RESEARCH ARTICLE

Risk Factors for Oral Cancer in Northeast Thailand

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Abstract

Oral cancer is a common site of head and neck cancer, and is relatively frequent in Northeast Thailand. The objective of this hospital-based, case-control study was to determine associations with risk factors. A total of 104 oral cancer cases diagnosed between July 2010 and April 2011 in 3 hospitals were matched with control subjects by age, sex and hospital. Data were collected by personal interview. There were significant associations between oral cancer and tobacco smoking (OR=4.47; 95%CI=2.00 to 9.99), alcohol use among women (OR=4.16; 95%CI=1.70 to 10.69), and betel chewing (OR=9.01; 95%CI=3.83 to 21.22), and all three showed dose-response effects. Smoking is rare among Thai women (none of the control women were smokers), but betel chewing, especially among older women, is relatively common. We did not find any association between practicing oral sex and oral cancer.

Keywords: Oral cancer - risk factors - betel quid - tobacco - alcohol - northeast Thailand

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Introduction

Oral cancer is the most common type of head and neck cancer. There were an estimated 15,300 new cases in South-Eastern Asia countries in 2008 (Ferlay et al., 2010). In Thailand, the age standardised incidence rate in 2001-2003 was 4.5 per 105 in males, and 3.7 per 105 in females (Khuhaprema et al., 2010). The incidence of oral cancer in the Northeast region of Thailand is the highest in the country (Khuhaprema et al., 2010), and, according to data from the population-based registry of Khon Kaen (One of the major provinces of the Northeast), incidence rates are increasing in females but not in males (Vatanasapt et al., 2011).

A large number of studies have confirmed the roles of tobacco smoking, alcohol drinking and betel quid chewing in aetiology (Lambert et al., 2011). Infection with Human papillomavirus (HPV) has also been shown to be a major risk factor for oral cancer in recent studies (Kreimer et al., 2005). However, the relative importance of these factors in Thailand, and especially in the higher risk area of the Northeast, has not been clarified. The present study aimed to determine strength of the association between potential risk factors - including tobacco smoking, alcohol drinking, betel quid chewing and oral sex behavior - and oral cancer.

Materials and Methods

We conducted a hospital-based case-control study. The participants in this study were new patients who visited three hospitals in the Northeast of Thailand (Srinagarind Hospital - Khon Kaen University teaching hospital, Khon Kaen Regional Hospital, and Sappasitthiprasong Ubon Ratchathani Hospital) between July 2010 and April 2011, and had been resident in the Northeast of Thailand for at least 5 years. Case subjects were those with oral cancer newly diagnosed by specialists, either otolaryngologists or plastic surgeons, within 1 month prior to the interview. Subjects-with cancers of the lips, base of tongue, other and unspecified parts of tongue, gum, floor of mouth, hard palate, other and unspecified parts of mouth, tonsil and oropharynx (ICD-O; C00-C10) were included, excluding those with salivary gland tumours (ICD-O; C07-C08), Only cases confirmed as squamous cell carcinomas by histopathology were included. Oral cancer patients who had multiple primaries and, or previously received treatment were excluded. Control subjects were patients with a diagnosis of non-cancer conditions, and no chronic illness of the head and neck regions and no history of head and neck surgery. They were selected from the general walk-in patients at the Out-Patient Department. In addition, controls were matched by age (±3 years), sex, and hospital visited of each case

Data on cases and controls was collected by questionnaire. It consisted of 2 parts: Part 1, collected data on socio-demographic characteristics of subjects, such as age, sex, education, occupation, household income per month, and family history of cancer. Part 2, collected data on risk factors of oral cancer, including tobacco smoking, alcohol drinking, betel quid chewing, and sexual behavior,

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especially oral sex behavior.

The participants were interviewed by interviewers the investigator (KL) and a research assistants using the appropriate local dialect of the subject.

