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Review article

Incorporating behavioral research to examine the relationship between betel quid chewing and oral cancer in Taiwan

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ABSTRACT

Cancer of the oral cavity is one of the most commonly diagnosed cancers and one of the leading causes of death among men in Taiwan. Extensive research findings have linked betel quid chewing with oral cancer and precancerous conditions. To date, no pharmaceutical or behavioral treatments exist for betel quid cessation. This paper discusses the potential benefits of applying behavioral research to better understand why betel quid chewers consume betel quid. Specifically, it discusses using behavioral research methods to examine betel quid chewing initiation, dependence, motivation, and withdrawal. Better understanding of these different aspects of betel quid chewing is likely to aid researchers in developing treatment programs.

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1. Introduction

Cancer of the oral cavity is one of the fastest growing cancers among men in Taiwan. Between 1979 and 2006, the age-adjusted incidence for oral cancer among men increased seven times, from 5.04 per 100,000 to 35.88 per 100,000, an increase that is greater than that of the other nine most common cancers among Taiwanese men [1]. In 2006, cancer of the oral cavity was the fourth most commonly diagnosed cancer and the fourth leading cause of cancer death among men in Taiwan.

The International Agency for Research on Cancer has identified tobacco smoking and betel quid (BQ) chewing, with or without tobacco, as Group 1 carcinogens to humans [2]. Both habits have been found to be significantly related to oral cancer among men in Taiwan. In this paper, we

review current research on BQ use in Taiwan and the evidence regarding the link between BQ chewing and smoking and oral cancer among Taiwanese men. We also discuss the need for cessation of BQ chewing and smoking as a form of primary cancer prevention and as reduction of risk for additional cancer following cancer diagnosis and treatment.

2. BQ chewing in Taiwan

It is estimated that some 600 million people use BQ worldwide [2]. BQ chewing is popular in many Asian countries. Three types of quid, *lao-hwa* quid, BQ, and stem quid, are typically found in Taiwan [2]. *Lao-hwa* quid and stem quid are prepared by adding, respectively, a piece of inflorescence of *Piper betle* L.

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with red lime paste or a piece of *Piper betle* L. stem to an unripe areca nut. A BQ is made by wrapping a split unripe areca nut with slaked lime paste with a piece of betel leaf. In contrast, the practice in many southeast Asian countries, tobacco is never added to BQ in Taiwan.

The 2005 Taiwan National Health Interview Survey [3] found that, among the 16,542 adult respondents (age 18–64 years), 9.2% reported that they were current BQ chewers, 4.5% indicated that they had quit in the last 6 months, 7.2% indicated that they had tried BQ but were not regular users, and 79.1% responded that they had never used BQ. Of the current chewers, 42% chewed BQ daily, 16% chewed BQ on 3–5 days/week, and 22% used BQ on 1–2 days/week, and 20% chewed <4 days/month. Most chewers were men. Although 17% of all men living in Taiwan reported chewing BQ, <1% of all women reported regular use of BQ. Several other studies have confirmed this gender disparity in BQ chewing among adults [4–6] and adolescents [7,8]. The National Health Interview Survey also found that the majority of chewers were aged 35–44 years, lived in rural and less urbanized areas, and reported a family income of lower than NT\$30,000. Furthermore, individuals who completed junior high school or less in education and those who worked in nonprofessional, blue-collar occupations were more likely to chew BQ [9].

Due to historical and cultural factors, BQ chewing is especially widespread among ethnic aborigines, who make up approximately 2% of the population in Taiwan [10]. A stratified random survey that examined 7144 individuals in over 50 aboriginal communities found that 53% of male and 38% of female aborigines reported current or former use of BQ [10]. Three other large-scale surveys that sampled both aborigines and nonaborigines have also confirmed a higher rate of BQ chewing among aborigines [5,9,11]. The prevalence was estimated to be as high as 61% for men and 79% for women in a study that surveyed BQ chewing in a single aboriginal community in southern Taiwan [12]. Thus, the gender disparity that is found in the Taiwanese general population does not exist and may even be reversed among the ethnic aboriginal population.

