



Original Contribution

Areca Nut Chewing and Mortality in an Elderly Cohort Study

Tzuo-Yun Lan¹, Wen-Chiung Chang¹, Yih-Jian Tsai², Yi-Li Chuang³, Hui-Sheng Lin⁴, and Tong-Yuan Tai¹

¹ Division of Gerontology Research, National Health Research Institutes, Taipei, Taiwan.

² Division of Child and Adolescent Health, Bureau of Health Promotion, Department of Health, Taichung, Taiwan.

³ Center for Population and Health Survey Research, Bureau of Health Promotion, Department of Health, Taichung, Taiwan.

⁴ Department of Public Health, Chung Shan Medical University, Taichung, Taiwan.

Received for publication May 3, 2006; accepted for publication August 26, 2006.

Compared with the well-documented association with betel-related cancer, little is known about the long-term effect of areca nut chewing on other fatal diseases. The authors' analyses were based on a population-based cohort study in Taiwan, including 4,049 participants aged 60 years or older enrolled in 1989 and 2,462 participants aged 50–66 years enrolled in 1996. Information regarding betel quid chewing and covariates was collected at baseline and was updated at subsequent interviews. Proportional hazards analysis was performed to determine the effect of chewing on all-cause and cause-specific deaths. During a mean follow-up of 9.5 years, 2,309 deaths occurred. Ever chewers were at higher risk of only total (hazard ratio = 1.19, 95% confidence interval: 1.05, 1.35) and cerebrovascular (hazard ratio = 1.66, 95% confidence interval: 1.19, 2.30) deaths. Furthermore, increased chewing-years or quid-years appeared to be associated with increased mortality risk (linear trend: $p = 0.02$ for total mortality and $p = 0.001$ for cerebrovascular mortality). The authors found that, although betel quid chewing resulted in a statistically significant increase in the risk of total and cerebrovascular deaths in the elderly population, the associations were weak and should be interpreted with caution. Further studies are needed to confirm these findings and to better understand the possible mechanisms of death.

aged; areca; cohort studies; mortality

Areca nut chewing is an indigenous habit common in habitats of the tropical palm trees bearing the nut, notably in Central, South, and Southeast Asia, and some South Pacific islands (1). It is estimated that the habit is practiced by 200–600 million persons around the globe, accounting for 10–20 percent of the world's population (1, 2). With the growing number of immigrants from those areas, consumption of areca nut is increasing in western Europe and North America (2), where areca nut chewing, compared with tobacco use and alcohol intake, remains an underrecognized public health issue.

Across countries, areca nut is prepared in different ways from different forms of areca nut to betel quid—a mixture of areca nut and flavoring ingredients with or without processed tobacco leaves. For example, in India, Pakistan, Ban-

gladesh, and Sri Lanka, the fresh, dried, or cured areca nut is commonly chewed with slaked lime, some flavorings, and cut tobacco leaves or powder wrapped in betel leaf (1, 3). However, in Taiwan, the unripe areca nut is often chewed with slaked lime, sometimes together with betel inflorescence or betel leaf, but tobacco is not added (3, 4). Although areca nut or betel quid is used as a psychoactive substance (5), its carcinogenic effect has been observed in both animal and epidemiologic studies (6). In 2004, the International Agency for Research on Cancer confirmed areca nut and betel quid as human carcinogens with sufficient evidence of increased risk of precancerous oral fibrosis and cancer of the oral cavity, pharynx, and esophagus (3).

Except for cancer of the upper digestive tract, population-based studies examining the long-term association of areca

Correspondence to Dr. Tzuo-Yun Lan, Division of Gerontology Research, National Health Research Institutes, Room 4110, 4F, No. 161, Ming-Chuan East Road, Sec. 6, Taipei 114, Taiwan (e-mail: tylan@nhri.org.tw).

nut chewing with other types of cancer or other diseases have been relatively rare. Only a few cross-sectional surveys have attempted to examine the association between areca nut and psychological symptoms (5) or diabetes (7). A major reason is lack of cohort studies to facilitate longitudinal assessment of their causal relation and to eliminate the confounding effect of tobacco potentially existing in the study because areca nut is often chewed with tobacco (8, 9). It therefore remains unclear whether areca nut chewing has effects similar to those for cigarette smoking on the development of different diseases such as cardiovascular diseases (10). As mentioned, in Taiwan, betel quid is chewed without tobacco, which provides an opportunity to better understand the independent effect of betel quid on diseases (8, 9). Using nationwide health data, we previously identified the link between betel quid chewing and obesity (11), a predisposing factor for cardiovascular, metabolic, and other chronic diseases. In the present cohort study, we extended our analyses to prospectively examine the relations of betel quid chewing with total and cause-specific mortality.