Smokers were defined as those who had smoked at least once cigarette per day for a period of six months continuously. Frequency was grouped as daily, weekly, monthly, and less than once a month. Frequency and amount smoked were combined into number of pack-years. Alcohol drinking was defined as drinking alcohol at least once a month continuously, including beer, wine, wort (The product of fermentation of rice), rice whisky, hard liquor (Lao Dang) and herbal liquor (Lao Ya Dong). Betel quid chewing was defined as chewing all the betel nut at least six month continuously [Or keeping the betel nut in the buccal cavity (sulcus)]. Sexual behavior was investigated as a potential method of infection with HPV: we investigated the number of sexual partners and oral sex partners.

This study was approved by the Khon Kaen University Ethics Committee in Human Research.

Statistical analysis

Data were analyzed by logistic regression, which included the following modelling strategy: 1) Univariate analysis of risk factors. This process tested the main effects of potential risk factors, and defined as clinically or biological meaningful those for which an association with a p-value <0.25 (p-value 0.10-0.20) was found (Hosmer and Lemeshow, 2000). 2) Multivariable analysis for consideration of the factors identified in (1) at the same time. 3) Using logistic regression (LR) models with backwards selection to choose a final model. Backward elimination involves inputting all variables into the model, then selection of the variables removal of which has a non-significant effect on the strength of the association.

Results

The numbers of matched pairs were 76, 16 and 12 from each of the three participating hospitals. Three-fourths of participants were aged 55 or more, with more males than females (Table 1). Primary school was the highest education level for most participants in both case and control subjects. There was an inverse association between level of education and risk of oral cancer (P for trend=0.001). Moreover, most participants were farmers and had less than 5,000 Thai Baht (~160 USD) household income per month, but inverse for control subjects who had high (10,001 Baht or more) household income per month, as shown in Table 1.

Overall 24% of control subjects were smokers, but habit is much more common in men (64.1% of smokers among controls) than among women (none). Ever smokers had a 1.82-fold risk (95%CI=0.99-3.35, p-value=0.05) in univariate analysis when compared with never smokers and the risk increased with duration of smoking (P for trend=0.02) (Table 2). There was a very strong dose-response effect, with those smoking 10-20 pack-years having a 2.86-fold (95%CI=1.10-7.42, p-value=0.02) increased risk of developing oral cancer.

Some 42.3% of control subjects were alcohol drinkers, but alcohol consumption is much more common in men (87.2% ever-drinkers among controls) than among women (15.4%). The drinkers had a 2.10-fold (95%CI=1.19-3.68, p-value=0.01) increased risk compared with never drinkers in univariate analysis (Table 2). There was no clear effect of increased frequency or duration of drinking. In addition, the alcoholic beverage with the strongest association with oral cancer was rice whisky (OR=3.8; 95%CI=1.99-7.25, p-value <0.001) when compared with never drinkers (of rice whisky). We found the risk in females, however, was 4.16 (95%CI 1.7-10.7), whereas the risk was weaker and not significant in males. The difference between the sexes is significant (p-value for interaction between patient's sex and alcohol drinking=0.002).

Chewing of betel quid is a relatively common habit, especially among older women. Although only 22.1% of all control subjects were chewers, it was 35.9% among women, and all were over the age of 55. Ever chewers had a 4.11-fold (95%CI=2.16-7.78, p-value <0.001) increased risk when compared with never chewers in univariate analysis. There is a strong relationship with the duration of chewing (P for trend <0.001). We also found red lime conveyed the strongest risk factor among all components of the betel quid (OR=10.67, 95%CI=2.27-50.08).

No significant association was found between the risk of oral cancer and number of sexual partners, use of condoms, or the practice of oral sex, although it was not significant, use of condoms was potentially found to be a protective factor in our study population.

