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Intercountry prevalences and practices of betel-quid use in south, southeast and eastern Asia regions and associated oral preneoplastic disorders: an international collaborative study by Asian betel-quid consortium of south and east Asia

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Health risks stemming from betel-quid (BQ) chewing are frequently overlooked by people. Updated epidemiological data on the increased BQ use among Asian populations using comparable data collection methods have not been widely available. To investigate the prevalence, patterns of practice and associated types of oral preneoplastic disorders, an intercountry Asian Betel-quid Consortium study (the ABC study) was conducted for Taiwan, Mainland China, Malaysia, Indonesia, Nepal and Sri Lanka. A random sample of 8,922 subjects was recruited, and the data were analyzed using survey-data modules adjusted for the complex survey design. Chewing rates among men (10.7–43.6%) were significantly higher than women (1.8–34.9%) in Taiwan, Mainland China, Nepal and Sri Lanka, while women's rates (29.5–46.8%) were higher than that for men (9.8–12.0%) in Malaysia and Indonesia. An emerging, higher proportion of new-users were identified for Hunan in Mainland China (11.1–24.7%), where Hunan chewers have the unique practice of using the dried husk of areca fruit rather than the solid nut universally used by others. Men in the Eastern and South Asian study communities were deemed likely to combine chewing with smoking and drinking (5.6–13.6%). Indonesian women who chewed BQ exhibited the highest prevalence of oral lichen planus, oral submucous fibrosis and oral leukoplakia (9.1–17.3%). Lower schooling, alcohol drinking and tobacco smoking were identified as being associated with BQ chewing. In conclusion, the ABC study reveals the significant cultural and demographic differences contributing to practice patterns of BQ usage and the great health risks that such practices pose in the Asian region.

Epidemiology

Key words: Asia, areca nut, betel-quid, epidemiology, oral disorders, substance abuse

Abbreviations: AN: areca nut; BQ: betel-quid; OL: oral leukoplakia; OLP: oral lichen planus; OSF: oral submucous fibrosis; TA-BQ: tobacco-added betel-quid; TF-BQ: tobacco-free betel-quid

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Betel-quid (BQ), a mixture of areca nut (AN) in combination with betel leaf and slaked lime, packed with flavoring ingredients like condiments and sweetening agents, is a chewing (masticatory) substance that is extensively used by diverse Asian populations. Although it is prepared with regional variations, AN is the most important component of BQ. There are an estimated 600 million BQ users in the world, predominantly on the Indo-Pakistan subcontinent, in countries in South and Southeast Asia, on islands around the Pacific Rim and in migrant populations in Africa, Europe and North America.[1]

While in many parts of the Indian subcontinent, habitual chewers often add tobacco to the BQ, in Taiwan and Papua New Guinea, for example, tobacco is never added. Due to long-standing cultural perspectives, its use has been viewed as publicly acceptable among all strata of society, including women and children.[2,3] Epidemiological surveys have reported that in the past 2 to 3 decades, 20–40% of the population in India, Nepal and Pakistan have customarily used BQ.[4] Although a decreased trend in the consumption of BQ has been observed in certain countries or regions, such as in Thailand, an alarmingly high chewing prevalence has been found among the Palauans of the West Pacific (a 72–80% use of BQ, with 80% found to be consumers of tobacco-added mixtures).[4,5] To our knowledge, population data in regard to BQ usage stemming from comparable data collection tools have not been available.

There is sufficient evidence that both tobacco-added (TA-BQ) and tobacco-free (TF-BQ) BQ are carcinogenic to humans.[6] Furthermore, the mastication of AN is associated with the development and onset of several premalignant lesions in the oral cavity, such as oral submucous fibrosis, which have a high potential for malignant transformation.[6,7] Evaluations performed by the International Agency for Research on Cancer (IARC) have shown that BQ consumption is causally linked to cancer of the oral cavity, pharynx and esophagus and, with restricted evidence, to liver cancer.[8] Recent epidemiological studies have shown that BQ use is associated with a 1.8–2.1-, 1.6–2.0-, 1.2–1.9-, 1.3- and 2.6-fold higher risk of suffering from obesity,[9] metabolic syndromes,[10] cardiovascular disease,[11] type 2 diabetes[12] and chronic kidney disease,[13] a 2.4–3.7-fold risk of delivering low birth weight infants[14,15] and a 3.6-fold risk of developing cirrhosis of the liver.[16] It is increasingly clear that there are multidimensional health consequences to the use of BQ.

In recent years, the marketing of industrially manufactured BQ products in Asia that contain a variety of areca mixtures with and without tobacco has made the use of this substance common and popular, especially to children and adolescents.[4] Comprehensive data on the prevalence, usage patterns and conditions of associated oral neoplasia had previously been limited in numerous Asian populations. Such information is warranted to recognize contemporary problems so as to better facilitate the strategic development of prevention and the control of AN-related health consequences in this region.

