2. Studies of Cancer in Humans

2.1 Oral cancer

2.1.1 *India, Pakistan and Sri Lanka*

(*a*) *Descriptive studies and case series*

In this section, the subsites included in oral cancer were rarely specified, but mostly included lip, tongue and mouth. The reports summarized in the previous monograph on betel-quid and areca-nut chewing (IARC, 1985a) are given in Table 33, which shows that the percentage of oral cancer among all cancers diagnosed in hospitals or groups of hospitals in Asia was always much higher than that usually found in western countries (3–5%; Parkin *et al.*, 2003), where the habit of chewing betel quid, with or without tobacco, is virtually unknown.

In many descriptive studies, investigators have obtained histories of chewing betel quid with tobacco from series of patients with oral cancer (Table 34). In most of these studies, the percentage of patients who practise chewing habits is extremely large. Several authors also commented that the cancer generally develops at the place where the quid is kept.

A high incidence of oral, oro- and hypopharyngeal cancer is observed in regions of the world where a high proportion of the population practises betel-quid chewing (Parkin *et al*., 2003). Of the 267 000 new oral cancers estimated to occur around the year 2000 throughout the world, 128 000 (48%) occur in South and South-East Asia; of the 123 000 cases of oro- and hypopharyngeal cancer estimated to occur globally annually, 63 000 (51.2%) are accounted for in South and South-Easts Asia (Figures 3 and 4).

In India, the age-standardized incidence rates (ASR) of oral cancer (ICD 9: 140–145) per 100 000 population are 12.8 in men and 7.5 in women (Ferlay *et al*., 2001).

Table 33. Chewing habit and percentage of oral cancer among all cancers

Location	Habit	All cancers (years)	Oral cancer	Reference
Papua New Guinea	Betel quid without tobacco	1175 (1958–63)	209 (17.8%)	Atkinson *et al*. (1964)
Papua New Guinea	Betel quid without tobacco	2300 (1958–65)	(17.1%); 29 (9%) oral cancers were verrucous carcinoma	Cooke (1969)
Papua New Guinea	Betel quid without tobacco	6186 (1958–73)	890 (14.4%)	Henderson & Aiken (1979)
Travancore, South India	Betel quid with tobacco	1700 (5 years)	989 (58%)[a]	Bentall (1908)
Neyoor, South India	Betel quid with tobacco	377 epithelial cancers (2 years)	346 (91.5%)[b]	Fells (1908)
Mumbai, India	Betel quid with tobacco	2880 carcinomas (1941–43)	1000 (34.7%)[c]	Khanolkar (1944)
Mumbai, India (Parsees)	Betel-quid chewing very rare	1705 (1941–65)	160 (9.4%)[d]	Paymaster & Gangadharan (1970)
Sri Lanka	Betel quid	2344 (1928–48)	1130 (48.2%)[e]	Balendra (1949)
Thailand	Betel quid	1100	155 (14.1%)[f]	Piyaratn (1959)
Malaysia (Indians)	Betel quid with tobacco	–	219[g]	Marsden (1960)
Singapore	Betel quid with tobacco	7131	(8%)[h]	Muir (1962)
Philippines	Betel leaf, tobacco chewing, reverse cigarette smoking	– (1957–61)	186	Tolentino *et al*. (1963)
Malaysia	Betel quid with and without tobacco	4369 (1961–63)	476 (10.9%)[i]	Ahluwalia & Duguid (1966)
Indians	Betel quid with tobacco	912	306 (33.6%)	
Malays	Betel quid without tobacco	777	74 (9.5%)	
Bangladesh	Betel quid	3650	672 (18.4%)[j]	Huq (1965)
Pakistan	Betel quid with tobacco, cigarette smoking	14 350 (1960–71)	2608 (18.2%)	Zaidi *et al.* (1974)

[a] Lip, tongue, buccal mucosa
[b] Epithelial cancers of the buccal cavity
[c] Lip, buccal mucosa, alveolus, tongue, palate
[d] Lip, tongue, alveolus, floor of mouth, buccal mucosa, palate
[e] Cheek, tongue, palate and tonsil, jaw, floor of mouth, pahrynx and larynx, lip
[f] Lip, tongue, oral cavity
[g] 'Betel cancers'
[h] Buccal cavity and pharynx
[I] Lip, tongue, floor of mouth, cheek, palate
[j] Buccal cavity

Table 34. Case series of oral cancer and chewing habits

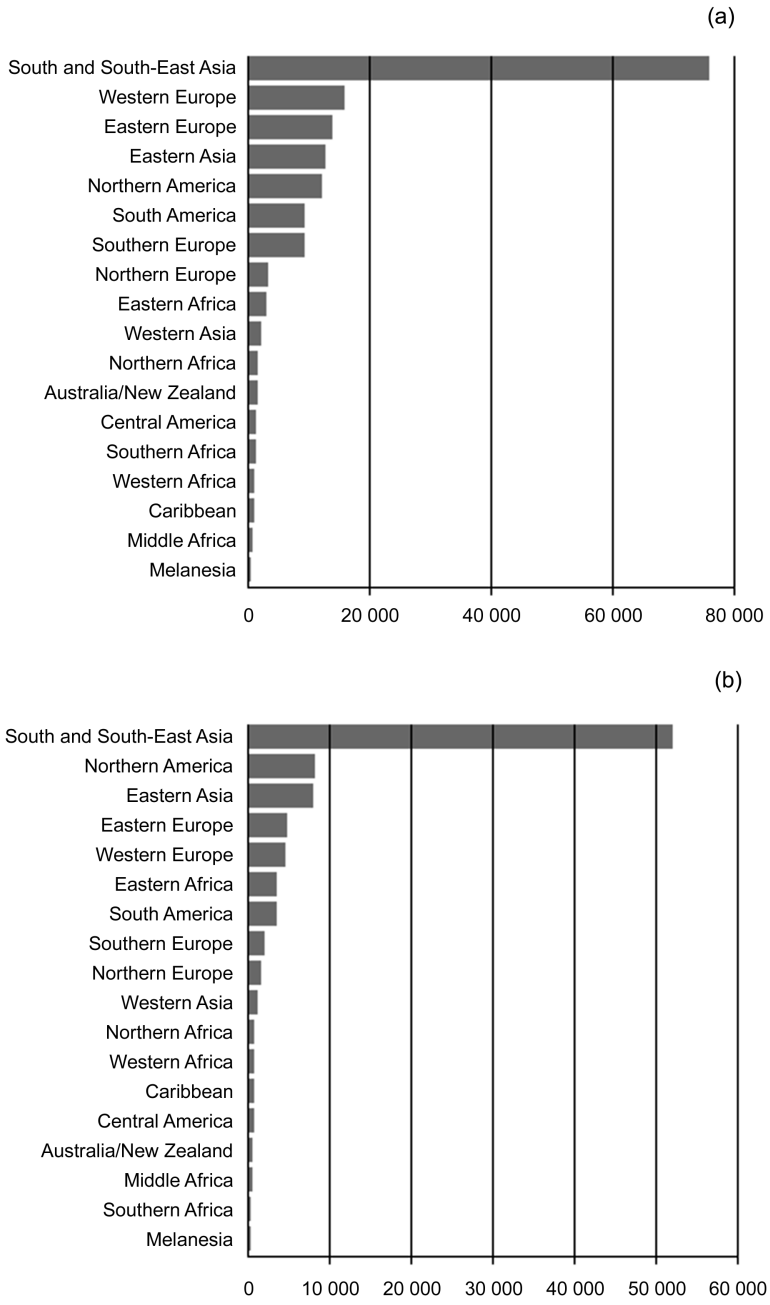
Location	Habit	All cancers (years)	Oral cancer	Reference
South-west Pacific Islands – New Britain	Betel quid without tobacco	60 (1921–40)	7 (11.7%)	Eisen (1946)
Papua New Guinea	Betel quid without tobacco (98%)	–	110	Farago (1963a)
Papua New Guinea	Betel quid without tobacco (129/130)	1160 (1960–61)	210 (18.1%)	Farago (1963b)
Mumbai, India	Tobacco and betel-quid chewing (excessive in 35%)	3627 intra-oral malignant tumours (1941–47)	650 (buccal mucosa)	Paymaster (1956)
Guntur, India	Betel-quid chewers; 9 (3.6%) Betel-quid + tobacco chewers; 29 (12%) Tobacco chewers; 20 (8%)	– (1957–59)	250 (17.4%) (oral + pharyngeal)	Padmavathy & Reddy (1960)
Mumbai, India	36.5% chewers (tobacco + betel) 21.9% chewers and smokers 23.2% smokers 18.4% no habit (among oral-cavity tumour patients)	30 219 carcinomas (1941–55)	14 162 (46.9%) (oral + pharyngeal)	Paymaster (1962)
Mumbai, India	100% tobacco + betel-quid chewers 55.7% chewers and smokers	519	210 (40.5%) (oropharyngeal)	Agarwal & Arora (1964)
Madras, India	76.7% chewers with tobacco 18.6% without tobacco 4.7% non-chewers	13 626 (1950–59)	6728 (49.4%) (oral cavity)	Sidiq *et al*. (1964)
Madras, India	95% betel-quid chewers (83% with tobacco) 34% smokers	3529 (1962–63)	362 (10%) (buccal mucosa)	Singh & von Essen (1966)
Mainpuri, India	26.6% tobacco with lime 15.6% smokers 53.9% both 3.9% no habit 2% betel quid	– (1950–62)	154 (oral + oropharyngeal)	Wahi *et al*. (1966)
Agra, India	32.5% tobacco with lime 30.1% smokers 18.1% both 19.3% no habit 12% betel quid	–	83 (oral + oropharyngeal)	Wahi *et al*. (1966)

Table 34 (contd)

Location	Habit	All cancers (years)	Oral cancer	Reference
Agra, India	85% betel quid with tobacco 51% smokers (85 gingival cancer patients)	6790 (1957–65)	3173 (46.7%) (intra-oral), 85 (gingival)	Srivastava & Sharma (1968)
Jabalpur, India	84% (100 oral cancers) tobacco chewers 28% smokers	– (1958–67)	814 (oral + pharyngeal) (33.8%)	Gandagule & Agarwal (1969)
Kanpur, India	14.8% betel quid without tobacco 22% betel quid with tobacco 49% tobacco + lime 5.4% smoking 5% smoking and chewing	2332 (1958–66)	630 (27%) (oral)	Samuel *et al*. (1969)
Philippines	52 buyo[a] chewers 2 non-chewers 21 uncertain	–	75 (49 of the cheek)	Davis (1915)
Thailand	100% betel quid + tobacco	53 (1922–23)	25 (47%) (oral)	Mendelson & Ellis (1924)
Taiwan	59% betel-quid chewers 82% smokers	– (1953–1963)	89	Chang (1964)
Sri Lanka	Only 3 (1.5%) betel-quid chewers among cases 38 smokers	– (1945 on) 400 new cases seen during 3 months in 1960	508 (buccal mucosa) 214 (53.5%) (buccal mucosa)	Balendra (1965)

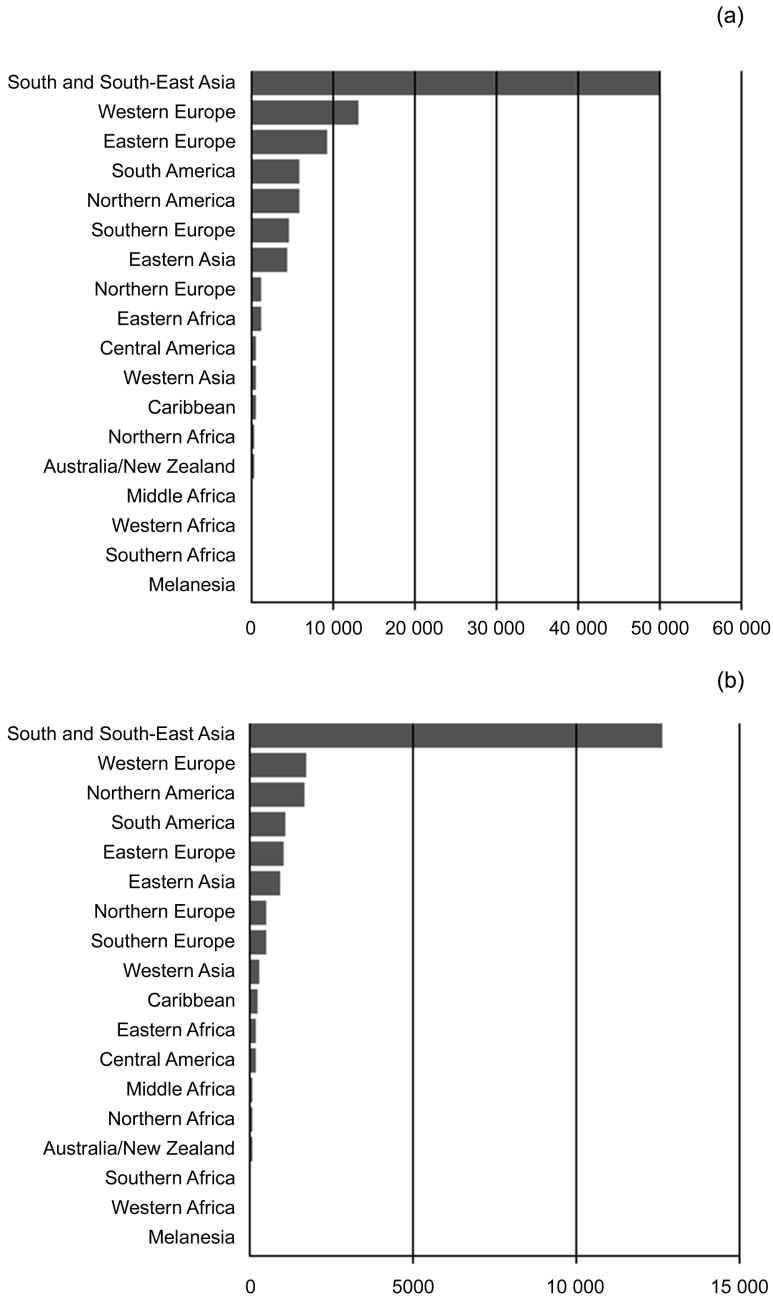
[a] Buyo can consist of betel leaves, areca nut, slaked lime and tobacco or any combination of these constituents.

Figure 3. Cancer of the oral cavity (ICD-9: 140–145) in (a) men and (b) women



From Ferlay *et al.* (2001) – GLOBOCAN 2000

Figure 4. Oropharyngeal and hypopharyngeal cancers (ICD-9: 146, 148–149) in (a) men and (b) women



From Ferlay *et al.* (2001) – GLOBOCAN 2000

A study from Mumbai, India, in 1993–97 compared the incidence rates of oral cancer among Parsi and non-Parsi communities (Yeole *et al*., 2001). Parsis form a very small subgroup (about 0.8%) of the population of the city of Mumbai; few smoke and very few chew (for religious reasons), whereas chewing and smoking are common in the population of Mumbai as a whole. The annual age-adjusted incidence rates (per 100 000) in 1995 of cancers at several sites were lower among Parsi men than among the male population of Mumbai as a whole: tongue and mouth, 4.5 versus 11.9; pharynx, 2.6 versus 10.6; oesophagus, 2.6 versus 8.7; stomach, 2.8 versus 6.6; larynx, 2.2 versus 7.2; and lung, 4.2 versus 12.6.

Gupta (1999) reported an increase in the incidence rates of mouth cancers (ICD 9: 143–145) in 1995 compared with 1983–87 among inhabitants under the age of 50 years in the city of Ahmedabad, India, which is consistent with the hypothesis of an increase in oral cancer among the young due to increased use of *gutka* and *pan masala*.

In Karachi, Pakistan's largest city, the ASR of cancer of the oral cavity per 100 000 population is 17.9 in men and 16.3 in women (Bhurgri, 2001).

(*b*) *Cohort studies*

A population-based prospective study was reported by Wahi (1968) from a temporary cancer registration system established in Uttar Pradesh (Mainpuri district), India. Over a period of 30 months (1964–66), a total of 346 cases of oral and oropharyngeal cancer were detected and confirmed histologically. Exposure data were obtained from these patients by questionnaire, and a house-to-house interview survey was conducted on a 10% cluster sample of the district population. The numbers in various exposure categories were then extrapolated to the population as a whole and used as denominators for calculating oral cancer period prevalence. Chewing *Mainpuri* tobacco was distinguished from other chewing habits. Prevalence rates for the two kinds of chewing habits and for combinations of alcohol and smoking habits are summarized in Table 35. Prevalence rates were highest among users of *Mainpuri* tobacco and higher for all other chewing habits than for no chewing habit, after adjusting for smoking and drinking. The strength of the association between chewing and oral cancer was studied in many ways [frequently intercorrelated] (Table 36) and was reported to be positive by every criterion. [The Working Group of *IARC Monographs* Volume 37 noted that differences in age between cancer patients and the population sample do not seem to have been taken into account; it is possible that the prevalence of habits within the population was age-dependent.]

Mehta *et al.* (1972a) examined a cohort of 4734 policemen in Mumbai, India, for oral precancers, at baseline in 1959, and 5 and 10 years later. Of the 3674 policemen followed successfully, 49% chewed (mostly betel quid with tobacco) and 12% chewed and smoked. Oral cancer was found in one man who chewed and smoked.

Of 57 518 textile industry workers in Ahmedabad, India, examined in the first phase of a study conducted in 1967–71, Bhargava *et al.* (1975) re-examined 43 654 workers 2 years later. They diagnosed 13 new cases of oral cancer, all of which had developed among individuals chewing betel quid with tobacco and/or smoking tobacco (Table 37).

Table 35. Numbers of oral cancers and prevalence per 1000 population in a study in Mainpuri district, India[a]

Habit	No tobacco		Mainpuri tobacco		Other kinds of tobacco	
	No. of cases	Prevalence	No. of cases	Prevalence	No. of cases	Prevalence
No habit	27	0.18	59	4.51	32	0.80
Alcohol drinking	0	0	6	6.59	2	1.08
Smoking	54	0.57	78	8.12	47	1.76
Drinking and smoking	9	1.56	30	11.45	2	0.58
Total	90	0.36	173	6.60	83	1.15

[a]From Wahi (1968)

Gupta *et al.* (1980) followed a random sample of 10 287 individuals in Kerala (Ernakulam district) for a period of 10 years (1966–77) in house-to-house surveys, with a follow-up rate of 87%. Chewing betel quid with tobacco was a common habit in that area, and all 13 new cases of oral cancer were diagnosed among either chewers only or chewers who also smoked. The person–years method was used for data analysis and incidence rates were age-adjusted (Table 37).

