Original Article

Betel Nut Chewing Is Associated with Hypertension in Taiwanese Type 2 Diabetic Patients

Chin-Hsiao TSENG[1)-5)]

Betel nut chewing is associated with oral cancers and diabetes. This study investigated whether betel nut chewing could be associated with hypertension in Taiwanese patients with type 2 diabetes mellitus (T2DM). The data of a total of 81,226 (37,226 men and 44,000 women) patients with T2DM obtained from a cross-sectional telephone survey in a national sample of diabetic patients in Taiwan were analyzed. Hypertension was defined by a positive history or reported systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Analyses were performed in separate sexes with consideration paid to the potential confounding effects of age, diabetic duration, body mass index and smoking. The prevalences of betel nut chewing in men and women were 20.4% and 1.1%, respectively. Betel nut chewing was more common in the younger age groups of the male sex. The multivariate-adjusted odds ratios for hypertension in chewers *vs.* non-chewers were 1.067 (1.007–1.131) and 1.897 (1.534–2.346) for men and women, respectively. In multiple linear regression, although no adjustment was made for the use of antihypertensive agents, betel nut chewing was significantly associated with blood pressure, with regression coefficients of 0.958±0.163 (SEM) for systolic and 0.441±0.108 for diastolic blood pressure in men; and the respective values for women were 1.805±0.618 and 1.198±0.393. In conclusion, betel nut chewing was significantly associated with hypertension in Taiwanese patients with T2DM and the association was stronger in women. (*Hypertens Res* 2008; 31: 417–423)

***Key Words*: betel nut chewing, smoking, hypertension, type 2 diabetes mellitus, Taiwan**

Introduction

The areca nut is the seed of the palm tree *Areca catechu*, and is the fourth most commonly used psychoactive substance, after caffeine, nicotine and alcohol (*1*). Because areca nuts are always consumed with the leaves of the *Piper betle*, the chewing of areca nuts has always been referred to as "betel nut chewing" in the English literature (*2*). There are an estimated 600 million people who chew betel nuts worldwide (*3*). It is a common habit and is a means of social interaction in Asia, particularly the South Pacific islands, Southeast Asia, Papua New Guinea, Bangladesh, Pakistan and India (*1–4*). Chewing of betel nuts was forbidden in Taiwan during the Japanese reign more than 60 years ago (*4*), but the habit has become popular in Taiwan over the past several decades, and in 1997 it was estimated that about 2.4 million, or 11.4%, of the total population engaged in betel nut chewing (*5*). Moreover, the

From the [1)]Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan; [2)]Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [3)]Department of Medical Research and Development, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, Taiwan; [4)]School of Public Health, Taipei Medical University, Taipei, Taiwan; and [5)]Division of Environmental Health and Occupational Medicine of the National Health Research Institutes, Taipei, Taiwan.

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Address for Reprints: Chin-Hsiao Tseng, M.D., Ph.D., Department of Internal Medicine, National Taiwan University Hospital, No. 7 Chung-Shan South Road, Taipei, Taiwan. E-mail: ccktsh@ms6.hinet.net

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Table 1. Characteristics of Study Subjects by Betel Nut Chewing and by Sex

Characteristics	Total	Current or ex-chewers	Non-chewers	*p*
Men				
n (%)	37,226 (100.0)	7,585 (20.4)	29,641 (79.6)	
Age, years	61.3±11.9	57.3±11.0	62.4±11.9	<0.001
Diabetic duration, years	6.8±6.4	6.1±5.5	7.0±6.6	<0.001
Body mass index, kg/m^2	24.5±3.4	24.7±3.5	24.4±3.4	<0.001
Hypertension, %	53.0	50.9	53.6	<0.001
Smoking, %	62.4	92.7	54.8	<0.001
SBP, mmHg	133.2±12.0	133.5±11.2	133.2±12.2	0.057
DBP, mmHg	79.4±7.9	79.6±7.7	79.3±8.0	<0.01
Women				
n (%)	44,000 (100.0)	471 (1.1)	43,529 (98.9)	
Age, years	63.0±10.9	61.2±10.9	63.1±10.9	<0.001
Diabetic duration, years	7.3±6.4	6.6±5.7	7.3±6.4	0.017
Body mass index, kg/m^2	24.7±3.8	25.7±4.6	24.7±3.8	<0.001
Hypertension, %	54.9	69.6	54.7	<0.001
Smoking, %	3.2	42.0	2.8	<0.001
SBP, mmHg	132.6±13.3	134.9±14.6	132.6±13.3	<0.001
DBP, mmHg	79.0±8.4	80.7±7.9	79.0±8.4	<0.001