In 2008, in conjunction with the World Health Organization Collaborating Centre for Oral Cancer in the United Kingdom, the Center of Excellence for Environmental Medicine at Kaohsiung Medical University (KMU) in Taiwan initiated an international collaborative project to mobilize outreach activities in disease prevention focusing on the health effects of BQ in Asian communities (the Asian Betel-quid Consortium study, termed ABC study). Six large study centers participated in this international research consortium (East Asia: Taiwan and Mainland China; Southeast Asia: Malaysia and Indonesia; South Asia: Nepal and Sri Lanka), where the goals were to update the characteristics of usage prevalence and the patterns of use with other substances within the Asian region as well as the potential identification of genetic susceptibilities to oral malignancies. Our study represents phase I among a wide range of planned activities by this consortium. The specific aims herein were to outline the current prevalence of BQ use, the characteristics among the variations of practice, the lifestyle factors inherent in BQ usage and the types of associated oral preneoplastic disorders across the countries that were studied.

Material and Methods

Recruitment in the phase I study by this consortium commenced in January 2009 and ended in February 2010. The same research protocol was applied among the countries in the study, with the purpose of offering a comparative framework. This proposal was approved independently by the Research and Ethical Review Committees at the KMU (Kaohsiung) in Taiwan, the Central South University (Changsha) in Mainland China, the University of Malaya (Kuala Lumpur) in Malaysia, the Airlangga University (Surabaya) in Indonesia, the Kathmandu University (Kavrepalanchwok) in Nepal and the University of Peradeniya (Peradeniya) in Sri Lanka. Written informed consent was obtained from all of the participants prior to the collection of data.

Study population

The study populations comprised of residents from southern Taiwan; the Hunan Province of Mainland China; the Selangor, Sabah and Sarawak States of Malaysia; the North Sumatran, East Javan, Balese, West Nusa Tenggara, South Sulawesi and Papua Provinces of Indonesia; as well as the Middle of Nepal and the Central Province of Sri Lanka, as shown in Figure 1.

Using demographic data from census records and the household registry of individual participating countries, a multistage sampling approach was employed to select civilian, noninstitutionalized representative samples of the general population of the ages of 15 and older. In stage one, a number of cities and rural areas were independently selected to favorably make up and represent the geographic and economic status within each population to be studied. The resulting chosen regions were Kaohsiung and Pingtung of southern Taiwan; Changsha, Liuyang, Changde, Yongzhou,

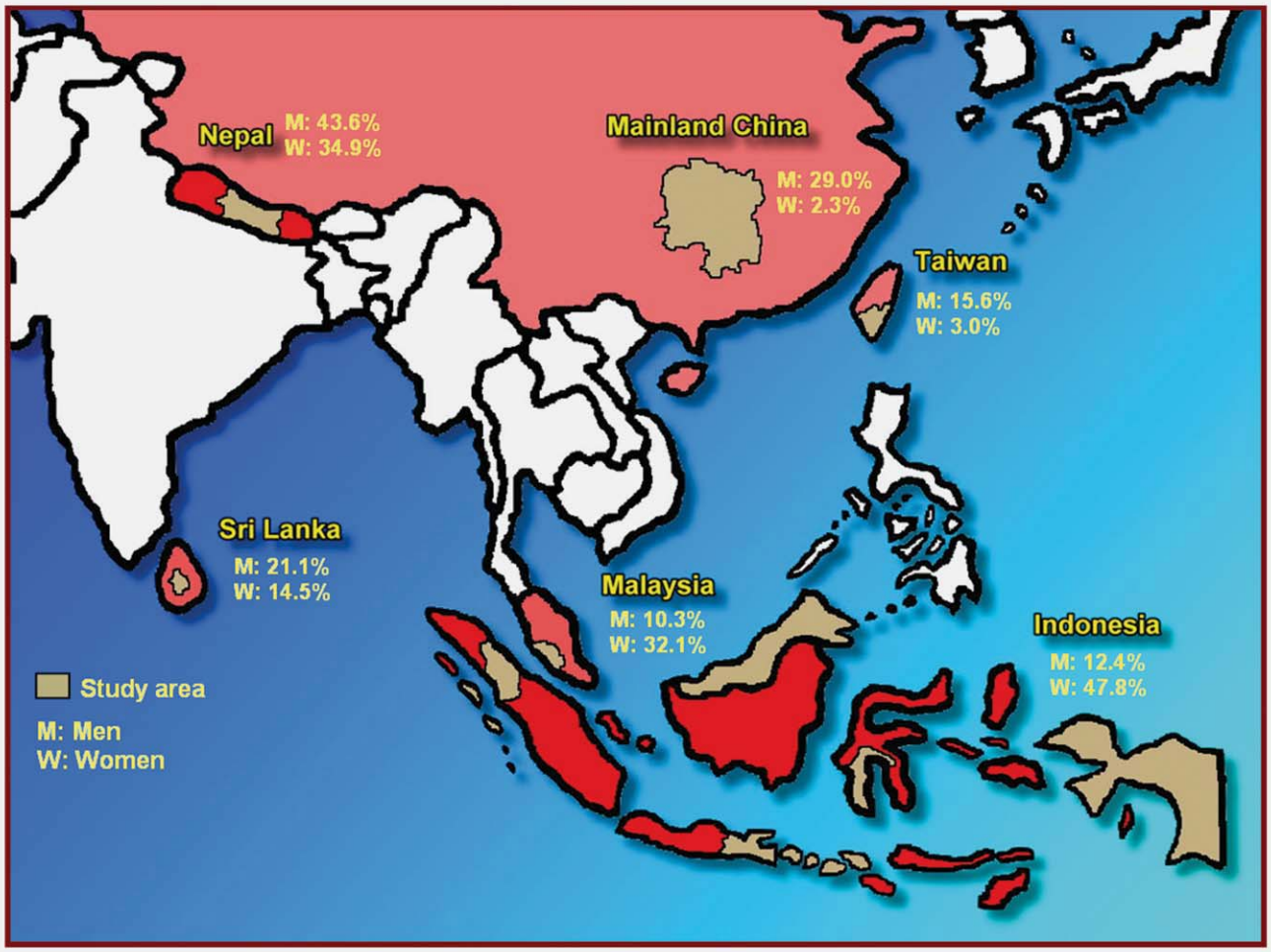

Figure 1. The geographic regions showing lifetime prevalence rate of betel-quid chewing by gender distribution in the Asian countries studied in the ABC study. The international mobilizing outreach activities in prevention of potentially malignant oral disorders. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