Apparently healthy subjects aged 35 years or older in rural Kerala were included from 1995–98 in an intervention trial, in which 59 894 individuals formed the screened group and 54 707 formed the non-screened group. Those in the screened group who chewed betel quid with tobacco, smoked or drank alcohol were advised to stop their habit; 31 and 44% of subjects in the screened and non-screened groups, respectively, reported no tobacco (chewing betel quid with tobacco or smoking) or alcohol habit. About 3 years after the start of the study, 47 cases of oral cancer (incidence, 56.1/100 000 person–years) were identified in the screened group and 16 (incidence, 20.3/100 00 person–years) in the non-screened group (Sankaranarayanan *et al.*, 2000).

(*c*) *Case–control studies*

Case–control studies for oral (comprising gum, floor of the mouth, buccal mucosa and palate; the tongue may also be included) and other cancers and their association with chewing betel quid with or without tobacco are described in Table 38 and the dose–response relationships found in these studies are summarized in Table 39. [Data for men and women were combined and relative risks were calculated by the Working Group of *IARC Monographs* Volume 37 from the data given in the papers published up to 1985, unless provided by the authors]. The derived relative risk estimates for use of betel quid ranged from 0.1 to 45.9 in different studies.

A case–control study was reported by Shanta and Krishnamurthi (1959), consisting of 206 cancers of the buccal mucosa and the floor of the mouth and 278 randomly selected

non-cancerous controls. The proportion of betel and areca-nut chewers was 8.7% in the cancer group and 51.8% in the control group. [The percentages of habits given for cases as well as for controls were inconsistent.]

Table 36. Prevalence of oral cancer by chewing habit

Chewing habit	Estimated population	No. of cases	Prevalence per 1000
Total	349 710	346	0.99
Non-chewers of tobacco	251 330	90	0.36
Frequency of tobacco chewing			
Occasionally	11 680	5	0.43
Daily	86 700	251	2.90
Age started chewing (years)			
≥ 30	38 290	69	1.80
25–29	15 000	28	1.87
20–24	22 230	61	2.74
15–19	16 030	58	3.62
5–14	6 870	40	5.92
Retention of each quid (min)			
1–20	69 030	133	1.93
21–30	18 680	69	3.69
≥ 31	9 650	53	5.49
Period of exposure (min) per day			
Up to 99	53 720	123	2.29
100–299	33 670	90	2.67
300–499	9 400	31	3.30
≥ 500	2 230	12	5.38
Sleeping with quid in mouth			
Never	85 790	175	2.04
Occasionally	10 790	58	5.38
Daily	1 740	23	13.22
Type of tobacco chewed			
Pattiwala	71 610	84	1.17
Mainpuri and *Pattiwala*	8 950	37	4.13
Mainpuri	17 160	134	7.81
Other (*Kapuri*, *Rampuri*, *Moradabadi*)	760	1	1.32
Amount of money (paisa)[a] *spent on tobacco per day*			
0–6	67 240	161	2.39
7–37	19 710	77	3.91
38–74	680	4	5.88
75–100	260	9	34.62

From Wahi (1968)

[a] 1 paisa = 0.01 rupee

Table 37. Chewing and smoking habits and oral cancer in two cohort studies, India

Habit	Ahmedabad[a]			Ernakulam[b]		
	Number re-examined[c]	New oral cancers	Incidence per 100 000	Person–years	New oral cancers	Age-adjusted incidence per 100 000
Chewing	3 266	1	31	23 416	9	23
Chewing and smoking	16 881	6	36	8 476	4	32
Smoking	15 378	6	39	20 222	0	0
None	7 065	0	0	30 962	0	0

[a] Industrial workers aged 35 years and over; data from Bhargava *et al*. (1975)
[b] House-to-house survey of individuals aged 15 years and over; data from Gupta *et al*. (1980)
[c] Approximately 2 years after the first examination

Chandra (1962) reported a study of 450 cases of cancer of the cheek (287 men, 163 women) and 500 hospital visitor controls (410 men, 90 women) conducted in 1955–59. The proportion of betel-quid chewers was 5.6% and that of chewers of betel quid with tobacco was 23.3% among male cases. Corresponding proportions among male controls were 13.4 and 10.7%, respectively. The proportions among female cases were 18.4 and 43.5% and those among female controls were 16.7 and 18.9%, respectively.

In another case–control study, Shanta and Krishnamurthi (1963) reported on 882 cancer cases (628 men, 254 women) and 400 (300 men, 100 women) controls. Cancer sites included lip (12 men, seven women), buccal mucosa (293 men, 152 women), anterior tongue (69 men, 18 women), posterior tongue (48 men, four women), pharynx (130 men, 25 women), hypopharynx (18 men, 12 women) and oesophagus (57 men, 36 women). For cancer of these different sites, the proportion of male cases who chewed betel quid without tobacco ranged from 8.4 to 38.5% and that among male controls was 49.1%; the proportion of female cases who chewed betel quid without tobacco ranged from 12.4 to 55.5% and that among female controls was 55.5%. [The authors pointed out that most chewers of betel quid without tobacco were occasional chewers and the percentage was high because it was very hard to find Indians who had not chewed betel quid without tobacco at one time or another. They opined that betel-quid and areca-nut chewing was of no statistical significance in etiology and is only a reflection of habit in the general population.]

Hirayama (1966) reported a case–control study of oral and oropharyngeal cancers conducted in India and Sri Lanka. The study included 545 cases of cancer of the buccal mucosa (369 men, 176 women), 143 cases of cancer of the anterior tongue (117 men, 26 women), 37 cases of cancer of the palate (28 men, nine women), 102 cases of cancer of the oropharynx (81 men, 21 women) and 440 controls (277 men, 163 women). The proportion of men who chewed areca nut (reported as betel nut) was 0.8% for cancer of the buccal

Table 38. Case–control studies of oral[a] and other cancers and their association with chewing of betel quid

Location (years)	Cancer site[b]	No. of cases	Habit	No. of controls	Habit	Relative risk (95% CI)	Reference
Up to 1985							
Travancore, India	Lip	100	Q, 98%	100	Q, 66%	25.2	Orr (1933)
Mumbai, India (1952–54)	Base of tongue, oropharynx, hypopharynx, oesophagus	289 (M + F) (oral)	Q, 12% Q + S, 39% S, 47% (M)	400 400	Q, 9% Q + S, 24% S, 50% (M)	Q, 10.2 Q, 4.0	Sanghvi *et al*. (1955)
		551 (M + F) (base of tongue, oropharynx, hypopharynx, oesophagus)					
Assam, India (1954–55)	Lip, pharynx, oesophagus, larynx	238 (108 larynx)	Q, 97%	3678	Q, 79%	7.6	Sarma (1958)
Mumbai, India (1952–54)	Base of tongue, oropharynx, lip	371	Q, 12% Q + S, 38% S, 48%		Q, 9% Q + S, 24% S, 50%		Khanolkar (1959)
		95 (oral)	Q, 28% Q + S, 42% S, 18%	288		Q, 8.0	
		276 (oropharynx and base of tongue	Q, 5% Q + S, 36% S, 58%	288		Q, 10.0	
Madras, India	Only cheek and floor of the mouth	206	BQ, 9% BQ + T, 85% S, 26%	278	BQ, 52% BQ + T, 13% S, 47%	BQ, 0.1 BQ + T, 39	Shanta & Krishnamurthi (1959)

Table 38 (contd)

Location (years)	Cancer site[b]	No. of cases	Habit	No. of controls	Habit	Relative risk (95% CI)	Reference
Calcutta, India (1955–59)	Cheek	450 (M + F)	BQ, 6% (M) BQ + T, 23% (M) T, 6% (M) BQ, 18% (F) BQ + T, 44% (F) T, 3% (F)	500	BQ, 13% (M) BQ + T, 11% (M) T, 40% (M) BQ, 17% (F) BQ + T, 19% (F) T, 2% (F)	BQ, 0.8 (M) BQ + T, 2.5 (M) T, 1.5 (M) BQ, 1.1 (F) BQ + T, 3.3 (F) T, 1.4 (F)	Chandra (1962)
Madras, India	Lip, oropharynx, hypopharynx, oesophagus, tongue	882	BQ, 20% (M) BQ + T, 64% (M) BQ, 50% (F) BQ + T, 71% (F)	400	BQ, 40% (M) BQ + T, 9% (M) BQ, 56% (F) BQ + T, 11% (F)	BQ, 0.3 (M) BQ + T, 17.2 (M) BQ, 0.8 (F) BQ + T, 20.1 (F)	Shanta & Krishnamurthi (1963)
Agra, India (1950–62)	Lip, tongue, tonsil	821	T, 73% T + S, 38% S, 55%	1916	T, 12% T + S, 6% S, 28%	T, 41.2	Wahi *et al*. (1965)
Sri Lanka	Oesophagus only	111	Q, 81%	1088	Q, 30%	9.9	Stephen & Uragoda (1970)
Varanasi, India (1966–70)	–	206	BQ + T, 39% T, 50%	100	Q, 25%	27.0	Khanna *et al*. (1975)
Mumbai, India	Anterior two-thirds of tongue, lip	214 M	Q, 29% Q + S, 32% S, 31%	230	Q, 15% Q + S, 20% S, 48%	Q, 4.2	Notani & Sanghvi (1976)
1985–2003							
Kerala, India (1983–84)	Tongue Floor of mouth	158 (M) 70 (F)	BQ + T, 58% (M) BQ + T, 76% (F)	314 (M) 139 (F)	BQ + T, 30% (M) BQ + T, 39% (F)	BQ + T, 6.1 (3.3–11.4) (M) BQ + T + S, 7.02 (3.6–13.5) (M) S, 4.98 (2.5–9.8) (M)	Sankaranarayanan *et al*. (1989a)

Table 38 (contd)

Location (years)	Cancer site[b]	No. of cases	Habit	No. of controls	Habit	Relative risk (95% CI)	Reference
Kerala, India (1983–84)	Gingiva	109 (M) 78 (F)	BQ + T, 80% BQ + T, 88%	546 (M) 349 (F)	BQ + T, 33% (M) BQ + T, 51% (F)	BQ + T, 8.8 (3.6–21.5) (M) BQ + T + S, 16.3 (6.5–40.9) (M) S, 3.8 (1.2–11.7) (M)	Sankaranarayanan *et al.* (1989b)
Kerala, India (1983–84)	Buccal and labial mucosa	250 (M) 164 (F)	BQ + T, 81% (M) BQ + T, 88% (F)	546 (M) 349 (F)	BQ + T, 33% (M) BQ + T, 51% (F)	BQ + T, 14.3 (8.2–24.8) (M) BQ + T + S, 21.5 (11.9–38.5) (M) S, 4.2 (2.09–8.5) (M)	Sankaranarayanan *et al*. (1990a)
Bangalore, India (1982–85)	Oral cavity excl. base of tongue	115 (M) 233 (F)	BQ, 13% (M) BQ + T, 28% (M) BQ, 4% (F) BQ + T, 88% (F)	115(M) 233 (F)	BQ, 13% (M) BQ + T, 10% (M) BQ, 13% (F) BQ + T, 25% (F)	Odds ratio not adjusted BQ, 1.5 (0.6–3.8) (M) BQ + T, 4.0 (1.8–8.9) (M) BQ, 2.2 (0.7–6.5) (F) BQ + T, 30.4 (12.6–73.4) (F)	Nandakumar *et al*. (1990)
Mumbai, India (1980–84)	Anterior 2/3 of tongue Posterior 1/3 of tongue	141 (M) 495 (M)	BQ + T, 54% BQ + T, 35%	631 (M)	BQ + T, 40%	BQ + T, 1.7(1.2–2.6) BQ + T, 0.9 (0.7–1.2)	Rao & Desai (1998)
Maharashtra, India	Oropharynx	123 (M + F)	T, 20% Areca, 4% T + areca, 11% BQ, 6% BQ + T, 42%	246 (M + F)	T, 4% Areca nut, 6% T + areca, 4% BQ, 7% BQ + T, 16%	Odds ratio not adjusted T, 15.9 (6.9–36.7) Areca nut, 2.6 (0.9–7.7) T + areca, 10.2 (4.1–25.5) BQ, 2.8 (1.09–7.4) BQ + T, 9.5 (5.1–17.5)	Wasnik *et al.* (1998)
Bhopal, India (1986–92)	Oral cavity	148	BQ, 3% BQ + T, 97% S + T, 33%	260	BQ, 10% BQ + T, 90% S + T, 17%	BQ + T, 5.8 (3.6–9.5) BQ, 1.7 (0.9–3.3)	Dikshit & Kanhere (2000)
Karachi, Pakistan (1996–98)	Oral cavity	79 (M + F)	BQ, 33% BQ + T, 52% Naswar, 17%	149 (M + F)	BQ, 11% BQ + T, 10% Naswar, 7%	BQ, 9.9 (1.8–55.6) BQ + T, 8.4 (2.3–30.6) Naswar, 9.5 (1.7–52.5)	Merchant *et al*. (2000)

Table 38 (contd)

Location (years)	Cancer site[b]	No. of cases	Habit	No. of controls	Habit	Relative risk (95% CI)	Reference
Chennai, Bangalore & Trivandrum, India (1996–99)	Oral cavity	309 (M) 282 (F)	BQ, 5% (M) BQ + T, 45% (M) BQ, 5% (F) BQ + T, 79% (F)	292 (M) 290 (F)	BQ, 2% (M) BQ + T, 13% (M) BQ, 2% (F) BQ + T, 11% (F)	BQ, 4.2 (1.5–11.8) (M) BQ + T. 6.1(3.8–9.7) (M) BQ, 16.4 (4.8–56.5) (F) BQ + T, 45.9 (25.0–84.1) (F)	Balaram *et al.* (2002)
Chennai & Trivandrum, India (1993–99)	Oral cavity	1563 (M)	BQ, 6% BQ + T, 48% S, 73%	3638 (M)	BQ, 5% BQ + T, 10% S, 51%	BQ, 2.2 (1.6–3.0) BQ + T, 5.1 (4.3–6.0)	Znaor *et al*. (2003)
	Tongue					BQ, 1.7 (1.1–2.6) BQ + T, 2.7 (2.2–3.4)	
	Mouth					BQ, 2.6 (1.8–3.7) BQ + T, 7.0 (5.7–8.5)	

M, men; F, women; Q, betel quid with or without tobacco; S, smoking only; BQ, betel quid without tobacco; T, tobacco
[a] Usually comprises gum, floor of the mouth, buccal mucosa and palate; the tongue may be also included.
[b] In addition to oral cancer

Table 39. Dose–response relationship [calculated by the Working Group] between chewing of betel quid with tobacco and oral cancer

Frequency of chewing	Relative risk	
	Hirayama (1966)	Orr (1933)
None	1.0	1.0
< 2 times a day	8.4	4.9
3–5 times a day	14.2	17.7
6 times or more	17.6	68
Retaining quid in sleep	63	212.5

mucosa, 1.7% for cancer of the anterior tongue, 2.5% for oropharyngeal cancer and 2.9% for controls. Among women, the percentage of areca-nut chewers was 4.5% for cancer of the buccal mucosa and 19.6% for controls. Controls were cases of other diseases [not specified] matched for age and sex. [The information on areca-nut use was obtained by interviewing patients and by using hospital records if considered reliable. The proportion of such cases was not mentioned.] A dose–response relationship was calculated by the Working Group of *IARC Monographs* Volume 37 using case–control studies reported by Orr (1933) and Hirayama (1966) and results are given in Table 39. Both studies showed a positive dose–response relationship, the highest relative risk being that of retaining the betel quid during sleep.

The case–control sltudy of Jussawalla & Deshpande (1971) on 2005 cancers of the upper aerodigestive tract also reported increased relative risks for several subsites of oral cancer. These results are described in detail in Section 2.3.

Jafarey *et al.* (1977) reported a case–control study of cancer of the oral cavity and oropharynx conducted in Karachi, Pakistan, in 1967–72, comprising 1192 cases (683 men, 509 women) and 3562 controls (1978 men, 1584 women). Population controls were matched for age, sex and place of birth. Among nonsmokers, the risk for oral cancer of chewing betel quid alone in men and women was 4.2 and 3.2, respectively. When betel quid was chewed with tobacco, the risk among nonsmokers increased to 20.0 in men and 29.9 in women. The joint effect of chewing betel quid with tobacco and smoking was 23 in men and 35.9 in women.

A case–control study on several oral cancer subsites was conducted in Kerala, India. The first part of the study (Sankaranarayanan *et al.*, 1989a) that focused on cancer of the anterior two-thirds of tongue and floor of mouth comprised 228 cases (158 men, 70 women) and 453 hospital non-cancer controls (314 men, 139 women) matched for age, sex and religion. The risk associated with chewing betel quid with tobacco was lower in men than in women. The second part of the study on cancer of the gingiva (Sankaranarayanan *et al.*, 1989b) comprised 187 cases, and the third part on cancer of buccal and labial mucosa comprised

414 cases (Sankaranarayanan *et al*., 1990a). Hospital controls (n = 895) with no cancers were used for both the second and third studies. Attributable risk in men for chewing betel quid with tobacco was estimated at 54% for gingival cancers. Statistically significant dose–response relationships were observed for all oral cancer sites, for duration of chewing betel quid with tobacco and for number of betel quids with tobacco consumed per day (Tables 38 and 40).

