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Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan

Ying-Chin Ko[1], Yung-Li Huang[2], Chien-Hung Lee[1], Mei-Ju Chen[1], Li-Min Lin[2] and Chih-Cheng Tsai[2]

[1]*School of Public Health,* [2]*School of Dentistry, Kaohsiung Medical College, Taiwan, Repulic of China*

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A hospital-based case-control study of matched pairs was conducted to explore (a) the relationship between the use of betel quid chewing, cigarette smoking, alcohol drinking and oral cancer and (b) synergism between these factors. The case group consisted of 104 male and 3 female oral cancer patients and these were compared with 194 male and 6 female matched controls. We found by univariate analysis that alcohol consumption, smoking, betel quid chewing, educational level and occupation were associated with oral cancer. The adjusted odds ratios were to be found elevated in patients who were smoking and betel quid chewing. After adjusting for education and occupation covariates, the incidence of oral cancer was computed to be 123-fold higher in patients who smoked, drank alcohol and chewed betel quid than in obstainers. The synergistic effects of alcohol, tobacco smoke and betel quid in oral cancer were clearly demonstrated, but there was a statistically significant association between oral cancer and betel quid chewing alone. Swallowing betel quid juice (saliva extract of betel quid produced by chewing) or including unripened betel fruit in the quid both seemed to enhance the risks of contracting oral cancer.

Key words: alcohol drinking; betel quid; oral cancer; smoking

Ying-Chin Ko, No. 100 Shih Chuan 1st Road, Kaohsiung Medical College, Kaohsiung, Taiwan, ROC

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It has long been known that tobacco smoking or alcohol abuse play a role in the etiology of oral cavity cancer and that the two agents may act synergistically (1–4). A working group of the International Agency for Research on Cancer (IARC) concluded that there was adequate evidence of an association between chewing betel quid together with tobacco use (chewing or smoking) and oral cancer, but evidence supporting a link between betel chewing alone and human cancer was not sufficient (5). In areas where the habit of betel quid chewing is widespread and chewers are also smokers and alcohol drinkers, the relationship of oral cancer to betel quid, tobacco and alcohol use is probably complex and requires further investigation.

Although the chewing of betel quid is practiced in several different ways in various countries, the major components are relatively consistent. As a rule, pieces of raw, cooked or roasted areca nut are wrapped into a betel leaf, smeared with lime and catechu. Frequently tobacco and/or spices are also added to the bundle. In Taiwan, areca nut plus pieces of unripe *Piper betel* fruit or areca nut are wrapped into a piece of betel leaf together with white or red lime. Thus the Taiwanese betel quid prepared entirely from fresh plants is quite different from the betel quid used in other countries (6). As it is free from tobacco, in the case-control study presented here we were able to investigate the independent and synergistic effects of betel quid chewing, tobacco use and alcohol consumption on the incidence of oral cancer.

Material and methods

Study population

The participants in this study were patients of Kaohsiung Medical College Hospital, used by all socioeconomic categories. Patients visiting the hospital's dentistry department were defined as the study population. All patients found to suffer from oral cancer with the diagnosis confirmed by histopathology during 1992 and 1993 formed the case group. In all, 104 men and three women oral cancer patients were registered with cancer sites coded as ICD (International Classification of Diseases) 140–141, 143–145. The control group consisted of non-carcinoma patients treated during the same period in the ophthalmology and physical check-up departments. Patients suffer-

ing from peptic ulcer were excluded from the control group, as betel quid is known to damage the gastric mucosa (7) and to cause stomach cancer in animal studies (5). As oral cancer patients were older people, each case was matched randomly by control patients of the same age and sex. Each of 93 cases was matched with two controls, 14 cases with one control. A few cases could only be matched for age within ±5 years. In all, 194 men and six women participated in this study as controls. A trained interviewer filled in for each participant a structured questionnaire, collecting information on demographic characteristics, occupation and historical information such as whether or not the patient was a habitual betel quid chewer (one quid or more daily for at least one year), cigarette smoker (one cigarette or more per day for at least one year) and regular alcohol drinker (drinking more than four days a week); the duration of habits and daily amounts consumed were also recorded. In addition, the risks of swallowing betel quid juice (saliva extract of betel quid produced by chewing) were also explored. The types of betel material chewed were recorded as areca nut with betel leaf, areca nut with betel fruit, or both mixed.

Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the risks of contracting oral cancer in relation to the risk factors in question. Those showing significant ORs were subsequently examined in conditional logistic models (8) that included a multivariate technique especially designed for a matched case-control study with varying numbers of controls (9). Stata computer packages were used for the analysis of collected data in this study (10).

Results

The average age of the 107 confirmed oral cancer cases was 48±12 years (range 18–86 years), the same as that of the 200 controls. A univariate comparison of the ORs between oral cancer cases and controls by residence, marital status, religious affiliation, ethnicity, dietary habit, educational level, occupation, cigarette smoking, alcohol drinking and betel quid chewing habits are displayed in Tables 1 and 2. The estimated ORs were found to be lower in better educated patients (OR=0.2, 95% CI 0.1-0.5) and white collar workers (OR=0.2, 95% CI 0.1-0.5) as compared to lesser educated patients and blue collar workers. The estimated ORs were elevated in cigarette smokers (OR=8.4, 95% CI 3.5–20.4), alcohol consumers (OR=3.2, 95% CI 1.8–5.6) and betel quid chewers (OR=8.5, 95% CI 4.4–16.2) as compared to abstainers. The adjusted ORs for factors such as alcohol drinking, cigarette smoking and betel quid chewing remained significantly elevated even after logistic regression

Table 1. Estimated odds ratios (ORs) and 95% confidence intervals (CIs) of demographics and dietary habit in oral cancer patients compared with matched hospital-based controls

Characteristics	Categories	Cases	Controls	OR	(95% CI)
Residence	Municipality	42	100	1.0	
	Urban	23	36	1.6	(0.8–3.2)
	Rural	42	64	1.5	(0.9–2.7)
Marriage status	Unmarried	12	16	1.0	
	Widowed, Separated	5	16	0.3	(0.1–1.5)
	Married	90	168	0.6	(0.2–1.6)
Religious	None	25	21	1.0	
	Folk religion	77	46	1.2	(0.5–2.5)
	Others	5	7	1.0	(0.2–4.1)
Ethnicity	Fukien	97	168	1.0	
	Hakka	4	12	0.6	(0.2–2.1)
	Mainlander	3	18	0.3	(0.1–1.1)
	Aborigines	3	2	2.6	(0.4–15.5)
Educational level (years)	None	26	36	1.0	
	1–9	59	82	0.8	(0.4–1.5)
	10+	22	80	0.2	(0.1–0.5)
Occupation	Blue collar	79	105	1.0	
	Farmer	20	47	0.6	(0.3–1.1)
	White collar	8	45	0.2	(0.1-0.5)
Dietary habit	Balanced	77	115	1.0	
	.Preferrence animal origin	17	33	0.8	(0.6–2.5)
	Preference vegetable origin	13	18	1.3	(0.6–2.8)

Table 2. Estimated odds ratios (ORs) and 95% confidence intervals (CIs) of substance use in oral cancer patients compared with matched hospital-based controls

Substance use	Categories	Cases	Controls	OR	(95% CI)	AOR*	(95% CI)
Alcohol drinking	No	25	89	1.0		1.0	
	Ex-drinker	14	37	1.2	(0.5–2.7)	1.0	(0.3–3.3)
	Yes	68	74	3.2	(1.8–5.6)	2.2	(1.0–4.9)
Cigarette smoking	No	11	72	1.0		1.0	
	Ex-smoker	11	30	3.5	(1.1–10.5)	3.6	(0.9–14.6)
	Yes	85	98	8.4	(3.5–20.4)	4.6	(1.5–14.0)
Betel chewing	No	31	153	1.0		1.0	
	Ex-chewer	5	5	4.6	(1.3–18.3)	4.7	(0.9–22.7)
	Yes	71	42	8.5	(4.4–16.2)	6.9	(3.1–15.2)

* Odds ratios adjusted for education, occupation and covariates in the table.

Table 3 Synergistic effect of cigarette smoking, alcohol drinking and betel chewing for oral cancer patients

	Alcohol drinking					
	User			Non-user		
Cigarette smoking	Cases/ Controls	AOR*	(95% CI)	Cases/ Controls	AOR*	(95% CI)
			Betel chewing user			
User	58/34	122.8	(17.1–880.5)	12/9	89.1	(10.0–790.7)
Non-user	3/2	54.0	(4.4–660.0)	3/2	28.2	(1.9–414.4)
			Betel chewing non-user			
User	18/56	22.3	(3.2–153.8)	8/29	18.0	(2.4–135.8)
Non-user	3/19	10.2	(1.2–86.4)	2/49	1.0	

* Odds ratios adjusted for education and occupation.

