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Betel quid not containing tobacco and oral cancer: A report on a case–control study in Papua New Guinea and a meta-analysis of current evidence

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Smoking and betel quid chewing are associated with increased risk of oral cancer but few studies have reported on associations in populations where betel quid does not contain tobacco. We conducted a case–control study in Papua New Guinea and a systematic review. Our case–control study recruited 143 cases with oral cancer and 477 controls. We collected information on smoking and betel quid chewing. Current smoking was associated with an increased risk of oral cancer with an adjusted odds ratio (OR) for daily smokers of 2.63 (95% confidence intervals (95% CI) 1.32, 5.22) and amongst heaviest smokers of 4.63 (95% CI 2.07, 10.36) compared to never-smokers. Betel chewing was associated with increased risk of oral cancer with an adjusted OR for current chewers of 2.03 (95% CI 1.01, 4.09) and in the heaviest chewers of 2.47 (95% CI 1.13, 5.40) compared to nonchewers. The OR in those who both smoked tobacco and chewed betel quid was 4.85 (95% 1.10, 22.25), relative to those who neither smoked nor chewed. The systematic review identified 10 previous studies that examined risk of oral cancer associated with betel quid chewing that controlled for smoking in populations where betel quid did not contain tobacco. In studies that reported results for non-smokers the combined OR was 2.14 (95% CI 1.06, 4.32) in betel quid chewers and in studies that adjusted for smoking the combined OR was 3.50 (95% CI 2.16, 5.65) in betel quid chewers. Preventive efforts should discourage betel quid chewing as well as smoking.

Key words: oral cancer; betel quid; case–control study; meta-analysis

Oral cancer is not uncommon and is an important cause of morbidity and mortality with 267,000 cases reported globally in 2000, 2/3 of them in men. There are marked international variations in reported incidence. Melanesia has the highest incidence in the world (36.3 per 10^5 in men and 23.6 per 10^5 in women) and oral carcinoma is the most common cancer in Papua New Guinea (PNG). Rates are also high in South Asia (13.0 per 10^5 in men and 8.6 per 10^5 in women).[1]

Smoking has been consistently associated with increased risk of oral cancer but smoking patterns do not adequately explain geographical variation of this cancer.[1] One factor that may explain these variations in disease risk is the chewing of betel quid. Betel quid constituents vary across cultures, but betel quid generally consists of Areca nut, part of the Piper betle plant (inflorescence, leaf or stem) and slaked lime (either as a powder or paste) with some populations including tobacco and other spices.[2] Several lines of evidence support the suggestion that the chewing of betel quid increases the risk of oral cancer. Betel quid has been shown to contain various carcinogens[2] and has been shown to be carcinogenic in animal models; areas where chewing of betel quid is common have higher rates of oral cancer and some case–control studies of oral cancer have reported increased risk in those who chew betel quid. For these reasons the International Agency for Research on Cancer decided that betel quid should be classified as a human carcinogen. But as betel quid in many countries contains tobacco and the chewing of betel quid is often associated with smoking, few studies have been able to estimate the role of betel quid as an independent risk factor for oral cancer reliably, and only one has reported a dose-response.[2,3]

To clarify the situation we report a large case–control study in PNG where betel quid use is common, does not contain tobacco, and where smoking and betel quid exposure have been accurately recorded. In addition, we report and extend the existing literature by systematically reviewing case–control studies estimating the risk of oral cancer among people chewing betel quid that does not contain tobacco.

Material and methods

This case–control study was conducted in Papua New Guinea (PNG) from January 1985 to July 1987. Cases were hospitalised with oral cancer and controls were hospital controls either admitted or related to someone admitted to the same hospital. Information on exposures was collected using an interviewer-administered questionnaire.

Case selection

Cases had a first diagnosis of clinically apparent oral squamous cell carcinoma diagnosed by a doctor within 3 months of interview. They were identified at 6 hospitals serving 6 provinces with high rates of oral cancer. Approval for the project was sought from the medical superintendents of participating hospitals and permission to approach patients was sought from the treating doctor. Hospitals were contacted every fortnight by telephone and asked to provide the names and details of any possible cases admitted. Hospitals were visited by the research team every 3 months and cases were interviewed in hospital. Following an explanation of the scope, aims and purpose of the study, all eligible cases who were approached agreed to participate. At each visit the local clinicians were approached to see if any possible cases had been missed: none were identified.

