RESEARCH ARTICLE

Prevalence and Factors Associated with Oral Pre-Malignant Lesions in Northeast Thailand

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Abstract

Background: Oral cavity cancer (OCC) is one of the most common cancers worldwide. No studies have reported on the prevalence and epidemiologic risk factors of oral premalignant lesions (OPLs) in Thailand. The purpose of this study was to investigate the prevalence of OPLs and associated factors in Roi Et Province, Thailand. Materials and Methods: To investigate the prevalence of OPLs, a cross-sectional descriptive study was conducted in which 2,300 subjects over 40 years of age were recruited and screened for the prevalence of OPLs. To identify factors associated with OPLs, a matched case-control study was used in which the subjects were 102 cases with OPL and 102 matched controls without OPLs. The studies were conducted in Roi Et Province during the period 1 February, 2014, to 30 April, 2014, and the data were collected by the use of a structured interview questionnaire and by extraction of information from medical records. Data analyses involved the use of descriptive statistics, McNemar's test, and conditional logistic regression. Results: The overall prevalence of OPLs was 3.8%, and no-one was diagnosed with more than one type of OPL. The factors found to be associated with a statistically significant higher risk of an OPL were betel nut chewing, smoking, and alcohol consumption. The associations with these factors were strong, especially for betel nut chewing and smoking. Conclusions: The habits of betel nut chewing, smoking, and alcohol use are confirmed as factors associated with OPLs in a population of Roi Et Province, Thailand. Campaigns to reduce such risk healthy behaviour are needed, but whether any actual decrease will prevent the eventual transformation of an OPL into an OCC remains an open question.

Keywords: Oral pre-malignant lesions - oral cavity cancer - Thailand

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Introduction

Oral cavity cancer (OCC) is one of the most common life-threatening diseases in some parts of the world, especially in developing countries. In 2012, there were estimated to have been more than 300,373 newly diagnosed cases and more than 145,353 deaths due to this disease globally. In Southeast Asia, OCC has been the third most common of all malignant tumors in males and the sixth in females, and the age-standardized incidence rates (ASR) for males and females were estimated to be 8.9 per 100,000 and 3.9 per 100,000, respectively (Ferlay et al., 2015). In Thailand, the mean annual ASRs for the years 2010-2012 were 5.1 per 100,000 in male and 3.6 per 100,000 in females (Imsamran et al., 2015).

According to the World Health Organisation's working group on oral cancer, there are six oral conditions described as potentially malignant: leukoplakia, erythroplakia, lichen planus, oral submucosus fibrosis, palatal lesion of reverse smoking and discoid lupus erythematosus (Warnakulasuriya et al., 2007). The prevalence of OPLs appears to vary considerably from one country to another: in a summary of the findings of 28 different studies conducted from 1971 to 2002 in many parts of the world, the prevalence of both OPLs and OCC (mainly the former) ranged from 0.2% to 20.4% (Lim et al., 2003). More recently, an Indian study reported a prevalence rate for OPLs as high as 22.2% (Gambhir et al., 2011).

With regard to factors associated with an increased risk of OPLs, many studies have reported that smoking, drinking alcohol, wearing dentures, and chewing betel nut can be risk factors (for example: Mikkonen et al., 1984; Shiu et al., 2000; Garcia et al., 2002; Thomas et al., 2003; Coelho et al., 2004; Chung et al., 2005; Tovosia

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et al., 2007; Thomas et al., 2008; Carrard et al., 2011). In addition, various demographic factors including age, gender, occupation, education level, and socioeconomic status have been associated with OPLs (Hashibe et al., 2003; Lim et al., 2003; Thomas et al., 2003; Carrard et al., 2011). It is also the case that human papillomavirus (HPV) infections have received considerable scrutiny in the aetiological basis of OPLs and oral cancer (D'Costa et al., 1998; Grinde and Olsen, 2010; Prabhu and Wilson, 2013). Oral squamous cell papillomas, which are caused by HPVs, are most commonly found on the tongue, lips, cheek mucosa, and hard and soft palates (Scully, Prime and Maitland, 1985; Syrjanen, 1992). These papillomas can turn into malignant lesions.

The early detection and therapeutic management of OPLs are crucial for the prevention of OCC, and knowledge of the risk factors for the development OPLs is an important issue for primary prevention (Gaphor and Sabri, 2014). To our knowledge, while the prevalence rates and potential factors associated with OPLs have often been reported in other parts of the world, there have been no published reports about these issues in Thailand since a study of northern rural Thais and hill tribes about 30 years ago (Reichart and Mohr, 1987). The purpose of this study was to investigate the prevalence of OPLs in one area of Northeastern Thailand and to investigate the factors associated with OPLs in this area.

