ERECTILE DYSFUNCTION

Association of Areca Nut Chewing With Risk of Erectile Dysfunction

Yung-Jui Huang, PhD,[1] and Bang-Ping Jiann, MD[2]

ABSTRACT

Introduction: Areca nut chewing has been shown to increase the risk of cardiovascular disease, but its association with erectile dysfunction (ED) has not been investigated.

Aim: To investigate the association between areca nut chewing and risk of ED.

Methods: Consecutive men at public health centers for oral malignancy screening or health checkup were invited to complete a questionnaire.

Main Outcome Measure: The Sexual Health Inventory for Men (SHIM).

Results: Of the 2,652 respondents, 1,038 (mean age = 43.8 ± 11.1 years) were eligible for the areca nut chewing group and 1,090 non-areca nut chewers were selected as the age-matched control group. In the areca nut group, the mean duration of chewing was 13.2 ± 9.6 years, 61.7% consumed more than 10 portions per day, and 76.2% used it with betel leaf, 16.7% used it with betel inflorescence, and 7.1% used it with betel leaf and inflorescence. Smoking, alcohol drinking, obesity, hypertension, and diabetes were more predominant in areca nut chewers compared with controls. ED defined by self-report and by SHIM score was more prevalent in areca nut chewers than in controls (13.7% vs 9.8% and 48.7% vs 43.3%, respectively; $P < .05$ for the two comparisons). Areca nut use with betel inflorescence was associated with a higher risk of ED (odds ratio = 2.25, 95% confidence interval = 1.55−3.28) with a dose-dependent effect, whereas using it with betel leaf was not (odds ratio = 1.00, 95% confidence interval = 0.79−1.26) after adjustment of possible confounders.

Conclusion: Areca nut chewing with betel inflorescence was associated with an increased risk of ED. These findings warrant further studies. **Huang Y-J, Jiann B-P. Association of Areca Nut Chewing With Risk of Erectile Dysfunction. Sex Med 2017;5:e163−e168.**

Key Words: Areca Nut; Betel Inflorescence; Erectile Dysfunction; Psychoactive Substance

INTRODUCTION

Areca nut is the fourth most commonly used psychoactive substance worldwide, after tobacco, alcohol, and caffeine, and its use is addictive.[1] The prevalence of areca nut chewing has been estimated to be 10% to 20% of the world's population.[2] The annual national survey in Taiwan showed that approximately 17% of men and 1% of women were areca nut chewers from 2005 through 2015.[3]

There are two popular ways of preparing areca nut for chewing in Taiwan. One is wrapping a split unripe areca nut with slaked lime paste in a betel leaf; the other is inserting a piece of betel inflorescence with red lime paste (slaked lime and some local flavoring) into an unripe areca nut. The most important chemical constituents in areca nut are areca alkaloids, including arecoline, arecaidine, guvacine, guacoline, among others.[4] Nitrosation of areca alkaloids after ingestion takes place in the mouth especially in the presence of bacteria owing to poor oral hygiene and in the acid condition of the stomach.[4] The areca-nut specific nitrosamines have toxic and mutagenic effects on DNA.[4] The International Agency for Research on Cancer[4] concluded that areca nut is carcinogenic to humans.

Areca nut was considered an aphrodisiac in ancient times. Feeding animals with areca nut was purported to enhance libido and potency.[5] The risk factors for erectile dysfunction (ED), a prevalent problem in men, such as obesity,[6] metabolic syndrome, diabetes, hypertension, and cardiovascular diseases,[7] are more

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prevalent in areca nut chewers than in non-chewers.[8] Whether the areca nut affects the chewers' erectile function has not been investigated. A cross-sectional study was conducted to compare the prevalence of ED between areca nut chewers and non-chewers.

OBJECTIVE

The aim of this research was to investigate the association between areca nut chewing and risk of ED.

METHODS

Participants

Each district in Taiwan has a public health center to promote public health. Consecutive men who were undergoing screening for oral malignancy with a history of areca nut chewing or for a health checkup were invited to participate in the study in four of these centers in south Taiwan from 2010 to 2011. The responsible nurses explained the purpose and methods of the study. Participants who consented to join the study were invited to complete a self-administered questionnaire anonymously without any compensation and an informed consent was not required. The protocol of this study was reviewed and approved by the institutional review board at our institution.