LouDi and Xiangxi prefecture, Hunan of Mainland China; Pulau Carey, Simpang Morib and Klang (Selangor), Kampung Sembirai and Kota Belud (Sabah), Kampung, Tebedu/Mongkos and Serian (Sarawak) of Malaysia; Deli Serdang (North Sumatra), Pacitan and Banyuwangi (East Java), Jembrana (Bali), Mataram (West Nusa Tenggara), Tana Toraja (South Sulawesi) and Wamena (Papua) of Indonesia; Kathmandu, Chitwan, Nawalparasi and Pokhara of middle Nepal and Gangawata Korale, Udunuwara, Yatinuwara of Sri Lanka.

In the second stage, projected numbers for administrative districts or townships were randomly selected. In stage three, researchers listed households within each district/township, and a sample of households was randomly drawn. In the final stage, subjects were chosen to participate in our study from a list of people residing in the selected households. On average, 2.2–2.6 people were selected per household in Taiwan, Malaysia, Indonesia and Sri Lanka. Due to logistic concerns, only one participant was randomly selected from each household in the populations of Mainland China and Nepal. With this exception, a similar sampling scheme was implemented in all of the areas that were studied.

Data collection

After the study samples were drawn, the research teams conducted door-to-door home visits to the participants' dwellings to conduct the interviews. Each survey team consisted of a principle investigator (PI), four to five trained interviewers and data-recording clerks. The purposes and procedures involved in the study were explained to all of the participants. The resulting total of those surveyed who completed the interviews was: 1,548 subjects in Taiwan, 2,356 in Mainland China, 1,003 in Malaysia, 1,941 in Indonesia, 1,002 in Nepal and 1,072 in Sri Lanka. The response rates were 68% for Taiwan, 79% for Mainland China, 71% for Malaysia, 100% for Indonesia, 99% for Nepal and 99% for Sri Lanka, respectively.

Data were collected by trained staff members who had recently successfully completed the necessary training

program as a prerequisite to working in each study center under the supervision of the country's PI. A standardized questionnaire was developed which was adapted from WHO surveys and sources such as national prevalence surveys. The original questionnaires were written in English and translated into the appropriate language or dialect for each country. They were later retranslated into English to verify their validity. The questions have been written in community-specific languages, and in the few situations where the participants were unable to understand the questions, study items were translated into local dialects by investigators with the assistance of local, native people. Pictograms were used to clarify constituents used to make the BQ. The interviewer-administered structured questionnaire gathered data on the sociodemographics and habits of lifetime BQ usage, alcohol intake and tobacco use (including tobacco smoking and smokeless tobacco use). In addition, information concerning the age at which subjects started using these substances, the daily consumption, duration of usage, as well as the types and frequency of substances consumed were collected. For the BQ users, further information was collected in regard to the materials added with AN. Chewers were also asked to report whether they had habitually swallowed fluids from such chewing. Moreover, in preparation for their work in the detection of oral lesions, the dentists or dental hygienists/medical officers received 1 month of standardized training in regard to performing oral cavity examination, and this was done under the supervision of the survey team's PI. The training programs included differential diagnosis for oral disorders where clinical pictures were used and pretest courses conducted in a clinical or field setting.

Our study defined BQ chewers as subjects who had consumed at least one quid per day of any type of betel/AN product for a minimum of 6 months. Alcohol drinkers and tobacco smokers were defined separately as individuals who had drunk any type of alcoholic beverage per week and/or had smoked/chewed one or more tobacco products per day for at least 6 months. Among them, current-users were those who had any of these habitual practices within the year prior to the interview; past-users were defined as those who had stopped any of the habits for at least a year before the interviews took place.

Statistical analysis

The study data was analyzed using survey-data modules implemented in Stata v11, a technique that adjusts for the complex survey design. All analyses, including means, percentages, standard errors, point estimates for prevalence and regression modeling were conducted on weighted data that took age and gender structure into account. For continuous and binary/multinomial outcomes, we respectively used multiple linear and logistic/polytomous regression models to assess across country differences in regard to the characteristics of BQ usage. A multivariate logistic regression model was employed to investigate the influence of age, gender, educational level, alcohol consumption and tobacco smoking on country-specific behaviors in BQ use. Because observed gender heterogeneity in the chewing prevalence was identified in most countries, the results were evaluated according to gender.

Results

The demographic characteristics with respect to gender, age, educational level and the status of the respective drinking and smoking are presented in Table 1. Significant differences in these factors were detected across the areas of study (all $p < 0.05$). The prevalence of tobacco smoking was found to be higher than that of alcohol drinking in every sampled country, with the highest rates occurring in Nepal for both smoking (55.2%) and drinking (29.9%).