MATERIALS AND METHODS

Study cohort

The Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan, a prospective cohort study jointly funded by the US National Institute on Aging and the Taiwan government, was conducted by the Taiwan Provincial Institute of Family Planning (now incorporated into the Bureau of Health Promotion, Department of Health, Taiwan) and the Population Studies Center at the University of Michigan. The study began in 1989 with a sample of 4,049 persons aged 60 years or older. The sample was re-interviewed in 1993. In addition to elderly persons, the near-elderly population has grown into a crucial constituent of the rapidly aging society. Taking this factor into consideration, with its 1996 interview, the study was extended to include a sample of 2,462 persons aged 50–66 years. The interview was conducted again in 1999 so that all 6,511 study participants were interviewed at 3- to 4-year intervals. Both samples were drawn, through a three-stage probability sampling method (12, 13), from the entire elderly or near-elderly population of Taiwan. Data used in this analysis comprise four waves (1989, 1993, 1996, and 1999) of in-person interviews for the 1989 elderly cohort and two waves (1996 and 1999) for the 1996 near-elderly cohort.

Betel quid chewing and covariates

In the initial interview, study participants were asked to report whether they chewed betel quid. Betel quid users were asked to provide information on starting age and average amount consumed daily. Former users were also asked their age at quitting. Those having tried chewing only one or two times in their lifetime were regarded as never chewers. A half quid per day was used to represent the amount of quid consumed per day for those who chewed less than one quid per day on average. Chewing status was updated in subsequent interviews throughout the study period so we could

calculate cumulative time and amount of chewing. Similar to pack-years or cigarette-years of smoking commonly used in smoking-related studies to evaluate long-term cumulative exposure, quid-years of chewing were calculated by multiplying the number of betel quids per day by the number of years of chewing reported at the last interview.

Other information collected at baseline through a pre-designed, pretested questionnaire included age, sex, living area as an indicator of geographic variations in social and health status, functional status, and selected history of chronic conditions reported by the physicians. Similar items in follow-up questionnaires were used to update information. Because questions regarding difficulties in daily functioning activities were not consistent across interviews, difficulty in bathing was used as the indicator of functional status. In addition, information regarding cigarette smoking and alcohol intake was also considered because use of these substances may confound the relation between betel quid chewing and diseases or mortality (4, 14).

To better control these confounders in the survival analyses, we used, in addition to smoking and drinking status, cumulative pack-years of smoking and average weekly ethanol consumption to quantify the use of cigarettes and alcohol. Cumulative pack-years of smoking were calculated as average daily use of cigarettes across interviews multiplied by cumulative smoking-years divided by 20. Level of cigarette smoking was further grouped into five categories: never, low (<12 pack-years), middle (12–36 pack-years), high (>36 pack-years), and ever smokers without detailed smoking information.

Average weekly ethanol consumption was defined as the average amount of ethanol consumed weekly across interviews. Because ethanol content is determined by both beverage type (4.5 percent in beer, 12 percent in wine, 40 percent in liquor, and 8 percent in Chinese medicinal wine) and unit per drink (600 ml in a large bottle, 300 ml in a small bottle, 350 ml in a can, 120 ml in a large glass, and 20 ml in a small glass), weekly ethanol amount for a consumed beverage was calculated as follows: ethanol content for the beverage \times total amount for each type consumed \times frequency per week. The weekly ethanol amounts for different consumed beverages were then added to produce weekly ethanol consumption. Similarly, level of ethanol consumption was categorized as never, low (<10 ml of ethanol), middle (10–85 ml of ethanol), high (>85 ml of ethanol), and ever drinkers without detailed drinking information.

