

RESEARCH ARTICLE

Betel Quid Chewing and Upper Aerodigestive Tract Cancers: A Prospective Cohort Study in Khon Kaen, Thailand**Wilas Kampangsri¹, Patravoot Vatanasapt^{2,4*}, Siriporn Kamsa-ard³, Krittika Suwanrungruang⁴, Supanee Promthet⁵****Abstract**

Background: This study aimed to determine the association between betel quid chewing and the occurrence of upper aerodigestive tract (UADT) cancers. **Methods:** A cohort of 17,388 subjects, recruited and interviewed over the 1990-2001 period, in Khon Kaen, Thailand, was followed up until 2011. The data were linked to the Khon Kaen Population-Based Cancer Registry. **Results:** The prevalence of betel quid chewing was 15.9%, with a female predominance (97.7%); the mean age of chewers was 57.7 years (SD 6.6). The overall incidence of UADT cancers from the cohort was 14.7 per 100,000 person-years, whereas the incidence among the chewers was 45.7. Betel nut chewing was the only major risk factor for UADT cancers in this population (HR=5.26, 95% CI=2.51-11.0), while weak associations were found for tobacco smoking and alcohol (HR=1.16, 95% CI=0.45-3.01 and 1.47, 95% CI=0.72-3.03 respectively). **Conclusions:** We found betel quid chewing to be a main risk factor for UADT cancers, resulting in a higher incidence in females. However, further study is required to explore the potential risk factors among non-chewers, non-smokers, and non-drinkers

Keywords: Betel nut chewing - upper aerodigestive tract cancers - cohort study - Thailand

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Introduction

Cancers of the upper aerodigestive tract (UADT), including mouth, pharynx and esophagus, is one of the major disease burdens in public health with more than 880,000 cases annually diagnosed world-wide (Ferlay et al., 2010). In Thailand, the incidence (ASR world) of UADT cancers is 10.1 and 4.40 per 100,000 in males and females respectively (Khuhaprema et al., 2012). In contrast to other regions, oral cancer in the Northeast of Thailand was found to be more common in females than in males (Khuhaprema et al., 2012). Moreover, a significantly increasing trend in incidence was found only in females (Vatanasapt et al., 2011). This begs the question: could this unique pattern of cancer incidence be explained by known risk factors?

Tobacco smoking and alcohol drinking are well-known as major risk factors for the UADT cancers. Betel quid chewing, in addition, was found to be a strong risk factor in certain countries in Asia, especially Taiwan, where this habit is prevalent (Lee et al., 2005; Yen et al., 2008; Lin et al., 2011). However, the evidence from South-East Asian countries is limited, despite the fact that betel quid chewing is one of the customs of people in rural areas.

This study, therefore, was primarily aimed to determine the association between betel quid chewing and UADT cancers in the Khon Kaen population.

Materials and Methods

A total of 24,528 subjects were included from the Khon Kaen Cohort study over the 1990-2001 period. The details of the cohort have been described in a previous publication (Sriamporn et al., 2005). In order to obtain sufficient information from the cohort, we further filtered the subjects to select only the age group 30 to 69 years old using available 13-digit identification numbers which were introduced in 1984 in Thailand. The cases of oral cavity, pharyngeal and esophageal cancer that occurred during the first year of the cohort were also excluded. The resulting number of subjects in the analysis was 17,388.

The data on determinants was obtained by questionnaire interview during the cohort recruitment phase, including demographic data, tobacco smoking, alcohol drinking, and betel-quid chewing. A betel quid habit was defined as a regular use at least every month.

The cohort was followed up until December, 31st, 2011 to detect the occurrence of the UADT cancers, including cancers of the oral cavity, oropharynx, hypopharynx, and esophagus (C00-15, excluding C07, 08 and 11). The 13-digit ID number was used to link the cohort to the Khon Kaen population-based cancer registry, and double-checked with the subjects name, birth date, and address in questionable cases. The medical records of all detected cases were reviewed to confirm the diagnosis.

