

# Association Between Betel Nut and Presence of Diverticulum: A Cross-Sectional Study

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## Research

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# Abstract

**Background:** Current studies reporting multiple systemic effect of betel nut (BN) chewing have little analysis on colonic system. The aim of our study was to analyze the association between BN chewing and diverticulosis.

**Method:** This cross-sectional study is conducted from 2010 to 2016 at a medical center in Taiwan. 5586 eligible participants were enrolled in our study (all of them underwent colonoscopy, and 349 with diverticulosis). The BN chewing behavior was recorded from assessment of personal history. The diverticulosis was categorized by the presence or not according to the colonoscopies done by trained physicians from health examinations in Tri-Service General Hospital. A logistic regression model with adjusted models, with covariates from Directed Acyclic Graph, was used to determine the association between BN chewing and diverticulosis. We also analyzed the association between different exposures, including cigarette, alcohol, and BN, and diverticulosis.

**Results:** Our study included 3161 males and 2425 females with significantly higher prevalence rates of BN chewing behavior among males than females (11.1% versus 0.3%). In men group, BN chewing had adjusted odd ratio: 1.65(95% CI:1.12-2.44) on the presence of diverticulosis. Among the combination of exposures of cigarette, alcohol and BN, only the group exposed to all showed significant association between diverticulosis with adjusted OR: 1.909(95% CI: 1.188-3.065). Further subgroup analysis displayed adjusted OR: 2.310(95% CI:1.245-4.287) in obesity Taiwanese male.

**Conclusion:** BN chewing is independently associated with diverticulosis in Taiwanese male.

## Introduction

Betel nut, also known as areca nut, is the seed of the areca palm (*Areca catechu*), which grows in much of the tropical Pacific region, Southeast and South Asia, and parts of Africa. Approximately 700 million people (about 10% of the world's population) have habit of chewing BN (or betel quid) in the world, and most of them resident in Asia-Pacific regions which is accord with the region where *Areca catechu* tree grows.<sup>1</sup> In fact, It is the fourth most widely (after alcohol, caffeine, and nicotine) used addictive substance and major addiction in the world<sup>2</sup>. Studied showed various compounds in the nut, including arecoline which is the main component thought to cause short-term euphoric/stimulant effects by the muscarinic activity.<sup>3</sup> Furthermore, BN was thought as group 1 carcinogen in human with links to multiple cancers of the digestive system, such as oral cavity, pharynx, esophagus, liver and biliary tracts in 2004.<sup>4</sup> Despite the strong between BN and oral cancer, in recent studies, multiple systemic effects among people who chew BN were reported, including hypertension<sup>5</sup>, metabolic syndrome<sup>6</sup>, even all-cause mortality.<sup>7</sup>

Diverticulosis is a commonly noted status in patients undergoing colonoscopy with or without any gastrointestinal symptoms, and modern studies say that the incidence of diverticula-related disease, such as diverticulitis, is increasing.<sup>8</sup> A person with diverticulosis was reported to have 10–25% lifetime risk

suffering diverticulitis.<sup>9</sup> Further complications come along with phlegmon or abscess (approximately 70% of patients with complications), peritonitis, obstruction, and fistula which offer increasing huge cost for health care use.<sup>10</sup> Moreover, a recent retrospective cohort study presented that diverticulosis (OR 3.874, 95% CI 1.843–8.144) had high risk of synchronous colorectal adenomas in colorectal cancer patients.<sup>11</sup>

To our knowledge, no research has examined the association between BN chewing and diverticulosis among human population. Thus, we analyze the associations between BN chewing and diverticulosis in a large general population in Taiwan by cross-sectional study.

## **Methods**

### **Design**

This retrospective cross-sectional study was investigated from health examinations in Tri-Service General Hospital from 2010 to 2016, and there were 69226 people undergoing comprehensive examinations during then.

Our protocol was based on the Declaration of Helsinki, and was verified by the TSGH Institutional Review Board. Before the study enrollment, all participants provided written informed consent by themselves. During the whole study, participants' characteristics were stayed anonymous, and any information about individual identification was eliminated.

### **Selection of participants**

Initially, we included participants who finished core elements of anthropometry measurement, serum laboratory examination, colonoscopy, and assessment for personal history about substance use, including BN chewing. After excluding those with missing information such as demographic and laboratory data, 5586 eligible participants were enrolled for further analysis.