Outcome measures

Deaths that occurred between the initial interviews in 1989 for the elderly cohort and 1996 for the near-elderly cohort and December 31, 2003, were reported by families of study participants at subsequent interviews and were confirmed by the national death registry at the Department of Health, Taiwan, from which detailed information about the death, including the dates and major causes, was also obtained. Causes of death were classified by using the coding system of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (15). In the analysis, all causes of death were grouped into cancer, diabetes,

TABLE 1. Characteristics of the study cohort at baseline* according to betel quid chewing status, Taiwan, 1989 and 1996

Characteristic	Betel quid chewing status								<i>p</i> value†
	Never chewer (<i>n</i> = 5,602)		Ever chewer (<i>n</i> = 901)						
			Former chewer (<i>n</i> = 373)		Current chewer (<i>n</i> = 528)		Total		
No.	%	No.	%	No.	%	No.	%		
Sex: male	2,839	50.7	331	88.7	407	77.1	738	81.9	<0.001
Age in years (mean (standard deviation))	64.6 (7.7)		63.0 (8.1)		61.6 (7.0)		62.2 (7.5)		<0.001
Living area									<0.001
North	1,702	30.4	63	16.9	57	10.8	120	13.3	
Central	1,814	32.4	145	38.9	178	33.7	323	35.8	
South and east	2,086	37.2	165	44.2	293	55.5	458	50.8	
Medical history									
Hypertension	1,398	25.1	82	22.0	104	19.7	186	20.7	0.004
Anemia	469	8.4	22	5.9	33	6.3	55	6.1	0.02
Heart disease	998	17.9	38	10.2	60	11.4	98	10.9	<0.001
Liver disease	310	5.5	28	7.5	40	7.6	68	7.6	0.02
Arthritis	1,402	25.1	59	15.8	112	21.3	171	19.0	<0.001
Smoking status									
Current or former smoker	2,192	39.2	328	87.9	423	80.3	751	83.4	<0.001
Alcohol intake									
Current or former drinker	1,798	32.2	264	70.8	330	62.6	594	66.0	<0.001
Physical function									
Has difficulty	264	4.7	17	4.6	12	2.3	29	3.2	0.04

* For the pooled cohort at baseline, we included data for 4,049 subjects aged 60 years or older collected in 1989 and for 2,462 subjects aged 50–66 years collected in 1996.

† *p* values represent differences between the never and the ever betel quid chewers.

cardiovascular conditions, liver cirrhosis, respiratory conditions, and other causes. Some of these groups were further classified into subgroups. Cancer was divided into oral cavity and esophagus, stomach, liver, lung, and others. Cardiovascular conditions were divided into coronary heart disease, cerebrovascular disease, and others. Respiratory conditions were categorized as pneumonia and chronic obstructive pulmonary disease. These groups or subgroups were the main causes of death commonly seen in Taiwan in recent years (16).

Statistical analysis

In the descriptive analysis of baseline information and chewing status, frequency distributions for categorical variables or means plus standard deviations for continuous variables were used. A chi-square test or independent *t* test, as appropriate, was used to compare never chewers with ever chewers. Survival data were modeled with Cox proportional hazards regressions to estimate hazard ratios associated with groups of deaths from different causes among groups of chewers. The assumption of proportional hazards, the constant hazard ratio or proportionality of hazards from one case to another over time, was tested graphically. The log survival probabilities plot stratified by chewing status showed two separate lines, indicating no violation of the

assumption. Results were consistent across the two cohorts in the models; the data were therefore combined.

In addition to age- and sex-adjusted models, multivariate models were also adopted to assess confounding in the association between betel quid and mortality with the adjustment of covariates that had previously been tested with significant differences between never- and ever-chewer groups in the descriptive analysis. Curves for overall survival were estimated by the Kaplan-Meier method (17). Cumulative years and quid-years of chewing, stratified into groups, were further used to examine the dose-response relation. Because 247 ever chewers were either uncertain about or failed to provide the exact number of quids per day, a category listed as “missing” was added in the analysis of quid-years of chewing. A test for trend was also conducted by treating cumulative chewing-years and quid-years of chewing as a continuous variable. *p* values for all tests were two tailed, and statistical differences were considered at the <0.05 level. All analyses were performed by using SPSS version 12 software (SPSS Inc., Chicago, Illinois).