Materials and Methods

Subjects and data collection

This research involved the use of two different study designs: a cross-sectional descriptive study was used to estimate the prevalence of OPLs and a matched case-control study to investigate factors associated with the presence of OPLs.

In the cross-sectional descriptive study, 2,300 screening subjects were recruited over the period 1st February, 2014, to 30th April, 2014, from those attending the dental clinic at Roi Et Hospital in Northeast Thailand and from the network for oral pre- malignant lesion screening in Muang District, Roi Et Province. All were over 40 years of age, all gave their informed consent to participate, and those found to have OCC were excluded. A required sample size of 2,270 subjects was calculated using the method of estimating a population proportion with specified relative precision described by Lwanga and Lemeshow (1991). The anticipated population proportion was set at 0.14 (adopted from data in Yen et al., 2007), the confidence level was 95%, and the relative precision was 10%. An additional 30 subjects were enrolled to allow for incomplete data. The diagnoses of OPLs were made according to the guidelines of the National Institute of Dental and Craniofacial Research ("Detecting Oral Cancer: A Guide for Health Care Professionals," 2013) and were obtained in a two stage process. In the first stage, the oral cavities of the subjects were clinically examined by a dental technician using the method of light-illuminated visualization. The participants who were considered to have an OPL (or an actual malignancy) by the dental technician were then referred to a qualified hospital dentist for confirmation of the OPL diagnosis or possible OCC.

In the matched case-control study, the subjects were a consecutive series from the cross-sectional study and comprised 102 cases of subjects with OPLs and 102 controls with no diagnosed OPLs matched for gender and age (± 3years). All of cases had been diagnosed with OPLs by a hospital dentist, and the controls were subjects who had never been diagnosed with OPLs. The required sample size was calculated using the sample size and power for pair-matched studies method (Schlesselman, 1982). Alpha and beta were set as 0.05 and 0.10, respectively, and the odds ratio was 6.4 (adopted from Thomas et al., 2003). The required sample size was 144 subjects, 72 in each group. A further 30 subjects were added to the cases and controls to allow for incomplete data so that the final number in each of the case and control groups was 102.

Data for the case-control study were collected by the use of a structured interview questionnaire and from medical records. The interviewers were blinded to the case-control status of the subjects. The content of the questionnaire was based on factors known from previous studies to be associated with OPLs. These were age, gender, monthly income, BMI (kg/m2), smoking, alcohol drinking, coffee drinking, betel nut chewing, and relevant oral behaviours such as teeth brushing and the wearing of dentures. Information about the betel nut staining or any colour staining was also recorded and was obtained from medical records and from the observations recorded by the dental technicians.

Statistical analysis

In addition to the use of descriptive statistics such as frequencies, percentages and medians (min : max), conditional logistic regression was used to investigate associations between potential risk factors and the presence of an OPL. The univariate analysis was performed with McNemar's test, and candidate variables for a multivariate analysis with backward elimination were factors which were statistically significant at the $p<0.25$ level in the univariate analysis and also factors found to have significant association with OPLs in previous studies. Statistical significance in the final model was set as $p<0.05$. All analyses were performed using Stata version 10.0 (Stata Corp LP, 2007).

Ethical Approval

The study was approved by the Khon Kaen University Ethics Committee for Human Research (reference number: HE562310).

Table 1. Distribution of Oral Premalignant Lesions among 2,300 Participants

Type of Oral premalignant lesions	No. (%)
Leukoplakia	34 (1.5)
Erythroplakia	19 (0.8)
Oral lichen planus	33 (1.4)
Oral submucous fibrosis	1 (0.1)
Actinic cheilitis	0 (0.0)
None	2213 (96.2)
Total	2300 (100)

Table 2. Demographic, Environmental, Dietary and Health-Related Characteristics of Participants

