011). Smoking and drinking in relation to oral potentially malignant disorders in Puerto Rico: a case-control study. BMC Cancer. 11(1):324. https://doi.org/10.1186/1471-2407-11-324 PMID:21801414

Li S, Lee YC, Li Q, Chen C-J, Hsu W-L, Lou P-J, et al. (2015). Oral lesions, chronic diseases and the risk of head and neck cancer. Oral Oncol. 51(12):1082–7. https://doi.org/10.1016/j.oraloncology.2015.10.014 PMID:26526128

Lin WJ, Jiang RS, Wu SH, Chen FJ, Liu SA (2011). Smoking, alcohol, and betel quid and oral cancer: a prospective cohort study. J Oncol. 2011:525976. https://doi.org/10.1155/2011/525976 PMID:21547265

Lockhart PB, Norris CM Jr, Pulliam C (1998). Dental factors in the genesis of squamous cell carcinoma of the oral cavity. Oral Oncol. 34(2):133–9. https://doi.org/10.1016/S1368-8375(97)00086-9 PMID:9682777

Loyha K, Vatanasapt P, Promthet S, Parkin DM (2012). Risk factors for oral cancer in northeast Thailand. Asian Pac J Cancer Prev. 13(10):5087–90. https://doi.org/10.7314/APJCP.2012.13.10.5087 PMID:23244115

Maasland DH, van den Brandt PA, Kremer B, Goldbohm RA, Schouten LJ (2014). Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands Cohort Study. BMC Cancer. 14(1):187. https://doi.org/10.1186/1471-2407-14-187 PMID:24629046

Maasland DH, van den Brandt PA, Kremer B, Goldbohm RA, Schouten LJ (2015). Consumption of vegetables and fruits and risk of subtypes of head-neck cancer in the Netherlands Cohort Study. Int J Cancer. 136(5):E396–409. https://doi.org/10.1002/ijc.29219 PMID:25220255

Madani AH, Dikshit M, Bhaduri D (2012). Risk for oral cancer associated to smoking, smokeless and oral dip products. Indian J Public Health. 56(1):57–60. https://doi.org/10.4103/0019-557X.96977 PMID:22684175

Madathil SA, Rousseau MC, Wynant W, Schlecht NF, Netuveli G, Franco EL, et al. (2016). Nonlinear association between betel quid chewing and oral cancer: implications for prevention. Oral Oncol. 60:25–31. https://doi.org/10.1016/j.oraloncology.2016.06.011 PMID:27531869

Mahapatra S, Kamath R, Shetty BK, Binu VS (2015). Risk of oral cancer associated with gutka and other tobacco products: a hospital-based case-control study. J Cancer Res Ther. 11(1):199–203. https://doi.org/10.4103/0973-1482.143332 PMID:25879362

Manoharan S, Nagaraja V, Eslick GD (2014). Ill-fitting dentures and oral cancer: a meta-analysis. Oral Oncol. 50(11):1058–61. https://doi.org/10.1016/j.oraloncology.2014.08.002 PMID:25169920

Mehrotra D, Kumar S, Agarwal GG, Asthana A, Kumar S (2013). Odds ratio of risk factors for oral submucous fibrosis in a case control model. Br J Oral Maxillofac Surg. 51(7):e169–73. https://doi.org/10.1016/j.bjoms.2012.08.001 PMID:22951384

Miranda J, Monteiro L, Albuquerque R, Pacheco JJ, Khan Z, Lopez-Lopez J, et al. (2017). Coffee is protective against oral and pharyngeal cancer: a systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 22(5):e554–61. https://doi.org/10.4317/medoral.21829 PMID:28809372

Mondal R, Ghosh SK, Choudhury JH, Seram A, Sinha K, Hussain M, et al. (2013). Mitochondrial DNA copy number and risk of oral cancer: a report from Northeast India. PLoS One. 8(3):e57771. https://doi.org/10.1371/journal.pone.0057771 PMID:23469236

Mork J, Lie AK, Glattre E, Hallmans G, Jellum E, Koskela P, et al. (2001). Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. N Engl J Med. 344(15):1125–31. https://doi.org/10.1056/NEJM200104123441503 PMID:11297703