RESULTS

For the 6,511 study participants enrolled, information on betel quid chewing was provided for 6,503 at baseline. At baseline (table 1), about 13.9 percent reported having a betel

TABLE 2. Numbers of deaths and hazard ratios* by cause of death and betel quid chewing status,† Taiwan, 1989 and 1996

Cause of death (ICD-9‡ code(s))	Betel quid chewing status								
	Never chewer (n = 5,586)			Ever chewer (n = 917)					
	No. of deaths	HR‡	No. of deaths	HR§	95% CI‡	p value	HR¶	95% CI	p value
Cancer (140–208)	418	1.00	71	1.10	0.85, 1.43	0.45	1.03	0.78, 1.34	0.86
Oral cavity and esophagus (140–150)	27	1.00	10	1.95	0.93, 4.11	0.08	1.60	0.73, 3.54	0.24
Stomach (151)	51	1.00	6	0.79	0.34, 1.86	0.59	0.78	0.32, 1.90	0.59
Liver (155)	79	1.00	10	0.69	0.35, 1.35	0.28	0.61	0.30, 1.27	0.19
Lung (162)	85	1.00	19	1.38	0.83, 2.29	0.21	1.15	0.68, 1.95	0.60
Other	176	1.00	26	1.09	0.72, 1.66	0.68	1.10	0.71, 1.72	0.673
Diabetes (250)	161	1.00	23	1.18	0.75, 1.84	0.47	1.14	0.71, 1.84	0.579
Cardiovascular conditions (390–459)	582	1.00	102	1.36	1.10, 1.69	0.004	1.41	1.12, 1.77	0.003
Coronary heart disease (410–414)	134	1.00	19	1.10	0.67, 1.78	0.71	1.22	0.73, 2.04	0.45
Cerebrovascular disease (430–439)	254	1.00	51	1.52	1.12, 2.06	0.008	1.66	1.19, 2.30	0.003
Other	194	1.00	32	1.35	0.92, 1.97	0.13	1.18	0.79, 1.78	0.41
Liver cirrhosis (571)	40	1.00	10	1.62	0.79, 3.31	0.19	1.69	0.78, 3.63	0.18
Respiratory conditions (460–519)	227	1.00	39	1.23	0.88, 1.74	0.23	1.22	0.85, 1.75	0.28
Pneumonia (480–486, 507)	100	1.00	17	1.29	0.77, 2.17	0.34	1.42	0.82, 2.47	0.22
Chronic obstructive pulmonary disease (490–496)	99	1.00	18	1.23	0.74, 2.04	0.43	1.11	0.65, 1.88	0.71
All other causes	554	1.00	82	1.18	0.93, 1.49	0.17	1.08	0.84, 1.38	0.54
Total	1,982	1.00	327	1.24	1.10, 1.39	<0.001	1.19	1.05, 1.35	0.007

* Hazard ratios are from a Cox proportional hazards model.

† Chewing status was measured throughout the last interview.

‡ ICD-9, *International Classification of Diseases*, Ninth Revision; HR, hazard ratio; CI, confidence interval.

§ Adjusted for age and sex.

¶ Adjusted for sex, age at baseline, living area, and the following factors updated until the last interview: presence or absence of hypertension, anemia, heart disease, liver disease, arthritis, and physical difficulty; and levels of cigarette smoking and alcohol intake.

quid chewing habit currently or in the past. Compared with never chewers, ever chewers were more likely to be men, be younger, live in southern and eastern areas, and have liver disease but were less likely to have hypertension, anemia, heart disease, arthritis, and physical difficulty. Chewers also tended to be cigarette smokers and alcohol users. A total of 2,309 deaths occurred during follow-up, including 489 from cancer, 184 from diabetes, 684 from cardiovascular conditions, 50 from liver cirrhosis, 266 from respiratory conditions, and 636 from other causes. The average follow-up period was 9.5 years (standard deviation, 4.2), with 10.9 years (standard deviation, 4.7) for the 1989 cohort and 7.2 years (standard deviation, 1.3) for the 1996 cohort.

Only a borderline significant association was detected between chewing status and cancer of the oral cavity and esophagus, with adjustment for age and sex. However, this weak association disappeared after adding other covariates, including living area, hypertension, anemia, heart disease, liver disease, arthritis, physical difficulty, cigarette smoking, and alcohol intake. Ever chewers were at a significantly higher risk than never chewers of dying from cardiovascular conditions, cerebrovascular disease, and all causes, both when age and sex and when age and sex together with other confounding factors were considered in the models

(table 2). The significant risk of cardiovascular conditions was fully attributable to cerebrovascular disease because the risk of other subgroups of cardiovascular conditions was not significant.