Table 2 compares the prevalence and BQ usage among the communities that were studied according to gender. Remarkable country-dependent differences in lifetime prevalence were observed for both genders (p for difference <0.005). As shown in Figure 1, the lifetime chewing rates for men (15.6–43.6%) were significantly higher than that for women (2.3–34.9%) in areas that were sampled in Taiwan, Mainland China, Nepal and Sri Lanka, while conversely the prevalence for women (32.1–47.8%) were notably higher than men (10.3–12.4%) in the Malaysian and Indonesian regions of investigation. In regard to the BQ ever-users, a high percentage of quitters (15.3–31.1%), with a >14 years of abstinence level was found among the Taiwanese. All of the BQ users in Nepal were current-chewers, and no quitters were identified. The Hunan (Mainland Chinese) BQ users had a shorter duration of usage (8.8–9.7 years), but a higher proportion of new consumers (usage of ≤2 years) among current-chewers (11.1–24.7%). A reported >49% chewing rate occurred in older Malaysian and Indonesian women (>40 years). In contrast, a higher prevalence of chewing (32.0%) was seen among younger Hunan men in Mainland China (<41 years).

Significant differences in the ingredients of BQ were found in the investigated communities in our study. To assess the possible carcinogenetic impact of BQ consumption, we categorized the BQ preparation according to the addition of tobacco or its being tobacco-free.[6] Table 3 shows that 100% of Nepalese chewers added tobacco to their BQ, and that, in Taiwan and the Hunan of Mainland China, tobacco is never added as an ingredient to BQ. An overwhelming majority of chewers in Taiwan consumed AN with a piece of betel leaf (84.4–93.3%), and all of the chewers in Hunan consumed the dried husk of the areca fruit (not the solid AN) marinated with flavored additives, such as lime, sweeteners, cassia oil and bittern. The highest daily quantity of BQ use by both men and women was found in Taiwan (16.2–19.5 quid). In addition, TA-BQ users chewed BQ more frequently (5.7–6.9 days per week) as compared to TF-BQ users, the latter of which reporting their chewing frequency at 4.3–5.9 days per week. AN chewers in Taiwan, Malaysia, Indonesia and Sri

Table 1. Characteristics for the study participants, the ABC study

Characteristics	Taiwan	Mainland China	Malaysia	Indonesia	Nepal	Sri Lanka
Study sample, No.	1,548	2,356	1,003	1,941	1,002	1,072
Gender (%)						
Male	47.6	52.0	38.2	49.7	66.3	35.9
Female	52.5	48.0	61.8	50.3	33.7	64.1
Age [years (%)]						
≤30	19.0	31.6	20.2	17.1	46.7	24.4
31–40	19.5	22.8	15.9	19.1	23.9	19.7
41–50	17.9	16.9	21.3	17.2	15.9	15.6
51–60	20.9	14.8	21.7	19.2	10.5	17.0
≥61	22.7	13.9	20.8	27.4	3.1	23.3
Education [years (%)]						
≤6	24.2	20.2	61.2	75.2	66.2	22.8
7–12	44.1	58.0	36.7	24.5	20.1	67.0
≥13	31.7	21.8	2.1	0.3	13.8	10.3
Alcohol drinker (%)						
No	87.1	78.3	84.7	77.1	70.1	88.0
Yes	12.9	21.7	15.4	22.9	29.9	12.0
Tobacco smoker (%)						
No	76.7	68.0	72.8	58.8	44.8	82.8
Yes	23.3	32.0	27.2	41.2	55.2	17.2

Lanka were found to be inclined to spit out the chewing quid juice; this is in stark contrast to those from Mainland China and Nepal, who swallowed it. Furthermore, in Eastern and South Asian study communities, male BQ users were found to have the highest prevalence for chewing that was combined with smoking and drinking (5.6–13.6%). With the exception of Nepal, only a handful of female chewers were found to concomitantly use cigarettes and alcohol. Among Malaysian and Indonesian women, a high proportion of substance users were observed to be exclusively BQ users (a prevalence of 27.8–45.7%).

The prevalence of oral mucosal lesions associated with BQ chewing is presented in Table 4. Indonesian women had the highest prevalences of oral lichen planus (OLP), oral submucous fibrosis (OSF) and oral leukoplakia (OL) (9.6–17.3%). Compared to nonchewers, Taiwanese male chewers had a remarkably higher likelihood of suffering from these oral preneoplastic disorders [an adjusted odds ratio of (aOR) = 13.5–137.4]. OSF appeared to be the most common oral premalignancy in Hunan, as indicated by the 3.5–6.6% among BQ users there.

The association between the practice of BQ chewing with educational levels and the habits of drinking and smoking are given in Figure 2. Compared to those who had only finished primary school (<7 years of schooling), subjects who had achieved a tertiary level of education (>12 years of education) were found to have a 0.3-fold less likelihood of being a chewer among men in Taiwan. Women with 7 to 12 years of schooling also had a reduced chance of becoming a chewer in Malaysia and Sri Lanka (aOR = 0.2–0.3, $p < 0.05$). With the exception of Indonesia, alcohol drinkers almost always had a higher tendency of being chewers, with a 2.1–8.9-fold increased risk observed in men, and a 5.2–21.2-fold elevated risk in women in Malaysia and Nepal. In Taiwan and Hunan, male smokers had an elevated propensity of becoming a BQ chewer. However, smokers in Malaysia and Indonesia were found to have a less likelihood of being a chewer (aOR = 0.1–0.4 in men, 0.2–0.4 in women).