Nandakumar *et al*. (1990) reported a case–control study conducted in Bangalore, India, using cases of cancer of the lip, tongue (excluding base of tongue), alveolus and mouth, registered at the Bangalore population-based cancer registry, and population controls with no evidence of cancer matched by age and area of residence. This study showed increased risk for oral cancer in both genders for chewing betel quid with tobacco (Table 38). Higher risk was seen among those who retained the quid in the mouth while asleep (odds ratio, 17.7; 95% CI, 8.7–36.1) than among those who did not (odds ratio, 8.5; 95% CI, 4.7–15.2). Risk increased with increase in duration of chewing betel quid with tobacco, with the number of tobacco quids consumed per day and with duration (period) of retention of the quid in the mouth (Table 40). Risks for chewing betel quid without tobacco were increased in men (odds ratio, 1.5; 95% CI, 0.6–3.8) and in women (odds ratio, 2.2; 95% CI, 0.7–6.5) and also in the combined analysis of men and women (odds ratio, 1.7; 95% CI, 0.9–3.5); however, these risks were not statistically significant. [The Working Group noted that the results were not adjusted for tobacco smoking. No information was available on other potential confounders.]

A study was conducted in Mumbai, India, of 142 male cases of cancer in the anterior two-thirds of the tongue, 495 male cases of cancer in the posterior third of the tongue and 635 hospital controls without cancer, infection or benign lesion. Information on chewing was available for 141 cases of cancer of the anterior two-thirds of tongue, all cases of cancer of the posterior third of the tongue, and 631 controls. A risk associated with chewing betel quid with tobacco was seen for the anterior two-thirds of the tongue but not for the posterior third (Rao & Desai, 1998) (Table 38).

Wasnik *et al*. (1998) reported a hospital-based case–control study conducted at three tertiary care centres in Nagpur city, Maharashtra, India, comprising 123 histologically confirmed cases of oropharyngeal cancer (73 men, 50 women), 123 cancer controls (sites other than oropharynx) and 123 non-cancer controls, matched by age and sex. Univariate analysis with both types of controls showed an elevated risk for chewing betel quid without tobacco and for chewing areca nut alone, as well as a more than ninefold risk for chewing tobacco alone or with betel quid. Multivariate analysis adjusting for tobacco smoking and occupation showed an eightfold risk (95% CI, 4.1–13.6) for chewing tobacco. The attributable risk for chewing tobacco was estimated at 87%.

A case–control study conducted on 148 cases of cancer of the oral cavity registered in the population-based Bhopal (India) Cancer Registry and 260 population controls showed a sixfold risk for chewing betel quid with tobacco for cancer of the oral cavity. An increased risk (odds ratio, 1.7; 95% CI, 0.9–3.3) was suggested for chewing betel quid without tobacco. The population attributable risk for developing cancer of the oral cavity

Table 40. Dose–response relationship associated with chewing habit

	Cases	Controls	Odds ratio (95% CI)	*p* for trend
Kerala Study				
I. Cancer of anterior 2/3 of tongue and floor of mouth (Sankaranarayanan *et al.*, 1989a)				
Men				
Duration of chewing (years)				
Never chewers	58	216	1.0	
≤ 10	8	8	3.9 (1.2–12.8)	
11–20	11	24	1.7 (0.7–3.96)	
21–30	29	26	4.6 (2.4–9.0)	
31–40	27	23	5.2 (2.5–10.7)	
> 40	17	13	5.6 (2.3–13.8)	< 0.001
Average daily amount (no. of quids/day)				
Never chewers	58	216	1.0	
< 5	32	33	4.0 (2.2–7.5)	
5–9	29	43	2.9 (1.6–5.3)	
≥ 10	31	18	5.5 (2.9–10.7)	< 0.001
Women				
Duration of chewing (years)				
Never chewers	13	84	1.0	
≤ 10	8	8	7.6 (1.97–29.1)	
11–20	9	11	3.5 (1.1–10.8)	
21–30	11	20	4.6 (1.5–13.8)	
31–40	10	7	15.9 (3.6–69.0)	
> 40	15	8	18.3 (4.7–71.4)	< 0.001
Average daily amount (no. of quids/day)				
Never chewers	13	84	1.0	
< 5	19	24	5.8 (2.2–15.2)	
5–9	20	22	6.6 (2.5–17.7)	
≥ 10	14	8	9.3 (3.1–27.6)	< 0.001
II. Cancer of the gingiva (Sankaranarayanan *et al.*, 1989b)				
Men				
Duration of chewing (years)				
Never chewers	19	360	1.0	
≤ 10	4	13	5.8 (1.6–20.7)	
11–20	9	54	2.9 (1.2–6.8)	
21–30	13	49	4.95 (2.3–10.8)	
31–40	28	40	13.6 (6.7–27.7)	
> 40	33	25	32.1 (13.9–73.8)	< 0.001

Table 40 (contd)

	Cases	Controls	Odds ratio (95% CI)	*p* for trend
Average daily amount (no. of quids/day)				
Never chewers	19	360	1.0	
< 5	21	61	5.95 (2.99–11.8)	
5–9	30	80	6.9 (3.7–12.9)	
≥ 10	36	40	15.1 (7.8–29.0)	< 0.001
Women				
Duration of chewing (years)				
Never chewers	6	168	1.0	
≤ 10	4	48	2.4 (0.6–9.3)	
11–20	10	49	5.9 (1.97–17.6)	
21–30	14	48	9.3 (3.3–26.6)	
31–40	18	19	32.3 (10.6–98.4)	
> 40	23	13	54.2 (16.3–180.4)	< 0.001
Average daily amount (no. of quids/day)				
Never chewers	6	168	1.0	
< 5	19	92	6.6 (2.5–17.7)	
5–9	39	63	18.5 (7.2–47.8)	
≥ 10	11	22	13.7 (4.4–42.5)	< 0.001
III. Cancer of the buccal and labial mucosa (Sankaranarayanan *et al.*, 1990a)				
Men				
Duration of chewing (years)				
Never chewers	37	360	1.0	
≤ 10	11	13	6.9 (2.8–16.8)	
11–20	35	55	5.8 (3.3–10.11)	
21–30	39	49	7.7 (4.4–13.4)	
31–40	48	40	13.2 (7.5–23.3)	
> 40	70	25	37.8 (19.5–73.1)	< 0.001
Average daily amount (no. of quids/day)				
Never chewers	37	360	1.0	
< 5	59	61	9.3 (5.6–15.2)	
5–9	75	80	9.04 (5.7–14.5)	
≥ 10	69	40	16.4 (9.7–27.7)	
Women				
Duration of chewing (years)				
Never chewers	19	168	1.0	
≤ 10	11	48	1.8 (0.8–4.1)	
11–20	22	49	3.8 (1.9–7.8)	
21–30	38	48	7.7 (4.0–15.0)	
31–40	33	19	21.3 (9.6–47.4)	
> 40	39	13	54.9 (21.2–142.4)	

Table 40 (contd)

	Cases	Controls	Odds ratio (95% CI)	*p* for trend
Average daily amount (no. of quids/day)				
Never chewers	19	168	1.0	
< 5	36	92	3.7 (1.99–7.0)	
5–9	72	63	10.8 (6.0–19.6)	
≥ 10	35	22	14.2 (6.9–29.5)	
Bangalore study (Nandakumar *et al.*, 1990)				
Men and women				
Duration of chewing (years)				
Never chewers	111	278	1.0	
1–5	4	6	1.7 (0.3–9.3)	
6–15	23	7	10.3 (3.6–29.6)	
16–25	56	20	12.4 (5.6–27.2)	
> 25	154	37	15.95 (8.4–30.2)	
Average daily amount (no. of quids/day)				
Never chewers	111	278	1.0	
1–4	82	33	9.3 (4.9–17.5)	
5–9	98	28	12.8 (6.6–25.0)	
≥ 10	35	8	16.6 (6.3–44.3)	
Chewing period (min)				
Never chewers	111	278	1.0	
≤ 5	5	3	6.4 (0.9–45.1)	
6–10	67	20	9.7 (4.7–19.8)	
11–20	59	13	16.5 (7.2–37.4)	
21–30	54	17	13.2 (5.8–30.0)	
> 30	11	6	6.6 (1.6–27.0)	
Bhopal study (Dikshit & Kanhere, 2000)				
Men				
Duration of chewing (years)				
Never chewers	28		1.0	
1–20	12		1.1 (0.5–2.4)	
21–30	32		5.5 (2.9–10.6)	
> 30	72		23.9 (12.0–47.3)	
Average daily amount (no. of quids/day)				
Never chewers	28		1.0	
1–5	19		2.0 (1.0–3.8)	
6–10	47		6.7 (3.7–12.1)	
> 10	15		13.9 (7.1–27.2)	

Table 40 (contd)

	Cases	Controls	Odds ratio (95% CI)	*p* for trend
Multicentre study in South India: Chennai, Bangalore and Trivandrum (Balaram *et al.*, 2002)				
Men				
Age started chewing (years)				
≥ 25	51	21	1.0	
20–24	42	10	1.5 (0.6–4.2)	
< 20	27	6	1.5 (0.5–5.0)	0.39
Average daily amount (no. of quids/day)				
Never chewers	127	232	1.0	
Former chewers				
< 5	28	11	4.2 (1.9–9.6)	
≥ 5	31	9	5.8 (2.5–13.2)	
Current chewers				
< 5	40	18	3.1 (1.6–5.9)	
5–9	46	12	8.2 (3.9–16.9)	
≥ 10	34	7	7.9 (3.2–19.4)	< 0.001
Women				
Age started chewing (years)				
≥ 25	56	13	1.0	
20–24	74	12	1.9 (0.7–5.3)	
< 20	73	4	5.4 (1.5–19.7)	0.01
Average daily amount (no. of quids/day)				
Never chewers	29	251	1.0	
Former chewers				
< 5	17	6	20.2 (6.4–63.9)	
≥ 5	31	3	60.4 (15.8–230.7)	
Current chewers				
< 5	51	13	22.1 (10.1–48.5)	
5–9	101	13	58.6 (26.6–129.0)	
≥ 10	51	3	112.4 (30.9–409.6)	< 0.001
Study in South India: Chennai and Trivandrum (Znaor *et al.*, 2003)				
Men				
Never chewing	711	3079	1.0	
Duration of chewing (years)				
0–19	250	286	3.1 (2.5–3.9)	
20–39	432	209	5.3 (4.3–6.5)	
≥ 40	170	64	5.2 (3.7–7.3)	
Average daily amount (no. of quids/day)				
1–3	279	343	2.06 (1.7–2.5)	
4–5	273	135	6.02 (4.7–7.7)	
> 5	300	800	11.9 (8.9–15.96)	

Table 40 (contd)

	Cases	Controls	Odds ratio (95% CI)	*p* for trend
Cumulative exposure to chewing				
< 1000	354	158	3.8 (2.95–4.8)	
> 1000	211	26	13.3 (8.5–20.9)	
Time since quitting chewing (years)				
Current chewers	640	460	1.0	
2–4	93	41	1.2 (0.8–1.8)	
5–9	59	20	1.6 (0.9–2.8)	
10–14	30	19	0.7 (0.4–1.4)	
≥ 15	30	19	0.7 (0.4–1.3)	

CI, confidence interval

was 66% for chewers of betel quid with tobacco (Dikshit & Kanhere, 2000) (Tables 38 and 40).

Merchant *et al*. (2000) reported a case–control study in three hospitals in Karachi, Pakistan, comprising 79 (54 men, 25 women) histologically confirmed cases of oral squamous-cell carcinoma and 149 controls (94 men, 55 women) matched for age, gender, hospital and time of occurrence, without past or present history of cancer. An eight- to ninefold risk for developing oral cancer was associated with ever chewing betel quid with or without tobacco, and ever chewing naswar, after adjustment for oral submucous fibrosis, cigarette smoking, alcohol and other chewing habits where appropriate. A dose–response relationship was observed between tertiles of *pan*–years without tobacco (average number of quids per day × average years of use) and the risk for oral cancer (*p*-value for trend = 0.0008), after adjustment for smoking, oral submucous fibrosis, alcohol drinking, and chewing naswar or pan with tobacco. [Possible limitations of the study are the use of hospital controls without exclusion of betel quid-related diseases and adjustment for oral submucous fibrosis, which is a disease that is strongly related to chewing betel quid.]

Balaram *et al*. (2002) reported a multicentre study conducted in three Indian centres, Bangalore, Chennai and Trivandrum, in 1996–99 on 591 cases of cancer of the oral cavity (309 men, 282 women) and 582 hospital controls (292 men, 290 women). Controls were frequency-matched with cases by centre, age and sex. Controls were identified and interviewed in the same hospital as cases. In Chennai and Bangalore, controls were visitors of patients admitted for cancers other than oral cancer. In Trivandrum, controls were non-cancer patients attending the hospital for diagnosis or treatment. The results showed that 80% of male and female chewers combined chewed quid with tobacco; the odds ratio for chewing betel quid without tobacco versus non-chewers was 4.2 (95% CI, 1.5–11.8) in men and 16.4 (95% CI, 4.8–56.5) in women after adjusting for age, centre and education for men and women and smoking and alcohol drinking for men only. The risk associated with chewing betel quid with or without tobacco was higher among women than among men. A significant dose–response relationship with the number of betel quids with or

without tobacco chewed per day was found in both sexes ($p < 0.001$), while early age at starting chewing was significantly associated with the risk for oral cancer in women only ($p = 0.01$). Only 13 (eight cases, five controls) and 11 (six cases, five controls) women in the study were smokers and alcohol drinkers, respectively; therefore, results among women had little chance of being confounded by smoking or alcohol drinking. There was a slight decrease in risk 10 years after quitting the habit of chewing (Tables 38 and 40).

Znaor *et al*. (2003) reported a study conducted in two centres in South India, Chennai and Trivandrum, on 1563 male oral cancer cases and 3638 controls (1711 male cancer controls from Chennai and Trivandrum and 1927 healthy male hospital visitor controls from Chennai), during the period 1993–99. Although the two centres involved in this study are the same as those in the study of Balaram *et al*. (2002), different cases and controls were used in the two studies. All cancer cases and cancer controls were histologically confirmed and controls were identified and interviewed in the same hospital as the cases. Odds ratios were adjusted for age, centre, level of education, alcohol consumption and smoking. The risks for chewing betel quid without tobacco were 2.2 (95% CI, 1.6–3.0) for cancer of the oral cavity, 1.7 (95% CI, 1.1–2.6) for cancer of the tongue and 2.6 (95% CI, 1.8–3.7) for cancer of the mouth excluding tongue. The analysis stratified by smoking and alcohol drinking showed the risk for chewing betel quid without tobacco to be 3.4 (95% CI, 2.04–5.7) in nonsmokers and non-drinkers of alcohol. Statistically significant dose–response relationships were observed for duration of the combined habit of chewing betel quid with or without tobacco, average daily amount of betel quid with or without tobacco chewed and cumulative years of chewing betel quid with or without tobacco ($p < 0.001$). The risk associated with oral cancer decreased with duration since quitting the combined habit of chewing betel quid with or without tobacco, but the odds ratios for time since quitting were not statistically significant (Tables 38 and 40).

(*d*) *Cross-sectional surveys*

Cross-sectional studies summarized in Volume 37 of the *IARC Monographs* (IARC, 1985a) are given in Table 41. These studies provide information on prevalence of oral cancer among persons chewing betel quid with or without tobacco, as well as combined or not with smoking. No new prevalence studies were available to the Working Group of this monograph.

(*e*) *Synergism*

Jayant *et al.* (1977) examined the possibility of interaction between chewing and smoking habits in the etiology of cancer of the upper alimentary tract using the data of Jussawalla and Deshpande (1971). It was found that chewing and smoking habits interacted synergistically for cancers of the oral cavity, oropharynx, hypopharynx, larynx and oesophagus.

A significant interaction with the smoking of bidis was observed in the studies from Kerala, India (described in detail in Section 2.1.1(*c*)). The unadjusted relative risk for chewing betel quid with and without tobacco and smoking bidis in the case–control study

Table 41. Cross-sectional surveys of oral cancer in India

Location	Individuals examined	Habit	No. of cancer cases detected	Prevalence per 1000[a]	Reference
Lucknow	10 000 in dental clinic	Q and/or S, 33%	24	73	Pindborg *et al*. (1965)
Ernakulam district, Kerala	10 000 by random sampling	BQ + T, 25.9% BQ, 0.4% BQ + S, 10.8% S, 22.1%	 6 6 –	 2.2 5.4 –	Mehta *et al*. (1971)
Bhavnagar district, Gujarat	10 000	Mishri, 7.1% BQ + T, 3.0% BQ, 1.6% BQ + S, 3.2% S, 29.1%	– – – 1 2	– – – 3.1 0.7	
Darbhanga district, Bihar	10 000	BQ, 1.3% BQ + T, 15.2% BQ + S, 14.3% S, 33.2%	– – 1 –	– – 0.7 –	
Srikakulam district, Andhra Pradesh	10 000	BQ, 0.6% BQ + T, 2.8% BQ + S, 7.9% S, 63.0%	– – 1 9	– – 0.8 1.9	
Poona (Pune) district, Maharashtra	101 761 villagers	BQ, 0.7% (M) BQ + T, 52.1% (M) Mishri, 0.8% (M) BQ + S, 2.4% (M) S, 5.6% (M) BQ, 0.5% (F) BQ + T, 9.5% (F) Mishri, 38.9% (F)	Total of 12	0.2 (M) – – 1.1 0.6 0.3 (F)	Mehta *et al*. (1972b)
Ahmedabad, Gujurat	57 518 industrial workers	Q, 4.7% Q + S, 22.0% S, 35.7% No habit, 15.1%		– 0.9 0.6 0.2	Smith *et al*. (1975)

Q, betel quid with or without tobacco; S, smoking; BQ, betel quid without tobacco; T, tobacco
[a] Prevalence rates calculated by the Working Group

of oral cancers of the tongue and floor of mouth was 7.02 (95% CI, 3.6–13.5) in men, compared with nonsmokers and non-chewers (p for interaction < 0.01) (Sankaranarayanan *et al.*, 1989a). In the second part of the study on cancer of the gingiva (Sankaranarayanan *et al*., 1989b), the risk associated with mixed habits of chewing betel quid with tobacco and bidi smoking was 16.5 (95% CI, 7.5–36.1) in men, compared with nonsmokers and non-chewers (p for interaction < 0.05). Risk estimates were not adjusted for age. In the third study on cancer of the buccal and labial mucosa, the risk in men of chewing and smoking bidis was 21.5 (95% CI, 11.9–38.5) compared with nonsmokers and non-chewers (p for interaction < 0.05) (Sankaranarayanan *et al.*, 1990a)

The study by Balaram *et al*. (2002) conducted in southern India with 591 cases of cancer of the oral cavity and 582 hospital controls (described in Section 2.1.1(*c*)) showed a sevenfold risk for developing oral cancer among men who were current chewers of betel quid with or without tobacco and who smoked 20 or more cigarettes/bidis or equivalents per day, and a ninefold risk among those who were current chewers and current drinkers. This study showed a negative interaction between chewing tobacco and smoking (Table 42).