Data are mean±SD or %.

chewing population continues to increase in Taiwan, especially among younger males (*6*, *7*). In Taiwan, unripe areca nuts are commonly chewed with a mixture of lime and the leaves or flowers of the *Piper betle*, but without tobacco (*4*).

Betel nut chewing has been linked to a variety of health problems, including oral lesions of leukoplakia, submucosal fibrosis, squamous cell carcinoma and periodontal disease (*8*, *9*), albuminuria in diabetic patients (*10*), disruption of gastric mucosal barriers (*11*), aggravation of asthma (*12*), induction of extrapyramidal syndrome (*13*), milk-alkali syndrome (*14*), induction of uterine cervical dysplasia (*15*), cancers of the esophagus (*16*) and liver (*17*), and low birth weight of babies born to mothers chewing betel nut (*18*). In more recent population-based studies in Taiwan, betel nut chewing has also been associated with a higher risk of type 2 diabetes mellitus (T2DM) (*19*) and total and cerebrovascular deaths (*20*).

Studies on the cardiovascular effects of betel nut chewing are rare, and there has not been any population-based epidemiologic study evaluating this aspect of the habit. In an earlier study evaluating the cardiovascular response associated with betel nut chewing in a group of subjects in Taiwan, Chu found that betel nut chewing was associated with an elevated systolic blood pressure (SBP) in fresh chewers but not in habitual chewers (*21*). However, a more recent study by the same group did not confirm this effect (*7*), but rather showed a significant drop of diastolic blood pressure (DBP) and an insignificant increase of SBP in 30 healthy men (*7*). The small number of cases and the use of exclusively healthy subjects in the later study could have been responsible for the discrepancy in the observations. Although experimental studies will be needed to investigate the pathogenetic mechanisms, it may prove highly difficult to reach satisfactory conclusions on the associations between betel nut chewing and clinical diseases, due to the complex constituents of the nuts and leaves and the interactions among various active compounds that occur during chewing. Moreover, any immediate effects observed following betel nut chewing would not necessarily impact human health over the long-term. For this reason, epidemiologic studies are needed to evaluate the link between betel nut chewing and medical conditions. To the best of our knowledge, there has not been any previous epidemiologic study evaluating the effect of betel nut chewing on hypertension status. The purpose of this study was to evaluate whether betel nut chewing in patients with T2DM could be associated with the prevalence of hypertension by analyzing the data obtained in a national cohort of diabetic patients in Taiwan.

Methods

Study Subjects

The study was approved and supported by the ethics committee of the Department of Health of Taiwan and conducted following the local regulations. All subjects who submitted to the telephone interview were first informed of the purpose of the study and gave their consent to participate. Because more than 96% (after exemption of persons involved in military services and those subject to criminal sanction, *etc.*) of the total population of Taiwan has been covered by the compulsory and universal National Health Insurance (NHI) plan

Table 2. Distribution of Case Number by Betel Nut Chewing and by Age and Sex

Age, years	*n*	*n* (%)			*p**
		Current chewers	Ex-chewers	Non-chewers	
Men					
<40	1,474	327 (22.2)	88 (6.0)	1,059 (71.8)	<0.001
40–49	5,231	1,064 (20.3)	497 (9.5)	3,670 (70.2)	
50–59	8,447	1,366 (16.2)	869 (10.3)	6,212 (73.5)	
60–69	11,891	1,142 (9.6)	1,218 (10.2)	9,531 (80.2)	
≥70	10,183	395 (3.9)	619 (6.1)	9,169 (90.0)	
Total	37,226	4,294 (11.5)	3,291 (8.8)	29,641 (79.6)	
Women					
<40	1,077	14 (1.3)	1 (0.1)	1,062 (98.6)	<0.001
40–49	3,952	43 (1.1)	8 (0.2)	3,901 (98.7)	
50–59	10,177	101 (1.0)	31 (0.3)	10,045 (98.7)	
60–69	15,934	122 (0.8)	45 (0.3)	15,767 (99.0)	
≥70	12,860	61 (0.5)	45 (0.3)	12,754 (99.2)	
Total	44,000	341 (0.8)	130 (0.3)	43,529 (98.9)	