Table 4. Types of betel material chewed in oral cancer patients compared with matched hospital-based controls

Types	Categories	Cases	Controls	AOR*	(95% CI)
Type of material	Non-user	31	160	1.0	
	With betel leaf	1	7	0.1	(0.0–6.3)
	With unripe betel fruit	41	13	11.6	(3.7–36.9)
	Mixed	34	25	8.5	(2.7–26.3)
Juice swallowing	Non-user	31	160	1.0	
	Non-swallowing	3	15	0.2	(0.0–2.9)
	Swallowing	73	31	11.4	(4.0–32.0)

* Odds ratios adjusted for education, occupation, smoking and drinking.

analysis (Table 2). Betel quid chewing was shown to be the most potent risk factor for oral cancer.

Educational level and occupation were found to be significant exogenous factors and were adjusted as covariates for the relationship between oral cancer and smoking, alcohol drinking, and betel quid chewing. The association of betel quid chewing alone with oral cancer was statistically significant, even after adjusting for education level and occupation covariates. The adjusted ORs of patients who indulged in at least two of the three habits studied were significantly elevated as compared with the ORs of patients with a single habit. The synergistic effect was the greatest for betel quid chewers who smoked cigarettes and consumed alcohol. The incidence of oral cancer among individuals who were betel quid chewers, alcohol drinkers and smokers was 123-fold (95% CI 17.1–880.5) higher than that among abstainers (Table 3). The risk of contracting oral cancer tended to decline among those who had quit betel quid chewing. Chewing betel quid without betel fruit seemed less risky than with betel fruit included. Swallowers of betel juice were more likely to contract oral cancer than non-swallowers (Table 4).

Discussion

The IARC identified alcoholic beverages, betel quid with tobacco and tobacco smoke as human carcinogens, with target organs including the oral cavity, pharynx, larynx and esophagus (11). The carcinogenicity of alcohol beverages and tobacco smoke has been established from evidence presented in Western reports. The carcinogenic nature of betel quid is based mostly on epidemiologic observations made in India, where betel quid nearly always includes tobacco, a known cause of oral cancer in its own right. An association between tobacco-free betel quid chewing and oral cancer has never been observed, either because none of the usual betel quid ingredients (areca nut, betel leaf, catechu and lime) contain carcinogens or because the sample size of betel quid chewers who did not drink or smoke was not sufficiently large to unravel the association. In Taiwan, the independent and combined use of these substances is common and attempts had already been made to analyze the relationship between betel quid chewing and oral cancer in 1976 (12). The IARC was, however, unable to estimate the relative risks based on this study because of the lack of a suitable control group (5).

In the present investigation, a significant relationship was found between oral cancer and betel quid chewing alone. However, the Taiwanese betel quid often includes the unripe *Piper betel* fruit, which contains about 1% safrole, a possible human carcinogen (group 2B) incriminated by ample evidence obtained in animal experiments (11). Chewing betel quid consisting of areca nut wrapped in betel leaf but excluding the betel fruit seems to be less risky according our study. Not only does betel leaf contain no safrole, but it has been shown to include two compounds, eugenol and hydroxycavicol, which are thought to be antimutagenic and/or anticarcinogenic agents (13, 14), lending the betel leaf an antagonistic role against the tobacco carcinogens (15). As a matter of interest, both the betel leaf and fruit are from the same *Piper* plant, parts of which evidently contain carcinogenic and others anticarcinogenic substances.

As the incidence of oral cancer was significantly higher among swallowers of betel juice than among non-swallowers, the juice may be assumed to contain carcinogens or pro-carcinogens causing the onset of cancer in the upper alimentary tract; examination for cancer of the oesophagus, larynx, pharynx and stomach in such individuals is recommended. In this study patients who combined the habits of betel quid chewing with cigarette smoking and alcohol drinking ran the highest risks of contracting oral cancer; the combination of betel quid chewing and cigarette smoking came second, followed by betel quid chewing and drinking. The risks were similar to those who indulged in betel quid chewing alone, or cigarette smoking or a combination of cigarette smoking and alcohol consumption. The weakest risk factor was alcohol consumption on its own. These findings are not dissimilar to those observed in some Indian studies (16, 17). According to SANKARANARAYANAN *et al.* (17), although alcohol consumption alone was not independently associated with oral cancer, it did seem to enhance the risk of developing the disease when used in combination with the other two habits. Tobacco quid chewing was the most potent risk factor for buccal and labial cancers, although the separation of risks due to tobacco and betel quid chewing alone was difficult. In addition to the three habits discussed, recently the human papilloma virus-6 has been postulated as another possible cause of oral cancer (18).

