

**Table 2.10. Case-control studies of betel quid chewing and cancer of the upper aerodigestive tract published after IARC (2004)**

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
<b>Nasopharynx</b>								
Yang XR <i>et al.</i> (2005) Taiwan, China	Naso-pharynx (ICD-10 C11) – code not given in the paper	325 sporadic cases* (69.8% male) (86.0% of eligible) in two large hospitals and Tumour registries * From Hildesheim <i>et al.</i> (1997) Sporadic = non-familial	327 population-based controls* (~69% male) from Taipei (out of 374 eligible =87.4%) selected by two stage random sampling in the National Household Registration System (matched on age, sex). * From Hildesheim <i>et al.</i> (1997)	Interviewer-administered standardized questionnaire	<i>Duration of betel quid use without tobacco* (year)</i> Never < 20 ≥20	1.00 1.08 (0.57-2.07) 1.37 (0.61-3.10)	Cigarette smoking, Guangdong salted fish consumption during childhood and cumulative wood exposure.	*The authors refer to this exposure as areca nut
	Naso-pharynx (ICD-10 C11)	502 cases identified from nationwide tumour registry, tertiary hospitals and specialized outpatient clinics; proxy interviews used for the deceased (N=203 = 42.5% deceased); age range not shown; apparently 100% response rate.	327 population-based controls* from Taipei selected by two stage random sampling in the National Household Registration System (no matching in this study), 1991-94. * From Hildesheim <i>et al.</i> (1997).	Interviewer-administered standardized questionnaire	<i>Duration of betel quid use without tobacco* (year)</i> Never < 20 ≥ 20	1.00 1.22 (0.65-2.30) 1.83 (1.08-4.67)	Cigarette smoking, Guangdong salted fish consumption during childhood and cumulative wood exposure.	*The authors refer to this exposure as areca nut

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Yang XR <i>et al.</i> (2005) (contd)	Naso-pharynx (ICD-10 C11)	502 cases identified from nationwide tumour registry, tertiary hospitals and specialized outpatient clinics; proxy interviews used for the deceased (N=203 = 42.5% deceased); age range not shown; apparently 100% response rate.	1944 unaffected family members	Interviewer-administered standardized questionnaire	<i>Duration of betel quid use without tobacco* (year)</i> Never < 20 ≥20	1.00 0.68 (0.42-1.10) 1.36 (0.81-2.27)	Cigarette smoking, Guangdong salted fish consumption during childhood and cumulative wood exposure. Degree of relationship among family members generated similar results.	All cases and controls were EBV positive *The authors refer to this exposure as areca nut
e	Naso-pharynx (ICD-10 C11)	227 late age onset cases (out of 502 identified from nationwide tumour registry, tertiary hospitals and specialized outpatient clinics; proxy interviews used for the deceased; age range not shown; apparently 100% response rate.	963 unaffected family members	Interviewer-administered standardized questionnaire	<i>Duration of betel quid use without tobacco* (year)</i> Never < 20 ≥ 20	1.00 0.62 (0.25-1.52) 2.44 (1.16-5.13)	Cigarette smoking, Guangdong salted fish consumption during childhood and cumulative wood exposure. Degree of relationship among family members generated similar results	This study is the more highly powered of the four *The authors refer to this exposure as areca nut

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Chelleng <i>et al.</i> (2000) Assam & Nagaland, India	Naso-pharynx (147)	47 cases (34 men, 13 women) in two hospitals	94 controls (68 men, 26 women) from the population, matched on sex, age, and ethnicity	Interviewer-administered standardized questionnaire	Never Frequently (34 cases)	1.0 1.8 (0.8-4.4)	Smokeless tobacco, smoking, smoked meat, nasal drops, fuel, etc.	Occasional Users (3 cases) had estimated RR 3.7 (0.5-25.8)
<b>Hypopharynx</b>								
Znaor <i>et al.</i> (2003) Chennai and Trivandrum, India	Hypopharynx (148)	A subset of the 636 total pharyngeal cancer cases (all men.), all histologically confirmed.	3638 controls consisting of 1711 men with non tobacco related cancers reported during the same study period, all histologically confirmed; 1927 healthy male hospital visitors	Interviewer administered, standardized questionnaire	Chewing betel quid Never Without tobacco With tobacco	1.00 1.34 (0.78-2.30) 1.98 (1.46-2.68)	Age, centre, education tobacco smoking and alcohol consumption	