*χ^2 test.

since March 1995, almost all diabetic patients in Taiwan have been using the NHI (*22–25*). Therefore, the NHI database of insurance claims submitted by clinics and hospitals is appropriate to derive a national sample of diabetic patients. The assembly of such a national sample has been described in detail elsewhere (*22–25*). In brief, the total case number of diabetic patients identified by using the NHI database was 536,159, from which a total of 256,036 diabetic patients were identified from 66 hospitals and clinics located evenly throughout Taiwan. The clinical settings were selected under the consideration of homogeneous geographical distribution. To create a cohort of 90,000 patients (approximately one-sixth of the total number of diabetic patients in Taiwan during the period) for long-term follow-up, 128,572 cases from the 256,036 patients were randomly selected, anticipating a response rate of 70%.

Telephone Interview

The telephone surveys were conducted between March 1, 1995 and April 30, 2002 by well-trained interviewers using a structured questionnaire. The interviewers tried up to three times to reach subjects before giving up. In order to obtain all required information from the patients and keep missing data as minimal as possible, the interviewers handed in the completed questionnaires each week, and all returned questionnaires were checked by an assistant and then double-checked by the investigator.

The information obtained from the interview included the onset age of diabetes, onset symptoms and treatment modality for the distinction between type 1 diabetes mellitus (T1DM) and T2DM, body height, body weight, history of hypertension, self reported SBP and DBP, smoking and betel nut chewing.

The classification of T1DM was based on either one of the following two criteria: 1) diabetic ketoacidosis at the onset of diabetes mellitus; and 2) requirement of insulin injection within 1 year of diagnosis of diabetes mellitus. If a patient was not diagnosed with T1DM, he/she was viewed as having T2DM. Patients identified as having T1DM were not included in the present study. Hypertension was defined by self-reported history and also by reported SBP ≥140 mmHg and/or DBP ≥90 mmHg. Diabetic duration was calculated as the age at the time of interview minus the onset age of diabetes; and body mass index (BMI) was calculated from the body weight in kg divided by the squared body height in m.

Statistical Analyses

Data were analyzed separately for either sex. Age, diabetic duration, BMI and cigarette smoking were considered as potential confounders. Although tobacco is not added to the betel quid in Taiwan, a smoking habit is generally associated with the habit of betel nut chewing. Therefore, cigarette smoking was analyzed as one of the potential confounders.

The characteristics between the diabetic men and women were compared by Student's *t*-test and χ^2 test for continuous and categorical variables, respectively. The age- and sex-specific prevalences of betel nut chewing were calculated and tested by χ^2 test. Age- and sex-specific prevalences of hypertension by betel nut chewing and smoking were tested by χ^2 test. Logistic regression was used to estimate the multivariate-adjusted odds ratios and their 95% confidence intervals for hypertension with the following variables entered as independent variables in the models: age, diabetic duration, BMI, smoking and betel nut chewing. Multiple linear regression models for estimating SBP and DBP were generated using similar independent variables. Data were expressed as the

Table 3. Age- and Sex-Specific Prevalence of Hypertension by Betel Nut Chewing and Cigarette Smoking