Figure 1 shows the Kaplan-Meier estimates of time of death or the end of follow-up for the two cohorts. The probabilities of survival for the 1989, 1996, and combined cohorts were significantly lower for ever chewers than for never chewers. The *p* values for the log-rank test were 0.003, 0.033, and less than 0.001, respectively. Similar results were also observed for death from cerebrovascular disease; *p* values were 0.003, 0.049, and 0.005, respectively.

The hazard ratios of total death and death from cerebrovascular disease according to level of betel quid consumption in years are shown in table 3. After adjustment for confounders, betel quid chewing-years was associated with both total (*p* = 0.02 for trend) and cerebrovascular (*p* = 0.001 for trend) mortality. A significant increase in the risk was observed for chewers who had chewed for 25–39 years and for 40 years or longer when never chewers (chewing year = 0) were considered the reference group. Similarly, quid-years of chewing was related to death from all causes (*p* = 0.02 for trend) and cerebrovascular disease (*p* = 0.001 for trend) after the same adjustment. There was

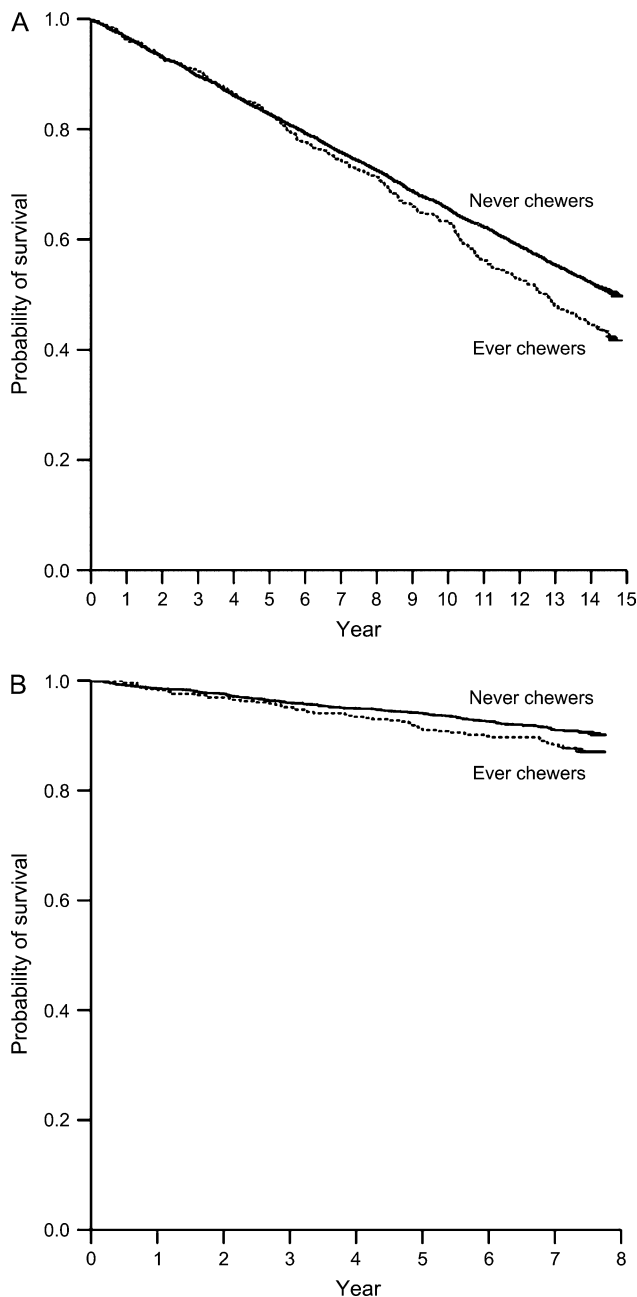


FIGURE 1. Kaplan-Meier estimates of survival for the 1989 cohort (A) and 1996 cohort (B) of study subjects according to betel quid chewing status, Taiwan.

a significantly increased risk for chewers with 350 quid-years or more of chewing (table 4).

DISCUSSION

In this population-based cohort study in Taiwan, we found betel quid chewing to be associated with mortality from all causes and cerebrovascular disease, but not with

mortality from cancer and other causes among near-elderly and elderly persons. Our results also showed dose-response relations in which the increased risks were mainly for chewers who chewed for 25 years or for 350 quid-years or longer compared with those who never chewed. Overall, our findings may provide new evidence linking elevated mortality risk with long-term betel quid chewing.