Control selection

Controls were people with an unrelated condition and no evidence of oral cancer or precancer, recently admitted to the same hospital as the index case. Towards the end of the study, guardians of these inpatients were also recruited if suitable patient controls were not available. Controls were recruited at visits to the hospitals over the course of the study, and were selected to have a similar

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distribution of age, sex and geographical location as the cases with a case–control ratio of about 1:3. The controls were approached in a similar manner to the cases and none refused to participate.

Interview methodology

Our study was conducted among a predominantly preliterate population (*i.e.* a culture not having a written language) with some particular methodological challenges in assessing duration and frequency of exposures. All subjects were interviewed by trained investigators fluent in Melanesian Pidgin, trained in a standard manner using a detailed instruction manual and monitored using tape recordings of the interviews. The timing of key events, such as the Second World War, was used to estimate age of the participants and as milestones to judge duration of exposure. To obtain frequency data on smoking and betel quid chewing, each person was first asked about their daily activities from waking until going to sleep. A typical day was divided into 24-hourly periods and then the interviewee was asked whether they chewed betel quid or smoked during this period. The history of chewing betel quid and smoking documented the specific components of the quid or type of tobacco in Melanesian Pidgin and the local language (*Tok Ples*) along with duration of use. The subjects were also asked whether they had ever been to school, whether they had a job that paid money and recorded whether they lived in an urban or rural setting.

Exposure data

Age was estimated within 5-year age groups with those aged below 40 years placed into a single category. Urban and rural residence was classified according to census division of residence. Those residing in the same census division as the provincial administrative centre were classified as urban; otherwise they were classified as rural. The reference group for all analyses was never smokers or never chewers unless the numbers in this group were too small, in which case it was expanded to include exsmokers or exchewers. Exsmokers or exchewers were smokers or chewers who had stopped for more than one year prior to the interview. Occasional smokers or chewers were those who reported smoking or chewing weekly or less often. Current daily smokers and chewers were people who still smoked or chewed daily or had been daily smokers or chewers within 1 year of the interview. Current smokers and chewers were split into 3 categories according to frequency of use and daily smokers of different types of tobacco were identified. Lifetime tobacco exposure was calculated as the product of daily frequency and duration of smoking and then the combined distribution was dichotomised for analysis. To provide a summary estimate of tobacco exposure from the different types of tobacco smoked throughout a subject's lifetime, total tar exposure was computed using frequency and duration of use for each tobacco and the estimated tar content of each type. The lifetime tar consumption was grouped into thirds based on the joint distribution of cases and controls.

Statistical methods

Unconditional multiple logistic regression was used to estimate odds ratios (ORs), and 95% confidence intervals (CIs) for the association between smoking and betel quid chewing, and to adjust for the effects of confounding variables. Unadjusted ORs, and ORs adjusted for age, sex, province, urban or rural residence, education and income and either smoking or betel chewing were estimated.

Systematic review and meta-analysis

Studies were located by searching MEDLINE, (from inception to January 2006), and the reference lists of relevant texts and reviews. A hierarchical literature search in MEDLINE used the following National Library of Medicine MeSH terms (Medical Subject Headings): 'Oral Neoplasms', 'Mouth', 'Betel' and 'Areca'. The additional keywords oral, oropharynx and cancer or carcinoma were also used in MEDLINE (truncated where necessary). Eligible studies were case–control studies of oral squamous cell carcinoma that had documented exposure to betel quid in populations where betel quid did not contain tobacco. To identify potentially eligible studies the title and abstract of each study identified by the literature search was assessed. Full papers of potentially relevant studies were reviewed. Data extracted included numbers of cases and controls who were and were not exposed to betel quid without tobacco, evidence for a dose-response with betel quid chewing without tobacco, exposure to tobacco smoke, adjustment for tobacco smoking in the analysis, year of publication, country and sample size.

We used inverse-variance weighted fixed-effect metaanalysis, and DerSimonian and Laird random-effects meta-analyses[4] to derive summary OR in nonsmokers who chewed betel quid and for betel quid chewing after adjustment for smoking. Between-study heterogeneity was assessed using I^2 statistics.[5] Stata version 8.2 was used for all analyses.

Results

A total of 620 subjects were recruited into the study: 143 cases (102 men) and 477 controls (342 men). The distribution of oral cancer cases and controls by age, sex, province, urban rural status, education and income are summarised in Table I. Cases were less likely to reside in an urban area and less likely to have been to school but were similar in terms of having a job that paid money.