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The incidence of UADT cancers was calculated by cases per year. The association between betel quid chewing, including other potential relevant factors, and UADT cancers was analysed by cox-proportional hazard regression (Qiu et al., 2012) using STATA version 10.0 software. According to the recruited subjects in the cohort, the power of study was calculated to be greater than 99%.

Results

Baseline information

The cohort of 17,388 eligible subjects comprised 5,359 males (30.8%) and 12,029 females (69.2%), with a mean age of 50.9 years (SD 8.44).

Betel quid chewing

A betel quid chewing habit was found in 2,767 subjects (15.9%). Most subjects did it everyday (94.9%). The chewers started this habit at a mean age of 33.5 years (SD 12.8). The majority of chewers were females (97.7%). The common components of a betel quid include Koon or Cassia fistula (92.6%), slaked lime (92.3%), fresh betel leaf (88.9%), and dried areca nut (68.7%). The chewers tended to be of lower socioeconomic status. Betel quid chewing was found with tobacco smoking in 2.57%, and with alcohol drinking in 28.6%.

Incidence of UADT cancers

At the end of the follow up period, 35 cases of UADT cancers had been found in the cohort of 17,388 subjects (incidence rate 14.7 per 100,000 person-years). The incidence was significantly higher in those with lower education, older age, and in betel quid chewers (Table 2).

By adjusting for alcohol drinking, tobacco smoking,

Table 1. Characteristics of the Study Population from the Khon Kaen Cohort in Relation to Betel Quid Chewing

Characteristics	Chewer		Non-chewer	
	n	%	n	%
Total study population (n=17,388)	2,767	15.9	14,621	84.1
Personal data				
Gender				
Male	63	2.3	5,296	36.2
Female	2,704	97.7	9,325	63.8
Age (years)				
30-45	117	4.2	4,645	31.8
46-51	373	13.5	4,142	28.3
52-57	730	26.4	3,166	21.6
58-69	1,547	55.9	2,668	18.3
mean (SD)	57.7	(6.6)	49.6	(8.1)
Marital status				
Single	50	1.8	342	2.3
Married	2,717	98.2	14,271	97.7
Education				
Never attended school	207	7.5	246	1.7
Ever attended school	2,560	92.5	14,375	98.3
Average household income (Baht per month)				
<1,500	1,310	47.4	5,292	36.2
1,500-3,000	1,033	37.3	6,039	41.3
>3,000	424	15.3	3,290	22.5
mean (SD)	2,274.25		3,103.97	
	(3,030.9)		(5,391.2)	
Behaviors				
Tobacco Smoking				
Ever	71	2.6	4,280	29.3
Never	2,696	97.4	10,341	70.7
Alcohol Drinking				
Ever	791	28.6	6,869	47.0
Never	1,976	71.4	7,752	53.0

Table 2. Incidence and Association between Potential Risk Factors; Crude Analysis

Characteristics	Case	Person-years	IR	HR (95% CI)
Sex (p value=0.54)				
Male	9	72591.1	12.4	1.00
Female	26	165762.9	15.7	1.26 (0.60-2.70)
Age (years) (p value=0.004)				
30-45	6	72098.8	8.3	1.00
46-51	6	61124.6	9.8	1.33 (0.43-4.15)
52-57	6	51027.0	11.8	1.64 (0.52-5.11)
58-69	17	54103.7	31.4	4.41 (1.73-11.25)
Marital status (p value=0.06)				
Single	3	5539.9	54.1	1.00
Married	32	232814.1	13.7	0.26 (0.08-0.85)
Education (p value=0.012)				
Never attended	4	6004.7	66.6	1.00
Ever attended	31	221972.9	14.0	0.19 (0.07-0.55)
Average household income (p value=0.47)				
>3,000	5	47896.0	10.4	1.00
1,500-3,000	12	96340.6	12.5	1.12 (0.40-3.17)
<1,500	18	94117.5	19.1	1.62 (0.60-4.40)
Tobacco Smoking (p value=0.52)				
Never	28	179446.8	15.6	1.00
Ever	7	58907.2	11.9	0.76 (0.33-1.75)
Alcohol Drinking (p value=0.68)				
Never	19	135279.3	14.1	1.00
Ever	16	103074.7	15.5	1.15 (0.59-2.23)
Betel quid Chewing (p value<0.001)				
Never	18	201169.1	8.9	1.00
Ever	17	37184.9	45.7	5.15 (2.66-10.01)