Of Taiwanese betel quid chewers, 86% were smokers and 75% were alcohol drinkers (6). About 10% of the general population aged over 15 years were found to combine betel quid chewing with smoking and drinking at one time in their life. Strategies of prevention or control of betel quid use should therefore include: 1) cessation of both chewing and smoking, 2) reduction of amounts used, 3) removal of carcinogenic components from the products, 4) change to a safe substitute, 5) persuade young people not to take up the habits by public education and law enforcement (some patients in our study were younger than 20 years of age), and 6) encourage the consumption of green vegetables and beta-carotene.

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References

1. BLOT WJ, MCLAUGHLIN JK, WINN DM, *et al.* Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988; **48**: 3287–7.
2. MERLETTI F, BOFFETTA P, CICCONE G,

MASHERG A, TERRACINI B. Role of tobacco and alcoholic beverages in the etiology of cancer of the oral cavity/oropharynx in Torino, Italy. *Cancer Res* 1989; **49**: 4919–24.

3. CHOI SY, KAHYO H. Effect of cigarette smoking and alcohol consumption in the aetiology of cancer of the oral cavity, pharynx and larynx. *Int J Epidemiol* 1991; **20**: 878–85.
4. OREGGIA F, DE STEFANI E, CORREA P, FIERRO L. Risk factors for cancer of the tongue in Uruguay. *Cancer* 1991; **67**: 180–3.
5. IARC. Betel-quid and areca-nut chewing. International Agency for Research on Cancer, Lyon, Monographs 1986; **37**: 141–291.
6. KO YC, CHIANG TA, CHANG SJ, HSIEF SF. Prevalence of betel quid chewing habit in Taiwan and related socio-demographic factors. *J Oral Pathol Med* 1992; **21**: 261–4.
7. HUNG CR, CHENG JT. Betel quid chewing damaged gastric mucosa: protective effects of cimetidine and sodium bicarbonate. Symposium on betel quid chewing and its health effect, December, 1993, p.19–20, Kaohsiung Medical College.
8. BRESLOW NE, DAY NE. Statistical methods in cancer research. Volume I – the analysis of case-control studies. *IARC Sci Publ* 1980; 32: 248–79.
9. ROTHMAN KJ. Matching. In: ROTHMAN KJ, ed. *Modern epidemiology*. Boston: Little, Brown, 1986; 237–83.
10. STATA STATISTICS SOFTWARE. STATA Corporation. Release 3.1, 1993.
11. VAINIO H, WILBOURN J. Identification of carcinogens within the IARC monograph program. *Scand J Work Environ Health* 1992; **18** Suppl 1: 64–73.
12. KWAN HW. A statistical study on oral carcinomas in Taiwan with emphasis on the relationship with betel nut chewing: a preliminary report. *J Formosan Med Assoc* 1976; **75**: 497–505.
13. AMONKAR AJ, NAGABHUSHAN M, D'SOUZA AV, BHIDE SV. Hydroxychavicol: a new phenolic antimutagen from betel leaf. *Food Chem Toxicol* 1986; **24**: 1321–4.
14. PADMA PR, AMONKAR AJ, BHIDE SV. Antimutagenic effects of betel leaf extract against the mutagenicity of two tobacco-specific N-nitrosamines. *Mutagenesis* 1989; **4**: 154–6.
15. PADMA PR, LALITHA VS, AMONKAR AJ, BHIDE SV. Anticarcinogenic effect of betel leaf extract against tobacco carcinogens. *Cancer Lett* 1989; **45**: 195–202.
16. SANKARANARAYANAN R, DUFFY SW, DAY NE, NAIR MK, PADMAKUMARY G. A case-control investigation of cancer of the oral tongue and the floor of the mouth in southern India. *Int J Cancer* 1989; 43: 617–21.
17. SANKARANARAYANAN R, DUFFY SW, PADMAKUMARY G, DAY NE, NAIR MK. Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India. *J Epidemiol Commun Health* 1990; **44**: 286.
18. MADEN C, BECKMANN AM, THOMAS DB, *et al.* Human papillomaviruses, herpes simplex viruses, and the risk of oral cancer in men. *Am J Epidemiol* 1992; **135**: 1093–102.