Age, years	Total	Betel nut chewing		*p*	Cigarette smoking		*p*
		Current or ex-chewer	Non-chewer		Smokers	Non-smokers	
Men							
<40	24.5	27.1	23.4	>0.1	24.7	24.1	>0.1
40–49	37.6	42.1	35.7	<0.001	38.8	35.5	0.022
50–59	46.9	49.2	46.1	<0.05	48.4	44.5	0.001
60–69	58.0	58.5	57.9	>0.1	57.6	58.8	>0.1
≥70	64.2	60.3	64.6	<0.01	63.2	65.7	0.012
Total	53.0	50.9	53.6	<0.001	53.1	52.9	>0.1
Women							
<40	17.3	40.0	17.0	<0.05	20.9	17.2	>0.1
40–49	36.4	66.0	36.0	<0.001	41.6	36.2	>0.1
50–59	48.8	70.5	48.5	<0.001	53.9	48.6	0.058
60–69	58.1	73.2	57.9	<0.001	64.5	57.9	0.007
≥70	64.7	68.7	64.7	>0.1	63.6	64.7	>0.1
Total	54.9	69.6	54.7	<0.001	57.8	54.8	0.026

Data are shown in %.

means±SD or percentages, and values of $p<0.05$ were considered statistically significant.

Reliability of Questionnaire Information

In order to understand whether the information obtained from the questionnaire interview was reliable, a repeated interview by different interviewers was completed in 728 patients out of a random sample of 1,000 patients within 12 months (*22*). The continuous variables of onset age of diabetes, body height, body weight, SBP and DBP were analyzed by correlation coefficients; and the categorical variables of personal history of smoking, hypertension and betel nut chewing were analyzed by percent agreement.

Results

A total of 93,484 (response rate: 72.7%) participants completed the interview. The age and sex distributions of the responders did not differ significantly from those in the original cohort of 256,036 patients: age 61.2±11.9 *vs*. 61.2±15.2 years, and % men 46.2% *vs*. 46.4%, respectively. The questions on betel nut chewing were added some time after the start of the interview. Therefore, the earlier interviews did not include data on betel nut chewing. After excluding patients with T1DM ($n=3,528$) and those with an unknown history of betel nut chewing ($n=8,730$), there were a total of 81,226 (37,226 men and 44,000 women) patients with T2DM included in this study.

Table 1 shows the characteristics of the study subjects and the comparison of these characteristics between chewers and non-chewers. The habit of betel nut chewing was more common in the diabetic men (20.4%) than in the women (1.1%). The chewers were significantly younger and had a shorter diabetic duration than the non-chewers in both sexes. Cigarette smoking was significantly associated with the habit of betel nut chewing, and this association was more remarkable in the diabetic men. In men, the prevalence of hypertension was significantly lower in the chewers than in the non-chewers, probably because the chewers were younger and had a shorter diabetic duration than the non-chewers; but in women, the prevalence of hypertension remained significantly higher in chewers than in non-chewers. BMI was significantly higher in the chewing groups in both sexes. Although the differences were small, both SBP and DBP were higher in the chewing groups in both sexes.

Table 2 shows the prevalences of betel nut chewing by age and sex. The results showed that betel nut chewing was a more common habit in the younger patients than in the older patients in both sexes.

Table 3 shows the age- and sex-specific prevalence of hypertension by betel nut chewing and cigarette smoking. In the diabetic men, betel nut chewing and smoking were significantly associated with a higher prevalence of hypertension in the age groups of 40–49 and 50–59 years; but in the diabetic women, betel nut chewing was significantly associated with hypertension for all age groups except those ≥70 years and smoking was significant only for the age group of 60–69 years.

Table 4 shows the regression coefficients for estimating SBP and DBP and the adjusted odds ratios for hypertension for the independent variables entered separately into the models for either sex. Age, BMI, diabetic duration and betel nut chewing (*i.e.*, all the variables except for smoking) were all significantly associated with SBP and DBP; and also with significantly higher odds ratios for hypertension.

The information obtained from the questionnaire interview was very reliable. The correlation coefficients for two differ-

Table 4. Multiple Linear Regression for Systolic and Diastolic Blood Pressure and Logistic Regression for Hypertension