Cigarette smoking and alcohol drinking have been found to be significantly associated with BQ use [5,8–10]. For example, Wen et al [13] analyzed data collected in the 2001 National Health Interview Survey in Taiwan and found that 93% of BQ chewers were current cigarettes smokers. It was also estimated that 50–67% of betel quit chewers consumed alcohol regularly [9,10].

We identified three surveys that examined unaided BQ cessation [9,10,14]. One study, which classified chewers as successful quitters if they had not chewed any BQ in the last 12 months, reported quit rates of 8.2% in male aborigines and 6.7% in female aborigines [10]. Using a less stringent criterion in which successful quitters were defined as chewers who had not chewed any BQ in the last 6 months, Lai et al [14] found that 49% of the Chinese (i.e., nonaborigine) chewers in their study had quit successfully. Similarly, Yap et al [9] reported that 28.6% of male nonaborigine chewers and 15.7% of female nonaborigine chewers had quit chewing in the last 6 months. Aborigine chewers had less success in quitting, with 7.8% of male and 9.8% of female chewers stopping chewing for at least 6 months. No information on relapse was discussed in any of the three studies.

Several factors, including gender, alcohol use, and level of education, have been found to be predictive of BQ cessation. Regarding gender, while one study found that male chewers were significantly more likely than female chewers to quit [odds ratio (OR) = 4.22, 95% confidence interval (CI) = 3.74–4.77] [9], another study found that although men quit at a higher rate than women, the odds ratio only approached significance (OR = 1.25, 95% CI = 0.95–1.64) [10]. These studies also found that those who drank alcohol and chewers who completed less education were significantly less likely to quit [9,10,14]. Younger chewers were more successful than older chewers in quitting [9,10]. The findings on the association between smoking and BQ cessation were mixed. One study found that chewers who did not smoke were more successful in quitting than those who did [9], whereas another failed to find significant difference in quitting success between smoking and non-smoking chewers [10].

3. BQ chewing, cigarette smoking, and cancer

A high incidence of oral cancer has been observed in countries where tobacco was routinely added to BQ [2]. In Taiwan, where tobacco is never added to BQ, numerous studies have found that BQ chewing, by itself or in combination with smoking, is significantly associated with precancerous oral lesions, cancer, and cancer death.

3.1. Oral submucous fibrosis and oral leukoplakia

Oral mucosal lesions such as oral submucous fibrosis (OSF) and oral leukoplakia (OL) are risk factors for and have been found to transform malignantly to oral cancer [15,16]. Two case-control studies have investigated the effects of BQ chewing and cigarette smoking on OSF and OL [17,18]. One study that examined 62 histologically diagnosed OSF patients and 62 matched controls found that BQ chewers were 4.51 times (95% CI = 1.20–16.94) more likely than nonchewers to have OSF [18]. Individuals with both smoking and chewing habits had even higher risk of OSF (OR = 8.68, 95% CI = 1.87–40.23). A significant dose response effect was found, with chewers who used between 10 and 29 quids/day having a 4.55-fold (95% CI = 1.16–17.84) increase in risk and chewers who used 30 or more quids/day having a 10.34-fold (95% CI = 2.39–44.73) increase in risk for developing OSF compared to matched controls.

In another study that included 219 patients with histologically confirmed OL or OSF and 876 community controls, the risk for developing OL was 22.3 (95% CI = 11.3–43.8) times higher for current chewers than never chewers and the risk for developing OSF was 40.7 times (95% CI = 16.0–103.7) higher for current chewers than never chewers [17]. Significant dose response effects were also found for the development of both OL and OSF. A synergistic effect of BQ chewing and cigarette smoking on OL and OSF was also reported. Compared to individuals who neither chew BQ nor smoke cigarettes, those with both habits had a 40-fold (95% CI = 16.3–99.2) increase in risk of OL and a 57.9-fold (95% CI = 16.0–209.6) increase in risk for OSF.