Znaor *et al*. (2003) reported the results of a study in men conducted in two centres (Chennai and Trivandrum) in South India that included 1563 cases of oral, 636 cases of pharyngeal and 566 cases of oesophageal cancer, 1711 disease controls and 1927 healthy controls (see Section 2.1.1(*c*)). Table 43 shows the joint effects of smoking, drinking and chewing habits. Compared with subjects who did not smoke, chew betel quid with or

Table 42. Risk for cancer of the oral cavity among men: interaction between chewing and smoking, and chewing and drinking

	Paan chewing			
	Never		Current chewers	
	Cases/ controls	Odds ratio[a] (95% CI)	Cases/ controls	Odds ratio[a] (95% CI)
Tobacco smoking				
Never smokers	25/106	1.0	49/16	9.2 (4.4–19.3)
Current smokers (cig./day)				
1–19	33/55	1.8 (0.93–3.5)	35/10	8.9 (3.6–21.8)
≥ 20	48/35	3.7 (1.9–7.2)	22/8	6.7 (2.5–18.3)
Alcohol drinking				
Never drinker	64/174	1.0	48/18	7.3 (3.8–14.1)
Current drinker	48/38	2.8 (1.6–5.1)	46/13	8.6 (4.1–18.1)

From Balaram *et al*. (2002)

[a] Unconditional logistic regression adjusted for age, centre, education, oral hygiene, chewing and smoking and drinking habits, as appropriate

CI, confidence interval

Table 43. Odds ratios for oral cancer and combinations of smoking, chewing and alcohol drinking

Habit			Oral cavity cancer			
Smoking	Chewing	Alcohol	Controls	Cases	Odds ratios	95% CI
No	No	No	1471	122	1.0	–
No	Yes T–	No	83	24	3.4	2.04–5.7
No	Yes T+	No	127	159	9.3	6.8–12.7
Yes	No	No	1084	268	2.5	1.9–3.1
No	No	Yes	75	16	2.6	1.4–4.6
Yes	Yes T–	No	49	25	4.8	2.8–8.3
Yes	Yes T+	No	102	161	8.5	6.1–11.9
No	Yes T–	Yes	15	6	4.4	1.6–12.3
No	Yes T+	Yes	26	95	24.3	14.9–39.7
Yes	No	Yes	449	287	4.8	3.7–6.2
Yes	Yes T–	Yes	34	33	8.1	4.7–14.0
Yes	Yes T+	Yes	119	342	16.3	12.1–22.0

From Znaor *et al.* (2003)
Adjusted for age, center and level of education
CI, confidence interval; T+, with tobacco; T–, without tobacco

without tobacco or drink alcohol, the risks were 3.4 (95% CI, 2.04–5.7) for chewing betel quid without tobacco, 9.3 (95% CI, 6.8–12.7) for chewing betel quid with tobacco, 4.8 (95% CI, 2.8–8.3) for both smoking and chewing betel quid without tobacco, 4.4 (95% CI, 1.6–12.3) for both drinking alcohol and chewing quid without tobacco and 8.1 (95% CI, 4.7–14.0) for smoking, drinking alcohol and chewing quid without tobacco. In all estimates related to interaction between two habits, the third habit was controlled for in addition to age, centre and level of education. Likelihood ratio tests were statistically significant ($p < 0.05$) for the combination of the different habits — drinking and smoking, chewing and smoking, but not chewing and drinking.

2.1.2 *Taiwan, China*

(*a*) *Descriptive study*

One ecological study in Taiwan, China, found that the increase in incidence trends of oropharyngeal cancer parallels the time trend of consumption of areca nut, which almost doubled from 1985 to 1993 and which was much greater than the trend for the consumption of tobacco and alcohol (Ho *et al*., 2002). As the majority of betel-quid chewers are men, the large increasing trend of these cancers in men also supports the possibility of the cause being consumption of areca nut. Age-standardized incidence rates for men have

increased from 5.4 (95% CI, 5.05–5.8) in 1979–83 to 15.95 (95% CI, 15.3–16.6) in 1994–96 and those for women from 1.6 (95% CI, 1.4–1.8) in 1979–83 to 2.1 (95% CI, 1.8–2.4) in 1994–96 (Ho *et al*., 2002).

(*b*) *Case–control studies*

Kwan (1976) reported a case–control study of oral cancer in Taiwan, China, in which, out of 103 cases, 20 were betel chewers and 35 were betel chewers with other habits. No control subject chewed betel. [Therefore, it was not possible to estimate the relative risk.]

Three recent case–control studies in Taiwan, China, are summarized in Table 44.

Ko *et al*. (1995) conducted a hospital-based case–control study to assess the effects of betel quid without tobacco, smoking and alcohol on the incidence of oral cancer. A total of 107 oral cancers (104 men, three women) confirmed by histopathology (ICD 140–141, 143–145) between 1992 and 1993 were ascertained from patients at the dental department at Kaohsiung Medical College Hospital, in southern Taiwan, China. Controls were selected from ophtalmology and physical check-up departments in the same period as cases; 93 cases were matched with two controls and 14 cases with one control according to age (± 5 years) and sex. Information on demographic variables, the habit of betel-quid chewing, cigarette smoking and alcohol drinking was collected by a structured questionnaire administered by a trained interviewer. After controlling for education and occupation with a conditional logistic regression model, betel-quid chewing was considered to be the most important risk factor for oral cancer, compared with alcohol drinking and cigarette smoking. The association between chewing betel quid and oral cancer was significant for current chewers, with a sevenfold increase in risk, but was of borderline significance for former chewers, with a fivefold increase. The association between smoking and oral cancer was statistically significant for current smokers (fivefold increase in risk) and of borderline significance for former smokers (fourfold increase). Being a current drinker was also statistically significantly associated with risk for oral cancer, whereas no elevated risk was found for former drinkers. By stratified analysis incorporating the three factors simultaneously, relative risks were estimated at 122.8 (95% CI, 17.1–880.5) for the combination of the three factors, 89.1 (95% CI, 10.0–790.7) for chewing betel quid and smoking, 54.0 (95% CI, 4.4–660) for chewing betel quid and drinking and 28.2 (95% CI, 1.9–414.4) for chewing betel quid only, as compared with participants abstaining from all three habits. The relative risk for combined areca-nut chewing, smoking and alcohol is greater than the risk associated with the three risk factors independently. [A synergistic effect is suggested, but no assessment of interaction was made in this study.] With regard to the type of material chewed, chewers who used *lao-hwa* quid and mixed chewers (*lao-hwa* quid and betel quid) had a 12-fold and ninefold risk, respectively, both of which were statistically significant. Betel-quid chewers with the habit of swallowing the juice had an 11-fold statistically significant risk for oral cancer.

Another matched case–control study was conducted in the central area of Taiwan, China. A total of 40 consecutive histopathologically diagnosed oral cancers (34 men, six women) were ascertained from patients at Changhua Christian Hospital between 1990

Table 44. Case–control studies of betel quid-chewing and oral cancer in Taiwan, China

Reference, place, period	Characteristics of cases and controls	Oral cancer site	Exposure	Cases/ controls	Odds ratio (95% CI)	Comments
Ko *et al.* (1995), Kaohsiung, 1992–93	107 cases (104 men, 3 women) and 200 non-cancer hospital controls (194 men, 6 women) matched on age and sex	ICD 140–141 (lip, tongue), 143–145 (gum, mouth)	Non-drinker	25/89	1.0	Adjusted for education, occupation and each covariate
			Former drinker	14/37	1.0 (0.3–3.3)	
			Current drinker	68/74	2.2 (1.0–4.9)	
			Non-smoker	11/72	1.0	
			Former smoker	11/30	3.6 (0.9–14.6)	
			Current smoker	85/98	4.6 (1.5–14.0)	
			Non-chewer	31/153	1.0	
			Former chewer	5/5	4.7 (0.9–22.7)	
			Current chewer	71/42	6.9 (3.1–15.2)	
			Non-chewer	31/60	1.0	Adjusted for education, occupation, smoking and drinking
			Betel quid	1/7	0.1 (0.0–6.3)	
			Lao-hwa quid	41/13	11.6 (3.7–36.9)	
			Betel + *lao-hwa*	34/25	8.5 (2.7–26.3)	
			Not swallowing juice	3/15	0.2 (0.0–2.9)	
			Swallowing juice	73/31	11.4 (4.0–32.0)	
			Multivariate analysis			Adjusted for education and occupation; reference category: no habit
			D + S + BQ	58/34	122.8 (17.1–880.5)	
			D + BQ	3/2	54.0 (4.4–660.0)	
			S + BQ	12/9	89.1 (10.0–790.7)	
			S + D	18/56	22.3 (3.2–153.8)	
			BQ	3/2	28.2 (1.9–414.4)	
			S	8/29	18.0 (2.4–135.8)	
			D	3/19	10.2 (1.2–86.4)	

Table 44 (contd)

Reference, place, period	Characteristics of cases and controls	Oral cancer site	Exposure	Cases/ controls	Odds ratio (95% CI)	Comments
Lu *et al.* (1996), Changhua, 1990–92	40 cases (34 men, 6 women) and 160 population controls with no cancer (136 men, 24 women) matched on age, gender, residence and education	[subsite not specified]	Betel quid			Adjusted for age, gender, residence, education and other covariates
			Non-chewers	7/122	1.0	
			Chewers	33/38	58.4 (7.6–447.6)	
			Tobacco smoking			
			Nonsmokers	8/59	1.0	
			Smokers	32/101	2.7 (0.4–19.6)	
			Alcohol drinking			
			Non-drinkers	22/111	1.0	
			Drinkers	18/49	0.7 (0.3–2.2)	
			Duration of betel-quid chewing (years)			Adjusted for age, gender, residence, education, alcohol consumption and tobacco smoking
			Never	7/122	1.0	
			1–20	6/24	12.9 (1.3–128.1)	
			21–40	19/10	93.7 (10.1–868.0)	
			> 40	8/4	397.5 (19.5–8120.2)	
			Number of quids/day			
			0	7/122	1.0	
			1–9	8/27	26.4 (2.9–239.7)	
			10–20	16/9	51.2 (6.2–423.4)	
			> 20	9/2	275.6 (14.8–5106.5)	
Chen *et al.* (2002), Taichung, 1994–97	29 cases and 29 negative hospital controls from paraffin-embedded biopsies	Oral squamous-cell carcinoma [subsite not specified]	Betel-quid chewing	19/5	17.1 (23–129.0)	Adjusted for gender, age, smoking, HPV6 and HPV11
			HPV16	24/8	11.2 (1.2–103.2)	
			HPV18	20/3	6.6 (0.8–53.3)	

CI, confidence interval; BQ, betel quid; D, alcohol drinking; S, cigarette smoking

and 1992 (Lu *et al*., 1996). Each case was matched to four neighbourhood non-cancer controls (136 men, 24 women) in Changhua County according to four criteria: sex, age, living in the same community residence as the case for at least 5 years and educational background. Information was gathered from a questionnaire administered by a social worker that covered demographic and socioeconomic factors, duration, type and daily amount of smoking, chewing and alcohol drinking. After adjustment for each individual risk factor, the authors showed that chewing betel quid without tobacco was highly associated with risk for oral cancer but that only a moderate non-significant association was noted for smoking and that no association was found for alcohol drinking. Adjusted odds ratios increased with duration of chewing and quantity of betel quid chewed per day, suggesting a trend for increasing duration and amount.

A case–control study on the association between human papillomavirus (HPV) infection, chewing betel quid without tobacco and cigarette smoking was conducted using biopsies from 29 cases of oral squamous-cell carcinoma and those from 29 controls that included normal or inflammatory mucosa obtained from a negative biopsy, teeth extraction or excision of a benign lesion (mucocele and haemangioma). Case and control biopsies were collected from the archives of the Medical and Dental University Hospital from 1994 to 1997. Betel-quid chewing remained the most significant factor, giving a 17-fold increase in risk after adjusting for HPV sequences 6, 11, 16 and 18, sex, age and smoking (Chen *et al.*, 2002).

2.1.3 *South-East Asia*

Epidemiological data from South-East Asia on the association between oral cancer and the habit of chewing betel quid are rare. However, age-standardized rates for oral cancer in men and women are available for some countries (Tables 45 and 46). Some descriptive studies on oral cancer without details on betel-quid chewing habits have been published from the South-East Asian region (Piyaratn, 1959; Lay *et al*., 1982; Warnakulasuriya *et al.*, 1984; Kuek *et al*., 1990; Ikeda *et al*., 1995; Budhy *et al*., 2001).

(*a*) *Malaysia*

Ahluwalia and Duguid (1966) reported on the distribution of cancers in different ethnic groups of the Malay Peninsula (Malays, Chinese and Indians), using records from the Kuala Lumpur Institute for Medical Research. Of 4369 cases of cancer (1961–63), 476 (10.9%) were oral cancers in chewers of betel quid with and without tobacco. Of 912 cancers at all sites in Indians who are known to chew betel quid with tobacco, 306 (33.6%) were oral cancers. Of 776 cancers at all sites in Malays who are known to chew betel quid without tobacco, 74 (9.5%) had oral cancer.

Ramanathan and Lakshimi (1976) reported on racial variations of cancer in Indian, Malay and Chinese populations in Malaysia. Of a total of 898 cases of oral carcinoma, 31.1% occurred in Indian women, 29.1% in Indian men, 10.6% in Malay men, 11.1% in Malay women, 14.1% in Chinese men and 4% in Chinese women. Chewing and smoking

Table 45. Cancer of the oral cavity (men, all ages) in South-East Asia in 2000

Country	Cases	Crude rate	ASR (W)	Deaths	Crude rate	ASR (W)
Cambodia	113	2.1	4.6	66	1.2	2.8
Indonesia	1176	1.1	1.5	657	0.6	0.8
Lao	42	1.5	2.6	24	0.9	1.5
Malaysia	191	1.7	2.4	108	1.0	1.4
Myanmar	1387	6.1	8.6	805	3.5	5.1
Philippines	1304	3.4	5.8	755	2.0	3.4
Singapore	68	3.8	3.7	29	1.7	1.7
Thailand	1240	4.0	5.3	735	2.4	3.1
Viet Nam	920	2.3	3.7	520	1.3	2.1

From Ferlay *et al.* (2001)
ASR (W), age-standardized rates (world standard population)

Table 46. Cancer of the oral cavity (women, all ages) in South-East Asia in 2000

Country	Cases	Crude rate	ASR (W)	Deaths	Crude rate	ASR (W)
Cambodia	123	2.1	3.4	71	1.2	2.0
Indonesia	883	0.8	1.0	485	0.5	0.5
Lao	90	3.3	6.0	53	2.0	3.6
Malaysia	156	1.4	1.8	85	0.8	1.0
Myanmar	653	2.8	3.5	371	1.6	2.0
Philippines	1250	3.3	5.4	732	1.9	3.2
Singapore	38	2.1	1.9	16	0.9	0.8
Thailand	1139	3.7	4.0	673	2.2	2.4
Viet Nam	914	2.3	2.8	526	1.3	1.6

From Ferlay *et al.* (2001)
ASR (W), age-standardized rates (world standard population)

habits were not studied in particular. Ethnic differences in the pattern of oral carcinoma were evident and partly attributed to different oral habits such as betel-quid chewing, which is more prevalent in the Indian and Malay populations compared with the Chinese.

Ng *et al*. (1986) studied the betel-quid chewing and smoking habits, as well as alcohol consumption of 100 Indian, Chinese and Malay patients (39 men, 61 women) with histologically confirmed oral squamous-cell carcinoma. Betel-quid chewing was the most common single habit (85%), followed by alcohol consumption (55%) and smoking (29%). Seventy-one per cent of chewers used betel quid with tobacco. The location of the

squamous-cell carcinoma in betel-quid chewers was associated with the site where the quid was retained in the mouth.

In one prevalence study of oral mucosal lesions in out-patients at two dental schools in Chiang-Mai, Thailand, and Kuala Lumpur, Malaysia, Axéll *et al*. (1990) found one case of oral carcinoma among 96 women from Kuala Lumpur (1.0%). This case was diagnosed in a 45-year-old Indian woman who had been chewing betel quid with tobacco daily for many years.

(*b*) *Myanmar*

Sein *et al*. (1992) reported on 70 cases of oral cancer (35 men, 35 women) associated with smoking and betel-quid chewing (with or without tobacco) habits. Information was gathered from records of the Institute of Dental Medicine in Yangon (1985–88). The proportion of persons with oral cancer was 58.6% in regular betel-quid chewers, 12.8% in occasional users, 28.6% in non-chewers, 65.7% in regular smokers and 32.9% in non-smokers.

(*c*) *Thailand*

A multivariate regression analysis was conducted in a case–control study in Thailand (Simarak *et al*., 1977). Over a period of 16 months (1971–72) at the University Hospital in Chiang Mai, patients with a confirmed diagnosis of cancer of the oral cavity and oropharynx (50 men, 38 women), of the larynx and hypopharynx (84 men, 12 women) or of the lung (60 men, 55 women) were selected as cases; 1113 controls (697 men, 416 women) were selected from among patients attending a radiology clinic, mainly with uro-genital, respiratory or locomotor disorders; a small proportion of controls (7% of men, 15% of women) had cancers at sites other than those under study. Histological confirmation was obtained for about 50% of cases. A questionnaire administered by nurses provided information on personal habits and demographic factors. Variables that showed a significant relationship with cancer, after adjusting for age and residence, and that were included in the multivariate analysis comprised agricultural employment, rural residence and betel chewing for patients of each sex, lack of formal schooling, and cigarette and cigar smoking for men. After adjusting for the effects of covariables, the relative risk estimates for chewing betel were 2.3 ($p < 0.05$) for men and 3.2 ($p < 0.05$) for women for oral and oropharyngeal cancers and 2.4 ($p < 0.01$) for men for cancer of the larynx and hypopharynx. Among cancer cases who chewed betel, 25/26 added tobacco to the quid, whereas less than two-thirds of the control chewers used betel quid with tobacco.