Betel-related cancer, mainly including that of the oral cavity, pharynx, and esophagus, usually occurs in persons aged 45–65 years. The 5-year survival rate varies from 6 percent to 10 percent for esophagus cancer to 40–50 percent for oral cancer (18). In Taiwan, results from several studies have indicated that betel quid chewers who had these cancers were significantly younger than nonchewers (9). For example, the mean age of oral cancer patients with a betel quid chewing habit was 50 years, more than 10 years younger than patients without the habit (19). Betel quid chewers also reported a poorer prognosis, yielding a significantly lower survival rate than for nonchewers (19). Moreover, the effect of chewing on oral-related cancer was significantly strong in persons aged 50 years or younger, suggesting a relatively lower risk for those who were older (20). These characteristics of early age at onset, low survival rate, and different age susceptibility for betel quid chewers probably explain why mortality from cancer, especially betel-related cancer, was not associated with betel quid chewing in our study, because we observed only near-elderly and elderly persons.

Betel quid chewers who might have escaped the risk of betel-related cancer and reached older age, however, were not free from other diseases. In our study, they were at a relatively higher risk of death in later life from either all causes or cerebrovascular diseases. Of course, it is curious and crucial to understand why long-term chewing of betel quid is linked with cerebrovascular diseases, including stroke. Betel quid consumed without tobacco consists, in addition to areca nut, of a complex range of accompaniments covering slaked lime, betel leaf, spices, sweeteners, inflorescence, and/or catechu. Chewing these materials results in exposure to areca nut alkaloids (mainly arecoline and arecaine), polyphenols, tannin, trace elements (e.g., copper), areca-nut-derived nitrosamines that have been found in chewers' saliva, and other chemicals.

Most of these chemicals' relations with diseases have yet to be identified. Some studies have attempted to unravel the exact mechanisms involved in oral cancer (6) or obesity (21). As noted previously, the association of areca nut chewing with obesity and diabetes has been observed cross-sectionally. It is possible that the contribution of areca nut chewing to cardiovascular, mainly cerebrovascular, death lies in the fact that some of the chemicals from alkaloids may trigger increased appetite and glucose intolerance (7, 11), which in turn lead to obesity, diabetes, and subsequent death from cardiovascular conditions. The detailed mechanism by which the chemicals singly or jointly induce the specific disease remains unclear and merits further investigation.

On the other hand, the possible cause may have no direct link to these chemicals of betel quid. In recent years, increasing attention has been paid to investigating periodontal disease and its association with cardiovascular conditions,

TABLE 3. Hazard ratios of total and cerebrovascular mortality by cumulative years of betel quid chewing,* Taiwan, 1989 and 1996

No. of years of chewing	Total mortality				Cerebrovascular mortality			
	No. of deaths	HR†,‡	95% CI†	p value	No. of deaths	HR‡	95% CI	p value
Never chewer (n = 5,586)	1,982	1.00		0.02§	254	1.00		0.001§
1–9 (n = 207)	69	1.18	0.93, 1.51	0.18	9	1.27	0.65, 2.51	0.48
10–24 (n = 204)	58	1.01	0.77, 1.32	0.95	6	0.95	0.42, 2.16	0.90
25–39 (n = 259)	80	1.28	1.02, 1.62	0.04	14	2.05	1.17, 3.59	0.01
≥40 (n = 247)	120	1.25	1.03, 1.51	0.02	22	2.10	1.33, 3.32	0.002

* Chewing-years for chewers were categorized based on a quartile distribution.

† HR, hazard ratio; CI, confidence interval.

‡ Adjusted for sex, age at baseline, living area, and the following factors updated until the last interview: presence or absence of hypertension, anemia, heart disease, liver disease, arthritis, and physical difficulty; and levels of cigarette smoking and alcohol intake.

§ p values are for linear trend across all categories of years of betel quid chewing.

especially cerebrovascular events (22, 23). For example, the results of a meta-analysis of nine cohort studies indicate that the relative risks of future cardiovascular events and stroke for persons with periodontal disease were 1.44 and 2.85, respectively (24). Periodontal disease has also been linked with betel quid chewing. In Taiwan, a significantly higher prevalence of periodontal problems was observed in betel quid chewers than in nonchewers (25), suggesting that betel quid chewers may be at a higher risk of chronic microbial infection (e.g., subgingival infection) that can lead to subsequent cerebrovascular events (26).