Discussion

Our study offers the most up-to-date and comprehensive information on the prevalence, practice patterns and related factors in regard to BQ usage for six Asian populations. The findings further reveal the most affected populations and types of potentially malignant oral disorders among the studied regions where BQ use is widely practiced.

In this investigation, a remarkable discrepancy in gender prevalence for BQ use was recognized in the countries studied. Malaysian and Indonesian women had a particularly high chewing rate (29.5–46.8%), with female chewers in these two countries having reported an average history of >23 years of BQ usage, and such women tending to have a lower educational level (Fig. 2). Further, women aged >40 years in Malaysia and >30 years in Indonesia showed a 35.9–95.9%

Table 2. Prevalence and characteristics of betel-quid chewing, stratified by gender, the ABC study

	Men							Women						
Prevalence/category	Taiwan *n* = 736	Mainland China *n* = 1225	Malaysia *n* = 383	Indonesia *n* = 965	Nepal *N* = 664	Sri Lanka *n* = 385	*p* for diff.[1]	Taiwan *n* = 812	Mainland China *n* = 1131	Malaysia *n* = 620	Indonesia *n* = 976	Nepal *n* = 338	Sri Lanka *n* = 687	*p* for diff.[1]
Nonchewer (%)	84.4	71.0	89.7	79.5	61.8	78.8		97.0	97.7	67.9	32.1	63.3	83.1	
Chewer in lifetime (%)	15.6	29.0	10.3	12.4	43.6	21.2	**	3.0	2.3	32.1	47.8	34.9	14.5	**
Chewing status														
Past-chewer (%)	4.8	5.1	0.5	0.4	0.0	3.2		0.5	0.5	2.6	1.0	0.0	0.9	
Proportion of quitter in ever-chewers (%)	31.1	17.5	5.2	3.5	0.0	15.2	**	15.3	21.4	8.1	2.1	0.0	6.5	**
Years of quitting[2]	14.8 ± 1.9	3.6 ± 0.6	4.0 ± 3.2	9.0 ± 2.2	NA	13.8 ± 4.2	**	26.0 ± 2.1	2.4 ± 0.5	13.1±2.7	17.4±2.7	NA	10.6 ± 3.1	**
Current-chewer (%)	10.7	23.9	9.8	12.0	43.6	18.0		2.5	1.8	29.5	46.8	34.9	13.5	
Age at starting use[2]	20.7 ± 0.8	23.7 ± 0.6	20.9 ± 1.5	33.3 ± 0.9	18.9 ± 0.7	26.2 ± 1.5	**	25.4 ± 3.5	29.6 ± 2.6	23.1±0.8	25.5 ± 0.6	18.7 ± 0.6	31.6 ± 1.5	**
Years of chewing[2]	21.1 ± 2.0	8.8 ± 0.4	30.1 ± 2.0	15.3 ± 1.2	15.4 ± 1.9	21.7 ± 2.0	**	33.8 ± 5.3	9.7 ± 1.7	25.2 ± 1.3	23.8 ± 1.6	16.0 ± 2.0	23.9 ± 2.1	**
Proportion of new user in chewers (%)[3]	7.7	11.1	0.0	14.7	13.1	15.5	NS	0.0	24.7	10.7	7.7	18.2	20.3	**
Age-specific prevalence (%)							**							**
≤30	6.7	32.0	1.8	1.1	46.1	4.3		0.0	1.3	4.7	18.9	29.1	3.4	
31–40	16.0	32.0	3.0	14.4	40.4	24.2		0.0	2.5	28.8	35.9	34.3	5.2	
41–50	13.0	20.6	16.2	17.4	41.5	35.8		3.8	2.6	49.1	61.2	46.5	17.4	
51–60	13.2	8.6	32.7	22.3	34.3	23.2		4.0	1.0	68.7	81.5	57.0	22.8	
≥61	4.9	3.9	20.0	20.0	53.0	19.7		7.7	1.4	61.3	95.9	56.2	36.5	

*$p < 0.05$.** $p < 0.005$. [1]p for the difference in characteristics of betel-quid chewing across study areas was obtained adjusted for age. [2]Mean ± SE. [3]New-users, defined as those who regularly used betel-quid for ≤2 years.
Abbreviations: NA: nonappreciable; NS: nonsignificant.