Most people had smoked tobacco (91% of cases and 82% of controls) and nearly everyone had chewed betel quid (99% of cases and 98% of controls). The majority of people were current smokers (78% of cases and 62% of controls) and current betel quid chewers (87% of cases and 79% of controls). Current smoking was nearly twice as common among male controls (72%) as females (35%), whereas the percentage reporting current betel quid chewing was similar in male (80%) and female (75%) controls.

The risks of oral cancer associated with smoking are summarised in Table II. The risk of oral cancer was elevated in all categories of smoking exposure. Relative to nonsmokers, the risk was highest in current smokers and lower but still elevated in exsmokers. There was a dose-response relationship with both current daily tobacco consumption and lifetime exposure to tobacco smoke ($p < 0.001$). Various types of tobacco were smoked. Locally and commercially grown air-dried 'Black' tobacco (*Brus or Stik*) was most commonly smoked while commercial flue-cured machine rolled 'Blond'

TABLE I – CHARACTERISTICS OF CASES AND CONTROLS BY AGE, SEX, PROVINCE, RESIDENCE, EDUCATION AND INCOME

Factors and subgroups	Cases		Controls	
	No	%	No	%
Total	143	100	477	100
Age in years				
<40	17	11.9	76	15.9
40–49	37	25.9	138	29.0
50–59	47	32.9	147	30.8
60–70	42	29.4	116	24.3
Sex				
Male	102	71.3	342	71.7
Female	41	28.7	135	28.3
Province				
New Ireland	33	23.1	94	19.7
East New Britain	15	10.5	64	13.4
Morobe	19	13.3	64	13.4
Madang	31	21.0	98	20.5
East Sepik	26	18.2	70	14.7
Milne Bay	20	14.0	87	18.2
Residence				
Urban	18	12.6	107	22.4
Rural	125	87.4	370	77.6
Education				
Yes	74	51.7	289	60.6
No	69	48.3	188	39.4
Income				
Yes	53	37.1	172	36.1
No	90	62.9	305	63.9

TABLE II – ODDS RATIO OF ORAL CANCER ASSOCIATED WITH TOBACCO SMOKING AND BETEL QUID CHEWING

Risk factors and subgroups	Cases (*n*)	Controls (*n*)	OR[1]	95%	OR[2]	95% CI
Tobacco smoking						
Never smoked	13	86	1.00		1.00	
Ever smoked	130	391	2.20	1.20, 4.04	2.19	1.12, 4.30
Exsmoker	12	45	1.76	0.75, 4.12	1.74	0.70, 4.33
Current occasional smoker	7	52	0.89	0.34, 2.32	0.88	0.32, 2.42
Current daily smoker	111	294	2.50	1.35, 4.61	2.63	1.32, 5.22
Smoking frequency						
Never	13	86	1.00		1.00	
1–14	30	106	1.87	0.93, 3.77	2.14	0.98, 4.67
15–21	31	97	2.11	1.05, 4.26	2.42	1.09, 5.35
22 or more	50	91	3.63	1.86, 5.21	4.63	2.07, 10.36
Lifetime exposure						
Never	13	86	1.00		1.00	
38–540 tobacco years	47	153	2.03	1.05, 3.93	2.47	1.18, 5.17
550–1595 tobacco years	64	141	3.00	1.58, 5.72	3.38	1.55, 7.37
Tobacco type (used daily)						
Never	13	86	1.00		1.00	
Air-cured 'Black' tobacco	93	232	2.65	1.41, 4.98	3.07	1.49, 6.03
Flue-cured 'Blond' tobacco	7	31	1.49	0.55, 4.09	1.82	0.64, 5.21
Both 'Black' and 'Blond' tobacco	11	31	2.35	0.95, 5.78	2.81	1.04, 7.60
Lifetime tar						
Nil	13	86	1.00		1.00	
Low	31	143	1.43	0.72, 2.86	1.56	0.74, 3.27
Medium	41	131	2.07	1.06, 4.05	2.36	1.12, 4.96
High	58	117	3.28	1.71, 6.31	3.49	1.62, 7.55
Betel quid chewing						
Never chewed	2	9	1.00		1.00	
Ever chewed	141	468	1.36	0.28, 6.35	1.10	0.22, 5.51
Exchewer	9	56	0.72	0.13, 3.90	0.57	0.10, 3.28
Current occasional chewer	8	37	0.97	0.18, 5.39	0.98	0.17, 5.74
Current daily chewer	124	375	1.49	0.32, 6.98	1.29	0.25, 6.51
Chewing frequency						
Nonchewer[3]	11	65	1.00		1.00	
Current chewer	132	412	1.89	0.97, 3.69	2.03	1.01, 4.09
Occasional	8	37	1.28	0.47, 3.46	1.57	0.56, 4.36
Low	28	122	1.36	0.63, 2.90	1.73	0.78, 3.84
Medium	47	141	1.97	0.96, 4.04	2.10	0.98, 4.47
High	49	112	2.59	1.26, 5.32	2.47	1.13, 5.40