In addition to case-control studies, three community surveys employed dentists to conduct oral examinations to diagnose OSF and OL in order to investigate the effects of BQ chewing on precancerous oral lesions. Yang et al [19] screened over 2000 participants and found that BQ chewing increased men's risk for OL and OSF, respectively, by 6.57-fold (95% CI = 3.51–12.28) and 22.86-fold (95% CI = 7.28–71.73), and increased women's risk for OL and OSF, respectively, by 15.63 fold (95% CI = 8.31–29.39) and 13.03-fold (95% CI = 5.21–32.62). The results also showed a significant positive association between chewing frequency and risks of OL and OSF, as well as between years of chewing and risks of OL and OSF. That is, heavier chewers with longer durations had higher risks of OL and OSF than lighter chewers with shorter durations of chewing.

A second large-scale study surveyed 1075 adults in southern Taiwan. It found that quid chewers' risk of oral precancerous lesions (OL, OSF, and verrucous lesions) were 8.4 times (95% CI = 5.13–13.75) higher than nonchewers [20]. This study also found a significant synergistic effect of BQ chewing, cigarette smoking, and alcohol drinking on OL. Compared to individuals who did not use BQ, cigarettes, or alcohol, those with reported regular use of all three substances had a 15.12-fold (95% CI = 6.34–36.05) increase in risk of OL.

Given the high prevalence of BQ chewing among aborigines, their risks of oral lesions were specifically examined in a study that screened 312 individuals from an aboriginal community in southern Taiwan [12]. Results showed that the odds of developing either OSF or OL were 8.21-fold (95% CI = 1.80–37.46) higher among chewers than among nonchewers.

So far, five studies have found significant results confirming the etiological role of BQ chewing in the development of oral precancerous conditions. These oral lesions have often been found to be precursors of oral cancer [15,16]. Two case-control studies that examined the effect of BQ chewing on the malignant transformation from oral lesions to oral cancer yielded mixed results. In one study that examined a cohort of 435 individuals diagnosed with OL, BQ chewers were 4.59 times (95% CI = 1.25–16.85) more likely than nonchewers to experience a malignant transformation to oral cancer [21]. However, another study that examined 104 histologically confirmed OSF patients failed to find a significant effect of BQ chewing on the development of oral cancer among OSF patients [22].

3.2. Oral, esophageal, and pharyngeal cancer

Four case-control studies investigated the association between BQ chewing and oral, esophageal, and pharyngeal cancer. In a study that enrolled 107 cancer patients and 200 matched noncarcinoma patients, researchers found that chewers had a significantly higher risk than nonchewers of developing oral cancer (OR = 6.9, 95% CI = 3.1–15.2) [23]. Among BQ chewers, those who also smoked cigarettes saw their risk of oral cancer increased from 6.9 times to 89 times (95% CI = 10.0–790.7) higher than those who did not use either BQ or cigarettes.

Two studies reported a positive association between BQ chewing and squamous-cell carcinoma of the esophagus.

Both case-control investigations paired patients with histologically confirmed esophageal cancer with hospital-matched noncancer (control) patients. Wu et al [24] recruited 104 cases and 277 controls and found a significant dose-response effect of BQ chewing on esophageal cancer. Compared to non-chewers, patients who consumed ≤ 495 betel-years (about 20 quids/day for 20 years) had a 3.6-fold (95% CI = 1.3–10.1) increase in risk of esophageal cancer; those who consumed >495 betel-years had a 9.2-fold (95% CI = 1.8–46.7) increase in risk of esophageal cancer.

Lee et al [25] found, in a multi-site case-control study that included 513 esophageal cancer and 818 hospital-matched control patients, that BQ chewers had a 2.3-fold (95% CI = 1.4–3.7) increase in esophageal cancer than non-chewers. They also found a significant association between risk of esophageal cancer and initiation age of BQ chewing, years of chewing, and average amount of quid consumed/day. Furthermore, a synergistic effect of BQ chewing and cigarette smoking was found. Compared to individuals who neither smoked nor chewed, adding cigarette smoking to BQ chewing increased patients' risk of esophageal cancer from 2.3-fold to 8.8-fold (95% CI = 5.2–14.8).