Muwonge R, Ramadas K, Sankila R, Thara S, Thomas G, Vinoda J, et al. (2008). Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: a nested case-control design using incident cancer cases. Oral Oncol. 44(5):446–54. https://doi.org/10.1016/j.oraloncology.2007.06.002 PMID:17933578

Nagao T, Ikeda N, Warnakulasuriya S, Fukano H, Yuasa H, Yano M, et al. (2000). Serum antioxidant micronutrients and the risk of oral leukoplakia among Japanese. Oral Oncol. 36(5):466–70. https://doi.org/10.1016/S1368-8375(00)00037-3 PMID:10964055

Nagao T, Warnakulasuriya S, Ikeda N, Fukano H, Yamamoto S, Yano M, et al. (2001). Serum antioxidant micronutrient levels in oral lichen planus. J Oral Pathol Med. 30(5):264–7. https://doi.org/10.1034/j.1600-0714.2001.300502.x PMID:11334461

Nasher AT, Al-Hebshi NN, Al-Moayad EE, Suleiman AM (2014). Viral infection and oral habits as risk factors for oral squamous cell carcinoma in Yemen: a case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol. 118(5):566–572.e1. https://doi.org/10.1016/j.oooo.2014.08.005 PMID:25442493

Param K, Kanchan M, Manish P, Satish K (2018). Assessment of serum paraoxonase-1 enzyme activity, malondialdehyde and vitamin-C in oral premalignancies. Int J Clin Biomed Res. 4(3):21–6. https://doi.org/10.31878/ijcbr.2018.43.05

Pavia M, Pileggi C, Nobile CG, Angelillo IF (2006). Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. Am J Clin Nutr. 83(5):1126–34. https://doi.org/10.1093/ajcn/83.5.1126 PMID:16685056

Pearson N, Croucher R, Marcenes W, O'Farrell M (2001). Prevalence of oral lesions among a sample of Bangladeshi medical users aged 40 years and over living in Tower Hamlets, UK. Int Dent J. 51(1):30–4. https://doi.org/10.1002/j.1875-595X.2001.tb00814.x PMID:11326446

Petti S, Masood M, Scully C (2013). The magnitude of tobacco smoking–betel quid chewing–alcohol drinking interaction effect on oral cancer in South-East Asia. A meta-analysis of observational studies. PLoS One. 8(11):e78999. https://doi.org/10.1371/journal.pone.0078999 PMID:24260143

Piemonte ED, Lazos J (2018). Evidence for chronic mechanical irritation as a causative factor in oral cancer: application of Bradford Hill criteria. Transl Res Oral Oncol. 3:1–10. https://doi.org/10.1177/2057178X18791034

Piemonte ED, Lazos JP, Brunotto M (2010). Relationship between chronic trauma of the oral mucosa, oral potentially malignant disorders and oral cancer. J Oral Pathol Med. 39(7):513–7. https://doi.org/10.1111/j.1600-0714.2010.00901.x PMID:20456614

Pintos J, Black MJ, Sadeghi N, Ghadirian P, Zeitouni AG, Viscidi RP, et al. (2008). Human papillomavirus infection and oral cancer: a case-control study in Montreal, Canada. Oral Oncol. 44(3):242–50. https://doi.org/10.1016/j.oraloncology.2007.02.005 PMID:17467327

Purdue MP, Hashibe M, Berthiller J, La Vecchia C, Dal Maso L, Herrero R, et al. (2009). Type of alcoholic beverage and risk of head and neck cancer – a pooled analysis within the INHANCE Consortium. Am J Epidemiol. 169(2):132–42. https://doi.org/10.1093/aje/kwn306 PMID:19064644

Quadri MF, Alharbi F, Bajonaid AM, Moafa IH, Sharwani AA, Alamir AH (2015). Oral squamous cell carcinoma and associated risk factors in Jazan, Saudi Arabia: a hospital based case control study. Asian Pac J Cancer Prev. 16(10):4335–8. https://doi.org/10.7314/APJCP.2015.16.10.4335 PMID:26028095