[1]Odds ratios unadjusted.–[2]Odds ratios adjusted for age, sex, province, rural *cf* urban residence, income, education and frequency of betel quid chewing for smoking variables or frequency of smoking for chewing variables.–[3]Never and exchewers.

tobacco cigarettes were the tobacco type least often smoked. Only *Brus* varied in the way it was smoked usually either wrapped in newspaper or banana or tobacco leaf and less frequently smoked in a pipe. The risk of oral cancer increased regardless of the type of tobacco smoked or the method of smoking. Although the point estimate of risk was higher with 'Black' tobacco than 'Blond' CIs overlap. When different types of tobacco were combined to estimate lifetime tar exposure there was a linear dose-response relationship with risk of oral cancer ($p < 0.001$). These associations were essentially unaltered after adjustment for potential confounders and adjustment for betel quid chewing.

Betel quids in this population did not contain tobacco and were unwrapped. The constituent areca nut, slaked lime and the inflorescence of the piper betle plant (the flower stalk of the plant) were placed separately in the mouth. The nut was chewed first, (the pericarp was sometimes included if the youngest *kulau* nuts were chewed). Powdered slaked lime was then repeatedly added to the mouth. Most people used a piper betle inflorescence, which was also chewed, to add the lime while others added lime using a wooden spatula. If a stick or spatula was used, the inflorescence or leaf of the piper betle was still chewed. The quid when chewed was intensely sialogenic and turned bright red. It was usually chewed for about 15 min and expectorated when its flavour diminished, although around a quarter of cases and controls reported swallowing the remnants and around twenty percent reported sleeping with the quid in their mouth on occasion. Only 2 cases and 1 control reported that they did not usually add lime.

The risks of oral cancer associated with betel quid chewing are summarised in Table II. Risk of oral cancer was higher in current daily betel quid chewers. To explore the association with dose of betel quid the never and exchewers were combined to create a reference category of nonchewers. There was statistical evidence of a dose-response association with betel quid consumption ($p = 0.016$). These associations were essentially unaltered after adjustment for potential confounders and adjustment for smoking.

The risk of oral cancer with smoking and betel quid chewing are compared in smokers and nonsmokers and in chewers and nonchewers in Table III. The risk was higher in smokers and in betel chewers and highest in people who smoked tobacco and chewed betel quid when compared to people who did neither.

Systematic review and meta-analysis

Fourteen case–control studies were identified[6–19] that examined risk of oral cancer associated with chewing betel quid in populations where betel quid did not contain tobacco. Four were excluded because they did not report on nonsmokers or did not adjust for tobacco smoking in the analysis.[6–9] Therefore, 10 studies were included in the review together with the results of the present study.[10–19] These provided a total of 367 cases of oral cancer in people who were nonsmokers and 2,123 cases of oral cancer in studies in which smoking was adjusted for in the analysis.

Table IV shows characteristics of the studies including numbers of cases and controls exposure to betel quid without tobacco and adjustment for tobacco smoking. The majority of studies were hospital based. In one study, cases were identified from a population cancer registry[10] and controls were selected from the same population. Three other studies used population-based controls.

The proportion of oral cancer cases exposed to betel quid without tobacco ranged from 11 to 92% and from 3 to 86% in controls. Five studies, including the present one, reported on betel quid without tobacco chewing in nonsmokers, potential confounding factors were considered in 2 of these studies. Eight studies including the present one reported effect estimates adjusted for smoking amongst other potential confounders. All 11 studies reported dichotomous outcomes, 3 reporting never *versus* ever and the remaining studies yes *versus* no.