In a case-only study in southern Thailand (1996–98), Kerdpon and Sriplung (2001) investigated the risk for developing advanced-stage oral squamous-cell carcinoma. Of 161 patients (117 men, 44 women) with early- or advanced-stage carcinoma of the oral cavity and lip (ICD-9 140–141, 143–145), 59/99 cases (59.6%) who presented the advanced stage were betel-quid chewers. [The composition of the betel quid (with or without tobacco) was not specified.] No significant association was observed between chewing

and the development of advanced-stage cancer (crude odds ratio, 1.7; 95% CI, 0.9–3.2) at the time of diagnosis nor, upon further analysis, between dose or duration of chewing.

2.1.4 *Papua New Guinea*

In Papua New Guinea, the predominant habit is chewing betel quid with areca nut and slaked lime without tobacco, and oral cancer is generally the most common form of cancer. The earliest study (Eisen, 1946) concluded that betel-quid chewing does not appear to cause cancer of the buccal cavity. [The Working Group noted that this conclusion appeared to be based on the finding of no oral cancer in a cross-section of subjects.] In two reports by Farago (1963a,b), 99% and 98% of oral cancer patients were chewers of betel quid. Smoking was also reported to be common.

Two studies (Atkinson *et al*., 1964; Henderson & Aiken, 1979) were based on a cancer survey and a continuing cancer registration system. Atkinson *et al*. (1964) proposed that, since the occurrence of oral cancer correlated very well with the known distribution of the habit of betel-quid chewing, areca nut and slaked lime may have carcinogenic effects even when chewed without tobacco. [The Working Group noted that the authors did not take into consideration cigarette smoking, which was reported to be common.] Henderson and Aiken (1979) observed that the site distribution of their oral cancer cases was consistent with that reported of oral cancer among betel chewers from other parts of the world. Cooke (1969) observed that only 5% of all oral cancers occurred in people in the highlands [where 50% of the population lived, but where areca nut did not grow and betel-quid chewing was less popular (Henderson & Aiken, 1979)]. Cigarette smoking was reported to be common in both the highlands and lowlands.

In a study in 1971–78 from Papua New Guinea, the age-adjusted incidence rates of oral cancer were compared for different geographical areas (Atkinson *et al.,* 1982). In the highlands, where very few people chew areca nut with slaked lime, the age-adjusted incidence of oral cancer per 100 000 compared with that in the lowlands, where a very high percentage of people practise this habit, was 1.01 versus 6.83 for men and 0.41 versus 3.03 for women. It was observed that, in a part of lowland western Papua, inhabited by a specific tribe among whom very few chew, the incidence of oral cancer was very low. The authors, while pointing out that the numbers were very small, noted that the finding had been consistent for 21 years.

In another study (Scrimgeour & Jolley, 1983), the changes in the incidence of oral cancer were compared with the changes in smoking and tobacco consumption during the periods 1965–69 and 1975–79. It was found that the incidence of oral cancer had increased among men as well as among women; the increase for men was not statistically significant, but that for women was ($p < 0.01$). During the same period, the proportion of adult women in a specific area of Papua who smoked commercial cigarettes had increased from 34 to 76%, although their betel-quid chewing habits had not changed greatly. Smoking habits among men had not changed significantly.

2.1.5 *Migrant populations*

Studies of migrant populations have proved of considerable interest to cancer epidemiologists in suggesting the extent to which environmental exposures are important in the etiology of specific cancers. Migrant studies on oral cancer risk have included several Asian groups who have migrated and settled in Britain.

(*a*) *South Africa*

van Wyk *et al.* (1993) conducted a study among Indians in Natal, South Africa, during the period 1983–89, including 54 men and 89 women with oral and oropharyngeal cancer (ICD 140, 141, 143–146). Information on areca-nut chewing for the cases was obtained directly by patient interview ($n = 75$), from families or friends ($n = 42$) or was only available from hospital records ($n = 26$). Controls were of the same ethnicity, obtained from a random sample of households. The proportion of smokers among female cases was 7%, and 93% chewed areca nut with or without tobacco. Seventy per cent chewed areca nut without tobacco. The crude odds ratio in women (89 oral cancer cases, 735 controls) for chewing areca nut with or without tobacco was 47.4 (95% CI, 20.3–110.5) and that for chewing areca nut without tobacco was 43.9 (95% CI, 18.6–103.6). Of the male cases, 17% reported chewing betel quid with tobacco and 6% without tobacco. The proportion of smokers among male cases was 87%. [The percentage of female smokers was small, and it is known that drinking among these women is rare. This analysis is therefore close to a stratified analysis, but with no adjustment for age.]

(*b*) *United Kingdom*

Marmot *et al*. (1984) reported on 15 oral cancer deaths in England and Wales between 1970 and 1972 among male Indian ethnic migrants. A higher than expected proportionate mortality ratio of 221 was observed in this ethnic group. Donaldson and Clayton (1984) reported a significant excess in the number of incident oral cancers during 1976–82 in Asian-named individuals in Leicestershire compared with what they referred to as non-Asians. From 1973 to 1985, Swerdlow *et al*. (1995) examined the risk of cancer mortality in persons born in the Indian subcontinent who migrated to England and Wales. Of the numerous cancers examined, highly significant risks in Indian ethnic migrants were noted for cancers of the mouth and pharynx (odds ratio, 5.5; 95% CI, 3.7–8.2). A later study in the Thames region, which has dense pockets of Asian ethnic communities, supported these observations (Warnakulasuriya *et al*., 1999). There was a significantly higher proportion of cancers of the oral cavity and pharynx among Asian ethnic migrant groups compared with other natives (for oral cancer in Asian versus other ethnicities, $\chi^2 = 13.6$; $p < 0.01$).

The incidence of oral cancer among migrant Asians is similar to that of Asians in the countries of birth; Asians also appear to retain their habit and their increased risk for oral cancer even several decades after migration (Swerdlow *et al.*, 1995).

2.2 Some betel quid-associated lesions, and precancerous lesions and conditions

2.2.1 *Introduction*

Studies on the natural history of oral cancer suggest that several potentially malignant lesions and conditions precede the development of cancer of the oral cavity. Precancerous conditions include oral submucous fibrosis and oral lichen planus and oral precancerous lesions of relevance are leukoplakia and erythroplakia (Pindborg *et al.*, 1996; see Glossary B). There is no evidence to suggest that tobacco use (smoked or chewed) is associated with the development of oral submucous fibrosis (Murti *et al*., 1995; Shah & Sharma, 1998).

The studies summarized here include those carried out in Asia and South Africa, with particular reference to the use of betel quid and areca nut with or without tobacco.

2.2.2 *Betel quid-associated oral lesions*

Besides oral precancerous lesions (oral leukoplakia and erythroplakia) and oral precancerous conditions (oral submucous fibrosis, oral lichen planus), some other betel quid-associated lesions of the oral mucosa may be observed. These include betel chewer's mucosa and oral lichenoid lesions, which are of some importance in differential diagnosis.

Areca-induced lichenoid lesions, mostly involving buccal mucosa or the tongue, have been reported at the sites of betel-quid retention (Daftary *et al*., 1980). In areca-nut chewers, they are found at the site of quid placement and are unilateral in nature. The histology is suggestive of a lichenoid reaction and the lesion resolves following cessation of areca use.

Betel chewer's mucosa was first described by Mehta *et al*. (1971) and is characterized by a brownish-red discoloration of the oral mucosa. This discoloration is often accompanied by encrustation of the affected mucosa with quid particles, which are not easily removed, and a tendency for desquamation and peeling. The lesion is usually localized in and associated with the site of quid placement in the buccal cavity, and is strongly associated with the habit of betel-quid chewing, particularly in elderly women (Reichart *et al*., 1996). Several epidemiological studies have shown that the prevalence of betel chewer's mucosa may vary between 0.2 and 60.8% in different South-East Asian populations (Table 47). At present, betel chewer's mucosa is not considered to be potentially malignant.

2.2.3 *Leukoplakia and erythroplakia*

The prevalence of oral leukoplakia among chewers of betel quid with or without tobacco in selected population samples in India, Malaysia and the Pacific area reported before 1984 is shown in Table 48.

Table 47. Prevalence of betel chewer's mucosa in different populations

Country	Year	No.	Prevalence (%)	Reference
Cambodia	1991	1319 (M + F)	< 1	Ikeda *et al*. (1995)
	NG	102 (F)	60.8	Reichart *et al*. (1996)
	NG	48 (F)	85.4	Reichart *et al*. (2002)
Malaysia	1993/94	NG	5.2	Rahman *et al.* (1997)
	1993/94	187 (M + F)	1.6	Zain *et al.* (1997)
Thailand	1979–84	1866 (M + F)	13.1	Reichart *et al*. (1987)

M, men; F, women; NG, not given

(*a*) *India*

Gupta *et al*. (1995, 1997) reported on a cohort study conducted in Ernakulam district of Kerala state, India, that comprised 12 212 tobacco users, including betel-quid chewers and smokers, who were followed up for 10 years from 1977–78. All participated in a health education programme on cessation of tobacco use (chewing and smoking). The incidence of leukoplakia dropped significantly following cessation: the incidence among those who stopped chewing was 107 per 100 000 person–years compared with those who did not change their habit (265 per 100 000 person–years, men and women combined).

Gupta (1984) reported a dose–response relationship between the development of leukoplakia and chewing betel quid with or without tobacco. The age-adjusted prevalence of leukoplakia was higher among men than women and the prevalence increased with the number of quids chewed per day (Table 49).

Hashibe *et al*. (2000a) reported on a cross-sectional study in Kerala, India, that included 927 cases of oral leukoplakia (411 women, 516 men) and 47 773 population-based controls without oral disease (29 876 women, 17 897 men). A case–control study design was applied to the baseline data for a population screened by oral visual inspections and interviewed with structured questionnaires by health workers. Clinical diagnosis of oral precancers was confirmed by dentists and oncologists. Cases of leukoplakia who had other oral precancers or oral cancer were excluded. Elevated odds ratios for oral leukoplakia were observed for betel-quid chewing with tobacco, after adjustment for age, sex, education, body mass index, pack–years of smoking and years of alcohol drinking (Table 50). [The majority of chewers in this population chewed betel quid with tobacco.] The adjusted risk was higher for women than for men and higher for patients who swallowed the juice while chewing, or kept the quid in their mouth overnight. Dose–response relationships were observed for both the frequency (times per day, p-value for trend = 0.0001) and duration (years; p-value for trend = 0.0001) of betel-quid chewing and the risk for oral leukoplakia.

Within the same study population, 100 cases of erythroplakia (49 women, 51 men) were identified and included in a case–control study with the same 47 773 controls

Table 48. Prevalence of oral leukoplakia among chewers in selected studies in Asia and the Pacific

Reference	Location	Chewing habit	Size of sample	Prevalence	
				No.	%
Gerry *et al*. (1952)	Guam	Betel quid	822	4	0.5
Mehta *et al*. (1961)	Mumbai, India (police)	Betel quid with tobacco	1898	80	4.2
		Betel quid and smoking	595	42	7.1
		No habit	1112	1	0.001
Forlen *et al*. (1965)	Papua New Guinea	Areca nut and smoking	610	–	9.7–36.3
Pindborg *et al*. (1967)	Lucknow, India (out-patient clinic)	Tobacco alone	206	15	7.3
		Betel quid with tobacco	672	30	4.5
		Betel quid without tobacco	181	6	3.3
		No habit	6699	2	0.03
Pindborg *et al*. (1968)	Papua New Guinea	Areca nut	162	2	1.2
		Areca nut and smoking	767	29	3.8
		No habit	165	–	–
Chin & Lee (1970)	Perak, West Malaysia	Betel quid with tobacco	167	67	40.1
		Betel quid without tobacco	45	9	20.0
		Betel quid with *gambir*	45	5	11.1
Mehta *et al*. (1971)	Ernakulam (Kerala), India	Betel quid with tobacco	2661	47	1.8
		Betel quid without tobacco	38	–	–
		Chewing and smoking	1106	67	6.1
		No habit	4210	8	0.2
	Srikakulam (Andhra Pradesh), India	Betel quid with tobacco	281	–	–
		Betel quid without tobacco	56	–	–
		Chewing and smoking	803	23	2.9
		No habit	2620	3	0.1
	Bhavnagar (Gujarat), India	Betel quid with tobacco	299	3	1.0
		Betel quid without tobacco	157	1	0.6
		Mishri	714	2	0.3
		Chewing and smoking	320	19	5.9
		No habit	5647	–	–
	Darbhanga (Bihar), India	Betel quid with tobacco	1572	6	0.4
		Betel quid without tobacco	138	2	1.4
		Chewing and smoking	1485	6	0.4
		No habit	3719	–	–
	Singhbhum (Bihar), India	Betel quid with tobacco	1293	5	0.4
		Betel quid without tobacco	41	–	–
		Gudakhu	832	–	–
		Chewing and smoking	730	2	0.3
		No habit	4454	1	0.02

Table 48 (contd)

Reference	Location	Chewing habit	Size of sample	Prevalence	
				No.	%
Smith *et al*. (1975)	Ahmedabad (Gujarat), India (mainly textile-mill workers)	Tobacco chewing	1515	193	12.7
		Smoking and tobacco chewing	2319	300	12.9
		Betel quid/areca nut without tobacco	2687	144	5.4
		Smoking and betel quid	12 907	2264	17.5
		No habit	8710	112	1.3
Lin *et al*. (1983) (cited in Pindborg *et al*., 1984a)	Hainan Island, China	Betel quid	954	–	2.5

Table 49. Age-adjusted prevalence of leukoplakia in India by number of quids chewed per day

Gender	1–10 quids per day			> 10 quids per day		
	No. in study	No. of leukoplakias	Age-adjusted prevalence/1000	No. in study	No. of leukoplakias	Age-adjusted prevalence/1000
Men	1059	34	26.6	195	12	49.1
Women	3099	35	8.4	261	5	14.6

From Gupta (1984)

(Hashibe *et al*., 2000b). An association was observed between chewing betel quid with tobacco and the risk for erythroplakia, after adjustment for age, sex, education, body mass index, pack–years of smoking and years of alcohol drinking (Table 50). [The majority of chewers in this population chewed betel quid with tobacco.] An increase in the risk for erythroplakia was observed with an increase in the frequency and duration of betel-quid chewing, as well as for swallowing the juice and keeping the quid in mouth overnight. [Cases of erythroplakia were clinically diagnosed by dentists and oncologists without histopathological exclusion of other possible oral erythematous lesions. This may contribute to non-specific oral lesions being included in this clinical category.]

(*b*) *Taiwan, China*

Three recent studies addressed the association between chewing betel quid and the occurrence of oral leukoplakia. The details of design, method and results are summarized in Table 51.

Table 50. Epidemiological studies of the association between chewing betel quid and oral precancerous lesions in India

Reference, place	Methods	Precancerous lesion	Exposure measurement	Odds ratio (95% CI)	Comments
Hashibe *et al.* (2000a) Kerala	Cross-sectional study within large intervention study on oral cancer screening. Case–control design with 927 cases (411 women, 516 men) and 47 773 controls (29 876 women, 17 897 men) from intervention cohort	Oral leukoplakia	Non-chewers	1.0	Adjusted for age, sex, education, body mass index, smoking and drinking
			Ever chewers	*Men + women* 7.0 (5.9–8.3) *Women* 37.7 (24.2–58.7) *Men* 3.4 (2.8–4.1)	
			Current chewers	9.4 (8.0–11.2)	
			Former chewers	3.9 (2.8–5.6)	
			Occasional chewers	2.4 (1.7–3.3)	
			Swallowed chewed tobacco fluid		
			No	7.5 (6.4–8.8)	
			Yes	13.3 (9.0–16.9)	
			Kept quid in mouth overnight		
			No	7.6 (6.5–8.9)	
			Yes	13.8 (9.3–20.3)	

Table 50 (contd)

Reference, place	Methods	Precancerous lesion	Exposure measurement	Odds ratio (95% CI)	Comments
Hashibe *et al.* (2000b) Kerala	Same study base as Hashibe *et al.* (2000a) 100 cases (49 women, 51 men) and 47 773 controls	Oral erythroplakia	Non-chewers	1.0	Adjusted for age, sex, education, body mass index, smoking and drinking
			Ever chewers	19.8 (9.8–40.0)	
			Current chewers	27.6 (10.8–70.4)	
			Former chewers	25.8 (12.6–52.8)	
			Occasional chewers	2.3 (0.5–10.9)	
			Frequency of chewing (times per day)		
			Continuous	1.04 (1.02–1.06)	
			1–10	28.6 (14.0–58.7)	
			11–20	49.8 (22.0–113.1)	
			> 20	130.8 (52.5–326.3)	
			p for trend	0.0001	
			Duration of chewing (years)		
			Continuous	1.01 (0.99–1.03)	
			1–20	29.3 (14.2–60.8)	
			21–40	53.3 (24.7–114.8)	
			> 40	52.8 (18.3–152.6)	
			p for trend	0.0001	
			Swallowed chewed tobacco fluid		Also adjusted for tobacco chewing (years and times per day)
			No	20.8 (9.8–44.4)	
			Yes	50.6 (17.9–143.4)	
			Kept quid in mouth overnight		
			No	21.2 (10.0–45.2)	
			Yes	36.3 (11.9–111.6)	

CI, confidence interval

Table 51. Epidemiological studies of the association between chewing betel quid and oral precancerous lesions and conditions in Taiwan, China