### **Diagnosis of diverticulosis**

Trained physicians were responsible for colonoscopy and digital rectal examination was examined routinely before the endoscope examination. Those who were going to receive colonoscopy were told to take two doses of laxative. The first dose was taken at the previous night of examination and they should stay fasting after the first dose. The other dose was taken on the day for colonoscopy in the morning. Participants did not follow the protocol were told to hold the colonoscopy or excluded from the study. The presence of diverticulum was recorded by the operator, and we categorized the result into two groups by the presence of diverticulum, diverticulosis, through the whole procedure.

### **Measurement of covariates**

It was always not easy to clarify confounding for causal inferences from observational data. A confounder is defined as a factor that influences both the exposure and the outcome, causing a spurious

association. We presented our Directed Acyclic Graph analysis of the study according to the correlations and previous evidences in Fig. 1. The patient information, such as age, sex, personal history of cigarette use, BN chewing and alcohol consumption were assessed using the self-report questionnaire. The BMI value of a participant was derived from the body mass (weight) divided by the square of the height in units of  $\text{kg}/\text{m}^2$ . Serum total cholesterol, triglyceride, fasting glucose, and creatinine levels were assessed by standard methods.

## Definition of obesity

We defined the obesity as  $\text{BMI} \geq 27$  according to Health Promotion Administration, Ministry of Health and Welfare in Taiwan.

## Statistical analysis

The associations between diverticulosis and the BN chewing were evaluated using an adjusted logistic regression model (Model 1 was unadjusted; Model 2 included Model 1 and age, serum triglyceride, serum creatinine, serum total cholesterol, serum fasting glucose, and BMI; Model 3 included Model 2 and history of alcohol consumption and cigarette use). We analyzed the present study by SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc., and defined statistically significant as two-sided P-value below 0.05.

## Results

The participants comprised 3161 males and 2425 females; their demographic and laboratory data shown in Table 1. The mean ages were  $51.67 \pm 12.33$  years and  $50.52 \pm 11.82$  years for males and females, respectively. The male participants had significantly higher levels of creatinine, triglyceride, fasting glucose, and body mass index than female participants. In addition, a prominent higher prevalence of alcohol drinking, BN chewing and cigarette use were observed in the male population than female population.

### Relationship between BN chewing and diverticulosis in different gender

In table 2, we display the associations between BN chewing and diverticulosis after categorizing BN chewer by gender. A positive relationship was observed between BN chewing and diverticulosis in male group with OR:1.59(95% CI:1.11–2.28). Moreover, significant associations were noted in Model 2 and 3 after adjusting covariates with OR of 1.708(95% CI:1.18–2.48) and 1.65(95% CI:1.12–2.44), respectively. However, no significant association was observed between BN chewing and diverticulosis in the female group.

### Comparison of odd ratios for diverticulosis in male with different substances

For detail realizing different exposure effects on the presence of diverticulosis, we reveal the odd ratios in different combination of smoking, drinking and BN chewing. In table 3, small number of participants (< 50) in the group of BN chewing only, smoking plus BN chewing, and drinking plus BN chewing was noted. Among all combination, only the group exposed to cigarette, alcohol, and BN simultaneously showed significant association between diverticulosis with OR: 1.598(95% CI: 1.015–2.514) and adjusted OR:

1.909(95% CI: 1.188–3.065) while the group exposed to cigarette and alcohol (without BN) showed OR of 0.994(95% CI: 0.698–1.416) and adjusted OR of 1.0991(95% CI: 0.759–1.569).

Association between BN chewing and diverticulosis in male with obesity

We perform subgroup analysis to demonstrate the significant association between BN chewing and diverticulosis in obesity male group, in Table 4. Due to the repetition of covariates, we delete the BMI factor in Model 2 in the subgroup analysis. Statically significant adjusted OR in Model 1, 2 and 3 is 2.502(95% CI:1.418–4.416), 2.601(95% CI: 1.441–4.694) and 2.310(95% CI:1.245–4.287) respectively.