Meta-analysis stratified by tobacco smoking (Table IV, Fig. 1) shows an increased risk of oral cancer when exposed to betel quid without tobacco when the person was not a current smoker (random-effects summary OR 2.14, 95% CI 1.06, 4.32). There was evidence of between-study heterogeneity in these effects (I^2 = 77%, p = 0.002). The risk of oral cancer was increased among chewers of betel quid without tobacco after adjusting for tobacco smoking (random-effects summary OR 3.50, 95% CI 2.16, 5.65) with evidence of between-study heterogeneity in these effects (I^2 = 70.6%, p = 0.001).

Only 2 studies, Lu et al.[18] and the present study, had reported a dose-response. Both studies demonstrated an increased risk with exposure to betel quid after adjusting for the effect of smoking.

TABLE III – ODDS RATIOS FOR ORAL CANCER ACCORDING TO BETEL CHEWING AND SMOKING AMONG CURRENT DAILY CHEWERS AND SMOKERS

Current daily smoking		Current daily betel chewing	
		No[1]	Yes
No[2]	OR[3]	1.00[4]	1.76
	(95% CI)	–	(0.35, 8.92)
	Cases/Controls	2, 20	11, 66
Yes	OR[3]	1.81	4.85
	(95% CI)	(0.27, 10.89)	(1.10, 22.25)
	Cases/controls	4, 22	107, 272

[1]Nonbetel quid chewer; this includes never chewers and exchewers.–[2]Nonsmoker; never-smokers.–[3]Referent category.–[4]ORs adjusted for age, sex, province, education, urban *cf* rural residence and income.

Discussion

We have confirmed that smoking is a strong independent risk factor for oral cancer and have shown that betel quid (that does not contain tobacco) is also an independent, but weaker, risk factor for oral cancer.

Our study is one of the largest case–control studies of betel quid without tobacco to date, but despite our attempts to characterise the exposures accurately the lack of variation in exposure to tobacco and betel quid reduced our power to detect associations and the CI are therefore wide, particularly for betel quid chewing. All eligible cases and controls approached agreed to take part in our study and taped interviews were conducted by trained interviewers, thus minimising the likelihood of selection and information bias. Furthermore the size, anatomical site or the duration of the patients' awareness of the tumour were not related to reported smoking or betel quid chewing.

A disadvantage of hospital controls is that they differ from the referent population or may be a biased sample of people in that referent population. In PNG, betel quid chewing was not known to be associated with diseases other than oral cancer. Diseases attributable to smoking were less easily defined in PNG than in a Western population. Lung cancer was uncommon, as was cardiovascular disease and it is difficult to make a causal extrapolation between tobacco smoke and chronic lung disease because of the confounding effect of wood smoke in poorly ventilated houses.[20] Other than exclusion of people with oral cancer, diagnosis of controls was not routinely documented in our study. The inclusion of people with a wide variety of conditions presenting to the general wards in PNG would serve to dilute any bias that would occur if one disease were related to the exposure of interest even if the relationship was not obvious. In Western populations, hospitalised patients are more likely to smoke and in 1991 a report of a survey of Angau Provincial Hospital PNG, found 80% of 2000 patients were smokers.[20] As smoking and betel quid chewing were highly correlated in the present study high prevalence of betel quid chewing is also likely. Guardians of patients are likely to share similar attitudes and behaviours with controls attending as patients; in particular, friendship may be a determinant of study exposure or visa versa. Although no systematic differences were found between patients and guardians because of the small numbers the opportunity to explore this were limited. On balance, the selection forces leading to hospitalisation have probably led to underestimation of the true risk of oral cancer associated with smoking and chewing.

TABLE IV – CASE-CONTROL STUDIES ASSESSING RISK OF ORAL CANCER AMONG CHEWERS OF BETEL QUID WITHOUT TOBACCO. CHARACTERISTICS AND ODDS RATIOS (OR) IN STUDIES OF NONSMOKERS AND THOSE ADJUSTED FOR SMOKING