Table 3. Types of betel-quid (BQ) chewed and habits practiced among current-chewers, stratified by gender, the ABC study

Betel-quid chewing/category	Men						*p* for diff.[1]	Women						*p* for diff.[1]
	Taiwan	Mainland China	Malaysia	Indonesia	Nepal	Sri Lanka		Taiwan	Mainland China	Malaysia	Indonesia	Nepal	Sri Lanka	
	n = 731	*n* = 1225	*n* = 383	*n* = 965	*N* = 664	*n* = 385		*n* = 812	*n* = 1131	*n* = 620	*n* = 976	*n* = 338	*n* = 687	
Type of betel-quid[2]														
Tobacco-free BQ														
Prevalence (%)	10.7	23.9	3.6	1.6	0.0	11.6	**	2.5	1.8	17.5	15.0	0.0	10.4	**
% in all types	100.0	100.0	36.4	29.7	0.0	64.6		100.0	100.0	59.4	31.3	0.0	76.7	
Nut + leaf	84.4	0.0	36.4	2.3	0.0	0.0		93.3	0.0	54.6	16.5	0.0	6.7	
Nut + inflorescence	8.0	0.0	0.0	6.2	0.0	1.0		0.0	0.0	0.4	11.7	0.0	0.9	
Nut + stem	3.3	0.0	0.0	0.6	0.0	0.0		0.0	0.0	0.3	0.0	0.0	0.0	
Nut husk + favorites	0.0	100.0	0.0	0.0	0.0	0.0		0.0	100.0	0.0	0.0	0.0	0.0	
Nut + local favorites	4.3	0.0	0.0	0.6	0.0	63.6		6.7	0.0	4.1	3.1	0.0	69.1	
Daily amount of chewing[3]	19.5 ± 2.7	10.0 ± 0.6	3.6 ± 1.0	3.9 ± 0.5	NA	2.1 ± 0.2	**	16.2 ± 2.2	4.9 ± 0.8	4.6 ± 0.4	3.5 ± 0.3	NA	2.0 ± 0.2	**
Usage day per week[3]	5.7 ± 0.3	5.8 ± 0.1	4.4 ± 0.9	4.3 ± 0.4	NA	5.0 ± 0.4	**	6.1 ± 0.5	5.7 ± 0.5	5.9 ± 0.3	5.7 ± 0.4	NA	4.4 ± 0.3	**
Tobacco-added BQ														
Prevalence (%)	0.0	0.0	6.2	10.4	43.6	6.4	**	0.0	0.0	12.0	31.7	34.9	3.2	**
% in all types	0.0	0.0	63.6	70.4	100.0	35.5		0.0	0.0	40.6	68.7	100.0	23.3	
Daily amount of chewing[3]	NA	NA	5.7 ± 0.6	6.5 ± 0.4	9.0 ± 0.3	6.9 ± 1.1	**	NA	NA	6.8 ± 0.4	6.1 ± 0.3	9.0 ± 0.9	6.2 ± 0.9	NS
Usage day per week[3]	NA	NA	6.4 ± 0.4	6.8 ± 0.1	6.0 ± 0.1	6.8 ± 0.1	**	NA	NA	6.8 ± 0.1	5.7 ± 0.2	5.8 ± 0.1	6.9 ± 0.1	**
Habit in chewers (%)							**							**
Spit out the juice	41.2	15.2	82.3	72.5	0.0	76.9		64.4	16.7	89.1	71.8	0.0	65.6	
Swallow the juice	43.5	78.7	4.8	13.2	95.0	9.7		25.8	77.2	3.3	7.6	94.4	19.5	
Spit/swallow alternately	15.3	6.1	12.9	14.3	5.0	13.3		9.8	6.1	7.6	20.6	5.6	14.9	
Prevalence of combined habits (%)							**							**
Chewing only	1.4	2.9	1.7	10.1	13.7	3.7		2.4	1.5	27.8	45.7	8.1	13.4	
Chewing + smoking	0.8	2.5	3.8	0.1	10.4	2.7		0.0	0.1	1.2	0.0	7.7	0.2	
Chewing + drinking	2.9	8.8	0.2	1.0	6.0	4.3		0.0	0.1	0.4	1.0	6.6	0.0	
Chewing + smoking + drinking	5.6	9.8	4.1	0.8	13.6	7.3		0.1	0.1	0.1	0.1	12.6	0.0	

* $p < 0.05$.** $p < 0.005$. [1]*p* for the difference in characteristics of betel-quid chewing across study areas was obtained adjusted for age. [2]There were missing data in the type of betel-quid chewed. [3]Mean ± SE.

Table 4. Prevalence rate (PR) and adjusted odds ratio (aOR) of oral lichen planus (OLP), oral submucous fibrosis (OSF) and oral leukoplakia (OL) associated with betel-quid (BQ) chewing, stratified by gender, the ABC study

	Study number		PR of OLP (%)				PR of OSF (%)				PR of OL (%)			
Gender/country	Nonchewer	Chewer	Nonchewer	Chewer	aOR[1]	*p*	Nonchewer	Chewer	aOR[1]	*p*	Nonchewer	Chewer	aOR[1]	*p*
Men														
Taiwan	585	91	0.1	5.5	57.5	**	0.0	7.3	13.5	*,[2]	0.1	6.4	137.4	*
Mainland China	886	339	0.1	0.3	2.3	NS	0.0	6.6	91.8	**,[2]	0.1	0.6	8.1	NS
Malaysia	337	45	0.0	0.0	NA	–	0.0	0.0	NA	–	0.0	0.0	NA	–
Indonesia	718	196	6.5	9.6	5.7	**	4.8	5.5	2.7	*	9.6	6.6	1.7	NS[3]
Nepal	410	254	0.0	0.0	NA	–	0.0	0.0	NA	–	0.3	1.6	4.7	NS
Sri Lanka	283	99	0.0	0.0	NA	–	0.0	0.0	NA	–	0.0	0.8	NA	–
Women														
Taiwan	715	15	0.0	0.0	NA	–	0.0	0.0	NA	–	0.0	0.0	NA	–
Mainland China	1105	26	0.1	0.0	NA	–	0.1	3.5	26.7	NS	0.0	0.0	NA	–
Malaysia	345	275	0.0	0.0	NA	–	0.0	0.0	NA	–	0.0	0.0	NA	–
Indonesia	277	660	0.8	17.3	28.4	**	1.2	9.6	6.8	*	0.2	9.1	212.8	**
Nepal	214	124	0.0	0.0	NA	–	0.2	0.0	NA	–	0.0	0.0	NA	–
Sri Lanka	571	114	0.0	0.0	NA	–	0.1	0.0	NA	–	0.0	0.0	NA	–

