RESEARCH ARTICLE

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Is Periodontitis Independently Associated with Potentially Malignant Disorders of the Oral Cavity?

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Abstract

Objective: To examine if periodontitis is independently associated with oral potentially malignant disorders (OPMD) in a rural Indian adult population aged 35-54 years. **Methods:** A population-based cross-sectional study was conducted in rural India from 2011 to 2012. Multistage stratified cluster random sampling was followed to recruit 1401 participants aged 35-54 years. Face-to-face interviews were conducted to collect data on sociodemographic factors, tobacco and alcohol use. Oral examinations were done to record OPMD, periodontal findings and missing teeth. Univariate, bivariate and multivariable analyses were achieved using SPSS version 16 Chicago, SPSS Inc. OPMDs (leukoplakia, erythroplakia, oral submucous fibrosis (OSF) and suspicious malignant lesion) whether present or absent were selected as outcome variables; age, sex, socioeconomic factors, smoking, tobacco-chewing status, alcohol use, and periodontitis were considered as the predictor variables. **Results:** Among 873 participants, 44 demonstrated 47 lesions. Leukoplakia (n=21), erythroplakia (n=3), OSF (n=21), and suspicious malignant lesions (n=2) were present, strongly associated with past tobacco-chewing status [OR=9.22 (2.57-33.15)], current tobacco-chewing status [OR=15.49 (6.20-38.74)] and moderate/severe periodontitis [OR=3.19 (1.11-9.12)]. **Conclusion:** Periodontitis is a risk indicator for OPMD, independent of socioeconomic factors and tobacco-chewing. Tobacco-chewing status, both past and current, was strongly associated with OPMD in our rural Indian population.

Keywords: Oral potentially malignant disorders- periodontitis- prevalence- rural- socioeconomic position

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Introduction

Oral cancer is a public health problem in many countries (Rao et al., 2013). Annually around 300,000 new cases of oral cancer are detected worldwide and majority of them occur in developing countries. About one third of the cases are seen in the Indian subcontinent. The number continues to increase in developed countries (Chaturvedi et al., 2013). In the United States 30,000 new oral cancer cases occur every year and adds to the increase in cancer-related mortality (Tezal et al., 2005). Nearly 90% of oral cancers are squamous cell carcinoma. Oral squamous cell carcinomas (OSCC) could develop from oral potentially malignant disorders (OPMD). The term OPMD includes around 20 lesions and conditions that vary in the potential for malignant transformation (Warnakulasuriya et al., 2007). Some of the prominent OPMD linked to oral squamous cell carcinoma are Leukoplakia, Erythroplakia, Lichen Planus and Oral Submucous Fibrosis (OSF) (Mortazavi et al., 2014). Global prevalence of leukoplakia and erythroplakia are 2.6% and 0.11% respectively (Petti, 2003; Villa et al., 2011). OSF is common in Southeast Asia and its prevalence varies between 3.2-17.6% respectively (Gupta et al., 1998; Yang et al., 2001). Malignant transformation depends on the type of lesion. Leukoplakia, erythroplakia and OSF have prominent risk factors such as tobacco, arecanut, slaked lime and alcohol (Tanaka and Ishigamori, 2011). Interestingly, these are also the risk factors for OSCC. Several other factors apart from use of tobacco and alcohol have been associated with oral cancer, and prominent among them are Human Papilloma Virus infection (Ringstrom et al., 2002), stress (Shah et al., 2009), low socioeconomic conditions (Hashibe et al., 2003). Oral factors such as poor oral hygiene, use of denture and periodontitis (Meyer et al., 2008) have been indicated as risk factors for OSCC. Research has already shown the association between periodontitis and oral cancer and suggesting immune-inflammatory pathway (Feller et al., 2013; Tezal et al., 2007). A study by Tezal et al., (2005) has shown that leukoplakia, erythroplakia and non-specific ulcers to be associated with periodontal attachment loss in the American population. Another study conducted in Pomerania demonstrated that leukoplakia is associated with gingival bleeding on probing after adjusting for other predictors (Meisel et al., 2012).

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The two studies have examined association between periodontitis with mainly leukoplakia and erythroplakia. As mentioned above there are other OPMD having immuno-inflammatory pathogenesis processes that could plausibly have association with periodontitis. Considering the above reasons the present study was conducted to examine if periodontitis is associated with OPMD in a rural Indian adult population.