In a study that examined 148 patients with histologically confirmed pharyngeal cancer, 128 patients with histologically confirmed laryngeal cancer, and 255 matched control patients, the results showed that BQ chewing was significantly associated with pharyngeal (OR = 6.9, 95% CI = 3.4–14.3) but not laryngeal cancer [26]. Compared to non-chewers, patients who chewed more than 20 quids/day (OR = 7.2, 95% CI = 3.6–14.8) were also found to incur a significantly higher risk of pharyngeal cancer than those who chewed less than 20 quids/day (OR = 2.5, 95% CI = 1.0–3.8). Adding cigarette smoking to BQ chewing significantly increased patients' risk of pharyngeal cancer from 6.9-fold to 19.0-fold (95% CI = 5.7–70.6). Chewers who swallowed the BQ juice had higher odds (OR = 8.7) of developing pharyngeal cancer than nonswallowers (OR = 6.2). The pharynx, which is located immediately posterior to the mouth, may be more likely than the larynx, which is located in the upper air way and is inferior to the pharynx, to come into direct contact with BQ. As such, the differential anatomical position of the two structures may explain why BQ chewing is significantly associated with pharyngeal but not laryngeal cancer.

In addition to the case-control studies, two cohort studies also found evidence that supported a significant association between BQ chewing and oral cancer. The first study screened 8356 male patients (191 patients were diagnosed with oral cancer) over 2 years at a Taichung hospital and found a significant effect of BQ chewing on the development of oral cancer (OR = 9.03, 95% CI = 3.22–37.34) [27]. The OR of oral cancer increased to 21.79 (95% CI = 11.08–42.85) for patients who chewed BQ and smoked cigarettes.

Finally, information from 177,271 men who participated in a medical screening program was included in a large cohort study that examined the relationship between BQ chewing and cancer mortality [28]. In this study, the majority (90%) of those who chewed BQ also reported cigarette smoking. Compared to men who did not chew BQ or smoke cigarettes, BQ chewers were found to have a significantly higher risk of oral cancer

death [hazard ratio (HR) = 12.52, 95% CI = 5.45–28.77]. BQ chewers were also found to have elevated risk for esophageal cancer death (HR = 5.64, 95% CI = 2.25–14.12), liver cancer death (HR = 2.27, 95% CI = 1.12–4.60), pancreatic cancer death (HR = 2.67, 95% CI = 1.23–5.78), larynx cancer death (HR = 6.24, 95% CI = 1.03–37.44), and lung cancer death (HR = 2.43, 95% CI = 1.73–3.41). Since 90% of the BQ chewers also smoked cigarettes, efforts were made to tease apart the unique contribution of BQ chewing to cancer mortality. Compared to smokers who did not chew BQ, smokers who chewed had a significantly higher hazard of oral cancer death (HR = 4.84, 95% CI = 2.68–8.72), esophageal cancer death (HR = 2.20, 95% CI = 1.12–4.02), liver cancer death (HR = 1.73, 95% CI = 1.35–2.23), and larynx cancer death (HR = 4.09, 95% CI = 1.33–12.55).

In summary, findings from case-control, survey, and cohort studies have revealed a significant effect of BQ chewing on the development of precancerous oral lesions, oral cancer, esophageal cancer, and pharyngeal cancer. These risks were found to be considerably compounded if BQ chewers also smoked cigarettes. Both chewing BQ and smoking have been found to be associated with oral, esophageal, liver, pancreatic, larynx, and lung cancer mortality.

4. Behavioral research program on BQ chewing

Although extensive research findings have linked BQ chewing with oral cancer and precancerous conditions, to date, no pharmacological or behavioral treatments exist for BQ cessation. Previous studies that examined Taiwanese BQ chewers have found that male gender [3–6], membership in an aboriginal tribe [5,9,11], low socio-economic status [3,9], cigarette smoking [13], and alcohol drinking [9,10] are significantly associated with BQ use [3]. While these findings provide valuable information about who uses BQ (i.e., the characteristics of BQ users) in Taiwan, they offer relatively few insights about why these users chew BQ. Better understanding of the reasons why chewers consume BQ is likely to aid researchers in developing treatment programs.