Smoking status Year, Country	Author	Controls	Number of cases (% chewers)	Number of controls (% chewers)	Betel quid chewing	Adjusted	OR	95% CI
Nonsmokers								
1962, India	Chandra	Hsp	181 (25)	326 (22)	Yes/no	No	1.3	0.8, 1.9
1966, India, SL	Hirayama	Pop	40 (33)	142 (28)	Yes/no	No	1.2	0.6, 2.6
1976, Pakistan	Jafarey	Pop	128 (31)	190 (6)	Yes/no	No	3.6	2.4, 5.3
1995, Taiwan	Ko	Hsp	5 (60)	51 (4)	Yes/no	Yes[1]	28.2	1.9, 414.4
2006, PNG	Thomas	Hsp	13 (85)	86 (77)	Yes/no	Yes[2]	1.8	0.4, 8.5
Adjusted for smoking								
1995, Taiwan	Ko	Hsp	102 (70)	195 (22)	Yes/no	Yes[3]	6.9	3.1, 15.2
1996, Taiwan	Lu	Pop	40 (83)	160 (24)	Yes/no	Yes[4]	58.4	7.6, 447.6
2000, India	Dikshit	Pop	32 (13)	152 (8)	Yes/no	Yes[5]	1.7	0.9, 3.3
2000, Pakistan	Merchant	Hsp	79 (53)	149 (11)	Never/ever	Yes[6]	9.9	1.8, 55.6
2002, India	Balaram	Hsp	142 (11)	283 (3)	Never/ever	Yes[7]	4.2	1.5, 11.8
2002, Taiwan	Chen	Hsp	22 (86)	29 (30)	Yes/no	Yes[8]	17.1	2.3, 129.0
2003, India	Znaor (a)	Hsp			Never/ever	Yes[9]	2.6	1.8, 3.7
2003, India	Znaor (b)	Hsp			Never/ever	Yes[9]	1.7	1.1, 2.6
2006, PNG	Thomas	Hsp	143 (92)	477 (86)	Yes/no	Yes[10]	2.0	1.0, 4.1

SL, Sri Lanka; PNG, Papua New Guinea; Hsp, Hospital controls; Pop, populations controls. (a) mouth; (b) tongue. Empty enteries represent numbers of cases and controls for tongue and mouth not reported (total cases for mouth and tongue combined is 1563, total controls is 3,638).

[1]Alcohol matched on age and sex.–[2]Age sex centre education income urban/rural.–[3]Smoking alcohol matched on age and sex.–[4]Smoking alcohol matched on age and sex.–[5]Smoking age.–[6]Smoking (cigarettes) alcohol matched on age and sex.–[7]Smoking alcohol age centre education.–[8]Smoking age sex.–[9]Smoking alcohol age sex centre education.–[10]Smoking age sex centre education income urban/rural.