Since the effect of drinking alcohol on oral cancer was modified by sex, we did not include the alcohol perse in the model. Instead, the interaction term was applied in multivariate analysis. Based on the results of a multivariable model including occupation, tobacco smoking, betel quid chewing, interaction term of sex and alcohol drinking, adjusting those variables results in

Table 1. General Characteristics of Incident Cancer Cases and Controls

Variables	Cases		Controls		OR	95%CI	p-value
	n=104	%	n=104	%			
Age (years old)							
25-34	3	2.9	2	1.9	NA*		
35-44	8	7.7	6	5.8			
45-54	15	14.4	18	17.3			
≥55	78	75	78	75			
Sex							
Male	39	37.5	39	37.5	NA*		
Female	65	62.5	65	62.5			
Education							
Never attended school	8	8.6	5	5.4	1.00		
Primary school	70	75.3	57	61.3	0.77	0.24-0.49	0.66
Secondary school	12	12.9	13	14	0.58	0.14-2.33	0.43
College/University	3	3.2	18	19.4	0.1	0.01-0.72	0.005
P-for trend							0.001
Occupation							
Non-farmer	20	19.2	40	38.5	1.00		
Farmer	84	80.8	64	61.5	2.62	1.37-4.99	0.002
Household income per month (Baht)							
≤5,000 (Low)	78	75	44	42.3	1.00		
5,001-10,000 (Medium)	14	13.5	15	14.4	0.47	0.23-1.20	0.12
≥10,001 (High)	12	11.5	45	43.4	0.17	0.06-0.33	<0.001
P-for trend							<0.001

*Not applicable for matching factors

Table 2. Univariate Analysis of Risk Factors for Oral Cancer

Variables	Cases		Controls		OR*	95% CI	p-value
	n=104	%	n=104	%			
Tobacco smoking							
Never	66	63.5	79	76	1		
Ever	38	36.5	25	24	1.82	0.99-3.35	0.05
Duration of smoking (years)**							
None	66	63.5	79	76	1		
<21	5	4.8	8	7.7	0.74	0.23-2.40	0.63
21-48	22	21.1	15	14.4	1.75	0.83-3.67	0.13
>48	11	10.6	2	1.9	6.58	1.35-32.0	0.007
P- for trend							0.008
Amount smoked (pack-years)							
None	68	65.4	80	76.9	1		
<10	10	9.6	14	13.5	0.84	0.35-2.02	0.7
10-20	17	16.3	7	6.7	2.86	1.10-7.42	0.02
>20	9	8.6	3	2.9	3.53	0.90-13.84	0.05
P - for trend							<0.05
Alcohol drinking							
Never	41	39.4	60	57.7	1		
Ever	63	60.6	44	42.3	2.1	1.19-3.68	0.01
Frequency of drinking							
Less than once month	44	68.8	32	72.7	1		
Monthly	5	7.8	5	11.4	0.73	0.19-2.75	0.64
Weekly	10	15.6	6	13.6	1.21	0.39-3.70	0.74
Daily	5	7.8	1	2.3	3.64	0.39-33.77	0.22
P - for trend							0.35
Duration of drinking (years)							
None	40	38.5	60	57.7	1		
<10	8	12.5	5	11.4	2.4	0.72-8.00	0.14
10-30	22	34.4	23	52.3	1.43	0.70-2.93	0.32
>30	34	53.1	16	36.4	3.19	1.51-6.71	0.001
Betel quid chewing							
Never	48	46.2	81	77.9	1		
Ever	56	53.9	23	22.1	4.11	2.16-7.78	<0.001
Keep a betel nut in the buccal cavity							
Never	70	67.3	93	89.4	1		
Ever	34	32.7	11	10.6	4.11	1.88-8.93	<0.001
Duration of chewing (years)							
None	48	46.1	81	77.9	1		
<10	3	2.9	6	5.8	0.84	0.20-3.55	0.82
10-30	20	19.2	5	4.8	6.75	2.24-20.35	<0.001
>30	33	31.7	12	11.5	4.64	2.10-10.27	<0.001
P - for trend							<0.001
Condom use							
Never	90	86.5	81	77.9	1		
Ever	14	13.5	23	22.1	0.55	0.26-1.14	0.1
Number of sexual partners							
One person	76	73.1	77	74	1		
Two person or more	28	26.9	27	26	1.05	0.56-1.94	0.87
Oral sex partners							
Never	92	88.5	96	92.3	1		
Ever	12	11.5	8	7.7	1.57	0.60-4.02	0.35