In tobacco research, findings from behavioral studies have contributed significantly to the understanding of nicotine addiction as well as to the development of smoking cessation interventions. For example, several behavioral models of drug addiction have been proposed, which have enriched our understanding regarding smokers' motivation to smoke [29,30] as well as the importance of smoking-related cues in eliciting smoking behaviors [31,32]. Behavioral studies have also uncovered a positive association between nicotine withdrawal symptoms and cessation failure [33–36]. Furthermore, behavioral researchers have found evidence that many behavioral and cognitive constructs (e.g., smoking outcome expectancies, self-efficacy) predict smoking relapse [37,38]. An enormous trove of studies exists on each of these topics and a comprehensive review is beyond the scope of the present article. Thus, we briefly review several areas of behavioral research on smoking and discuss their potential application to BQ chewing.

Considering the contributions that behavioral research has added to the understanding of smoking and smoking

cessation, we propose that similar efforts should be initiated to define the behavioral aspects of BQ chewing. To better understand the different facets of BQ chewing, we suggest that behavioral researchers: (1) examine the factors relating BQ chewing initiation; (2) develop a self-report instrument that measures BQ dependence; (3) investigate chewers' motivation to chew BQ; and (4) document withdrawal symptoms experienced by chewers upon stopping BQ.

4.1. Examination of factors for BQ chewing initiation

Earlier smoking research focused on individual differences in sensitivity to nicotine, personality, and psychopathology to explain differences in smoking initiation. For example, individuals who showed high sensitivity to their initial exposure to nicotine [39], those with neurotic personality [40], those who suffered from major depression or schizophrenia [41], and those who met criteria for conduct or oppositional defiant disorder [42–44] were at higher risk of becoming smokers. Other studies showed that differences in life experiences such as poor or abusive childhood [45,46], major negative life events [47], and acute or chronic life stressors [48,49] increased a person's risk of taking up smoking. Furthermore, energy-balance factors, such as weight control, have been found to influence adolescents, especially young women, in starting smoking [50,51].

While there are many cross-sectional studies that reported demographic differences between BQ chewers and non-chewers [3,5,10], relatively few studies (cross-sectional or longitudinal) have looked at the role that innate constitutional (e.g., sensitivity to arecoline), psychological, or life experiential factors play in BQ initiation. Understanding not only who but also how a person takes up BQ chewing, and how one progresses from experimental to dependent chewers is likely to prove useful in the future development of BQ cessation programs.

4.2. A self-report instrument to measure BQ dependence

Previous studies have shown that nicotine dependence is a significant inverse predictor of success in long-term smoking cessation [52–54]. That is, smokers with a high level of nicotine dependence are significantly less likely than those with a low level of dependence to achieve and maintain smoking abstinence. Furthermore, nicotine dependence has also been found to be associated with psychiatric and other drug dependence disorders [41,55–57].

Nicotine dependence is typically measured using the Fagerström Test for Nicotine Dependence [58], a six-item self-report instrument that assesses various components of smoking behavior such as daily intake, difficulty in refraining from smoking, and time to first cigarette of the day. The items were derived based on smokers' dose (e.g., number of cigarettes smoked/day) and on behaviors often observed in dependent smokers (e.g., earlier smoking in the morning, difficulty refraining from smoking in places where smoking is prohibited). The Fagerström Test for Nicotine Dependence has been shown to be reliable and smokers' scores on the measure are significantly correlated with biochemical markers of nicotine use [58].

BQ chewing is an addictive behavior and chewers are likely to differ in their dependence on the BQ. A self-report instrument to assess BQ dependence will provide researchers with an easy to administer and valid mean to quantify chewers' dependence. With such an instrument, researchers can begin to examine questions regarding dependence (e.g., are all BQ chewers dependent?), consumption (e.g., do more dependent chewers chew more BQs/day?), and abstinence (e.g., do more dependent chewers have more difficulty quitting than their less dependent counterparts?). A self-report dependence scale will also allow researchers to examine the role that active quid ingredients (e.g., arecoline, arecaidine) plays in BQ use, and the complex ways in which these ingredients interact with behavioral and sensory factors in determining BQ consumption.