Reference, place, period	Characteristics of cases and controls	Precancerous lesion and condition	Exposure measurement	Odds ratio (95% CI)			Comments
Shiu *et al.* (2000), Taipei, 1988–98	Nested case–control study; 100 cases selected among cohort of 435 leukoplakia patients, and 100 hospital controls matched on age, gender and date of diagnosis, selected among 25 882 patients with periodontal disease	Leukoplakia	No habit	1.0			Multivariate analysis adjusted for the effects of the three factors on each other
			Former chewer	2.4 (0.3–16.8)			
			Current chewer	17.4 (1.9–156.3)			
			Former smoker	1.04 (0.2–4.6)			
			Current smoker	3.2 (1.06–9.8)			
			Former drinker	0.3 (0.03–2.6)			
			Current drinker	3.0 (0.3–33.5)			
			Level of habit				
			Chewing Low	9.06 (1.0–81.6)			
			Chewing High	22.5 (1.4–351.0)			
			Smoking Low	1.7 (0.5–6.3)			
			Smoking High	3.1 (0.9–10.3)			
Yang *et al.* (2001), Pingtung, 1997	Prevalence study including 312 participants (119 men, 193 women) out of a source population of 3623 in Mutan country (aboriginal community)	Oral submucous fibrosis (OSF) and oral leukoplakia (OL)	*Duration of chewing (years)*	**OSF**	**OL**	**OL or OSF**	[Relative risks calculated by the Working Group]
			0–10	1.0	1.0	1.0	
			11–20	1.8 (0.7–4.8)	1.9 (0.9–4.1)	1.7 (0.9–3.1)	
			21–30	2.4 (1.01–5.6)	1.9 (0.9–3.9)	1.9 (1.09–3.3)	
			≥ 31	2.4 (1.1–5.0)	2.03 (1.1–3.7)	2.09 (1.3–3.4)	
			No. of quids/day				
			1–10	1.0	1.0	1.0	
			11–20	1.2 (0.7–2.04)	1.03 (0.6–1.7)	1.2 (0.8–1.8)	
			≥ 21	1.3 (0.7–2.2)	1.5 (0.9–2.2)	1.5 (1.04–2.08)	
			Multivariate analysis				Adjusted for each other, age and gender
			Areca/betel-quid chewing			8.2 (1.8–37.5)	
			Smoking			1.05 (0.5–2.2)	
			Drinking			1.8 (0.9–3.7)	
			Smoking/drinking			1.4 (0.6–3.1)	

Table 51 (contd)

Reference, place, period	Characteristics of cases and controls	Precancerous lesion and condition	Exposure measurement	Odds ratio (95% CI)		Comments
Lee *et al*. (2003), Kaohsiung, 1994–95	125 histologically confirmed cases of OL (118 men, 7 women) and 94 cases of OSF (93 men, 1 woman); 876 population controls (844 men, 32 women) matched on age and sex	Oral leukoplakia (OL) and oral submucous fibrosis (OSF)	*Betel-quid chewing*	**OL**	**OSF**	Adjusted for education and occupation
			Never chewed	1.0		
			Former chewer	7.1 (2.3–21.5)	12.1 (2.8–51.9)	
			Current chewer	22.3 (11.3–43.8)	40.7 (16.0–103.7)	
			Dose-response	4.6 (3.3–6.4)	6.2 (3.9–9.7)	
			Age started chewing (years)			
			≥ 26	20.6 (9.9–42.7)	32.3 (12.1–86.6)	
			< 26	19.5 (9.3–41.0)	39.4 (14.8–105.3)	
			Dose-response	4.3 (3.1–6.0)	5.8 (3.8–8.8)	
			Duration of chewing (years)			
			1–10	15.9 (7.1–35.6)	30.9 (11.3–84.7)	
			11–20	20.7 (8.9–48.2)	41.9 (14.1–124.9)	
			≥ 21	24.0 (10.8–53.4)	39.3 (11.7–131.7)	
			Dose-response	3.0 (2.3–3.9)	4.2 (3.0–6.1)	
			No. of quids chewed per day			
			1–10	16.6 (8.2–33.8)	31.4 (11.9–82.5)	
			11–20	21.0 (8.9–49.7)	37.4 (12.6–110.4)	
			≥ 21	38.5 (14.1–105.1)	53.5 (16.4–174.8)	
			Dose-response	3.8 (2.8–5.1)	4.1 (2.9–5.8)	
			Cumulative quid–years			
			1–10	12.0 (5.6–25.7)	26.5 (10.0–70.3)	
			11–20	23.7 (9.1–61.7)	47.0 (15.8–139.8)	
			≥ 21	31.4 (14.2–69.2)	51.4 (16.5–159.7)	
			Dose-response	3.1 (2.4–3.9)	4.1 (2.9–5.8)	
			Type of material			
			Lao-hwa	24.5 (11.8–50.7)	38.7 (14.7–101.9)	
			Betel quid	11.5 (4.2–32.0)	18.7 (5.3–66.1)	
			Mixed (betel quid + *lao-hwa*)	17.4 (7.6–39.8)	37.4 (13.1–107.2)	

Table 51 (contd)

Reference, place, period	Characteristics of cases and controls	Precancerous lesion and condition	Exposure measurement	Odds ratio (95% CI)		Comments
Lee *et al*. (2003) (contd)			**Synergistic effects**	**OL**	**OSF**	Adjusted for education, occupation and alcohol drinking
			Betel chewing/smoking			
			No habit	1.0		
			Smoking only	2.4 (1.0–5.5)	2.3 (0.6–9.1)	
			Chewing only	10.0 (3.1–32.7)	39.3 (7.5–206.9)	
			Chewing + smoking	40.2 (16.3–99.2)	57.9 (16.0–209.6)	
			Synergy index	3.8 (1.4–10.5)	1.4 (0.4–4.7)	
			Betel chewing/alcohol drinking			Adjusted for education, occupation and cigarette smoking. Synergy index estimated by an additive interaction model
			No habit	1.0	1.0	
			Drinking only	1.0 (0.4–2.6)	0.7 (0.1–3.4)	
			Chewing only	15.6 (7.1–34.3)	26.5 (9.5–74.1)	
			Chewing + drinking	16.8 (7.2–39.5)	31.7 (10.1–99.3)	
			Synergy index	1.1 (0.6–2.1)	1.2 (0.6–2.5)	

CI, confidence interval

Shiu *et al.* (2000) used a retrospective leukoplakia cohort that included 435 hospital patients diagnosed according to WHO criteria between June 1988 and February 1998 to study the effects of betel chewing, smoking and drinking on the occurrence of leukoplakia and malignant transformation to oral cancer. To investigate the association between betel quid and risk for oral leukoplakia, a nested case–control study was conducted with 100 cases randomly selected from among the leukoplakia cohort and 100 controls selected from patients with periodontal disease in the same hospital and period as the cases, and matched by age, sex and date of diagnosis. Information on betel-quid chewing (without tobacco), tobacco smoking and alcohol drinking was collected from medical charts and telephone interviews. Duration and frequency of the three habits was also ascertained. Level of chewing (frequency × duration) was classified as high or low according to the distribution of median values. After adjusting for tobacco smoking and alcohol drinking using conditional logistic regression, a 17-fold significant risk was observed among current betel-quid chewers, whereas the risk for former chewers was only twofold and was non-significant. The risk for oral leukoplakia also increased with the level of intensity, suggesting a dose–response relationship between areca-nut chewing and oral leukoplakia.

A population-based survey, using 312 samples obtained by stratified random sampling with a 62.3% response rate, selected from 2059 residents composed mainly of one aboriginal tribe (Paiwan) in southern Taiwan, China, found the prevalences of oral submucous fibrosis and leukoplakia to be 17.6 and 24.4%, respectively (Yang *et al.*, 2001). The prevalence of chewing areca/betel quid was 69.5% and more women (78.7%) than men (60.6%) chewed. Dose–response relationships between duration and frequency of chewing betel quid and precancerous lesions and conditions were also demonstrated [see Table 51; relative risks calculated by the Working Group]. In a multiple logistic regression analysis, the adjusted odds ratio for chewing areca/betel quid was 8.2 (95% CI, 1.8–37.5) for either oral leukoplakia or oral submucous fibrosis.

Lee *et al*. (2003) designed a case–control study to elucidate the relationships of betel-quid chewing, tobacco and alcohol with oral leukoplakia and oral submucous fibrosis. Cases were selected during 1994–95 among patients of the Kaohsiung Hospital dentistry department and were histologically confirmed. Patients with both oral leukoplakia and oral submucous fibrosis were excluded. There were 125 cases of oral leukoplakia (118 men, seven women) and 94 cases of oral submucous fibrosis (93 men, one woman). Population controls were recruited randomly in the greater Kaohsiung area, and matched to cases by age and sex. A total of 876 controls (844 men, 32 women) participated in the study. All subjects were interviewed by research workers. The major finding was that betel quid conferred a significantly increased risk not only for oral leukoplakia (adjusted odds ratio for current chewers, 22.3; 95% CI, 11.3–43.8), but also for oral submucous fibrosis (adjusted odds ratio for current chewers, 40.7; 95% CI, 16.0–103.7). Chewers of *lao-hwa* quid had the highest risk for oral leukoplakia (adjusted odds ratio, 24.5; 95% CI, 11.8–50.7) and oral submucous fibrosis (adjusted odds ratio, 38.7; 95% CI, 14.7–101.9). Significant dose–response relationships were also demonstrated with respect to duration and frequency of betel-quid chewing. Using an additive interaction model, the synergistic effects in terms of the interaction

between betel quid chewing and cigarette smoking were statistically significant for oral leukoplakia but not for oral submucous fibrosis. No synergistic effect between betel quid chewing and drinking was found for oral leukoplakia or oral submucous fibrosis. The proportion of betel-quid chewing contributing to precancerous lesions and conditions in the underlying population (population attributable proportion) was quantified as 73.2% for oral leukoplakia and 85.4% for oral submucous fibrosis.

(*c*) *South-East Asia*

(i) *Cambodia*

Among 953 Cambodian women, of whom 311 (32.6%) chewed betel quid [with or without tobacco not specified], oral leukoplakia was recorded in six (1.9%) (Ikeda *et al*., 1995).

In a study of 102 rural Cambodian women who chewed betel quid with tobacco, three (2.9%) showed homogeneous leukoplakia (Reichart *et al*., 1996). In another study in Cambodia that included 48 women who chewed betel quid with tobacco, four (8.3%) had oral leukoplakia (Reichart *et al*., 2002).

(ii) *Thailand*

In a field study, Reichart *et al*. (1987) investigated oral mucosal lesions in relation to smoking and chewing habits including betel quid with tobacco in northern Thai tribes. Among betel-quid chewers, oral leukoplakia was recorded in 1.5% of Lahu men, 2.3% of Karen men, 2.6% of Karen women and 3.1% of Lisu men.

(*d*) *Migrants*

Pearson (1994) reported areca-nut habits of Bangladeshi adults in London, United Kingdom, in a sample of 158 individuals attending general practices. Seventy-eight per cent chewed *paan* with or without tobacco, and the most common lesion was leukoplakia (22%). In a subsequent study on *paan* chewing and smoking habits among the same subjects, the prevalence of leukoplakia had increased to 24.8% (Pearson *et al*., 2001).

2.2.4 *Oral submucous fibrosis*

(*a*) *India and Pakistan*

In a survey of over 10 000 villagers in five areas of India, Mehta *et al*. (1971) found submucous fibrosis in people with various chewing and smoking habits. The prevalences are shown in Table 52.

In a 2-year follow-up study of 43 654 industrial workers in Gujarat, India (1969–71), Bhargava *et al.* (1975) found seven new cases of submucous fibrosis among 2105 (0.3%) people who chewed betel quid with areca nut, six new cases among 9506 (< 0.1%) who both chewed and smoked, three new cases among 1161 (0.3%) who chewed tobacco alone and 10 new cases among 7065 (0.1%) with no such habit.

Table 52. Prevalence of submucous fibrosis and lichen planus in five areas of India

Area	Chewing habit	No.	Prevalence of submucous fibrosis		Prevalence of lichen planus	
			No.	%	No.	%
Ernakulam (Kerala)	Betel quid with tobacco	2661	29	1.1	50	1.9
	Betel quid without tobacco	38	–	–	–	–
	Chewing and smoking	1106	5	0.4	41	3.7
	No habit	4210	2	0.05	3	0.07
Srikakulam (Andhra Pradesh)	Betel quid with tobacco	281	1	0.4	1	0.4
	Betel quid without tobacco	56	–	–	–	–
	Chewing and smoking	803	–	–	7	0.9
	No habit	2620	–	–	1	0.04
Bhavnagar (Gujarat)	Betel quid with tobacco	299	–	–	1	0.3
	Betel quid without tobacco	157	–	–	–	–
	Mishri	714	–	–	–	–
	Chewing and smoking	320	–	–	1	0.3
	No habit	5647	16	0.3	–	–
Darbhanga (Bihar)	Betel quid with tobacco	1572	–	–	5	0.3
	Betel quid without tobacco	138	2	1.4	–	–
	Chewing and smoking	1485	3	0.2	3	0.2
	No habit	3719	–	–	–	–
Singhbhum (Bihar)	Betel quid with tobacco	1293	–	–	4	0.3
	Betel quid without tobacco	41	–	–	–	–
	Gudakhu	832	–	–	–	–
	Chewing and smoking	730	–	–	–	–
	No habit	4454	–	–	2	0.04

From Mehta *et al.* (1971)

In the 10-year follow-up survey of Gupta *et al.* (1980), the age-adjusted incidences per 100 000 for submucous fibrosis were 7.0 for men and 17.0 for women in Ernakulam. The annual incidences per 100 000 were 2.6 for men and 8.5 for women in Bhavnagar; of the four new cases seen in 38 818 persons, two had no tobacco habit, one chewed and one smoked. In Ernakulam, all 11 new cases (out of 39 828 person–years) occurred among chewers of tobacco or of tobacco and betel quid or those with a mixed habit (including smoking).

Murti *et al*. (1990) calculated the incidence of oral submucous fibrosis from a 10-year prospective intervention study of 12 212 individuals in an intervention cohort and 10 287 in a non-intervention cohort. The intervention consisted in a health education programme

on cessation of tobacco habits (smoking and chewing) and betel-quid chewing. The intervention cohort consisted of tobacco chewers or smokers selected from a baseline survey undertaken in 1977–78 on 48 000 individuals from 23 villages. Controls were provided by an earlier random sample in Ernakulam district, followed up from 1966–67 but without health education. Two new cases occurred among men and nine among women in the intervention group and three new cases in men and eight in women among the non-intervention group. The annual incidence was 8.0 per 100 000 among men and 29.0 per 100 000 among women in the intervention cohort and 21.3 per 100 000 among men and 45.7 per 100 000 among women in the non-intervention cohort. However, there was only a small number of oral submucous fibrosis patients and the decrease in incidence in the intervention group was not statistically significant.

A case–control study was conducted at a dental clinic in Bhavnagar, Gujarat, and comprised 60 oral submucous fibrosis patients and an equal number of hospital controls matched on age, sex, religion and socioeconomic status. Relative risks were 78 for chewing areca nut without tobacco ($p < 0.01$), 106 for chewing *mawa* ($p < 0.01$) and 30 for chewing areca nut without *mawa* but with tobacco ($p < 0.01$) were observed. The relative risk increased with increasing frequency and duration of chewing (Sinor *et al.*, 1990).

Another case–control study was conducted in Karachi in 1989–90 comprising 157 histologically confirmed cases and 157 hospital-based controls matched on age, sex and ethnicity. Odds ratios for developing oral submucous fibrosis were similar in men and women, although women were predominant (ratio of men:women, 1:2.3). The risk associated with chewing areca nut alone was 154 (95% CI, 34–693) and that associated with chewing areca nut with tobacco was 64 (95% CI, 15–274). The risk increased with frequency of quids chewed, up to 10 per day, and duration of the habit, up to 10 years (Maher *et al.*, 1994).

Babu *et al*. (1996) reported on a clinico-pathological study of oral submucous fibrosis in Hyderabad. The study included 90 subjects consisting of 50 chewers of betel quid with tobacco and *pan masala* (alone or in combination) who had oral submucous fibrosis (cases) and 40 non-chewers without oral submucous fibrosis (randomly selected hospital controls). Smokers were excluded from the study. *Pan masala*/*gutka* chewers developed oral submucous fibrosis after 2.7 ± 0.6 years of use, whereas betel-quid chewers developed oral submucous fibrosis after 8.6 ± 2.3 years of use.

Gupta *et al*. (1998) found the highest prevalence of oral submucous fibrosis among users of *mawa* (10.9%) and the lowest among those who did not use areca nut, in a house-to-house survey conducted in 20 villages in Bhavnagar, Gujarat, that included 11 262 men and 10 590 women. This study also showed that the highest relative risk (age-adjusted) for developing oral submucous fibrosis was among users of *mawa* (75.6) followed by users of any kind of areca nut (60.6), including chewing *mawa*, smoking tobacco and chewing tobacco, compared with non-users of areca nut (Table 53).

Shah and Sharma (1998) reported a case–control study conducted in New Dehli on 236 cases of oral submucous fibrosis (188 men, 88 women) and 221 hospital controls (120 men, 101 women) without oral submucous fibrosis matched on age, sex and socio-

Table 53. Survey of areca-nut and tobacco use and oral submucous fibrosis, Gujarat, India

Areca nut habits	No. of users	No. of cases	Prevalence (%) (age-adjusted)	Relative risk (age-adjusted)
No areca nut use	3 232	4	0.12 (0.16)	1.0
Areca nut use	11 786	160	9.0 (9.7)	60.6
Mawa	1 326	144	10.9 (12.1)	75.6
With tobacco	136	2	1.5 (1.5)	9.4
With smoking	324	14	4.3 (5.0)	31.3
Total	15 018	164	3.2 (3.3)	–

From Gupta *et al*. (1998)

economic status. No case was found who did not practise any form of areca-nut chewing, whereas in the control group, 165 subjects (74.7%) had no chewing habit. Among cases, 34.7% chewed betel quid without tobacco, 46.2% chewed betel quid with tobacco and none of them smoked tobacco only. Among controls, 7.3% chewed betel quid without tobacco, 4.5% chewed betel quid with tobacco and 11% were tobacco smokers only. Oral submucous fibrotic changes occurred earlier in people who chewed *pan masala* (41.4 months) compared with those who chewed betel quid (77.9 months) [with or without tobacco not specified].

Hazare *et al.* (1998) reported the results of a case–control study conducted for 1 year (June 1996–May 1997) on 200 cases of oral submucous fibrosis (168 men, 32 women) and 197 age-matched hospital controls (122 men, 75 women) in Nagpur, Maharashtra, India. A statistically significant increase in risk was observed with an increase in the frequency of areca-nut use in the form of betel quid that almost always contained tobacco (Table 54).