**Crude OR, **Stratified by mean ±SD*

Table 3. Effect Modification of Alcohol Drinking on Oral Cancer

Factors	Cases	Controls	OR	95% CI
	n=104 (%)	n=104 (%)		
A Male (n=39); Alcohol drinking				
No	4 (10.2)	5 (12.8)		
Yes	35 (89.7)	34 (87.2)	1.29	0.25-7.04
Female (n=65);Alcohol drinking				
No	37 (56.9)	55 (84.6)		
Yes	28 (43.1)	10 (15.4)	4.16	1.70-10.69

Table 4. Oral Cancer and Association with Occupation, Tobacco Smoking, Betel Quid Chewing, and Interaction Term of Sex and Alcohol Drinking

Variables	Cases	Controls	OR*	OR**	95%CI***	p-value
	n=104 (%)	n=104 (%)				
A Occupation						
Non-farmer	20 (19.2)	40 (38.5)				
Farmer	84 (80.8)	64 (61.5)	2.65	1.78	0.82-3.85	0.14
Tobacco smoking						
Never	66 (63.5)	79 (76.0)				
Ever	38 (36.5)	25 (24.0)	1.82	4.47	2.00-9.99	<0.001
Betel quid chewing						
Never	48 (46.2)	81 (77.9)				
Ever	56 (53.9)	23 (22.1)	4.11	9.01	3.83-21.22	<0.001
Interaction term of sexand alcohol drinking				2.21	1.35-3.62	0.002

**Crude odds ratio, **Adjusted odds ratio (ORs), ***95%CI for Adjusted odds ratio*

increasing the strength of the association between oral cancer and tobacco smoking, and betel quid chewing.

Discussion

We found oral cancer cases were more common in females than males. Likewise, incidence of oral cavity cancer in the Northeast region reported from Nakhon Phanom, Ubon Ratchathani, Udon Thani, and Khon Kaen were higher in females than males (Khuhaprema et al., 2010). The mean age of the oral cancer patients (63 years) corresponded closely to the mean age of cases in the population (65 years), as recorded by the cancer registry of Khon Kaen (Khuhaprema et al., 2010). The case series is likely to be representative of oral cancer patients in the Northeast region.

Tobacco smoking; in our study we found that tobacco smoking increases risk of oral cancer, and that the risk increases with duration and amount smoked. This result is consistent with other studies (Applebaum et al., 2007). For alcohol drinking, as in many previous studies (Chung et al., 2005; Corrao et al., 2004) we found alcohol drinking was significantly associated with oral cancer. Moreover, we found a dose-response relationship to be apparently present for the frequency of alcohol consumed. However, alcohol drinking was not significantly associated with oral cancer in males, as the number of non-drinking males was too small to make a precise estimate of effect. Rice whisky in particular was significantly associated with oral cancer (OR was 3.80 and 95% CI was 1.99 to 7.25). The components of rice whisky consist of 40 percent ethanol, which can enhance the risk of oral cavity cancer. (IARC, 2007).

Betel quid chewing is quite strongly associated with oral cancer in women, especially in chewers of long duration. Moreover, all components of a betel nut can increase the risk of oral cancer, especially Red lime whose chemical compound acts through a relevant mechanism of carcinogenicity (IARC, 2004).

Oral sex behavior; Oral sex is thought to be one channel for HPV transmission. Cancers of the oro-pharynx and tonsil have been found to be associated with the number of sexual partners and number of lifetime oral sex

partners (Heck et al., 2010). We did not find a relationship between oral sex partners and oral cancer in our study. Only about a quarter of subjects admitted to having more than one sexual partner, and oral sex was relatively uncommon - at least by self report. These questions are quite sensitive within Thai culture, and one might question the accuracy of the responses.

In conclusion, there are significant associations between tobacco smoking, alcohol use, and betel chewing and oral cancer, and all three show dose-response effects. Smoking is rare among Thai women (none of control women was a smoker), but betel chewing, especially among older women, is relatively common. However, we could not demonstrate any association between oral sex behavior and oral cancer.

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