Outcome Measures

The questionnaire consisted of nine items, including age, marital status, a checklist of common comorbidities, smoking and alcohol drinking habits, history of areca nut chewing, mean frequency of sexual activity in the past 3 months, a global assessment question (GAQ) for ED, and the five-item Sexual Health Inventory for Men (SHIM). Body height (centimeters) and weight (kilograms) were measured by the nurses. Body mass index (BMI) was calculated as body weight (kilograms) divided by the square of body height (meters), and a BMI higher than 27 kg/m^2 was categorized as obesity according to the criteria provided by the Department of Health in Taiwan. The presence of smoking was defined as current smoking. The presence of alcohol drinking was defined as alcohol dinking every day or often. The existence of hypertension and diabetes was determined by self-report.

History of areca nut chewing was assessed by three questions. Question 1 was "Do you have a habit of areca nut chewing?" with choices of (i) yes, I have chewed it usually, for xx years; (ii) yes, I have chewed it occasionally for xx years; (iii) yes, I had chewed it for xx years but I quit it; and (iv) no, I have never chewed it before. Question 2 was "What was your average daily consumption of areca nut?" with choices of (i) no more than 10, (ii) 11 to 20, (iii) 21 to 50, (iv) 51 to 100, and (v) more than 100 portions per day. Question 3 was "What was (were) your usual preparation(s) of areca nut?" with choices of (i) with betel leaf and (ii) with betel inflorescence. A subject who chose answer i, ii, or iii for question 1 were defined as an areca nut chewer. The cumulative exposure to areca nut was estimated as the square root of (median daily consumption multiplied by years of chewing duration).

The presence of self-reported ED was defined as the participant responding yes to the GAQ, "Do you consider yourself to have ED?" Erectile function also was assessed by the SHIM. Participants who had a total SHIM score lower than 22 were categorized as having ED. To avoid misclassification as having ED only because of no sexual attempt, subjects who had a zero score for any item of the SHIM were excluded from the analysis.[9]

Statistical Analysis

The χ^2 test was used for comparison of categorical variables. Normality was assessed for continuous variables. The unpaired Student t-test or Mann-Whitney U-test was used to compare two continuous variables, depending on the normality of distribution. A receiver operating characteristic curve was obtained to estimate the best cutoff of cumulative exposure to areca nut chewing to predict the risk of ED. Multivariate logistic regressions were used to estimate the odds ratio (OR) of comorbidities (obesity, hypertension, diabetes, and ED) for chewing areca nut with adjustment of potential confounders (age, BMI, smoking, alcohol drinking, hypertension, or diabetes) as appropriate. Because there were a few incomplete responses, sample sizes of some calculations were decreased but were never less than 75% of the complete samples.

Data entry was performed using Excel 2003 (Microsoft, Redmond, WA, USA). Statistical analyses were executed using SPSS 17.0 (SPSS, Inc, Chicago, IL, USA). The null hypothesis was rejected for a P value lower than .05.

RESULTS

Of the 2,652 respondents, 43.4% (n = 1,152) reported a habit of areca nut chewing and 56.6% (n = 1,500) denied having such a habit. A total of 1,038 subjects were eligible for the areca nut group after excluding subjects who had no data on age or were younger than 20 years (n = 12), had incomplete SHIM data (n = 50), or had a zero score for the SHIM items (n = 52). An age-matched control group (n = 1,090) was selected from the 1,500 non-areca nut chewers.

The characteristics of the areca nut group and the control group are listed in Table 1. Their mean age was approximately 44 years (range = 20−86 years). The areca nut group was more likely to be divorced than the control group (7.7% vs 3.7%), whereas the two groups had a similar frequency of sexual activity in the past 3 months. Prevalences of smoking (66.8% vs 27.1%), alcohol drinking (35.3% vs 7.4%), and obesity (24.6% vs 18.4%) were greater in the areca nut group than in the control group, as were those of hypertension (22.5% vs 16.0%) and diabetes (8.8% vs 4.8%). The areca nut group had a higher prevalence of ED defined by the response to the GAQ (13.7% vs 9.8%, $P = .006$) or by SHIM scores (48.7% vs 43.3%, $P = .013$) than did the control group (Table 1).