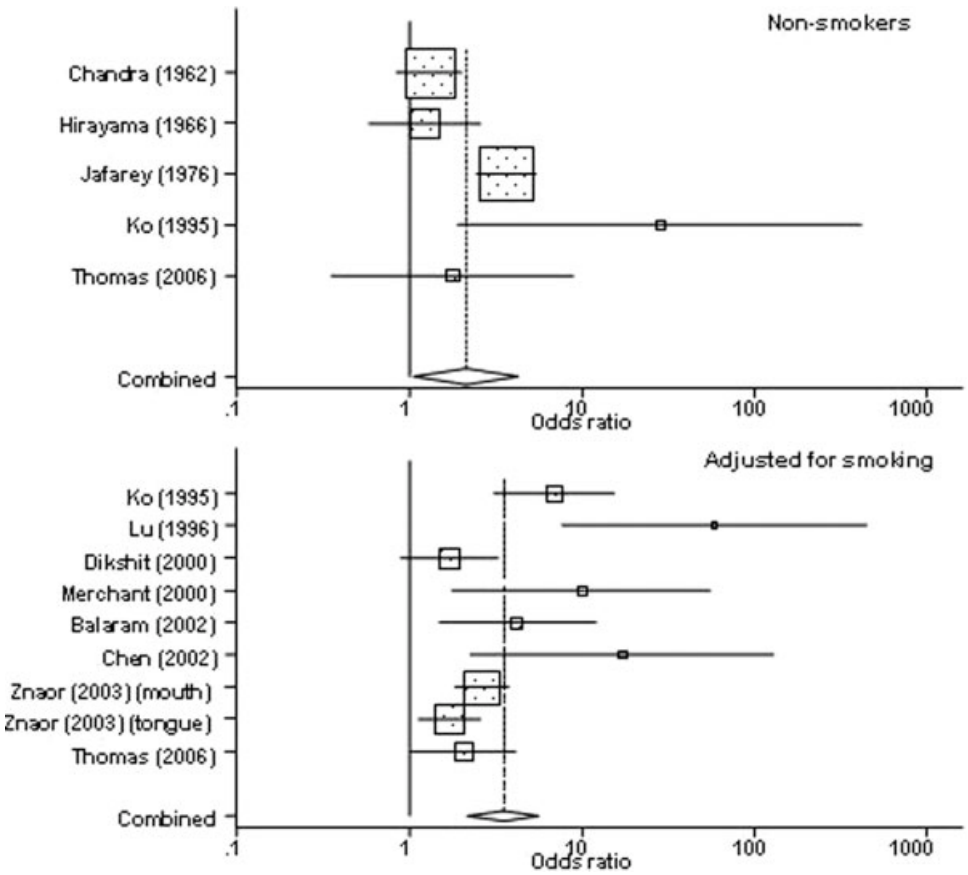

FIGURE 1 – Meta-analysis of studies of betel quid without tobacco.

PNG is a heterogeneous culturally diverse society where over 700 Austronesian and Papuan languages are spoken. The measures of social aspects of wealth and acculturation used in our study were necessarily crude but neither smoking nor betel quid chewing were strongly associated with any of these measures and adjustment for measures of these confounders did not alter the underlying associations making confounding less likely. It is of course possible that other unsuspected variables may have biased the results. It may be helpful in future studies to attempt to measure indicators of traditional lifestyle as well as acculturation. It is uncertain how such cultural factors affect habits such as smoking and betel quid chewing.

The association we observed with smoking in our study was strong and there was a dose-response relationship for both smoking frequency and lifetime tar exposure. These findings are consistent with previous results for increased frequency[17] and tar[21] and are biologically plausible. The different association we observed by tobacco type might reflect the high nitrosamine content which is a feature of air-cured tobacco.[22,23] The lower risk we observed in exsmokers is also consistent with the risks reported in studies in other populations.[24–26]

The relationship we observed with chewing of betel quid was weaker than that for tobacco smoking. Even so the risk was doubled in the highest exposure category and again there was evidence of a dose-response relationship. Only 10 studies have examined the risk of oral cancer in populations where betel quid does not contain tobacco and accounted for the potential confounding effect of smoking tobacco; 4 of these estimated risk in nonsmokers and 7 adjusted for the effect of smoking in the analysis. Exposure to smoking was estimated as a dichotomous outcome (yes *versus* no or never *versus* ever) in all of these, and the direction of effect was always towards an increased risk and is consistent with the present study. A meta-analysis of these studies (including the present study) showed evidence of between study heterogeneity, suggesting that effects vary and there is still some uncertainty about the magnitude (but probably not the reality) of the contribution of betel quid without tobacco to oral cancer in these populations. The heterogeneity may be explained in part by the variation in the proportion of the population exposed to betel quid without tobacco. In addition dichotomous outcomes offer only limited evidence of a causal link and ever chewing betel quid without tobacco does not exclude the inclusion of tobacco in the quid at other times. Again, only one of these previous studies reported a dose-response estimate for betel quid without tobacco,[18] which based on small numbers showed a very large but imprecise association for the heaviest chewers, (Adjusted OR 275.6 95% CI 14.8, 5106.5). The present study supports the finding of a dose-response, although the effect size is smaller the estimates are more precise. The value of testing for dose-response trends in judging causality is widely acknowledged, and so the lack of this information from so many reports is disappointing.

The present study thus adds to the literature as we have confirmed the importance of smoking as a dose-related risk factor for oral cancer. This further highlights the need for effective smoking prevention and cessation programmes in developing countries. We have also shown that betel quid chewing is associated in a dose-related manner with increased risk of oral cancer even in a population where the betel quid does not contain tobacco. The finding of a dose-response adds to the only other study reporting a dose effect for this exposure. We have previously reported that the type and use of slaked lime may modify the risk associated with betel quid chewing.[27] It may therefore be that modifications to the composition of betel quid could be an effective means of reducing the risk of oral cancer, but further studies are required, to assess this element of the quid. Here, we have extended previous reviews[3] by presenting previously unpublished data and combining this in a systematic review and meta-analysis.

We have shown that smoking and betel quid chewing are independent risk factors for oral cancer in large case–control study in PNG—a population where betel quid does not contain tobacco. Efforts to reduce the incidence of oral cancer in such populations should aim to reduce the smoking prevalence and discourage betel quid chewing and in particular the use of slaked lime as part of the betel quid.

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