Radoï L, Menvielle G, Cyr D, Lapôtre-Ledoux B, Stücker I, Luce D; ICARE Study Group (2015). Population attributable risks of oral cavity cancer to behavioral and medical risk factors in France: results of a large population-based case-control study, the ICARE study. BMC Cancer. 15(1):827. https://doi.org/10.1186/s12885-015-1841-5 PMID:26520570

Rajkumar T, Sridhar H, Balaram P, Vaccarella S, Gajalakshmi V, Nandakumar A, et al. (2003). Oral cancer in Southern India: the influence of body size, diet, infections and sexual practices. Eur J Cancer Prev. 12(2):135–43. https://doi.org/10.1097/00008469-200304000-00007 PMID:12671537

Ramaswamy G, Rao VR, Kumaraswamy SV, Anantha N (1996). Serum vitamins' status in oral leucoplakias – a preliminary study. Eur J Cancer B Oral Oncol. 32B(2):120–2. https://doi.org/10.1016/0964-1955(95)00076-3 PMID:8736174

Ranganathan K, Devi MU, Joshua E, Kirankumar K, Saraswathi TR (2004). Oral submucous fibrosis: a case-control study in Chennai, South India. J Oral Pathol Med. 33(5):274–7. https://doi.org/10.1111/j.0904-2512.2004.00116.x PMID:15078487

Ray JG, Ganguly M, Rao BS, Mukherjee S, Mahato B, Chaudhuri K (2013). Clinico-epidemiological profile of oral potentially malignant and malignant conditions among areca nut, tobacco and alcohol users in Eastern India: a hospital-based study. J Oral Maxillofac Pathol. 17(1):45–50. https://doi.org/10.4103/0973-029X.110720 PMID:23798829

Ren JS, Freedman ND, Kamangar F, Dawsey SM, Hollenbeck AR, Schatzkin A, et al. (2010). Tea, coffee, carbonated soft drinks and upper gastrointestinal tract cancer risk in a large United States prospective cohort study. Eur J Cancer. 46(10):1873–81. https://doi.org/10.1016/j.ejca.2010.03.025 PMID:20395127

Rezazadeh F, Haghighat S (2021). Serum vitamin profile in oral lichen planus patients in southwest of Iran. BioMed Res Int. 2021:8627435. https://doi.org/10.1155/2021/8627435 PMID:33708994

Rimal J, Shrestha A, Maharjan IK, Shrestha S, Shah P (2019). Risk assessment of smokeless tobacco among oral precancer and cancer patients in Eastern Developmental Region of Nepal. Asian Pac J Cancer Prev. 20(2):411–5. https://doi.org/10.31557/APJCP.2019.20.2.411 PMID:30803200

Rosenquist K (2005). Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. Swed Dent J Suppl. (179):1–66. PMID:16335030

Sankaranarayanan R, Duffy SW, Padmakumary G, Day NE, Padmanabhan TK (1989). Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva in Kerala, India. Br J Cancer. 60(4):638–43. https://doi.org/10.1038/bjc.1989.330 PMID:2803939

Scheifele C, Nassar A, Reichart PA (2007). Prevalence of oral cancer and potentially malignant lesions among shammah users in Yemen. Oral Oncol. 43(1):42–50. https://doi.org/10.1016/j.oraloncology.2005.12.028 PMID:16759897

Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM, et al. (1998). Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. J Natl Cancer Inst. 90(21):1626–36. https://doi.org/10.1093/jnci/90.21.1626 PMID:9811312

Shiu MN, Chen TH, Chang SH, Hahn LJ (2000). Risk factors for leukoplakia and malignant transformation to oral carcinoma: a leukoplakia cohort in Taiwan. Br J Cancer. 82(11):1871–4. https://doi.org/10.1054/bjoc.2000.1208 PMID:10839305

Singhvi HR, Malik A, Chaturvedi P (2017). The role of chronic mucosal trauma in oral cancer: a review of literature. Indian J Med Paediatr Oncol. 38(1):44–50. https://doi.org/10.4103/0971-5851.203510 PMID:28469336

Smith EM, Ritchie JM, Summersgill KF, Hoffman HT, Wang DH, Haugen TH, et al. (2004). Human papillomavirus in oral exfoliated cells and risk of head and neck cancer. J Natl Cancer Inst. 96(6):449–55. https://doi.org/10.1093/jnci/djh074 PMID:15026470