*$p < 0.05$. **$p < 0.005$. [1]*p* for OR of oral mucosal lesions was obtained adjusted for age, tobacco smoking and alcohol drinking. [2]The odds ratio was calculated using the median unbiased estimates with the aid of exact logistic regression. [3]Smoking conveys a negative confounding effect on the aOR of OL for BQ use.
Abbreviations: NA: nonappreciable; NS: nonsignificant.

high BQ chewing rate. As noted and released by the IRAC,[6] the length of BQ usage time is an important predictor in the development of oral precancerous and neoplastic lesions. Moreover, the health risk stemming from BQ chewing was generally less awareness among those women with a lesser educational level.[17] Consequently, Malaysian and Indonesian women from the study regions appear to be a high-risk group who require an increased amount of concern and educational assistance in regard to BQ-related health and disease prevention.

Although the raw areca used in Hunan is imported from Hainan in Mainland China, as well as from Thailand, the vast majority of BQ products in China, including commercial forms, are manufactured there. The Xiangtan city in Hunan province, where BQ chewing was reported to be very common (prevalence, 64.5–82.7%), is also where most BQ production factories and workshops are located.[18] In our study, we found that men (11.1%) and women (24.7%) from Hunan have a high percentage of BQ new-users. In contrast to other regions, the prevalence of BQ chewing in Hunan men was higher in the younger age groups, suggesting that Hunan is an emerging region of BQ practice. The improving economy and easy access to BQ products there, along with some recently begun BQ advertising campaigns in Hunan, could be the factors for widespread use of this substance, particularly among young people.

There is great diversity in how people chew BQ due to quite a bit of habitual variation, the majority of such practices being associated with higher risks for tumor development. In 1985, TA-BQ has been deemed by the IARC to be carcinogenic to humans.[19] Moreover, AN-derived carcinogenic nitrosamines have been unequivocally identified in the saliva of TF-BQ chewers.[20] Currently, there is sufficient evidence that TF-BQ causes oral and esophageal cancers.[6,8] Recent epidemiological evidence has revealed that the use of TF-BQ with betel inflorescent (containing safrole, a Group 2B carcinogen) conferred a higher carcinoma risk in the oral cavity, pharynx and esophagus than any other accompanying ingredients.[21–24] BQ chewers who also have the habits of alcohol drinking and tobacco smoking were found to have a synergistic risk of contracting the three aforementioned cancers of the upper gastrointestinal tract (OR = 8.1–41.2).[21–23] For users who habitually swallowed the juice from BQ chewing, a greater cancer risk was also observed.[21,22]

The Nepalese subjects who resided in the investigative regions displayed a 34.9–43.6% high rate of BQ chewing, and all were observed to have consumed TA-BQ. The daily amount of TA-BQ used by both genders was found to be the most (nine quids) in our study, and the overwhelming majority of chewers (94.4–95.0%) typically swallowed the BQ juice. Further, 12.6–13.6% of these people practiced chewing, drinking and smoking concomitantly. This is consistent with the age-standardized incidence of oral cancer in Nepal, which is ranked at a relatively high level according to GLOBOCAN 2002 report (12.8 and 8.4 per 100,000 men and women, respectively).[25] Hence, BQ-associated health problems should be carefully observed and counteracted in regard to the Nepalese population.

In Taiwan, the most important campaign to prevent BQ usage was initiated in 1998 where the government named