Materials and Methods

A cross-sectional study was conducted between 2011 and 2012 in rural areas of India. Ethics approval was provided by the Human Research Ethics Committee, University of Adelaide. The article was prepared according to the STROBE guidelines.

A cluster-stratified random sampling was followed to recruit an estimated sample size of 1160 people aged 35-54 years (Bhat et al., 2015). Initially five taluks (sub provinces) from two districts of Karnataka state were selected. Fifty villages were later selected from the five taluks. In each village, the houses were enlisted and 28 houses were selected randomly and from each house a male or female participant was selected and consent sought. The potential participant who was dentulous, did not have any contraindication for periodontal examination and provided written informed consent was included in the study. Data on sociodemographic factors, habits and diabetes were collected using structured questionnaire through face to face interview. The interview was followed by oral examination that was done in natural day light with additional lighting using a head lamp. Periodontal findings such as recession and probing pocket depth were recorded for all teeth except third molars using a Hu-Friedy PCP-2 probe (Hu-Friedy USA). Oral mucosa was examined for presence of premalignant or suspicious-malignant lesions. The examiner (first author) was trained by the standard examiner (third author) of the university, who trains examiners recruited for national oral health surveys. The kappa values for intra-examiner reliability were 0.83, 0.96 and 0.89 for probing pocket depth, recession and OPMD respectively. Participants detected with premalignant/ suspicious malignant lesions were referred to the nearby hospitals for further investigation and diagnosis.

Statistical analyses: The data were analysed with SPSS version 16, Chicago, USA Inc., using complex sampling plan according to the sampling design. The explanatory variables were periodontitis, age, gender, education, occupation, monthly per-capita income, tobacco use, alcohol, diabetes and the community to which they belonged. Age was categorized into '35-44'and '45-54'year groups. Monthly per-capita income of the family was dichotomized into 'Low-Middle' (Rupees=<1949/month) and 'High' Rupees>=1950/month) groups. Education recorded as highest level of education attained and categorized into 'Secondary/less' and 'Post-secondary' levels. Smoking and tobacco-chewing (a form of smokeless tobacco chewed commonly in the Indian subcontinent) were categorized as 'Never', 'Former' and 'Current'. Alcohol use and self-reported diabetes were dichotomised as Yes/No. Periodontitis was classified according to CDC-AAP criteria given below (Eke et al., 2012).

CDC-AAP case definition

Case	Definition
None	No mild, moderate or severe periodontitis
Mild	≥2 interproximal sites with CAL ≥3 mm, and ≥2 interproximal sites with pocket depth ≥ 4 mm (not on same tooth) or one site with pocket depth ≥5 mm
Moderate	≥ 2 interproximal sites with CAL ≥ 4mm (not on the same tooth) or ≥ 2 interproximal sites with pocket depth ≥ 5mm (not on the same tooth).
Severe	≥ 2 interproximal sites with CAL ≥ 6mm (not on same tooth) and ≥ 1 interproximal site with pocket depth ≥ 5mm

This was later dichotomised as 'None/Mild' and 'Moderate/Severe'.

The outcome variable was presence of premalignant/ suspicious malignant lesions. Bivariate analysis was done using cross-tabs to examine the distribution of explanatory variables by prevalence of OPMD. Binary logistic regression was done to determine the factors associated with OPMD. Explanatory variables for the multivariable model were selected based on prior knowledge (Greenland, 2008) of risk factors for OPMD from the review of literature. However, a variable was still included in the multivariable model if it was regarded as a risk factor (age and sex) even if not significant at the bivariate level. The variables were introduced into the model using 'Enter' method because we conceptualised that there was no logical basis for one variable to occur before the other in this cross sectional study (Cohen et al., 2003). Confidence interval of 95% was estimated. Non-overlapping 95% CI for proportions and 95% CI of odds ratios (OR) not including unity were considered statistically significant.

Results

Totally 873 participants entered the study reaching a response rate of 62.3%. Nearly 5% (95% CI=3.8-6.7%, n=44) were found to have OPMD. The lesions detected were suspicious malignant lesion (n=2), leukoplakia (n=21), oral submucous fibrosis (n=21) and erythroplakia (n=3).

Table 1 shows that proportion of people with moderate/severe periodontitis have higher prevalence of OPMD compared to those with none/mild periodontitis. Higher proportion of people with lower levels of education, former and current smokers, tobacco chewers, and alcohol consumers presented with OPMD compared to their counterparts.