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Sapkota <i>et al.</i> (2007) Ahmedabad, Bhopal, Chennai & Kolkata, India,	Hypopharynx (C12, C13)	513 (430 men, 83 women) from four hospitals, 96.4% of eligible, 100% histologically confirmed	718 (601 men, 111 women), 88.6% between ages 35 to 74, matched on age, sex and geographical area	Interviewer-administered standardized questionnaire	<b>Chewing status</b>			Centre, age, sex, socio-economic status, alcohol consumption, tobacco snuffing, tobacco smoking (pack years).	Mawa and gutka contain tobacco	
					<i>All individuals</i>	Never chewer	1.00			
					Mawa	Pan with tobacco	1.33 (0.61-2.89)			1.65 (0.96-2.85)
					Gutka	<i>Never smokers only</i>	1.35 (0.56-3.27)			1.00
					Never chewer	Mawa	3.17 (1.06-9.53)			3.34 (1.68-6.61)
Pan with tobacco	Gutka	4.59 (1.21-17.49)								
<b>Oropharynx</b>										
Znaor <i>et al.</i> (2003) Chennai and Trivandrum, India	Oropharynx (146)	A subset of the 636 total pharyngeal cancer cases (all men), all histologically confirmed.	3638 controls consisting of 1711 men with non tobacco related cancers reported during the same study period, all histologically confirmed; 1927 healthy male hospital visitors	Interviewer administered, standardized questionnaire	Chewing betel quid		Age, centre, education tobacco smoking and alcohol consumption			
					Never	1.00				
					Without tobacco	1.45 (0.77- 2.74)				
					With tobacco	1.74 (1.25-2.43)				
Dikshit and Kanhere (2000) Bhopal, central India	Oropharynx (146)	247 men in the population-based cancer registry of Bhopal	260 men in the Bhopal population	Interviewer administered, standardizes questionnaire	Chewing		Age and tobacco smoking	RR for chewing without tobacco not computed due to small numbers		
					No	1.0				
					Without tobacco	- *				
					With tobacco	1.2 (0.8-1.8)				

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<b>Pharynx</b>								
Znaor <i>et al.</i> (2003) Chennai and Trivandrum, India	Pharynx (146,148, 149)	636 total pharyngeal cancer cases (all men), all histologically confirmed.	3638 controls consisting of 1711 men with non tobacco related cancers reported during the same study period, all histologically confirmed; 1927 healthy male hospital visitors	Interviewer administered, standardizes questionnaire	Chewing betel quid Never Without tobacco With tobacco  <i>All chewers</i> Duration of chewing New chewers 0-19 20-39 ≥ 40  Average daily amount (no. of quids) New chewers 1-3 4-5 > 5 Cumulative exposure < 1000 > 1000 Time since quitting (yr) Current chewers 2-4 5-9 10-14 ≥15	1.0 1.37 (0.89-2.10) 1.83 (1.43-2.33)  1.00 1.23 (0.89-1.71) 1.97 (1.46-2.67) 2.60 (1.60-4.20)  1.00 1.21 (0.91-1.61) 1.89 (1.29-2.76) 4.22 (2.71-6.56)  1.36 (0.97-1.90) 1.97 (1.05-3.68)  1.00 0.81 (0.40-1.66) 1.23 (0.51-3.01) 0.45 (0.15-1.33) 0.57 (0.24-1.39)	Age, centre, education level, tobacco smoking and alcohol consumption	

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Lee <i>et al.</i> (2005a) Kaosiung, Taiwan, China	Oropharynx (C10) and Hypopharynx (C13) Combined 'pharynx'	148 men aged 41-80 years; mean age 53 years; 100% histologically confirmed; 130 smokers; 120 alcohol consumers	255 men aged 40-92 years; mean age 53 years; selected from hospital patients	Interviewer-administered standardized questionnaire	<i>Betel quid chewing without tobacco</i>		Tobacco smoking, alcohol consumption and age.	Interaction with alcohol intake and smoking.
					Non-chewers	1.0		
					Chewers	7.7 (4.1-15.0)		
					Ex-chewers	9.5 (4.3-28.1)		
					Current chewers	6.9 (3.4-14.3)		
					<i>Starting Age</i>			
					Non-chewers	1.0		
					≥ 20 years	9.9 (4.4-23.8)		
					< 20 years	4.6 (2.2-9.9)		
					<i>Daily quantity</i>			
					Non-chewers	1.0		
					≤ 20 pieces	2.5 (1.0-3.8)		
					> 20 pieces	7.2 (3.6-14.8)		
					<i>p for trend</i>	<0.0001		
<i>Type of quid</i>								
Non-chewers	1.0							
With betel inflorescence	13.5 (4.3-52.5)							
With betel leaf	5.4 (2.5-11.7)							
Mixed	5.8 (2.3-15.7)							
<i>Betel juice swallow.</i>								
Non-chewers	1.0							
Never swallowed	6.2 (3.0-13.0)							
Swallowed	8.7 (3.2-26.0)							
Not sure	5.0 (1.6-16.8)							