Variables	Participants (2300)	
	with OPLs	without OPLs
	numbers (%)	numbers (%)
Gender		
Male	43 (5.4)	756 (94.6)
Female	44 (2.9)	1,457 (97.1)
Age (years)		
40-49	9 (1.8)	494 (98.2)
50-59	22 (3.1)	687 (96.9)
60-69	26 (4.1)	613 (95.9)
70-79	25 (6.5)	358 (93.5)
≥ 80	5 (7.6)	61 (92.4)
Median (Min : Max)	58 (40 : 96)	
Monthly income (baht)		
< 5,000	49 (3.0)	1,579 (97.0)
5,000-9,999	18 (4.2)	410 (95.8)
≥10,000	20 (8.2)	224 (91.8)
Median (Min : Max)	2,000 (500 : 60,000)	
BMI (kg/m2)		
<18.5	4 (4.3)	90 (95.7)
≥18.5 - 22.99	39 (4.6)	806 (95.4)
≥23	44 (3.2)	1,317 (96.8)
Betel nut stain or any colour stain		
No	64 (3.1)	2,015 (96.9)
Yes	23 (10.4)	198 (89.6)
Smoking		
Never	47 (2.5)	1,812 (97.5)
Smoker	40 (21.9)	143 (78.1)
Ex-smoker	0 (0.0)	258 (100.0)
Alcohol drinking		
Never	50 (2.6)	1,852 (97.4)
Drinker	30 (14.2)	181 (85.8)
Ex-Drinker	7 (3.7)	180 (96.3)
Tea Drinking		
Never	86 (3.8)	2,201 (96.3)
Drinker	1 (7.7)	12 (92.3)
Coffee Drinking		
Never Drink	50 (3.2)	1,533 (96.8)
Drinker	37 (5.2)	668 (94.8)
Ex-drinker	0 (0.0)	12 (100.0)
Betel nut chewing		
Never	50 (2.5)	1,948 (97.5)
Chewer	32 (15.1)	180 (84.9)
Ex-chewer	5 (5.6)	85 (94.4)
Teeth Brushing		
Never	7 (10.5)	60 (89.5)
Once per day	40 (4.4)	874 (95.6)
2 times per day	40 (3.2)	1,227 (96.8)
Every after meal and before sleep	0 (0.0)	52 (100.0)
Denture history		
Never	10 (3.4)	286 (96.6)
Denture wearer	77 (3.8)	1,927 (96.2)

OPLs = Oral Premalignant Lesions

Results

No subjects were diagnosed with an OCC and complete data was obtained for all recruited participants. The analyses were therefore based on 2,300 subjects in the cross-sectional study and 204 subjects in the case-control study.

The prevalences of the various OPLs among the 2,300 subjects in the cross-sectional study are shown in Table 1. No case was found to have more than one type of OPL, and the overall prevalence rate for an OPL was 3.8% (by subtraction, datum not shown). The three most common types of OPL were leukoplakia (1.5%), oral lichen planus (1.4%), and erythroplakia (0.8%). None were diagnosed with actinic cheilitis.

Table 2 summarises the demographic, health-related, and dietary characteristics of the participants in the cross-sectional study. The prevalence rates of OPL were found to be higher in males than females and highest in the oldest, top income and middle BMI groups.

Table 3 shows the characteristics of cases and controls, and Table 4 summarises the results of the univariate

Table 3. General Characteristics of Cases and Controls

Variables	Cases (n=102)	Control (n=102)
	Number (%)	Number (%)
Gender		
Male	48 (47.1)	48 (47.1)
Female	54 (52.9)	54 (52.9)
Age (years)		
40-49	9 (8.8)	9 (8.8)
50-59	27 (26.5)	27 (26.5)
60-69	33 (32.4)	33 (32.4)
70-79	28 (27.4)	28 (27.4)
80	5 (4.9)	5 (4.9)
Median (Min, Max)	63 (42,83)	
Monthly income (baht)		
< 5,000	58 (56.9)	75 (73.5)
5,000 - 9,999	20 (19.6)	13 (12.8)
>10,000	24 (23.5)	14 (13.7)
Median (Min, Max)	3,000 (500, 38,500)	

Table 4. Factors Associated with Oral Pre-Malignant Lesions

Variables	Crude OR	Adjusted OR	P-value*
	(95% CI)	(95% CI)	
Monthly income (baht)			
5,000	1	-	
<5,000	0.41 (0.17-0.90)	-	
BMI (kg/m^2)			-
<23	1	-	
23	0.7 (0.38-1.26)	-	
Betel nut stain or any colour stain			-
No	1	-	
Yes	3.33 (1.29-10.14)	-	
Smoking			0.001
Never	1	1	
Smoker	5.6 (2.13-18.57)	7.53 (2.38-23.78)	
Alcohol drinking			0.01
Never	1	1	
Drinker	5 (1.88-16.72)	4.57 (1.43-14.62)	
Coffee drinking			
Never	1	-	
Drinker	2 (0.96-4.38)	-	
Betel nut chewing			<0.001
Never	1	1	
Chewer	4.28 (1.84-11.55)	8.81 (3.17-24.45)	
Teeth Brushing			
2 times/day	1	-	
<2 times/day	1.62 (0.84-3.24)	-	
Denture history			
No	1	-	
Yes	2.28 (0.88-6.56)	-	

*p-value from conditional logistic regression

analysis which included monthly income, BMI (kg/m^2), betel nut staining or any colour staining, smoking, alcohol drinking, coffee drinking, betel nut chewing, teeth brushing and denture history.