Sex and independent variables	Interpretation	Regression coefficient		Odds ratio (95% CI)
		Systolic blood pressure	Diastolic blood pressure	
Men				
Constant		105.617±0.582**	62.809±0.387**	—
Age	Every 1-year increment	0.160±0.005**	0.063±0.004**	1.044 (1.042–1.046)**
Body mass index	Every 1-kg/m^2 increment	0.686±0.018**	0.495±0.012**	1.162 (1.154–1.170)**
Diabetic duration	Every 1-year increment	0.116±0.010**	0.060±0.007**	1.022 (1.018–1.025)**
Smoking	Yes *vs*. no	0.006±0.133	0.158±0.088†	1.005 (0.959–1.054)
Betel nut chewing	Yes *vs*. no	0.958±0.163**	0.441±0.108**	1.067 (1.007–1.131)*
Women				
Constant		100.949±0.574**	60.696±0.364**	—
Age	Every 1-year increment	0.203±0.006**	0.089±0.004**	1.044 (1.042–1.046)**
Body mass index	Every 1-kg/m^2 increment	0.724±0.017**	0.493±0.011**	1.134 (1.127–1.140)**
Diabetic duration	Every 1-year increment	0.130±0.010**	0.076±0.006**	1.017 (1.014–1.021)**
Smoking	Yes *vs*. no	0.543±0.360	0.443±0.228)†	1.077 (0.958–1.210)
Betel nut chewing	Yes *vs*. no	1.805±0.618**	1.198±0.393**	1.897 (1.534–2.346)**

Data are mean±SEM. $^\dagger p<0.1$; $*p<0.05$; $**p<0.01$. CI, confidence interval.

ent interviewers for onset age of diabetes, body height, body weight, SBP, and DBP were 0.972, 0.904, 0.935, 0.626, and 0.436, respectively (all p values <0.01). The percent agreement for smoking, hypertension, and betel nut chewing was 91.7%, 97.7%, and 96.1%, respectively.

Discussion

The findings suggested that betel nut chewing was significantly associated with hypertension in both sexes in Taiwanese patients with T2DM (Table 4). The effects seemed to be stronger in the diabetic women, although fewer women than men had a betel nut chewing habit (Tables 1 and 2). The data shown in Table 3 suggested that the higher prevalence of hypertension associated with betel nut chewing was more consistently observed in different strata of age in the diabetic women; and an extraordinarily high prevalence of 40% was seen even in those aged <40 years. The stronger association between betel nut chewing and hypertension in the diabetic women than in their male counterparts could be confirmed in the regression models evaluating odds ratios for hypertension and the multiple regression coefficients for SBP and DBP (Table 4). There are no explanations for this sexual difference in the impact of betel nut chewing at this time. The question of whether there is an interaction between estrogen and the ingredients or compounds formed during the chewing of betel nuts will require further investigation.

Because the chewers were significantly younger in age and they were always cigarette smokers (Tables 1 and 2), the distribution of other potential risk factors might also have differed among the subgroups. This might partly explain why the prevalence of hypertension was higher in non-chewers in the age group ≥70 years and in the total patients in the diabetic men (Table 3). However, the association between betel nut chewing and hypertension could be confirmed after multivariate adjustment, as shown in the multiple regression models.

Although smoking might also be associated with hypertension, its effect was not as remarkable as that observed for the association between betel nut chewing and hypertension, especially in the diabetic women (Table 3). In the regression models, smoking was not significantly associated with hypertension after adjustment for betel nut chewing and other potential confounders (Table 4). These results suggested that in countries where betel nut chewing is a common habit, the evaluation of health effects associated with smoking should always simultaneously include betel nut chewing as a potential confounder.

Although the real pathogenetic mechanism(s) remains unknown, some of the biological effects associated with the ingredients of areca nuts or the compounds formed during chewing might explain some of the possibilities. The common preparations of the betel nut quid in Taiwan consist of three major components: the nuts of *Areca catechu*, quicklime and the leaves or flowers of the *Piper betle* (*4*). Sympathetic overdrive is considered to be one of the possible mechanisms leading to the increase of blood pressure and cardiovascular disease (*26*). The areca nut contains arecoline, which exerts a cholinergic action at the muscarinic and nicotinic receptors (*27*). This cholinergic action on the central nervous system could possibly produce the cortical arousal and alertness which is always claimed as one of the merits experienced by the betel nut chewers. On the other hand, a study in rats suggested that arecoline might stimulate the hypothalamic-pituitary-adrenal axis through a centrally mediated corticotrophin-releasing hormone–dependent mechanism (*28*). In the presence of lime, arecoline is hydrolyzed to arecaidine, which lacks the parasympathomimetic effects of arecoline (*4*)