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<b>Larynx</b>								
Kapil <i>et al.</i> (2005b) New Delhi, India,	Larynx (C32)	305 (280 men, 25 women) 100% proven by biopsy and histopathology	305 matched on age, sex and place of residence (urban, rural), unrelated persons accompanying patients in other departments of the same hospital	Interviewer-administered semi-structured questionnaire	<i>Chewing betel leaf with tobacco</i> No Yes	1.00 2.37 (1.12-5.06)	Unadjusted	This was a dietary study. Low vegetable consumption and more spicy and fried foods are risk factors.
Lee <i>et al.</i> (2005a) Kaosiung, Taiwan, China	Larynx (C32)	128 men aged 43-89 years; mean 61 years; 100% histologically confirmed; 115 smokers; 72 alcohol drinkers	255 men aged 40-92 years; mean 53 years; selected from hospital patients	Interviewer-administered standardized questionnaire	<i>Betel quid chewing without tobacco</i> Non-chewers Chewers Ex-chewers Current chewers	1.0 1.3 (0.7-2.5) 1.5 (0.6-3.9) 1.3 (0.6-2.7)	Tobacco smoking, alcohol consumption and age	Interaction with smoking. probably interaction with alcohol consumption, but there were no patients who used betel quid by itself.

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Sapkota <i>et al.</i> (2007) Ahmedabad, Bhopal, Chennai & Kolkata, India,	Larynx – Glottis, Supraglottis, & Other (C32.0, C32.1, C32.9)	511 (478 , 33 women), 96.4% of eligible, 100% histologically confirmed  (Results also given sub-sitewise)	718 (601 men, 111 women), 88.6% aged 35-74 years, matched on age, sex and geographical area of residence	Interviewer-administered standardized questionnaire	<b>Chewing status</b>		Centre, age, sex, socio-economic status, alcohol consumption, tobacco snuffing, tobacco smoking (pack years).	Mawa and gutka contain tobacco
					<i>All individuals</i>	Never chewer		
					Mawa	0.59 (0.25-1.45)		
					Pan with tobacco	0.82 (0.43-1.55)		
					Gutka	1.11 (0.45-2.74)		
					<i>All never smokers</i>			
					Never chewer	1.00		
					Mawa	0.98 (0.26-3.75)		
					Pan with tobacco	1.06 (0.43-2.62)		
					Gutka	2.55 (0.62-10.44)		
Kapil <i>et al.</i> (2005b) New Delhi, India,	Larynx (C32)	305 (280 men, 25 women) 100% proven by biopsy and histopathology	305 matched on age, sex and place of residence (urban, rural), unrelated persons accompanying patients in other departments of the same hospital	Interviewer-administered semi-structured questionnaire	<i>Chewing betel leaf with tobacco</i>		Unadjusted	This was a dietary study. Low vegetable consumption and more spicy and fried foods are risk factors.
					No	1.00		
					Yes	2.37 (1.12-5.06)		

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Lee <i>et al.</i> (2005a) Kaosiung, Taiwan, China	Larynx (C32)	128 men aged 43-89 years; mean 61 years; 100% histologically confirmed; 115 smokers; 72 alcohol drinkers	255 men aged 40-92 years; mean 53 years; selected from hospital patients	Interviewer-administered standardized questionnaire	<i>Betel quid without tobacco</i> Non-chewers Chewers Ex-chewers Current chewers	1.0 1.3 (0.7-2.5) 1.5 (0.6-3.9) 1.3 (0.6-2.7)	Smoking, drinking and age	Interaction with tobacco smoking. probably interaction with alcohol consumption, but there were no patients who used betel quid by itself.
Sapkota <i>et al.</i> (2007) Ahmedabad, Bhopal, Chennai & Kolkata, India,	Larynx – Glottis, Supraglottis, & Other (C32.0, C32.1, C32.9)	511 (478 , 33 women), 96.4% of eligible, 100% histologically confirmed  (Results also given sub-sitewise)	718 (601 men, 111 women), 88.6% aged 35-74 years, matched on age, sex and geographical area of residence	Interviewer-administered standardized questionnaire	<b>Chewing status</b> <i>All individuals</i> Never chewer Mawa Pan with tobacco Gutka <i>All never smokers</i> Never chewer Mawa Pan with tobacco Gutka	1.00 0.59 (0.25-1.45) 0.82 (0.43-1.55) 1.11 (0.45-2.74)  1.00 0.98 (0.26-3.75) 1.06 (0.43-2.62) 2.55 (0.62-10.44)	Centre, age, sex, socio-economic status, alcohol consumption, tobacco snuffing, tobacco smoking (pack years).	Mawa and gutka contain tobacco
<b>Oesophagus</b>								
Chitra <i>et al.</i> (2004) Coimbatore, India,	Esophagus (C15)	90 (62 men, 28 women) 90% between 31 and 70 years of age, at Coimbatore Medical College and Hospital.	90 hospital matched on age sex.	Interviewer-administered standardized questionnaire	<i>Chewing status</i> Non users Betel nut chewing	1.0 (implied) 2.8 (1.3-5.9)	None	