Two studies have shown that arecoline can be reliably detected, using high-performance liquid chromatography, in BQ chewers' saliva [59] and blood [60]. Wu et al [60] further demonstrated that the levels of plasma arecoline and plasma arecaidine found in BQ chewers' blood were positively correlated with the amount of BQ consumed, making them ideal biochemical markers of BQ use. Future behavioral research should consider employing plasma arecoline or arecaidine levels to validate self-report dependence measure or to verify self-report BQ use and cessation.

4.3. Chewers' motivation to chew BQ

Smoking behaviors are often influenced by smoking outcome expectancies. It has been hypothesized that while smokers with high expectancies for positive outcome of smoking (e.g., positive mood enhancement, alleviation of negative mood) are likely to increase their cigarette consumption, those with high expectancies for negative smoking outcome (e.g., smoking is detrimental to one's health) are likely to reduce their cigarette intake. Several studies have found that positive smoking outcome expectancies significantly predict the occurrence of smoking lapse and relapse [61–63].

Many BQ chewers expect that chewing can improve their mood, heighten their alertness, quench their thirst, warm their body, curb their appetite, and increase their stamina [64]. They also know that chewing increases their risk of oral cancer [3]. Nevertheless, it is unclear whether or not these positive and negative outcome expectancies of chewing influence chewers' behaviors. To better understand chewers' motivation to use or to quit BQ, it is imperative for behavioral researchers to begin to examine these factors and their effects on chewing.

4.4. BQ withdrawal symptoms

When smokers stop smoking, they experience nicotine withdrawal symptoms that may include a negative affect (e.g., depression), urge to smoke, irritability, anxiety, cognitive and attention deficits, sleep disturbance, and increased appetite. The nature of postcessation withdrawal symptoms may have important implications for smoking relapse. If postcessation withdrawal symptoms resolve quickly, abstinent smokers may be less motivated to smoke and may have better success in maintaining their abstinence. However, if postcessation

withdrawal symptoms are unrelenting, abstinent smokers may be more driven to smoke and may eventually resort to smoking for withdrawal relief. Numerous studies have found evidence that supports a strong link between postcessation withdrawal symptoms and smoking lapse or relapse. For example, Piasecki et al [33–36] identified several different trajectories of nicotine withdrawal and found that abstinent smokers who had prototypical withdrawal profile (transient course with quick resolution of symptoms) were significantly less likely to lapse than those who had the atypical profiles (extended course of unrelieved symptoms).

Specific nicotine withdrawal symptoms have also been found to be directly and indirectly associated with smoking and smoking relapse. At least one model of addiction has examined the effects of negative affect on smoking [29] and postcessation negative affect has been found to be one of the most potent predictor of relapse [65–69]. In addition to negative affect, smoking urge has also received a lot of attention in smoking cessation research. Several studies have found a positive link between urge and smoking relapse [70,71]. Finally, smokers often use smoking as a mean to control their body weight. Several studies have found evidence suggesting that smokers, especially women, who quit smoking resumed their cigarette consumption to curb increased appetite, a symptom of nicotine withdrawal [72–75].

Given this evidence regarding the effect of withdrawal symptoms on smoking relapse, we argue that it is important to study BQ withdrawal symptoms and to track changes in them across the postcessation period. Anecdotal evidence suggests that BQ chewers may experience withdrawal symptoms when they stop chewing. However, to date, no systematic efforts have been made to investigate what constitutes BQ withdrawal. Thus, we suggest that behavioral researchers to begin to identify the nature and frequency of all symptoms of withdrawal that BQ chewers experience when they abstain from chewing, and to track these overtime.

5. Summary

As many as 10% of people in Taiwan chew BQ. A typical chewer is male, middle-aged, living in a rural area, has a low level of education, and works in a blue-collar occupation. Among chewers, those who do not use alcohol and have a higher level of education are more successful in quitting. Despite a strong link between BQ chewing and oral cancer, relatively few efforts have been made to examine why chewers use BQ and the behavioral sequelae that are related to BQ addiction. We suggest several areas (dependence, drug use motivation, and withdrawal symptoms) in which researchers can begin to study the behavioral aspects of BQ chewing.

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