## Discussion

In our colonoscopy-based study, diverticulosis showed a significant association with BN chewing in Taiwanese male. No obvious association in the female group was the fact of few participants had the habit of BN chewing which is compatible with low prevalence rates of BN chewing behavior among women in Taiwan.<sup>12</sup> Furthermore, BN chewing had prominent effect in logistic regression among the combination analysis among most seen substances: cigarette, alcohol and BN. Lin et al. had showed that BN consumption had significant dose-response effects on general obesity.<sup>13</sup> To better understanding how much the obesity played in the association between BN chewing and diverticulosis, our subgroup analysis found obesity weighting the BN chewing in the presence of diverticulosis. As far as we are concerned, we first examined the relationship between diverticulosis and BN chewing.

Diverticulosis is a condition with the presence of colonic diverticula, and previous study showed about 4% of patient will develop acute diverticulitis in 11-years follow-up.<sup>14</sup> Although the clear pathological mechanisms that cause the formation of colonic diverticula are still unknown, modern studies used to believe that there were complex interactions including lifestyle, colonic dysbiosis, colonic motility, genetic factors, and microscopic inflammation.<sup>15</sup> However, the chain between inflammation(systemic or mucosal) and the formation of asymptomatic diverticulosis was broken since Peery et al. claimed that colonic diverticulosis was not associated with mucosal inflammation.<sup>16</sup>

BN chewing, also known as betel quid or areca nut chewing, was thought to possess digestion improvement and refreshing by the users.<sup>2</sup> However, its health benefits is lack of evidence and on the other hand, reviewing evidence of BN toxicity, the IARC has deemed BN (with or without tobacco) as group 1 carcinogen to humans since 2004.<sup>4</sup> Furthermore, BN is not only an addictive substance but also causes systemic effects which are mainly due to the principle alkaloid arecoline with the activation of muscarinic receptors and acetylcholine receptors.<sup>17</sup>

There are some mechanisms linking diverticulosis and BN chewing. First, BN chewing is associated to increasing gastrointestinal motility which is noted among patients with diverticulosis.<sup>18</sup> The possible mechanism for arecoline causing increasing gastrointestinal motility may be the result of stimulation of M3 receptor at distal colonic smooth muscle.<sup>19</sup> Furthermore, substances in BN stimulate the release of inflammatory mediators: prostanoids, interleukin6, and tumor necrosis factor- $\alpha$ <sup>20</sup>, and reactive oxygen

species. They also activate nuclear factor- $\kappa\beta$ <sup>21</sup>, which are changes with the potential to cause chronic inflammation. The studies mentioned above could support our finding that BN chewing had higher prevalence of diverticulosis. In recent population-based study, Jarbrink-Sehgal et al. found no low-grade colonic inflammation in subjects with diverticulosis by pathologic evidence which highlighted the other possible mechanisms for the formation of diverticulosis.<sup>22</sup> Jones RB et al. also indicated no obvious alternation of gut microbiota with or without diverticulosis.<sup>23</sup> Through recent studies, the important association between colonic motility and diverticulosis goes without saying.

The present study has some notable limitations. First, it has a cross-sectional design; therefore, the causal relationship between BN chewing and diverticulosis was not assessed. A long-term observation period should be considered in future studies. Second, the presence of diverticulum was observed by colonic scope, and was recorded only with the presence without further subgroup analysis for the right, left, or sigmoid diverticulosis. Third, the questionnaire of daily quantity of betel use was not performed for further dosage effect evaluation. In addition, the participants in our study could not represent nationally, so further study for general population was necessary to obtain external validation.

## Conclusion

In conclusion, our study first reported the independently significant association between history of BN chewing and diverticulosis. Due to not fully understood main mechanism causing diverticulosis, the effect of BN on stimulation of gastrointestinal motility might break new ground for the underlying cause. Therefore, further study for association between quantity of BN exposure and diverticulosis are required.

## Abbreviation

Betel nut, BN; Body mass index, BMI; Odd ratio, OR; Confident interval, CI

## Declarations

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### *Contributions*

Yu-Hong Liu contributed to the design of the study, was responsible for the management and retrieval of data, contributed to initial data analysis and interpretation, drafted the initial manuscript. Yu-Hong Liu and Wei-Liang Chen decided upon the data collection methods. Yu-Hong Liu and Wei-Liang Chen were also responsible for the data analysis decisions. Wei-Liang Chen conceptualized and designed the study, supervised all aspects of the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors meet the [ICMJE](#) criteria for authorship.