Table 1. Characteristics of participants*

Variables	Control group (n = 1,090)	Areca nut group (n = 1,038)	*P* value†
Age (y)	44.0 ± 11.4 (20–86)	43.8 ± 11.1 (20–78)	.705
Body mass index (kg/m^2)	24.3 ± 3.0 (16.1–37.5)	25.0 ± 3.5 (16.1–51.9)	<.001
Obesity	18.4% (201)	24.6% (251)	<.001
Marital status			
Married	84.3% (869)	80.8% (790)	.001
Divorced	3.7% (38)	7.7% (75)	
Single	12.0% (124)	11.6% (113)	
Mean sexual frequency in past 3 mo			
No sexual activity	3.3% (36)	3.2% (33)	.229
>2 times/wk	18.9% (204)	22.1% (225)	
1–2 times/wk	28.7% (309)	25.5% (259)	
1–4 times/mo	32.7% (352)	31.2% (317)	
<1 time/mo	16.4% (177)	17.9% (182)	
Current smoker	27.1% (295)	66.8% (689)	<.001
Daily or frequent alcohol drinking	7.4% (81)	35.3% (364)	<.001
Hypertension	16.0% (173)	22.5% (229)	<.001
Diabetes	4.8% (52)	8.8% (90)	<.001
ED classified by SHIM score	43.3% (472)	48.7% (505)	.013
Self-reported ED	9.8% (104)	13.7% (140)	.006

ED = erectile dysfunction; SHIM = Sexual Health Inventory for Men.
*Data are presented as mean ± SD (range) or percentage (number). Obesity was defined as a body mass index higher than 27 kg/m^2. Diabetes and hypertension were based on self-report. Self-reported ED was defined by a global assessment question.
†The χ^2 test was used for categorical variables; unpaired Student t-test or Mann-Whitney U-test was used for continuous variables depending on the normality of distribution.

Of the areca nut group, 81.7% were current users and 18.3% were former users and the mean duration of their areca nut use was 13.2 ± 9.6 years (range = 0.5–50; median = 10, interquartile range = 5–20). For the amount of daily consumption, 38.3% chewed fewer than 10 portions, 32.4% chewed 11 to 20 portions, 21.3% chewed 21 to 50 portions, and 8.0% chewed more than 50 portions. For preparation types, 76.2% (n = 728) used areca nuts with betel leaf, 16.7% (n = 160) used areca nuts with betel inflorescence, and 7.1% (n = 68) used areca nuts with betel leaf and inflorescence (Table 2).

Table 2. History of areca nut use in the areca nut group

Variables	Results (n = 1,038)
Duration of areca nut use (y)	
Mean ± SD (range)	13.2 ± 9.6 (0.5–50)
Median (interquartile range)	10 (5–20)
History of areca nut use, % (n)	
Current user	81.7 (848)
Former user	18.3 (190)
Daily consumption of areca nut (portions), % (n)	
<10	38.3 (364)
11–20	32.4 (308)
21–50	21.3 (202)
51–100	5.6 (53)
>100	2.4 (23)
Type of preparation, % (n)	
With betel leaf*	76.2 (728)
With betel inflorescence†	16.7 (160)
Both	7.1 (68)

*Wrapping a split unripe areca nut with slaked lime paste in a betel leaf.
†Inserting a piece of betel inflorescence with red lime paste into an unripe areca nut.

Subjects consuming areca nuts with betel leaf and inflorescence (n = 68) were excluded from the following analysis to delineate the consequences of the different preparations. The prevalence rates of ED, based on SHIM score, were 44.8% in betel leaf users (n = 728), 62.5% in betel inflorescence users (n = 160), and 43.3% in controls ($P < .001$). Betel inflorescence consumers had increased risks for hypertension (OR = 1.74, 95% confidence interval [CI] = 1.09–2.76), diabetes (OR = 2.68, 95% CI = 1.47–4.88), and ED (OR = 2.25, 95% CI = 1.55–3.28), whereas betel leaf consumers had increased risks for obesity (OR = 1.37, 95% CI = 1.06–1.78) and diabetes (OR = 1.64, 95% CI = 1.05–2.56) but no increased risk of ED (OR = 1.00, 95% CI = 0.79–1.26) compared with the controls after adjustment of potential confounders (Table 3). The prevalences of smoking and alcohol drinking were 54.1% vs 70.8% ($P < .001$) and 30.0% vs 37.9% ($P = .06$) in the betel inflorescence chewers vs betel leaf chewers, respectively.