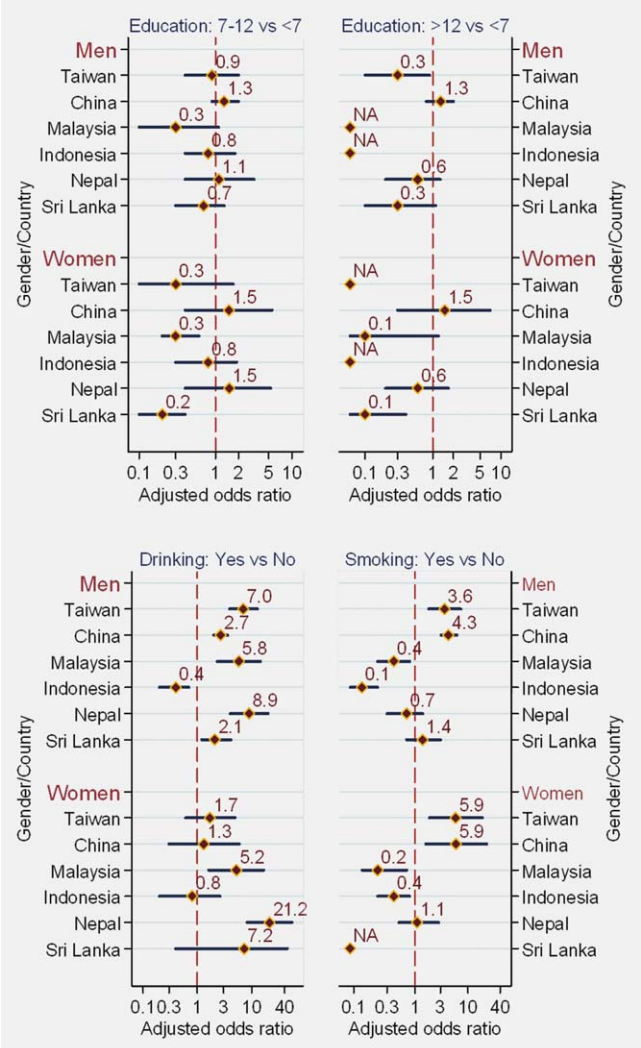

Figure 2. Adjusted odds ratio (aOR) showing the impact of education (schooling year), alcohol drinking and tobacco smoking upon the practice of BQ chewing, the ABC study. *Note*: aOR was adjusted for age and covariates in this figure. NA: nonappreciable, due to null BQ chewers in the group >12 years of schooling. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

December 3 as "Betel Quid Prevention Day" due to the finding that BQ chewers who concomitantly have the habits of alcohol drinking and cigarette smoking experienced a 123-fold increased oral cancer risk.[21] Although a reduced quantity of AN consumption has been observed in Taiwan,[26] health promotion campaigns have been continued. The high rate of BQ quitting that was noticed in our Taiwanese male samples (31.1%) is probably a result of such activities.

Compared to the results found in a population survey of the greater Kaohsiung area that was conducted in 1994,[7] the consumption of TF-BQ with betel inflorescence among chewers in Taiwan has substantially declined (from 51% in 1994 to 0–8% in our study). This indicates that people in Taiwan have noticed and considered the warnings about the higher cancer risks detected as a result of the intake of safrole-contained betel inflorescence.[21–23] On the other hand, the usage pattern for BQ chewers in Hunan differs greatly from that of other regions where BQ chewing is prevalent. All of the Hunan users chewed the dried husk of areca fruit,[27] and the majority (77.2–78.7%) of such users habitually swallowed the chewing quid juice as well. While current data has been limited in regard to the appraisal of the carcinogenetic consequences of consuming the dried areca husk,[18] a significant relationship between the consumption of this substance and OSF development was identified in our study for the male group from Hunan.

The IARC working group in 2004 reported that the prevalence of OLP, OSF and OL among BQ chewers in selected Asian populations was 0–3.7%, 0–3.0% and 0–40.1%, respectively.[6] The annual rate of malignant transformation was estimated to be <0.1%, 0.5% and 1% for the corresponding oral disorders.[28] Our study revealed that male Taiwanese TF-BQ chewers had a notably greater prevalence of exhibiting these potentially malignant oral disorders than nonchewers. In Hunan, an appreciably elevated OSF prevalence was detected in male chewers, despite the fact that they consumed tobacco-free areca husk. Approximately 6–17% of Indonesian BQ chewers suffered the above oral disorders, and a 7–213-fold risk was found for female chewers. The high prevalence of oral preneoplastic lesions and conditions in Indonesia reflect the current disease loadings and oral public health problems. With no reliable marker to predict malignant transformation[29] as yet, these data strengthen the great importance of disease prevention in Indonesia.

In line with several studies,[30,31] subjects with higher schooling in Taiwan, Malaysia, Indonesia and Sri Lanka were found to be correlated with a lesser likelihood to be BQ chewers. These results suggest that BQ-related health education programs should target less educated people in these study communities. In contrast, Hunan subjects with higher educational levels had a greater likelihood to use BQ (OR = 1.3–1.5, though nonsignificant), regardless of gender. As previously noted, the usage of this substance is more readily available in Hunan. This implies that the significance of extensive health education in this region is particularly important.

Large-scale epidemiological studies conducted in Taiwan have shown that drinking and smoking are significantly associated with an earlier onset age for the chewing of BQ.[32] Findings from a nationwide investigation further indicated that chewing practices are appreciably reduced among smokers who successfully quit smoking.[33] In this ABC study, alcohol drinking was the most important habit concomitant with BQ use. Male drinkers had a 2.1–8.9-fold likelihood of being a chewer in most countries, and female drinkers had a 5.2–21.2-fold probability of being a BQ user in Malaysia and Nepal. Interestingly, in the two Chinese populations, where chewers have been mostly men, male smokers showed a greater propensity to practice BQ chewing (aOR = 3.6–

4.3). As the habit of chewing is in sync with that of drinking and/or smoking, preventive policies should focus on BQ chewing and its link to individual alcohol and tobacco habits.[33]

In summary, we have outlined the significant country and gender differences contributing to BQ use and the great health risks that such practices pose in the Asian region. This international collaborative effort reveals the important BQ chewing-related demographic factors and regional-dependent factors, such as the emerging number of users in Hunan, and the overwhelming number of female chewers in Malaysia and Indonesia. It has also shed light on the importance of the inclusion of diverse ingredients like tobacco and nontobacco-based BQ and on the types of oral premalignant conditions associated with BQ chewing. We believe that the ABC study will greatly help to unify the awareness of the dangers of such diverse BQ practices. We also believe that it can provide an important framework to the development of more effective public health programs to help combat such serious practices

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