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### **Ethics declarations**

#### *Ethics approval and consent to participate*

Our protocol was based on the Declaration of Helsinki, and was verified by the TSGH Institutional Review Board.

#### *Consent for publication*

Not applicable.

#### Competing interests

There is no conflict of interest.

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## Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

## Figures

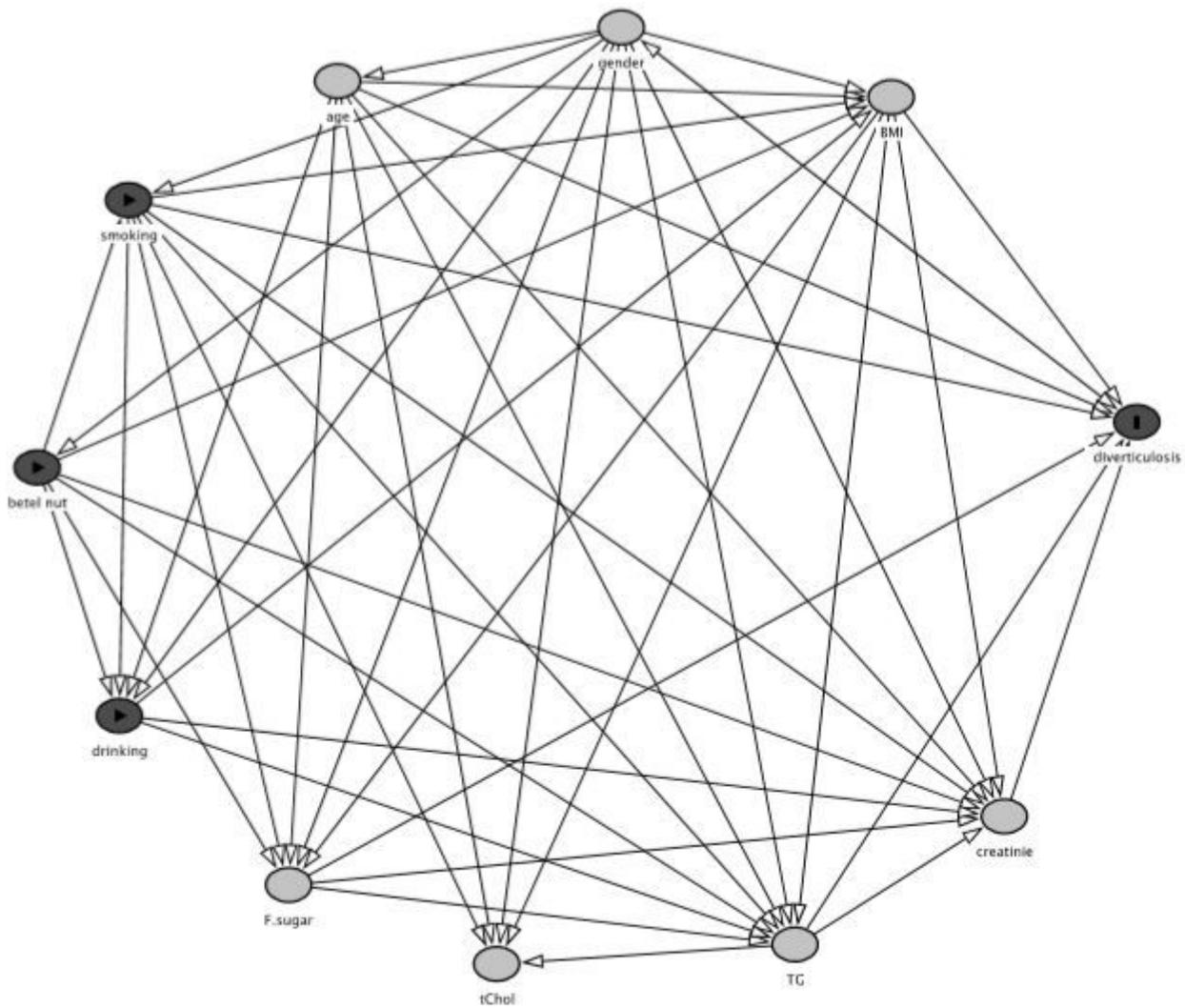


Figure 1

Figure 1

## Supplementary Files

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- [Table.pdf](#)