Of betel inflorescence consumers, the current and previous chewers had no significant difference in their ED prevalence, which did not change after adjusting potential confounders. A cutoff value of 6.516 for cumulative exposure to areca nut was

Table 3. Odds ratios of comorbidities for using areca nut with different preparations*

Variables	With betel leaf† (n = 728)	With betel inflorescence‡ (n = 160)	Control (n = 1,090)
Erectile dysfunction§	1.00 (0.79–1.26)	2.25 (1.55–3.28)††	Reference
Obesity‖	1.37 (1.06–1.78)#	1.21 (0.80–1.84)	Reference
Hypertension¶	1.32 (0.97–1.79)	1.74 (1.09–2.76)#	Reference
Diabetes¶	1.64 (1.05–2.56)#	2.68 (1.47–4.88)**	Reference

*Erectile dysfunction was defined as a Sexual Health Inventory for Men score lower than 22; diabetes and hypertension were based on self-report; obesity was defined as a body mass index higher than 27 kg/m^2. Data are presented as odds ratio (95% confidence interval).
†Wrapping a split unripe areca nut with slaked lime paste in a betel leaf.
‡Inserting a piece of betel inflorescence with red lime paste into an unripe areca nut.
§Controlled for age, body mass index, alcohol drinking, smoking, diabetes, and hypertension.
‖Controlled for age, alcohol drinking, and smoking.
¶Controlled for age, body mass index, alcohol drinking, and smoking.
#$P < .05$; **$P < .01$; ††$P < .001$.

chosen to evaluate its dose effect on ED risk according to the receiver operating characteristic curve (area under curve = 0.645, $P = .001$). A cumulative exposure to areca nut with betel inflorescence of at least 6.516 had an OR of 3.42 (95% CI = 2.06–5.67) for ED and exposure to less than 6.516 had an OR of 1.20 (95% CI = 0.56–2.57) for ED compared with controls after adjustment of potential confounders.

DISCUSSION

This study found that areca nut users had more problems with obesity, hypertension, diabetes, and ED than the non-chewers. Chewing areca nut with betel inflorescence increased the risk of ED in a dose-response relation after adjustment of possible confounders, whereas chewing it with betel leaf did not.

Link of Areca Nut Chewing to Obesity, Hypertension, and Diabetes

A meta-analysis of observational studies demonstrated that areca nut chewers had an adjusted relative risk of 1.47 for obesity and for diabetes ($P < .001$ for the two comparisons) and of 1.45 for hypertension ($P = .06$) compared with non-chewers.[8] These figures were comparable with ours (Table 3). Unhealthy lifestyles could be responsible in part for the link between them. Areca nut chewers were prone to have smoking and alcohol drinking habits in the present study. Other studies reported areca nut chewers had less physical activity and consumed a more unhealthy diet than non-chewers did.[10,11] The ingredients of areca nut and its additives also contribute to the increased risk of obesity, hypertension, and diabetes.[4,10,12–23]

Diabetes

The nitrosated derivatives of areca alkaloids damage DNA and generate reactive oxygen species.[4] This oxidative stress and DNA damage activate proinflammatory factors and promote insulin resistance.[12,13] Moreover, areca alkaloids inhibit the uptake of γ-aminobutyric acid (GABA)[14] and are strong blockers of the GABA receptor.[15] Because GABA suppresses the secretion of glucagon,[16] areca nut chewing can result in excessive secretion of glucagon, leading to hyperglycemia.

Hypertension

Areca nut and betel inflorescence can exert sympathomimetic effects.[17,18] The oxidative stress caused by nitrosated areca alkaloids could lead to increased risk of hypertension.[19] However, areca II-5-C, a fraction isolated from areca nut, exhibits potent angiotensin-converting enzyme inhibitory activity in vitro and produces a lasting dose-related antihypertensive effect in rats.[20]

Obesity

GABA can stimulate appetite.[21] The inhibitory effect of areca alkaloids on GABA[15] can suppress appetite. A decreased increment of BMI was observed after areca nut use in a cohort study.[22] In contrast, a cross-sectional study observed that areca nut chewers were likely to have general and central obesity, which did not change after adjustment of confounders including physical activity.[10] This could be attributed to the insulin resistance in areca nut chewers given that hyperinsulinemia contributes to obesity.[23]

Link of Areca Nut Chewing to ED

Because areca nut chewing increases the risks of diabetes, hypertension, and obesity, areca nut chewers were expected to be more likely to have ED. Our results showed that chewing areca nut only with betel inflorescence was associated with an increased risk of ED, which suggested that factors other than areca nut were responsible for the increased risk.