Stingone JA, Funkhouser WK, Weissler MC, Bell ME, Olshan AF (2013). Racial differences in the relationship between tobacco, alcohol, and squamous cell carcinoma of the head and neck. Cancer Causes Control. 24(4):649–64. https://doi.org/10.1007/s10552-012-9999-5 PMID:22674225

Subapriya R, Thangavelu A, Mathavan B, Ramachandran CR, Nagini S (2007). Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case-control study. Eur J Cancer Prev. 16(3):251–6. https://doi.org/10.1097/01.cej.0000228402.53106.9e PMID:17415096

Thomas G, Hashibe M, Jacob BJ, Ramadas K, Mathew B, Sankaranarayanan R, et al. (2003). Risk factors for multiple oral premalignant lesions. Int J Cancer. 107(2):285–91. https://doi.org/10.1002/ijc.11383 PMID:12949809

Tomar SL, Winn DM, Swango PA, Giovino GA, Kleinman DV (1997). Oral mucosal smokeless tobacco lesions among adolescents in the United States. J Dent Res. 76(6):1277–86. https://doi.org/10.1177/00220345970760060701 PMID:9168861

Toporcov TN, Znaor A, Zhang ZF, Yu GP, Winn DM, Wei Q, et al. (2015). Risk factors for head and neck cancer in young adults: a pooled analysis in the INHANCE consortium. Int J Epidemiol. 44(1):169–85. https://doi.org/10.1093/ije/dyu255 PMID:25613428

Tota JE, Gillison ML, Katki HA, Kahle L, Pickard RK, Xiao W, et al. (2019). Development and validation of an individualized risk prediction model for oropharynx cancer in the US population. Cancer. 125(24):4407–16. https://doi.org/10.1002/cncr.32412 PMID:31454434

Tramacere I, Negri E, Bagnardi V, Garavello W, Rota M, Scotti L, et al. (2010). A meta-analysis of alcohol drinking and oral and pharyngeal cancers. Part 1: overall results and dose-risk relation. Oral Oncol. 46(7):497–503. https://doi.org/10.1016/j.oraloncology.2010.03.024 PMID:20444641

Tuovinen V, Väänänen M, Kullaa A, Karinpää A, Markkanen H, Kumpusalo E (1992). Oral mucosal changes related to plasma ascorbic acid levels. Proc Finn Dent Soc. 88(3–4):117–22. PMID:1298961

Turati F, Garavello W, Tramacere I, Pelucchi C, Galeone C, Bagnardi V, et al. (2013). A meta-analysis of alcohol drinking and oral and pharyngeal cancers: results from subgroup analyses. Alcohol Alcohol. 48(1):107–18. https://doi.org/10.1093/alcalc/ags100 PMID:22949102

<other>Vaccarezza GF, Antunes JL, Michaluart-Júnior P (2010). Recurrent sores by ill-fitting dentures and intra-oral squamous cell carcinoma in smokers. J Public Health Dent. 70(1):52–7. https://doi.org/10.1111/j.1752-7325.2009.00143.x PMID:19694933

Velly AM, Franco EL, Schlecht N, Pintos J, Kowalski LP, Oliveira BV, et al. (1998). Relationship between dental factors and risk of upper aerodigestive tract cancer. Oral Oncol. 34(4):284–91. https://doi.org/10.1016/S1368-8375(98)80009-2 PMID:9813724

Voltzke KJ, Lee YA, Zhang ZF, Zevallos JP, Yu GP, Winn DM, et al. (2018). Racial differences in the relationship between tobacco, alcohol, and the risk of head and neck cancer: pooled analysis of US studies in the INHANCE Consortium. Cancer Causes Control. 29(7):619–30. https://doi.org/10.1007/s10552-018-1026-z PMID:29761303

Wasnik KS, Ughade SN, Zodpey SP, Ingole DL (1998). Tobacco consumption practices and risk of oro-pharyngeal cancer: a case-control study in Central India. Southeast Asian J Trop Med Public Health. 29(4):827–34. PMID:10772572