*HR=Hazard Ratios, IR=Incidence Rate (100,000pyrs), 95%CI=95% Confidence Interval

Table 3. Association between Potential Risk Factors and UADT Cancers; Multivariate Analysis by Cox-Hazard Regression

Variables	Crude HR	Adj.* HR	95%CI	p value**
Betel quid chewing				
Never	1.00	1.00		<0.001
Ever	5.15	5.26	2.51-11.01	
Tobacco smoking				
Never	1.00	1.00		0.76
Ever	0.76	1.16	0.45-3.01	
Alcohol drinking				
Never	1.00	1.00		0.29
Ever	1.15	1.47	0.72-3.03	
Education				
Never attended	1.00	1.00		0.077
Ever attended	0.19	0.32	0.11-0.93	

*adjusted for education, tobacco smoking, alcohol drinking, and betel quid chewing. **p value from Partial likelihood ratio test. HR=Hazard Ratios, IR=Incidence Rate, 95%CI= 95% Confidence Interval

and education, betel quid chewers had a 5.26 times greater risk of developing UADT cancers (95%CI 2.51-11.0). However, the associations of UADT cancers with alcohol drinking and tobacco smoking were slight and insignificant (Table 3).

Discussion

Our study showed the incidence of UADT cancers from the cohort was 14.7 per 100,000 person-years. This incidence is three-time greater than that obtained from the population-based cancer registry (Khuhaprema et al.,

2012), because the incidence for this cohort was calculated with an age limited denominator' ie not all age groups were included.

We found the prevalence of betel quid chewing was 15.9% and that it was more common in females, which is similar to the results of a previous study in Thailand which found a 17.0% prevalence (Gupta and Warnakulasuriya, 2002), with apparently higher rates in females in the North and Northeast of Thailand (Vatanasapt et al., 1995). This prevalence is still comparable to the latest case-control study in Khon Kaen, where the prevalence of betel quid chewing among the control group was 22.1% (Loyha et al., 2012). The gender proportion of betel quid chewing agrees with that for the UADT cancer incidence in this study. We found betel quid chewing increased the risk of the UADT cancers 5.26 times. The results from our cohort agree with those from previous case-control studies on betel quid in Thailand (Simarak et al., 1977; Prateepko, 1998; Boonyaphiphat et al., 2002; Loyha et al., 2012), as well as studies in other countries (Lee et al., 2005; Thomas et al., 2007; Yen et al., 2008; Amarasinghe et al., 2010; Lin et al., 2011; Akhtar et al., 2012). According to the IARC Working Group on Evaluation of Carcinogenic Risk to Humans, betel quid with or without tobacco and areca nut are considered as carcinogenic to humans (group 1) (IARC, 2004).

This may explain why UADT cancers, especially oral cancer, is more common in females in this population. However, after Prime Minister General Plaek Pibunsongkram, of the military government, declared the New Thai Cultural Mandates in 1941, the betel quid chewing habit seemed to fade away. The incidence of oral cancer in females increased (Vatanasapt et al., 2011) while betel quid chewing has become less common (Reichart et al., 2007). Further research is required to work out the potential risk factors among non-smokers, non-drinkers, and non-chewers, including the potential risk of the Human Papillomavirus (Herrero et al., 2003; Kreimer et al., 2005).

Drinking alcohol and smoking tobacco are known to be major risk factors for UADT cancers. However, we found their effect on the occurrence of UADT cancers was minimal. The association may be weakened by misclassification, as the exposure was obtained from one time interviews in this cohort, and it is possible for habits to change. Moreover, the residual confounders may also account for the apparent weakening of this well established association in the data from the present study.

In conclusion, chewing betel quid is a major risk factor for UADT cancers in a population with female predominance in its incidence. However, further studies are required to identify potential undetermined risk factors.

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