Table 54. Dose–response relationship between frequency of areca-nut use and oral submucous fibrosis in India

Frequency/day	Cases	Controls	Relative risk
Non-users	5	110	1.0
1	11	24	10.1
2–3	65	42	34.0
4–5	61	16	83.9
> 5	58	5	255.2
Total	200	197	p for trend < 0.01

From Hazare *et al*. (1998)

From the study population described in Section 2.2.3 on oral leukoplakia and erythroplakia (Hashibe *et al*., 2000a,b; Thomas *et al*., 2003), a case–control study was conducted in Kerala on 170 cases of oral submucous fibrosis (139 women, 31 men) and 47 773 controls (Hashibe *et al.*, 2002). Only nine cases of oral submucous fibrosis reported not to be occasional, past or current chewers of betel quid with or without tobacco. Betel-quid chewing (with and without tobacco) was associated with an increased risk for oral submucous fibrosis adjusted for age, sex, education, occupation, body mass index, pack–years of smoking, years of alcohol drinking and fruit and vegetable intake (Table 55). [The majority of chewers in this population chewed betel quid with tobacco.] Dose–response trends were apparent for the frequency and duration of betel-quid chewing.

Table 55. Association between chewing betel quid with and without tobacco and oral submucous fibrosis in India

Chewing habit	No. of cases/controls (women and men)	Odds ratio[a] (95% CI)
Non-chewer	9/34 373	1.0 (reference)
Ever chewer	161/13 400	44.1 (22.0–88.2)
Former chewer	29/1276	125.2 (56.7–276.3)
Occasional chewer	7/2625	12.7 (4.7–34.4)
Current chewer	125/9499	49.2 (24.3–99.6)
Frequency of chewing (times/day)		
1–20	114/8991	28.9 (16.5–50.5)
21–40	30/1443	46.8 (24.3–90.2)
> 40	8/271	84.3 (32.8–216.8)
p for trend		< 0.0001
Duration of chewing (years)		
1–20	88/5971	30.8 (17.6–53.8)
21–40	54/3470	34.7 (18.6–64.5)
> 40	9/1217	22.7 (9.0–57.5)
p for trend		< 0.0001

From Hashibe *et al.* (2002)
[a] Adjusted for age, sex, education, occupation, body mass index, drinking (years), smoking (pack-years), vegetable intake and fruit intake
CI, confidence interval

(*b*) *People's Republic of China*

In a population-based survey of 11 406 people in Xiangtan in 1986, using a method of cluster sampling, 3907 (35.4%) users of betel quid were found. All chewers used areca nut without tobacco. Among betel-quid chewers, a total of 335 cases of oral submucous fibrosis were diagnosed, indicating a prevalence of 3%. No case of oral submucous

fibrosis was found among those who did not chew betel quid. The development of oral submucous fibrosis was related to the duration and frequency of chewing (Tang *et al*., 1997).

On Hainan Island, no oral submucous fibrosis was found among 100 persons (44 men, 56 women) examined within a pilot survey of oral mucosa in betel-nut chewers [with or without tobacco not specified]. However, two cases were suggestive of an early-stage pre-cancerous lesion resembling leukoplakia (Pindborg *et al.*, 1984a).

(*c*) *Taiwan, China*

Two studies reporting on oral submucous fibrosis in Taiwan have been reported in Section 2.2.3 (Table 51).

(*d*) *South-East Asia*

(i) *Cambodia*

In a prevalence study of oral mucosal lesions, submucous fibrosis was diagnosed in two of 1319 individuals (0.2%), one man without any distinctive oral habit and one woman who reported betel chewing and tobacco smoking (Ikeda *et al*., 1995).

(ii) *Thailand*

Reichart *et al*. (1984) observed one case of submucous fibrosis among the Lisu hill tribe (n = 139) who chewed betel quid with tobacco.

(*e*) *Migrants*

(i) *South Africa*

In a survey of 1000 consecutive, unselected Indians from the municipal areas of Johannesburg and Pretoria, all five cases of oral submucous fibrosis detected were in women who chewed areca nut, giving an incidence of 0.5% (Shear *et al.*, 1967). In a further series, five cases of oral submucous fibrosis detected in hospitals by the same authors were also areca-nut chewers. The most frequent habit was chewing betel nut with tobacco in the form of *pan*.

In a stratified survey of 2058 randomly selected Indians in the Durban area in 1981–83, 5% were areca-nut chewers [with or without tobacco not specified]; 71 cases (70 women, one man) of oral submucous fibrosis were detected, all of whom chewed areca nut. Of the cases, 46% had established fibrous bands and 54% were early cases (Seedat & van Wyck, 1988). [The Working Group noted that the criteria for detection of oral submucous fibrosis included very early forms.]

(ii) *United Kingdom*

Canniff *et al*. (1986) described a large case series of 44 Asian patients (eight men, 36 women) treated at a London hospital (22 Indians, 17 Indians who arrived via East Africa and five non-residents including one Pakistani) for oral submucous fibrosis. All had chewed areca nut either alone or with additives of *pan*. The nature of their chewing habits

is shown in Table 56. The case series predominantly consisted of chewers of areca nut only (77%); tobacco was used by only a few, although some added other substances to the nut.

Table 56. Details of chewing habits in a case series of oral submucous fibrosis patients among migrants, United Kingdom

Material chewed	No. of patients (%)
Roasted areca nut	28 (64)
Raw areca nut	6 (14)
Roasted nut/slaked lime/betel leaf	4 (9)
Roasted nut/slaked lime/betel leaf/tobacco	2 (5)
Roasted nut/slaked lime/betel leaf/aniseed	1 (2)
Pan parag[a]	3 (6)

From Canniff *et al*. (1986)

[a] Preparation consisting in small pieces of roasted areca nut dusted with a powder of slaked lime and undisclosed flavouring agents

McGurk and Craig (1984) described three cases (two Indians and one Pakistani) of oral submucous fibrosis, two of whom had concomitant oral carcinoma, but whose chewing habits were not accurately recorded. Several other single case studies of oral submucous fibrosis have been reported in Asian migrants to Australia (Oliver & Radden, 1992), Canada (Hayes, 1985) and Great Britain (Zafarulla, 1985; Shah *et al*., 2001). Some of these cases were in young children who had never been exposed to tobacco or alcohol before and had consumption of areca nut only as a sole risk factor.

2.2.5 *Oral lichen planus*

(*a*) *India*

The prevalence of lichen planus in five areas of India (Mehta *et al.*, 1971) is given in Table 52.

In a house-to-house survey in Ernakulam (Kerala) of 7639 villagers, oral lichen planus was found in 1.5% of men and 1.6% of women. The prevalence in various habit groups is given in Table 57. The highest prevalence was found in chewers of betel quid with tobacco (Pindborg *et al.*, 1972).

In the 10-year follow-up survey of Gupta *et al*. (1997), age-adjusted incidences of lichen planus per 100 000 per year in Ernakulam were 251 for men with mixed habits (including smoking), 329 for men who chewed tobacco or betel quid plus tobacco, 146 for women with mixed habits and 385 for women who chewed betel quid with tobacco.

Table 57. Prevalence of lichen planus in subjects with various habits in Kerala, India

Habit	No. in study	Lichen planus	
		No.	%
Chewing			
Tobacco and lime	212	3	1.4
Betel quid without tobacco	24	–	–
Betel quid with tobacco	1925	61	3.2
Smoking			
Bidi	1334	10	0.7
Other	386	3	0.8
Chewing and smoking	845	31	3.7
None	2911	10	0.3

From Pindborg *et al*. (1972)

(*b*) *South-East Asia*

Among 953 Cambodian women studied for oral mucosal lesions, 365 chewed betel quid only or in combination with smoking. Oral lichen planus was recorded in 20 of these women (5.5%); 19 of the 20 women used betel quid with tobacco (Ikeda *et al*., 1995).

2.2.6 *Multiple and mixed lesions*

A case–control design was applied to analyse data collected from a screening programme conducted in Sri Lanka. Three hundred and fifty-nine precancer cases (316 men, 43 women, with leukoplakia and submucous fibrosis), age- and sex-matched to population controls from the same villages as the cases, were included in the study. Controls were disease-free following oral examination. The relative risk for chewing betel quid without tobacco among nonsmokers was 5.3 in men and 5.0 in women; both were statistically non-significant. The relative risk for chewing betel quid with tobacco among nonsmoking men was 15.0 ($p < 0.005$) and that among nonsmoking women was 33.0 ($p < 0.001$) (Warnakulasuriya, 1990). Chewers were at higher risk than smokers.

An additional 115 subjects with multiple premalignant oral lesions and conditions (defined as having one or more of the following: oral leukoplakia, erythroplakia, oral submucous fibrosis; 73 women, 42 men) from the Kerala, India, study population with the 47 773 controls described in Section 2.2.3 (Hashibe *et al*., 2000a,b) were included in another case–control study (Thomas *et al*., 2003). The odds ratios were 52.8 (95% CI, 22.4–124.4) for chewing betel quid with tobacco and 22.2 (95% CI, 6.6–74.0) for chewing betel quid without tobacco, after adjustment for age, sex, education, body mass index, pack–years of smoking, years of alcohol drinking and fruit and vegetable intake. Dose–response trends

were observed for the frequency (times per day; *p*-value for trend < 0.0001) and duration (years; *p*-value for trend < 0.0001) of chewing betel quid (with and without tobacco) and the risk for multiple premalignant oral lesions and conditions.

2.2.7 *Malignant transformation*

(*a*) *India and Pakistan*

In many of the earlier histological studies of oral cancer, e.g. Paymaster (1956), leukoplakia was seen concomitantly with the cancer.

In the 10-year follow-up study of Mumbai policemen (Mehta *et al.,* 1961, 1969, 1972a), one oral cancer developed among 117 cases of leukoplakia in an individual who chewed betel quid (presumably with tobacco) and who also smoked bidis.

In the follow-up of Bhargava *et al.* (1975) in Gujarat, India, 22 histologically confirmed cases of oral cancer were seen among 43 654 persons re-examined after 2 years. The authors stated that seven (0.13%) of the cases had developed from leukoplakia.

Of the 4762 persons with leukoplakia who were re-examined after 2 years by Silverman *et al.* (1976), six had developed oral carcinoma, giving an annual incidence of malignant transformation of leukoplakia of 63 per 100 000. One man chewed tobacco plus betel quid only, two both chewed (one tobacco, the other tobacco plus betel quid) and smoked bidis, two smoked bidis only and the one woman took nasal snuff only.

In a 10-year follow-up in Ernakulam (Kerala), South India, of 410 leukoplakia patients, all of whom were chewers of betel quid with tobacco, nine (six men, three women) developed oral carcinoma (Gupta *et al*., 1980). The crude annual rate of malignant transformation was 3.9 per 1000 in men and 6.0 per 1000 in women. Four other oral cancers were observed: two in patients who had been diagnosed with early leukoplakic changes (preleukoplakia), one in a patient with submucous fibrosis and the other in a case of lichen planus. No oral cancer was seen in subjects who had had normal mucosa at the previous examination.

In an 8-year follow-up of 12 212 tobacco users that started in 1977, the relative risk for developing oral cancer from nodular leukoplakia was 3243 (6 new cases of oral cancer among 13 cases), that from homogeneous leukoplakia was 25.6 (three new cases of oral cancer among 489 cases) and that from lichen planus was 15.8 (one among 344 cases). The relative risk for malignant transformation among individuals with oral submucous fibrosis was 397, based on three new cases of oral cancer among 25 cases of oral submucous fibrosis versus four new cases of oral cancer among 10 145 persons with no precancerous condition (Gupta *et al*., 1989). The risk for malignant transformation was significant for all lesions except lichen planus.

Gupta *et al*. (1980) also reported malignant transformation in one of 44 cases of oral submucous fibrosis in Ernakulam (Kerala); none were found among five cases in Srikakulam.

A follow-up study over 4–15 years of 66 patients with submucous fibrosis was carried out in Ernakulam. Malignant transformation was observed in three patients 3, 4 and 7

years after initial examination, giving an overall transformation rate of 4.5% (Pindborg *et al.,* 1984b).

In a population sample of 27 600 individuals in Ernakulam district, Kerala, 66 had oral submucous fibrosis and were followed up for 17 years. Five developed oral cancer, giving a malignant transformation rate of 7.6% (Murti *et al.*, 1985).

A study conducted in Karachi, Pakistan (1996–98), on 79 cases of oral squamous-cell carcinoma and 149 hospital controls showed that the risk for developing oral cancer was 19 times higher (95% CI, 4.2–87.7) among cases of oral submucous fibrosis than among subjects with no precancerous condition (Merchant *et al*., 2000).

Gupta *et al.* (1980) observed one oral cancer case among 332 individuals seen with lichen planus.

(*b*) *Taiwan, China*

In the study by Shiu *et al.* (2000), 60 cases of oral and pharyngeal cancer (including lip, tongue, gum, mouth floor, buccal palate, oropharynx and hypopharynx) were ascertained by linking a retrospective leukoplakia cohort consisting of 435 patients recruited from hospital between 1988 and 1998 to a population cancer registry. The risk for malignant transformation increased with time, particularly for areca-nut chewers. Using a Weibull survival model, the adjusted hazard ratio for chewing areca nut without tobacco was 4.6 (95% CI, 1.3–16.9) after adjusting for age and sex.

(*c*) *Migrants*

McGurk and Craig (1984) reported malignant transformation of submucous fibrosis in two Indian women living in the United Kingdom. Only one of the women had chewed areca nut and both had latent iron deficiency.

2.3 Other upper aerodigestive cancer

2.3.1 *India*

The study by Hirayama (1966) described in Section 2.1.1(*c*) reported a statistically significant six-fold increase in risk for oropharyngeal cancer among nonsmokers chewing betel quid with tobacco.

A comprehensive evaluation of cancer risk among betel-quid chewers and smokers was reported by Jussawalla and Deshpande (1971) in a case–control study in Mumbai. They selected 2005 histologically confirmed cancer patients with cancers of the oral cavity, pharynx, larynx and oesophagus. Equal numbers of controls were selected from the population using electoral roll and were matched to cases for age, sex and religion. Information was collected by interviewing patients and controls. Table 58 shows the assessment of risk for cancer at each site in chewers and non-chewers. The relative risks were highly significant for all studied cancers combined, oral cavity as a whole, and for cancers of the tongue, alveolus, buccal mucosa, hard palate, tonsils, oropharynx, hypopharynx, larynx

Table 58. Relative risks for oral cancer and other cancers of the upper aerodigestive tract among betel-quid chewers, assuming the risk among non-chewers to be unity

Group	Habit		Relative risk
	None (no.)	Chewing (no.)	
Controls	1340	665	
Cancer patients	853	1152	2.7***
Oral cavity	129	282	4.4***
Base of tongue	175	187	2.2***
Soft palate	35	18	1.0 NS
Tonsils	99	128	2.6***
Lip	8	6	1.5 NS
Anterior two-thirds of tongue	36	54	3.0***
Floor of mouth	10	4	0.8 NS
Alveolus	26	44	3.4***
Buccal mucosa	42	160	7.7***
Hard palate	7	14	4.0**
Oropharynx	309	333	2.2***
Nasopharynx	10	7	1.4 NS
Hypopharynx	21	49	4.7***
Larynx	246	314	2.6***
Oesophagus	138	167	2.4***

From Jussawalla & Deshpande (1971)
**, $p < 0.01$; ***, $p < 0.001$; NS, $p > 0.05$

and oesophagus. Table 59 shows the relative risks for cancers at different sites for chewers only, chewers and smokers and smokers only. The relative risks were highly significant for all cancers, except cancer of the nasopharynx, in all habit groups.

A summary of the case–control studies of other upper aerodigestive cancers in India published since 1984 is given in Table 60.

Sankaranarayanan *et al*. (1991) reported a case–control study of cancer of the oesophagus conducted in Kerala, India, in 1983–84, that included 267 cases (207 men, 60 women) and 895 controls comprised of 271 non-cancer cases from the cancer center and 624 patients diagnosed with acute respiratory, gastrointestinal or genitourinary infection. Sixty-seven per cent of cases were histologically confirmed (33% by radiology only). Only four men (controls) and six women (three cases, three controls) chewed betel quid without tobacco. Among men, an elevated risk was suggested for chewing betel quid with tobacco for the age group 31–40 years (odds ratio, 1.2; 95% CI, 0.6–2.1) and a significant risk for chewing betel quid with tobacco was observed for subjects over 40 years of age (odds ratio, 2.0; 95% CI, 1.03–3.9). Among women, risks were elevated for chewing betel quid with tobacco for the age group 30–40 years (odds ratio, 1.4; 95% CI, 0.5–4.3) and

Table 59. Relative risks for oral and other cancers by habit, assuming the risk among persons with no habit to be unity

Group	No habit (no.)	Chewing only (no.)	Relative risk	Chewing and smoking (no.)	Relative risk	Smoking only (no.)	Relative risk
Controls	925	521		144		415	
Cancer patients	243	557	4.1***	595	15.7***	610	5.6***
Oral cavity	57	192	6.0***	90	10.1***	72	2.8***
Oropharynx	49	91	3.3***	242	31.7***	260	11.8***
Nasopharynx	4	4	1.8 NS	3	4.8 NS	6	3.3 NS
Hypopharynx	8	28	6.2***	21	16.9***	13	3.6**
Larynx	55	142	4.6***	172	20.1***	191	7.7***
Oesophagus	70	100	2.5***	67	6.2***	68	2.2***

From Jussawalla & Deshpande (1971)
**, $p < 0.01$; ***, $p < 0.001$; NS, $p > 0.05$

for subjects over 40 years of age (odds ratio, 2.2; 95% CI, 0.6–8.1). [The Working Group noted that, among men, risk estimates were potentially confounded by bidi smoking.]