Wen CP, Tsai MK, Chung WS, Hsu HL, Chang YC, Chan HT, et al. (2010). Cancer risks from betel quid chewing beyond oral cancer: a multiple-site carcinogen when acting with smoking. Cancer Causes Control. 21(9):1427–35. https://doi.org/10.1007/s10552-010-9570-1 PMID:20458529

Worakhajit P, Fuangtharnthip P, Khovidhunkit SP, Chiewwit P, Klongnoi B (2021). The relationship of tobacco, alcohol, and betel quid with the formation of oral potentially malignant disorders: a community-based study from northeastern Thailand. Int J Environ Res Public Health. 18(16):8738. https://doi.org/10.3390/ijerph18168738 PMID:34444487

Wyss A, Hashibe M, Chuang SC, Lee YC, Zhang ZF, Yu GP, et al. (2013). Cigarette, cigar, and pipe smoking and the risk of head and neck cancers: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Am J Epidemiol. 178(5):679–90. https://doi.org/10.1093/aje/kwt029 PMID:23817919

Wyss AB, Hashibe M, Lee YA, Chuang SC, Muscat J, Chen C, et al. (2016). Smokeless tobacco use and the risk of head and neck cancer: pooled analysis of US studies in the INHANCE consortium. Am J Epidemiol. 184(10):703–16. https://doi.org/10.1093/aje/kww075 PMID:27744388

Yang CM, Chen HC, Hou YY, Lee MC, Liou HH, Huang SJ, et al. (2014). A high IL-4 production diplotype is associated with an increased risk but better prognosis of oral and pharyngeal carcinomas. Arch Oral Biol. 59(1):35–46. https://doi.org/10.1016/j.archoralbio.2013.09.010 PMID:24169152

Yang YH, Ho PS, Lu HM, Huang IY, Chen CH (2010). Comparing dose-response measurements of oral habits on oral leukoplakia and oral submucous fibrosis from a community screening program. J Oral Pathol Med. 39(4):306–12. https://doi.org/10.1111/j.1600-0714.2009.00820.x PMID:20149061

Yang YH, Lien YC, Ho PS, Chen CH, Chang JS, Cheng TC, et al. (2005). The effects of chewing areca/betel quid with and without cigarette smoking on oral submucous fibrosis and oral mucosal lesions. Oral Dis. 11(2):88–94. https://doi.org/10.1111/j.1601-0825.2004.01061.x PMID:15752081

Yen AM, Chen SC, Chen TH (2007). Dose-response relationships of oral habits associated with the risk of oral pre-malignant lesions among men who chew betel quid. Oral Oncol. 43(7):634–8. https://doi.org/10.1016/j.oraloncology.2006.05.001 PMID:17466570

Yen AM, Chen SL, Chiu SY, Chen HH (2011). Association between metabolic syndrome and oral pre-malignancy: a community- and population-based study (KCIS No. 28). Oral Oncol. 47(7):625–30. https://doi.org/10.1016/j.oraloncology.2011.04.011 PMID:21592847

Yen AM, Wang ST, Feng SW, Lin CT, Chen SL (2019). The association between fecal hemoglobin concentration and oral potentially malignant disorders. Oral Dis. 25(1):108–16. https://doi.org/10.1111/odi.12978 PMID:30216606

Zavras AI, Yoon AJ, Chen MK, Lin CW, Yang SF (2011). Metallothionein-1 genotypes in the risk of oral squamous cell carcinoma. Ann Surg Oncol. 18(5):1478–83. https://doi.org/10.1245/s10434-010-1431-3 PMID:21128001

Zhou H, Wu W, Wang F, Qi H, Cheng Z (2018). Tea consumption is associated with decreased risk of oral cancer: a comprehensive and dose-response meta-analysis based on 14 case-control studies (MOOSE compliant). Medicine (Baltimore). 97(51):e13611. https://doi.org/10.1097/MD.0000000000013611 PMID:30572470

Znaor A, Brennan P, Gajalakshmi V, Mathew A, Shanta V, Varghese C, et al. (2003). Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. Int J Cancer. 105(5):681–6. https://doi.org/10.1002/ijc.11114