Our study finds its major strengths in its ability to control tobacco use and other potential confounders, to perform a substantial and complete mortality follow-up for as long as 14 years, and to make available the responses to a repeated questionnaire that helped to assess the continuous conditions of betel quid chewing and other covariates.

Some methodologic issues should be considered when interpreting the results. First, although the number of study participants was large, the low prevalence of betel quid

chewing in the older population, partly due to the survival effect, may have resulted in an underestimate of the association with mortality. Second, some values for betel quid amount in the analysis of quid-years and mortality were missing, which inevitably reduced the power to evaluate the association. Third, measurement errors in self-reported questions of betel quid chewing as well as other health information, such as chronic conditions included in the study, might have biased the association between betel quid chewing and mortality. Similarly, our results could have been influenced by inaccuracies in identifying the primary cause of death. However, previous reviews found that death certificates and codes in the national death registry files were in overall agreement (27).

Fourth, certain health-related factors that could also affect chewing habits and other objective measures of physiological conditions, such as blood pressure and biochemical indicators, were not included in the study, which may also have biased the estimation of mortality hazard. Finally, our study was originally designed to understand factors

TABLE 4. Hazard ratios of total and cerebrovascular mortality by quid-years of betel quid chewing,* Taiwan, 1989 and 1996

No. of quid-years of chewing	Total mortality				Cerebrovascular mortality			
	No. of deaths	HR†,‡	95% CI†	p value	No. of deaths	HR‡	95% CI	p value
Never chewer (n = 5,586)	1,982	1.00		0.02§	254	1.00		0.001§
<50 (n = 222)	62	1.11	0.85, 1.43	0.45	7	1.09	0.51, 2.35	0.83
50–349 (n = 224)	68	1.18	0.92, 1.52	0.19	7	1.17	0.54, 2.52	0.69
≥350 (n = 224)	82	1.31	1.04, 1.64	0.02	16	2.43	1.42, 4.16	0.001
Ever chewer with no quid information (n = 247)	115	1.17	0.97, 1.42	0.11	21	1.79	1.13, 2.84	0.01

* Chewing-years for chewers were categorized based on a tertile distribution.

† HR, hazard ratio; CI, confidence interval.

‡ Adjusted for sex, age at baseline, living area, and the following factors updated until the last interview: presence or absence of hypertension, anemia, heart disease, liver disease, arthritis, and physical difficulty; and levels of cigarette smoking and alcohol intake.

§ p values are for linear trend across all categories of quid-years of betel quid chewing except the category of "Ever chewer with no quid information."

associated with general health and living arrangements, not to determine mortality risks. Our data therefore could not fully control for all potential factors affecting mortality, including diet. As a result, we cannot rule out the possibility of residual confounding by factors that were not evaluated or were not adequately measured or controlled.

In conclusion, these prospective data represent the first report, to our knowledge, from a population-based study of the impact of exposure to betel quid consumption on mortality from different causes. Betel quid chewing is associated with total and cerebrovascular mortality among middle-to-old-aged ever chewers. These data also suggest that the effects of betel quid chewing on mortality from all causes and cerebrovascular disease may be cumulative. Nonetheless, we need to be cautious when interpreting these results because the significant, but weak associations still leave room for some skepticism, including possible bias from random error or misclassification. Obviously, more investigations, preferably with a larger sample size and longer follow-up time, are needed to further clarify our findings.

ACKNOWLEDGMENTS

The Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan was supported by funding from the US National Institute on Aging; the Department of Health, Taiwan; and the National Health Research Institutes, Taiwan.

The authors are indebted to Yu-Hsuan Lin, Dr. Tony Liang, and Bob Hsu for their comments on an earlier draft of this paper.

This study was based on data from the Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan provided by the Population and Health Research Center, Bureau of Health Promotion. The interpretation and conclusions contained herein do not represent those of authors' affiliations.

Conflict of interest: none declared.