and exerts a sympathetic effect by inhibition of γ-aminobutyric acid (GABA) uptake (*29*). However, a later study suggested that arecaidine may not cross the blood-brain barrier and the central effects may involve transmitters other than GABA (*30*). The aromatic substances (*e.g.*, eugenol, isoeugenol and hydroxychavicol) in the flowers or leaves of the *Piper betle* plant can stimulate the release of catecholamines from chromaffin cells *in vitro* (*31*), and circulating norepinephrine and epinephrine levels are elevated following betel nut chewing (*32*). However, these sympathomimetic effects of arecoline might be mediated by central cholinergic mechanisms (*33*). Therefore, both areca nuts and *Piper betle* flowers may exert sympathomimetic effects. A determination of whether these sympathomimetic effects may be responsible for the hypertension observed in the present study awaits further investigation.

Reactive oxygen species and *N*-nitroso compounds can also be formed in the oral cavity during the chewing of betel nuts (*34, 35*). *In vitro* studies have also demonstrated that betel nut components increased the release of inflammatory mediators such as prostanoids, interleukin-6 and tumor necrosis factor-α (*36, 37*). The production of these chemical agents might be the mediators responsible for the carcinogenicity and diabetogenicity associated with betel nut chewing. All of these chemicals are also potentially causative of hypertension and cardiovascular disease through the mechanisms of endothelial dysfunction, expression of vascular cell adhesion molecules, induction of insulin resistance and diminished fibrinolysis (*38–43*).

The principle strength of this study is its large sample size. However, some limitations deserve mentioning. This study was conducted in diabetic patients, and it is not known whether its results are directly extensible to the general population without diabetes. In addition, the dose-response relationship and duration of betel nut chewing were not considered, and future studies will be needed to address these variables. Longitudinal studies will also be needed to clarify the cause/effect relationship between betel nut chewing and hypertension. Another limitation in this study is that blood pressure measurements were not recorded. Measurements of blood pressure might not have been effective at providing an overview of the average blood pressure over time, which is why the use of self-reporting of general blood pressure in our patients might on the other hand have provided some advantage. This limitation did not change the conclusions, because the results were similar if hypertension was defined by a positive history without considering the reported blood pressure in secondary analyses (data not shown).

It is difficult to check the validity of a telephone interview, and we did not attempt to do so here. However, taking into account the reliability of two different interviews in most of the variables used in the study, the validity was believed to be good. Even if a recall bias did exist, it would probably only underestimate the risk because the misclassification bias might not be differential.

Our results showed that the prevalence of hypertension in the chewing group was lower than that in the non-chewing group in men aged ≥70 years (Table 3). Because we considered that the effect of age might not have been linear in the male group, we refitted the logistic regression model by entering age as a categorical variable. The odds ratio for hypertension for chewers *vs.* non-chewers remained significant without a remarkable change in magnitude: 1.079 (1.012–1.150) ($p=0.020$).

In this study, information on the use of antihypertensive agents was not gathered by the interviewers because it was deemed difficult to obtain such information by telephone interview. Therefore, the observed association between betel nut chewing and blood pressures in the regression models (Table 4) requires further confirmation in the absence of confounding by antihypertensive drugs. Future studies with a blinded and randomized clinical trial will surely better demonstrate the hypertensive effect of areca nut chewing and the preventability of hypertension after withdrawal from the chewing habit.

In conclusion, betel nut chewing in Taiwanese patients with T2DM was associated with hypertension. Although the diabetic women had a lower prevalence of betel nut chewing, the magnitudes of association with hypertension were actually more remarkable than those observed in their male counterparts. While the chewing of betel nuts is decreasing in some countries, such as Thailand (*44*), the prevalence keeps on increasing in Taiwan, especially in the younger generation. It is thus urgent that policy makers implement health education programs for younger men and women to curb the increasing prevalence of betel nut chewing and its associated health problems.