From 1997 to 1998, a hospital-based case–control study on oesophageal cancer in Assam, India, included 502 cases (358 men, 144 women) and 994 controls (706 men, 288 women) who were attendants to cancer patients. Controls were matched on sex and age. The risk for chewing betel quid (with or without tobacco), adjusted for smoking and alcohol consumption, was 2.6 (95% CI, 1.3–7.4) for men and 1.9 (95% CI, 0.02–7.8) for women. The risk increased with increasing frequency of chewing betel quid with or without tobacco and increased substantially when the chewing habit had lasted 20 years or more. A dose–response relationship was also observed for age at starting the habit, with a higher risk for starting at a younger age (Phukan *et al*., 2001).

Znaor *et al*. (2003) reported a study conducted in men in two centres in South India, Chennai and Trivandrum, in 1993–99 that included 636 cases of pharyngeal cancer (except nasopharynx) and 566 cases of oesophageal cancer, who were compared with 1711 cancer controls and 1927 healthy hospital visitor controls. For oesophageal cancer, significantly elevated risks were found for chewing betel quid without tobacco (odds ratio,1.6; 95% CI, 1.1–2.5) and for chewing betel quid with tobacco (odds ratio, 2.1; 95% CI, 1.6–2.6). For pharyngeal cancer, the odds ratios (adjusted for age, educational level, smoking , alcohol consumption and centre) were 1.4 (95% CI, 0.9–2.1) for chewing betel quid without tobacco and 1.8 (95% CI, 1.4–2.3) for chewing betel quid with tobacco. Significant dose–response relationships were observed for duration of chewing with or without tobacco, number of quids consumed per day and cumulative years of chewing for both oesophageal and pharyngeal cancers (Table 61). A non-significant substantial decrease in risk was seen 10 years after quitting the chewing habit. Likelihood ratio tests

Table 60. Case–control studies of upper aerodigestive cancers other than oral cancers and risk associated with chewing betel quid in India (1985–2003)

Location (years)	Cancer site	ICD code	No. of cases	Habit	No. of controls	Habit	Relative risk (95% CI)	Reference	Comments
Kerala, South India (1983–84)	Oesophagus	150	207 (M) 60 (F)	BQ + T, 35.4% BQ + T, 45.5%	546 (M) 349 (F)	BQ + T, 33.5% BQ + T, 51.3%	BQ + T, 1.09 (0.8–1.5) BQ + T, 0.8 (0.4–1.4)	Sankaranarayanan *et al*. (1991)	Crude relative risk
Assam (1997–98)	Oesophagus	150	358 (M) 144 (F)	Q, 92% Q, 76%	706 (M) 288 (F)	Q, 65% Q, 47%	Q, 3.4 (1.2–9.5) Q, 3.5 (1.4–10.3)	Phukan *et al*. (2001)	Crude relative risk
Chennai & Trivandrum (1993–99), South India	Pharynx		636 (M)	BQ, 5% BQ + T, 28% S, 86%	3638 (M)	BQ, 5% BQ + T, 10% S, 51%	BQ, 1.4 (0.9–2.1) BQ + T, 1.8 (1.4–2.3)	Znaor *et al*. (2003)	Adjusted for age, center, education, drinking and smoking
	Oropharynx	146							
	Hypopharynx	148							
	Pharynx, unspecified	149							
	Oesophagus	150	566 (M)	BQ, 5% BQ + T, 25% S, 72%			BQ, 1.6 (1.1–2.5) BQ + T, 2.1 (1.6–2.6)		
Bhopal, Central India (1986–92)	Oropharynx	146	247 (M)	BQ, 1.6% BQ + T, 42.1% S + T, 32.8%	260 (M)	BQ, 4.6% BQ + T, 41.5% S + T, 16.5%	BQ + T, 1.2 (0.8–1.8)	Dikshit & Kanhere (2000)	Adjusted for age and smoking
Kerala, South India (1983–84)	Larynx	161	171 (M)	BQ + T, 29%	541 (M)	BQ + T, 33%	BQ + T, 0.8 (0.6–1.2)	Sankaranarayanan *et al*. (1990b)	Crude relative risk

CI, confidence interval; M, men; F, women; BQ, betel quid without tobacco; T, tobacco S, smoking only; Q, betel quid with or without tobacco

Table 61. Odds ratio for pharyngeal and oesophageal cancer by duration, level and cumulative chewing, South India

Site	Pharynx				Oesophagus		
	Controls	Cases	Odds ratio [a]	95% CI	Cases	Odds ratio[a]	95% CI
Never chewed	3079	424	1.0	–	371	1.0	–
Duration of chewing (years)							
0–19	286	67	1.2	0.9–1.7	71	1.8	1.3–2.5
20–39	209	101	1.97	1.5–2.7	84	2.05	1.5–2.8
≥ 40	64	44	2.6	1.6–4.2	40	2.3	1.4–3.6
p for trend				< 0.001			< 0.001
Average daily amount (no. of quids)							
1–3	343	101	1.2	0.9–1.6	81	1.2	0.9–1.6
4–5	135	55	1.9	1.3–2.8	51	2.2	1.5–3.2
> 5	800	56	4.2	2.7–6.6	63	6.1	4.0–9.1
p for trend				< 0.001			< 0.001
Cumulative exposure to chewing							
< 1000	158	101	1.4	0.97–1.9	69	0.9	0.7–1.3
> 1000	26	31	1.97	1.05–3.7	23	1.7	0.9–3.3
p for trend				= 0.03			= 0.029
Time since quitting chewing (years)							
Current chewers	460	171	1.0	–	160	1.0	–
2–4	41	15	0.8	0.4–1.7	12	0.5	0.2–1.1
5–9	20	10	1.2	0.5–3.0	8	0.9	0.4–2.3
10–14	19	6	0.5	0.2–1.3	8	0.6	0.2–1.6
≥ 15	19	10	0.6	0.2–1.4	7	0.4	0.2–1.1
p for trend				= 0.62			= 0.586

From Znaor *et al*. (2003)

[a] Adjusted for age, centre, level of education, alcohol consumption and smoking

CI, confidence interval

were statistically significant ($p < 0.05$) for (a) the combination of the three habits of chewing, smoking and drinking for oesophageal and pharyngeal cancers; (b) for chewing and drinking, and chewing and smoking, for oesophageal cancer and (c) for the interaction between drinking and smoking, and chewing and smoking, for pharyngeal cancer. Interaction was not tested separately for chewing betel quid without tobacco because only 33 oesophageal and 34 pharyngeal cancer cases had chewed betel quid without tobacco.

A case–control study conducted in 1986–92 on 247 cases of oropharyngeal cancer (all men) registered in the population-based Bhopal Cancer Registry and 260 population controls showed a non-significant risk for oropharyngeal cancer associated with chewing betel quid with tobacco. Those who chewed more than 10 quids with tobacco per day

(odds ratio, 3.6; 95% CI, 1.7–7.4) and those who had chewed quid with tobacco for more than 30 years (odds ratio, 3.1; 95% CI, 1.6–5.7) had statistically significant risks (Dikshit & Kanhere, 2000).

A case–control study was conducted in Kerala in 1983–84 on 191 men with histologically confirmed laryngeal cancer and 549 hospital controls; after excluding occasional chewers, the number of cases and controls (hospital patients without cancer) were 171 and 541, respectively. The risk associated with chewing betel quid with tobacco was not increased (Sankaranarayanan *et al*., 1990b).

2.3.2 *Taiwan, China*

One case–control study in Taiwan, China, in 1996–2000, included 104 cases of histologically confirmed oesophageal squamous-cell carcinoma (94 men, 10 women) and 277 age- and sex-matched controls (256 men, 21 women) without malignant disease from the same hospital. The results showed that subjects who chewed moderate amounts of betel quid without tobacco (lifetime consumption, 1–495 quid–years) had a 3.6-fold (95% CI, 1.3–10.1) risk and those who chewed greater amounts (lifetime consumption, ≥ 495 quid–years) had a 9.2-fold (95% CI, 1.8–46.7) risk for oesophageal cancer after controlling for cigarette smoking and alcohol consumption (Wu *et al*., 2001).

2.4 Other cancers

The studies from India on cancers of the stomach, lung or cervix are summarized in Table 62.

2.4.1 *Stomach cancer*

A case–control study of stomach cancer conducted in Chennai, India, in 1988–90 included 388 incident cases of stomach cancer (287 men, 101 women; 75% histologically confirmed) and an equal number of cancer controls matched on age, sex, religion and native language, showed a non-significantly increased risk, when adjusted for income group, level of education and area of residence, for current chewing of betel quid with or without tobacco (relative risk, 1.4; 95% CI, 0.96–1.93). This risk disappeared when further adjustment was made for smoking, alcohol drinking and dietary items (relative risk, 0.8; 95% CI, 0.5–1.4) (Gajalakshmi & Shanta, 1996).

2.4.2 *Lung cancer*

A case–control study conducted on 163 male lung cancer cases registered at the population-based Bhopal (India) Cancer Registry and 260 population controls showed no association between chewing betel quid with tobacco and lung cancer (Dikshit & Kanhere, 2000).

Table 62. Case–control studies of chewing betel quid and cancers of the stomach, lung and cervix, India

Location (years)	Cancer site	No. of cases	Habit	No. of controls	Habit	Relative risk (95% CI)	Reference	Comments
Chennai, South India (1988–90)	Stomach	287 (M) 101 (F)	Q, 38.9%	287 (M) 101 (F)	Q, 33.7%	Q, 1.3 (0.95–1.8) BQ, 1.3 (0.8–2.1) BQ + T, 1.3 (0.9–1.98)	Gajalakshmi & Shanta (1996)	Adjusted for income, education and residence
Bhopal, Central India (1986–92)	Lung	163	BQ, 2.5% BQ + T, 31.9% S + T, 27.6%	260 (M)	BQ, 4.6% BQ + T, 41.5% S + T, 16.5%	BQ + T, 0.7 (0.4–1.2)	Dikshit & Kanhere (2000)	Adjusted for age and smoking
Chennai and Trivandrum, South India (1993–99)	Lung	778 (M)	NS	3430 (M)	NG	Q, 0.8 (0.6–1.02)	Gajalakshmi *et al*. (2003)	Adjusted for age, education, centre and smoking
Chennai, South India (1998–99)	Cervix	205 (F)	BQ, 4.9% BQ + T, 13.7%	213 (F)	BQ, 2.8% BQ + T, 4.2%	BQ, 2.6 (0.7–9.8) BQ + T, 2.1 (0.8–5.9)	Rajkumar *et al*. (2003c)	

CI, confidence interval; M, men; F, women; Q, betel quid with or without tobacco; BQ, betel quid without tobacco; T, tobacco; S, smoking only; NG, not given

In a case–control study conducted in men in Chennai and Trivandrum, India, in 1993–99 comprising 778 lung cancer patients, 1711 cancer (non-tobacco related) controls and 1927 healthy controls, no significant association was found between chewing betel quid with or without tobacco and risk for lung cancer, nor was there evidence for increasing trend with prolonged duration of chewing (Gajalakshmi *et al*., 2003).

2.4.3 *Cervical cancer*

A case–control study of 205 cases of invasive cervical cancer and 213 age-matched hospital controls was conducted in Chennai, India, in 1998–99. A twofold non-significantly elevated risk was noted for chewing betel quid with and without tobacco. A statistically significant association was seen among those who chewed more than five quids with or without tobacco per day and the dose–response relationship was also significant ($p = 0.02$). [The Working Group noted that the number of subjects analysed for the dose–response relationship was small.] (Table 63) (Rajkumar *et al.*, 2003).

Table 63. Dose–response relationship: cervical cancer study in Chennai

Average daily amount (no. of quids)	Cases	Controls	Odds ratio[a]	95% CI
Never chewed	167	198	1.0	
< 5	16	9	1.4	0.5–4.1
≥ 5	22	6	4.0	1.2–13.3
Trend test, $p = 0.02$				

From Rajkumar *et al.* (2003)

[a] Adjusted for age, area of residence, education, occupation, marital status, age at first marriage, number of pregnancies and husband's extramarital affairs

2.4.4 *Liver cancer*

(*a*) *Taiwan, China*

An association was seen in one case report (Liu *et al*., 2000) of a histologically confirmed hepatocellular carcinoma in a 54-year-old Taiwanese man who had chewed betel quid without tobacco for at least 32 years. He also had an oral squamous-cell carcinoma. He had smoked 1.5 packs of cigarettes daily and consumed alcohol occasionally and in moderate amounts; he was not infected by hepatitis viruses. High concentrations of safrole (a product of the inflorescence of *Piper betle*)-like DNA adducts were detected in oral and liver cells. [The specificity of the DNA adducts was questioned by the Working Group.]

In a prospective study in Taiwan, China, Sun *et al*. (2003) followed a total of 12 008 men aged 30–64 years with no history of hepatocellular carcinoma at baseline from 1990 to 2001. At baseline, information on betel-quid chewing was available for 11 989 subjects; of these, 1463 (12.2%) had a history of chewing. Among the 1463 chewers and 10 526 non-chewers, 10 and 102 cases of hepatocellular carcinoma were ascertained, respectively, to give incidence rates of 74.8 per 100 000 person–years for chewers and 105.7 per 100 000 person–years for non-chewers, and a crude relative risk of 0.7 (95% CI, 0.4–1.3). In a multiple regression model with adjustment for age, smoking, hepatitis B virus surface antigen (HBsAg) status, and family history of liver cirrhosis and/or liver cancer, the relative risks for the combination of hepatitis C virus (HCV) infection and betel-quid chewing were 0.8 (95% CI, 0.4–1.6) for chewers without HCV infection, 2.6 (95% CI, 1.5–4.6) for non-chewers with HCV infection and 6.8 (95% CI, 1.7–28.2) for chewers with HCV infection, compared with non-chewers without HCV infection. The corresponding synergy factor was 4.2 (95% CI, 0.6–30.7), suggesting that the effect of HCV infection on the risk for hepatocellular carcinoma may be modified by betel-quid chewing.

Another case–control study in Kaohsiung in 1996–97 included 263 cases of hepatocellular carcinoma (205 men, 58 women), matched with 263 controls selected from community residents who received a health check-up in the same hospital and had normal serum aminotransferase levels and no space-occupying lesion in the liver (Tsai *et al.*, 2001). Chewing betel quid (without tobacco) was associated with the risk for hepatocellular carcinoma (odds ratio, 3.5; 95% CI, 1.7–7.0) after controlling for sex, age, alcohol drinking, smoking, HBsAg, anti-HCV and education, using a conditional logistic regression model. The risk for hepatocellular carcinoma increased with increasing duration of areca-nut chewing and with frequency of chewing (Table 64). The risk increased in subjects with HCV infection and an interaction between HCV infection and chewing was demonstrated. The risk was also strongly associated with the presence of HBsAg and chewing betel quid (Table 65). Both interactions, in terms of synergism index, were greater than 1, with 5.37 for HBV–areca-nut chewing and 1.66 for HCV–areca-nut chewing. [This finding suggests that the effect of areca-nut chewing on hepatocellular carcinoma may confer an increased risk among subjects who have HBV or HCV infections.]

(*b*) *Thailand*

A case–control study conducted in 1987–88 (Parkin *et al.*, 1991) included 103 cases (71 men, 32 women) of cholangiocarcinoma admitted to three hospitals in North-East Thailand and 103 hospital controls matched by age, sex and residence. The criteria for definition of cases included histology, typical findings on ultrasound examination or percutaneous cholangiography. Controls were selected from individuals visiting various clinics in the same hospital or from a variety of non-malignant diseases considered to be unrelated to tobacco or alcohol consumption. Interviews were conducted using a structured questionnaire, including information on family history, smoking, betel chewing, dietary habits and alcohol use. Blood specimens were examined for HBV serology, antibodies to *Opisthorchis viverrini* and aflatoxin–albumin adducts. The final conditional logistic regression model included anti-

Table 64. Dose–response relationship between duration and frequency of chewing and risk for hepatocellular carcinoma in Taiwan, China

Chewing habits	No. of cases/controls	Odds ratio (95% CI)
Non-chewer	192/241	1.0
Duration of chewing (years)		
< 20	8/14	0.7 (0.3–1.9)
20–30	27/5	6.8 (2.4–20.5)
> 30	36/3	15.1 (4.4–39.1)
p for trend		< 0.0001
Total amount consumed (quids × 1000)		
< 100	11/10	1.4 (0.5–3.6)
100–199	31/7	5.6 (2.3–14.2)
200–299	15/3	6.3 (1.7–20.7)
> 299	14/2	8.8 (1.9–34.0)

From Tsai *et al.* (2001)
CI, confidence interval

Table 65. Interactions between betel-quid chewing and anti-HCV, and betel-quid chewing and HBsAg, and risk for hepatocellular carcinoma in Taiwan, China

Betel-quid chewer	Anti-HCV	HBsAg	No. of cases/controls	Odds ratio (95% CI)	Synergy index
–	–		121/230	1.0	
–	+		71/11	12.3 (6.0–25.5)	
+	–		57/21	5.2 (2.9–9.3)	
+	+		14/1	26.6 (3.6–116.6)	1.66
–		–	74/187	1.0	
–		+	118/54	5.5 (3.6–8.6)	
+		–	18/18	2.5 (1.2–5.4)	
+		+	53/4	33.5 (11.1–72.7)	5.37

From Tsai *et al.* (2001)
Anti-HCV, antibodies to hepatitis C virus; HBsAg, hepatitis B surface antigen; CI, confidence interval

O. viverrini status, rice consumption and betel-quid chewing with or without tobacco. The odds ratio for betel-quid chewing, comparing weekly to less than monthly use, was 6.4 (90% CI, 1.1–39.3).

A case–control study conducted within the same investigation of liver cancer in Thailand (Parkin *et al.*, 1991) included 65 cases (47 men, 18 women) of hepatocellular carcinoma admitted to the same three hospitals in North-East Thailand and 65 controls matched by age, sex and residence (Srivatanakul *et al.*, 1991). The criteria for definition of cases included cytology, typical findings on ultrasound, or radiological examination. Controls were selected from the same source as in Parkin *et al.* (1991) and interviews were conducted similarly. Blood specimens were examined for HBV and HCV serology, antibodies to *O. viverrini* and aflatoxin–albumin adducts. The final conditional logistic regression model included HBsAg status, alcohol consumption, some dietary items and betel-quid chewing with or without tobacco. The odds ratio for betel-quid chewing, comparing weekly to less than monthly use, was 11.0 (90% CI, 1.0–115.8; $p < 0.05$).