REFERENCES

- Gupta PC, Warnakulasuriya S. Global epidemiology of areca nut usage. *Addict Biol* 2002;7:77–83.
- Trivedy C, Warnakulasuriya S, Peters TJ. Areca nuts can have deleterious effects. (Letter). *BMJ* 1999;318:1287.
- Betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 85. Lyon, France: International Agency for Research on Cancer, 2004.
- Wen CP, Tsai SP, Cheng TY, et al. Uncovering the relation between betel quid chewing and cigarette smoking in Taiwan. *Tob Control* 2005;14(suppl 1):i16–22.
- Winstock AR, Trivedy CR, Warnakulasuriya S, et al. A dependency syndrome related to areca nut use: some medical and psychological aspects among areca nut users in the Gujarat community in the UK. *Addict Biol* 2000;5:173–9.
- Jeng JH, Chang MC, Hahn LJ. Role of areca nut in betel quid-associated chemical carcinogenesis: current awareness and future perspectives. *Oral Oncol* 2001;37:477–92.
- Tung TH, Chiu YH, Chen LS, et al. A population-based study of the association between areca nut chewing and type 2 diabetes mellitus in men (Keelung Community-based Integrated Screening programme No. 2). *Diabetologia* 2004;47:1776–81.
- Warnakulasuriya S, Trivedy C, Peters TJ. Areca nut use: an independent risk factor for oral cancer. (Editorial). *BMJ* 2002;324:799–800.
- Wu MT, Lee YC, Chen CJ, et al. Risk of betel chewing for oesophageal cancer in Taiwan. *Br J Cancer* 2001;85:658–60.
- Howard G, Wagenknecht LE, Burke GL, et al. Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA* 1998;279:119–24.
- Chang WC, Hsiao CF, Chang HY, et al. Betel nut chewing and other risk factors associated with obesity among Taiwanese male adults. *Int J Obes (Lond)* 2006;30:359–63.
- Population Studies Center. 1989 survey of health and living status of the elderly in Taiwan: questionnaire and survey design. Ann Arbor, MI: Population Studies Center, University of Michigan, 1989. (Comparative study of the elderly in Asia report no. 89-1).
- Zimmer Z, Martin LG, Chang MC. Changes in functional limitation and survival among older Taiwanese, 1993, 1996, and 1999. *Popul Stud (Camb)* 2002;56:265–76.
- Ko YC, Chiang TA, Chang SJ, et al. Prevalence of betel quid chewing habit in Taiwan and related sociodemographic factors. *J Oral Pathol Med* 1992;21:261–4.
- Department of Health and Human Services. The international classification of diseases. Ninth Revision. Clinical modification: ICD-9-CM. Vol 1. Diseases: tabular list. Washington, DC: Government Printing Office, 1980. (DHHS publication no. (PHS) 80-1269).
- Department of Health. Summary of statistics on causes of death in Taiwan. Taipei, Taiwan: Department of Health, Taiwan, 1994.
- Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York, NY: John Wiley, 1980.
- National Cancer Institute. SEER cancer statistics review, 1973–1996. Bethesda, MD: National Cancer Institute, 1999.
- Lee JJ, Jeng JH, Wang HM, et al. Univariate and multivariate analysis of prognostic significance of betel quid chewing in squamous cell carcinoma of buccal mucosa in Taiwan. *J Surg Oncol* 2005;91:41–7.
- Sankaranarayanan R, Duffy SW, Padmakumary G, et al. Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India. *J Epidemiol Community Health* 1990;44:286–92.
- Johnston GA, Krogsgaard-Larsen P, Stephanson A. Betel nut constituents as inhibitors of gamma-aminobutyric acid uptake. *Nature* 1975;258:627–8.
- Joshiyura KJ, Hung HC, Rimm EB, et al. Periodontal disease, tooth loss, and incidence of ischemic stroke. *Stroke* 2003;34:47–52.
- Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet* 2005;366:1809–20.
- Janket SJ, Baird AE, Chuang SK, et al. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;95:559–69.
- Ling LJ, Hung SL, Tseng SC, et al. Association between betel quid chewing, periodontal status and periodontal pathogens. *Oral Microbiol Immunol* 2001;16:364–9.
- Pussinen PJ, Alfthan G, Rissanen H, et al. Antibodies to periodontal pathogens and stroke risk. *Stroke* 2004;35:2020–3.
- Lu TH, Lee MC, Chou MC. Accuracy of cause-of-death coding in Taiwan: types of miscoding and effects on mortality statistics. *Int J Epidemiol* 2000;29:336–43.