References

1. Gupta PC, Ray CS: Epidemiology of betel quid usage. *Ann Acad Med Singapore* 2004; **33**: 31–36.
2. Gupta PC, Warnakulasuriya S: Global epidemiology of areca nut usage. *Addict Biol* 2002; **7**: 77–83.
3. Nelson BS, Heischober B: Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34**: 238–243.
4. Chu NS: Effects of betel chewing on the central and autonomic nervous systems. *J Biomed Sci* 2001; **8**: 229–236.
5. Huang A: Betel nuts, better not. *Free China Rev* 1997; **47**: 18–27.
6. Yang MS, Su IH, Wen JK, Ko YC: Prevalence and related risk factors of betel quid chewing by adolescent students in southern Taiwan. *J Oral Pathol Med* 1996; **25**: 69–71.
7. Lin SK, Chang YJ, Ryu SJ, Chu NS: Cerebral hemodynamic responses to betel chewing: a Doppler study. *Clin Neuropharmacol* 2002; **25**: 244–250.
8. Trivedy CR, Craig G, Warnakulasuriya S: The oral health consequences of chewing areca nut. *Addict Biol* 2002; **7**: 115–125.
9. Mehta FS, Sanjana MK, Baretto MA: Relation of betel leaf chewing to periodontal disease. *J Am Dent Assoc* 1955; **50**:

531–536.
10. Tseng CH: Betel nut chewing is independently associated with urinary albumin excretion rate in type 2 diabetic patients. *Diabetes Care* 2006; **29**: 462–463.
11. Hung CR, Cheng JT: Betel quid chewing damaged gastric mucosa: protective effects of cimetidine and sodium bicarbonate. *Chin J Physiol* 1994; **37**: 213–218.
12. Taylor RF, al-Jarad N, John LM, Conroy DM, Barnes NC: Betel-nut chewing and asthma. *Lancet* 1992; **339**: 1134–1136.
13. Deahl M: Betel nut–induced extrapyramidal syndrome: an unusual drug interaction. *Mov Disord* 1989; **4**: 330–332.
14. Lin SH, Lin YF, Cheema-Dhadli S, Davids MR, Halperin ML: Hypercalcaemia and metabolic alkalosis with betel nut chewing: emphasis on its integrative pathophysiology. *Nephrol Dial Transplant* 2002; **17**: 708–714.
15. Chakrabarti RN, Dutta K, Ghosh K, Sikdar S: Uterine cervical dysplasia with reference to the betel quid chewing habit. *Eur J Gynaecol Oncol* 1990; **11**: 57–59.
16. Wu MT, Wu DC, Hsu HK, Kao EL, Lee JM: Relationship between site of oesophageal cancer and areca chewing and smoking in Taiwan. *Br J Cancer* 2003; **89**: 1202–1204.
17. Sun CA, Wu DM, Lin CC, *et al*: Incidence and cofactors of hepatitis C virus–related hepatocellular carcinoma: a prospective study of 12,008 men in Taiwan. *Am J Epidemiol* 2003; **157**: 674–682.
18. de Costa C, Griew AR: Effects of betel chewing on pregnancy outcome. *Aust N Z J Obstet Gynaecol* 1982; **22**: 22–24.
19. Tung TH, Chiu YH, Chen LS, Wu HM, Boucher BJ, Chen TH: 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**: 1776–1781.
20. Lan TY, Chang WC, Tsai YJ, Chuang YL, Lin HS, Tai TY: Areca nut chewing and mortality in an elderly cohort study. *Am J Epidemiol* 2007; **165**: 677–683.
21. Chu NS: Cardiovascular responses to betel chewing. *J Formos Med Assoc* 1993; **92**: 835–837.
22. Tseng CH: Prevalence of lower-extremity amputation among patients with diabetes mellitus: is height a factor? *CMAJ* 2006; **174**: 319–323.
23. Tseng CH: Exogenous insulin use and hypertension in adult patients with type 2 diabetes mellitus. *Arch Intern Med* 2006; **166**: 1184–1189.
24. Tseng CH: Higher risk of hypertension in indigenous type 2 diabetic patients in Taiwan. *J Hypertens* 2006; **24**: 1817–1821.
25. Tseng CH, Tseng CP, Chong CK, *et al*: Increasing incidence of diagnosed type 2 diabetes in Taiwan: analysis of data from a national cohort. *Diabetologia* 2006; **49**: 1755–1760.
26. Grassi G: Sympathetic overdrive and cardiovascular risk in the metabolic syndrome. *Hypertens Res* 2006; **29**: 839–847.
27. Nieschulz O: Pharmacology of the active substances in betel. 3. Experiments with arecaidine. *Arzneimittelforschung* 1970; **20**: 218–229 (in German).
28. Calogero AE, Kamilaris TC, Gomez MT, *et al*: The muscarinic cholinergic agonist arecoline stimulates the rat hypothalamic-pituitary-adrenal axis through a centrally-mediated corticotropin-releasing hormone–dependent mechanism. *Endocrinology* 1989; **125**: 2445–2453.
29. Johnston GA, Krogsgaard-Larsen P, Stephanson A: Betel nut constituents as inhibitors of gamma-aminobutyric acid uptake. *Nature* 1975; **258**: 627–628.
30. Lodge D, Johnston GA, Curtis DR, Brand SJ: Effects of the areca nut constituents arecaidine and guvacine on the action of GABA in the cat central nervous system. *Brain Res* 1977; **136**: 513–522.
31. Wang CK, Hwang LS: Effect of betel quid on catecholamine secretion from adrenal chromaffin cells. *Proc Natl Sci Counc Repub China B* 1997; **21**: 129–136.
32. Chu NS: Sympathetic response to betel chewing. *J Psychoactive Drugs* 1995; **27**: 183–186.
33. Nurnberger JI Jr, Jimerson DC, Simmons-Alling S, *et al*: Behavioral, physiological, and neuroendocrine responses to arecoline in normal twins and "well state" bipolar patients. *Psychiatry Res* 1983; **9**: 191–200.
34. Nair U, Bartsch H, Nair J: Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. *Mutagenesis* 2004; **19**: 251–262.
35. Boucher BJ, Mannan N: Metabolic effects of the consumption of *Areca catechu*. *Addict Biol* 2002; **7**: 103–110.
36. Peng JP, Su CY, Chang HC, Chai CY, Hung WC: Overexpression of cyclo-oxygenase 2 in squamous cell carcinoma of the hypopharynx. *Hum Pathol* 2002; **33**: 100–104.
37. Jeng JH, Wang YJ, Chiang BL, *et al*: Roles of keratinocyte inflammation in oral cancer: regulating the prostaglandin E2, interleukin-6 and TNF-alpha production of oral epithelial cells by areca nut extract and arecoline. *Carcinogenesis* 2003; **24**: 1301–1315.
38. Tanaka C, Mannami T, Kamide K, *et al*: Single nucleotide polymorphisms in the interleukin-6 gene associated with blood pressure and atherosclerosis in a Japanese general population. *Hypertens Res* 2005; **28**: 35–41.
39. Ono H, Ichiki T, Ohtsubo H, *et al*: CAMP-response element-binding protein mediates tumor necrosis factor-alpha–induced vascular cell adhesion molecule-1 expression in endothelial cells. *Hypertens Res* 2006; **29**: 39–47.
40. Iwai M, Mogi M, Horiuchi M: The role of tumor necrosis factor-alpha in inducing insulin resistance in the renin-angiotensin system. *Hypertens Res* 2005; **28**: 701–702.
41. Dong J, Fujii S, Goto D, *et al*: Increased expression of plasminogen activator inhibitor-1 by mediators of the acute phase response: a potential progenitor of vasculopathy in hypertensives. *Hypertens Res* 2003; **26**: 723–729.
42. Ishimitsu T, Tsukada K, Minami J, Ono H, Matsuoka H: Variations of human adrenomedullin gene and its relation to cardiovascular diseases. *Hypertens Res* 2003; **26** (Suppl): S129–S134.
43. Furumoto T, Saito N, Dong J, Mikami T, Fujii S, Kitabatake A: Association of cardiovascular risk factors and endothelial dysfunction in Japanese hypertensive patients: implications for early atherosclerosis. *Hypertens Res* 2002; **25**: 475–480.
44. Reichart PA: Oral cancer and precancer related to betel and miang chewing in Thailand: a review. *J Oral Pathol Med* 1995; **24**: 241–243.