In the multivariate analysis, three factors were found to have a statistically significant association with an increased risk of an OPL: betel nut chewing (ORadj= 8.81; 95% CI: 3.17-24.45), smoking (ORadj= 7.53; 95% CI: 2.38-23.78), and the drinking of alcohol (ORadj= 4.57; 95% CI: 1.43-14.62). Whereas all the confidence intervals were wide, the adjusted ORs indicated strong associations, especially for betel nut chewing and smoking. The odds of a betel nut chewer or smoker developing an OPL were almost eight to nine times higher than for those who did not engage in these habits.

Discussion

The objective of this study was to investigate the prevalence of OPLs and the factors associated with OPLs in Thailand, and this is the first study to explore these issues in a Thai population for almost 30 years.The prevalence rate of an OPL (3.8%) found in this study is similar to those reported in England and Germany (Lim et al., 2010; Carrard et al., 2011), but exceptionally high rates have been found in some other parts of the world (Gambhir et al., 2011; Kumar et al., 2015), and OPL prevalences have a highly variable distribution globally (Chung et al., 2005). One possible explanation for this is that, while the precise aetiology of OPLs is not known (Vlková et al., 2012), the role of various behavioural, demographic and environmental risk factors is well-documented, and the pattern of risk factors to which people are exposed will vary geographically and culturally (Yardimci et al., 2014; Kumar et al., 2015) A good example, is the pronounced socio-cultural habit of betel nut chewing among certain socio-ethnic populations in some parts of the world, especially in South and Southeast Asia. In India, for example, the areca (betel) nut is commonly regarded as a fruit of divine origin. The fruit plays an important part in Hinduism, and it is used in religious ceremonies and at important social events such as weddings. It is also believed to have beneficial health effects and plays a role in traditional ayurvedic medicine (Auluck et al., 2009).

In the present study, it is not surprising that betel nut chewing, smoking and alcohol consumption were found to be strongly associated with an increased risk for OPLs. Similar findings have been previously reported worldwide (Shiu et al., 2000; García-Pola Vallejo et al., 2002; Thomas et al., 2003; Chung et al., 2005; Tovosia et al., 2007; Thomas et al., 2008; Carrard et al., 2011). The betel nut is known to produce mutagenic and genotoxic effects on tissues of body which may lead to various malignant and premalignant lesions (Trivedy, Craig and Warnakulasuriya, 2002; Shah, Chaturvedi and Vaishampayan, 2012). Over 60 carcinogens have found in tobacco smoke (Hecht SS, 2003), and not only are smoking and alcohol use well-established independent risk factors for intra-oral cancer, but their combined harmful effects seem to be greater than the sum of their individual effects (Hecht, 2003). In some parts of the world such as Taiwan, betel nut chewers are also more likely to be smokers and alcohol drinkers (Lin et al., 2006).

While lifestyle habits such as betel nut chewing, smoking and alcohol play a focal part in the development of OPLs, they may not necessarily be significant factors in the transformation of an OPL into a malignancy even if people with a diagnosed OPL change their habits (Ho et al., 2009). This is a key issue for the clinical management of patients with OPLs. Advising these patients to refrain from the habits known to promote OPLs may not have any impact on their prognosis. This appears to be a crucial issue for future research, and its importance is highlighted in a study which indicated that smoking and alcohol use are unrelated to the malignant transformation of leukoplakia (Liu et al., 2010).

Our findings of no statistically significant association with the wearing of dentures is apparently inconsistent with the outcomes of some other studies (see references cited earlier in the Introduction). However, a relatively recent meta-analysis suggests that it is an ill-fitting denture rather a denture per se which substantially increases the risk of developing of oral cancer (Manoharan, Nagaraja and Eslick, 2014). In the present study no attempt was made to find out how far denture wearers had received a professional check to ensure the optimum fitting of their dentures.

Our study had at least one potentially serious limitation. This was that no attempt was made to assess the reliability and validity of the diagnoses of the OPLs. Whereas the diagnoses were made according to the official Thai guidelines, no attempt was made to assess the degree of agreement between those making the diagnoses, and no 'gold standard' was used to check the validity of the diagnoses made by a combination of dental technicians the hospital dentists. Substantial doubts about the reliability and validity of the method of screening for OPLs used in the present study have been raised on behalf of the U.S. Preventive Services Task Force (Moyer, 2014). The possibility of recall bias in the case-control study was potential limitation, but this was avoided because the subjects completed the interview questionnaire before they were informed of their results of the screening examination (Moyer, 2014).

In conclusion, the results of this study confirm that the lifestyle behaviours of betel nut chewing, smoking and alcohol consumption are major risk factors for the development of oral pre-malignant lesions in a population of Roi Et Province, Thailand, and should be the main focus of relevant health education programmes, but it is not yet clear how far these same behaviours contribute to the eventual transformation of existing OPLs into cancer.

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