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Lee <i>et al.</i> (2005b) Taipei and Kaosiung, Northern and southern Taiwan, China	Oesophagus (ICD-9 150)	513 (468 men, 45 women), 64.5% of sequential cases (28-89 years).	818 (752 men, 66 women) hospital (26-89 years) matched on sex and age and from the same geographical area.	Interviewer-administered standardized questionnaire	<i>Betel quid w/o tobacco chewing:</i> Never Former Current <i>Age at start</i> ≥30 yrs <30 yrs <i>Years of chewing</i> 1-10 11-20 >20 <i>Average amount</i> 1-10 11-20 > 20 <i>Materials chewed</i> With inflorescence With leaf or stem Mixed <i>Years since quitting</i> Current 1-5 6-10 > 10 Never chewer <i>p for trend</i>	1.0 2.2 (1.3-3.9) 2.3 (1.4-3.7)* 1.3 (0.7-2.5) 2.7 (1.8-4.3)* 1.8 (0.9-3.8) 2.2 (1.1-4.2) 3.1 (1.9-5.1)* 1.6 (0.9-2.6) 3.3 (1.7-6.4) 3.9 (1.9-7.9)* 2.9 (1.8-4.7) 1.2 (0.4-3.7) 2.1 (1.1-3.9) 1.0 1.0 (0.4-2.4) 2.2 (0.7-7.0) 0.7 (0.3-1.7) 0.5 (0.3-0.8) 0.848	Age, sex, study hospital, education, consumption of vegetables and fruits, gram/day-year of alcohol drinking and pack-year of cigarette smoking	* <i>p</i> for trend <0.001

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Boonyaphiphat <i>et al.</i> , (2002) Songkhla, Thailand	Oesophagus (150)	202 cases, all histologically confirmed.	261 hospital controls, frequency matched on age sex and ethnicity	Interviewer administered, standardizes questionnaire	Betel quid chewing Non-chewers Betel chewers	1.0 [2.1]		Unspecified whether tobacco was add to the betel quid
Znaor <i>et al.</i> (2003) Chennai and Trivandrum, India	Oesophagus (150)	566 oesophageal cancer cases (all men), all histologically confirmed.	3638 consisting of 1711 men with non tobacco related cancers reported during the same study period, all histologically confirmed; 1927 healthy male hospital visitors	Interviewer administered, standardizes questionnaire	Betel quid chewing Never Without tobacco With tobacco Average daily amount (number of quids) 1-3 4-5 >5	1.00 3.30 (1.53-7.13) 5.74 (3.50-9.42) 1.19 (0.88-1.60) 2.18 (1.48-3.19) 6.07 (4.03-9.14)	Sex, age, alcohol consumption, tobacco smoking, genotype Age, centre, education tobacco smoking and alcohol consumption	Among non alcohol drinkers

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Wu <i>et al.</i> (2006) Kaosiung, Southern Taiwan	Oesophagus (C15)	165 men (35-92 years) 100% histopathologically proven	255 men (40-92 years) hospital outpatients (88% response rate)	Interviewer-administered standardized questionnaire	<i>Betel quid chewing without tobacco</i>	1.0	Unadjusted	Interaction between cigarette, alcohol consumption and betel nut use without tobacco	
					Chewers	7.2 (4.6-11.4)			
					<i>Betel quid chewing</i>	1.0			Age, education, alcohol consumption, cigarettes
					Chewers	1.7 (0.8-3.1)			
					<i>Type of betel quid</i>	1.0			Age, education, alcohol consumption, cigarettes
					Non-chewers with inflorescence	4.2 (1.4-16.0)			
					with leaf mixed	1.4 (0.7-3.0) 1.1 (0.4-3.1)			
					<i>Juice swallowing</i>	1.0			Age, education, alcohol consumption, cigarettes
					Non-chewers	1.0			
					Not swallowed	3.3 (1.3-9.3)			
Lee <i>et al.</i> (2007) Taipei and Kaosiung, Northern and Southern Taiwan, China	Oesophagus (ICD-9 150)	447 (men, women) (81.9% response rate) incident cases with information on subsite and only one subsite	1022 (all controls) (954 men, 68 women)  or 918 (89.8%) matched on hospital, sex and age.	Interviewer-administered standardized questionnaire	No habit*	1.0	Age, sex, hospital, education, consumption of vegetables and fruits, alcohol consumption, cigarettes	Linked to Lee <i>et al.</i> , (2005b)  *Did not chew, consume alcohol, or smoke tobacco	
					<i>Betel quid chewers without tobacco</i>	4.7 (2.7-8.3)			
					Upper	2.1 (1.4-3.3)			
					Middle	3.0 (1.8-5.0)			
					Lower	3.0 (1.8-5.0)			