Betel leaf and inflorescence come from a tropical plant named *Piper betel* Linn. Betel leaf was found to have some beneficial effects, such as antioxidant, anticancer, and anti-inflammatory, in vitro and in animal studies.[24] Betel inflorescence contains eugenol (6.2%) and safrole (78.9%).[4] Safrole is a possible human carcinogen.[25] Unlike the more popular preparation of areca nut with betel leaf, consumption of areca nut with betel inflorescence is common only in Taiwan and Melanesia.[4] Probably owing to

the public awareness of its carcinogenicity, the use of betel inflorescence has greatly decreased in recent years.[26]

Among the various preparations of areca nut, using betel inflorescence has the highest cancer risk.[27] No clinical research has compared the impact of different preparations of areca nut on metabolic disorders or cardiovascular diseases. The current results showed that the risks of diabetes and hypertension were greater in betel inflorescence users than in betel leaf users. Some other causes might be responsible for the increased ED risk in betel inflorescence users because it remained significant after adjusting for diabetes and hypertension. A plausible conjecture was that betel inflorescence chewers had more negative lifestyles than betel leaf users. This hypothesis seemed unlikely because the prevalences of smoking and alcohol drinking were not higher in the betel inflorescence chewers than betel leaf chewers. Another hypothesis was that the ED-associated stress and depression prompted men to chew betel inflorescence. A long duration of areca nut use (median = 10 years) implied the users began to use it at a young age before they developed ED. There was no reason to believe that men with ED were more likely to choose betel inflorescence to relieve the stress than to choose betel leaf.

The oxidative stress caused by safrole in betel inflorescence[28] can compromise penile vascular function and penile erection. Safrole can be used to produce 3,4-methylenedioxy-methamphetamine,[29] which was reported to impede erection and orgasm.[30] The spices contained in the red lime used with betel inflorescence possibly contributed to an increased risk of ED. The spices were exclusive and varied among vendors. Their real components could not be determined.

Limitations

There were several limitations to this study. In Taiwan, only unripe areca nut was adopted and the additives used in preparing areca nut vary among countries. The response rate to this survey was not known. Differences in socioeconomic status and educational background between the areca nut chewers and non-chewers were not assessed. However, the choice of betel inflorescence or leaf was believed to depend on individual taste and preference, rather than on lifestyle.

Caution should be taken in generalizing the results. This was a cross-sectional study and a direct causal effect could not be concluded. Timing of dosing (eg, acute or long-term use and active or withdrawal phase) was not assessed. The effect of duration of cessation was not assessed, yet no significant difference was found in the risk of ED between current chewers and former chewers. The presence of comorbidities relied on self-report and underestimation was probable; if this were the case, then the independent contribution of areca nut chewing to risk of ED would be an overestimation. Another limitation was we did not quantitatively evaluate the confounding factors of ED such as comorbidities and habits of smoking and alcohol drinking. The dosing effect of these confounders on ED risk could not be evaluated.

Subjects who had a zero score for any SHIM item were excluded from the analysis, which decreased cases of severe ED without sexual activity. The prevalence of ED was prone to be underestimated especially for severe ED. The impact of areca nut on sexual desire was not assessed; nevertheless, the mean frequency of sexual activity showed no difference between areca nut users and non-users.

CONCLUSION

ED prevalence increased among those chewing areca nut with betel inflorescence but not in those chewing it with betel leaf. The association of ED and chewing areca nut with betel inflorescence exhibited a dose-response effect, independent of obesity, hypertension, and diabetes. The effect of areca nut on users' erectile function was neutral. The increased diabetes, hypertension, and obesity and the additives with betel inflorescence and red lime contributed to an increased ED risk in subjects chewing areca nut with betel inflorescence. More research is needed to verify the association between areca nut chewing and sexual function.

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