Table 2 presents the crude and adjusted odds ratios of various factors. The crude OR show that periodontal disease, smoking, chewing, alcohol use and sex to be associated with OPMD. After adjusting for confounders moderate/severe periodontitis and tobacco chewing were associated with OPMD. Chewing tobacco showed a gradient in increase of OR; while current chewers have 15 times, the past chewers have 9 times higher odds for

Table 1. Distribution of Periodontitis, Habits and Sociodemographic Factors by the Prevalence of OPMD

Factors / Categories	n	Without OPMD	With OPMD
Periodontal disease			
No/Mild	464	98.5 (96.8-99.3)	1.5 (0.7-3.2)
Moderate/severe	405	90.9 (87.7-93.3)	9.1 (6.7-12.3)
Tobacco-chewing status			
Never	663	98.9 (97.9-99.5)	1.1 (0.5-2.1)
Past	24	83.3 (64.6-93.2)	16.7 (6.8-35.4)
Current	186	82.3 (75.1-87.7)	17.7 (12.3-24.9)
Smoking status			
Never	796	96.1 (94.5-97.2)	3.9 (2.8-5.5)
Past	31	80.6 (62.4-91.3)	19.4 (8.7-37.6)
Current	46	84.8 (68.6-93.4)	15.2 (6.6-31.4)
Alcohol use			
No	652	97.2 (95.4-98.4)	2.8 (1.6-4.6)
Yes	221	88.2 (83.2-91.9)	11.8 (8.1-16.8)
Education level			
Post-secondary	162	97.5 (92.9-99.2)	2.5 (0.8-7.1)
Secondary/less	710	94.4 (92.9-95.8)	5.6 (4.2-7.4)
Monthly per-capita income			
High	423	94.1 (91.2-96.1)	5.9 (3.9-8.8)
Low-Middle	397	96.0 (93.5-97.5)	4.0 (2.5-6.5)
Age (years)			
35-44	525	96.0 (94.1-97.3)	4.0 (2.7-5.9)
45-54	348	93.4 (90.1-95.6)	6.6 (4.4-9.9)
Sex			
Male	473	92.2 (89.6-94.2)	7.8 (5.8-10.4)
Female	400	98.3 (96.5-99.1)	1.8 (0.9-3.5)
Diabetes			
No	830	95.2 (93.5-96.4)	4.8 (3.6-6.5)
Yes	43	90.7(78.2-96.4)	9.3 (3.6-21.8)
Community			
Fishing	522	94.8 (92.7-96.3)	5.2 (3.7-7.3)
Farming	351	95.2 (92.4-96.9)	4.8 (3.1-7.6)

*non-overlapping 95% CI of proportion indicates statistical significance

Table 2. Factors Associated with OPMD

Factors / Categories	Crude Odds Ratio	Adjusted Odds Ratio
Periodontal disease		
No/Mild	Reference	Reference
Moderate/severe	6.56 (2.65-16.29)*	3.19 (1.11-9.12)*
Tobacco-chewing status		
Never	Reference	Reference
Past	18.74 (6.34-55.45)*	9.22 (2.57-33.15)
Current	20.21 (8.86-46.11)*	15.49 (6.20-38.74)*
Smoking status		
Never	Reference	Reference
Past	5.92 (2.14-16.37)*	1.55 (0.56-4.28)
Current	4.43 (1.57-12.52)*	2.43 (0.68-8.74)
Alcohol use		
No	Reference	Reference
Yes	4.70 (2.22-9.96)*	1.71 (0.71-4.15)
Education level		
Post-secondary	Reference	--
Secondary/less	2.36 (0.76-7.29)	
Monthly per-capita income		
High	Reference	--
Low-Middle	0.67 (0.33-1.35)	
Age (years)		
35-44	Reference	Reference
45-54	1.70 (0.90-3.20)	0.92 (0.38-2.22)
Sex		
Male	4.76 (2.21-10.28)*	0.98 (0.42-2.30)
Female	Reference	Reference
Diabetes		
No	Reference	--
Yes	2.03 (0.69-5.94)	
Community		
Fishing	Reference	--
Farming	0.93 (0.51-1.72)	

*, non-overlapping 95% CI of proportion indicates statistical significance; --, Not included in the model

OPMD compared to that of non-chewers.

Discussion

The present study was designed to examine the association of periodontitis with OPMD. The findings support a strong association between periodontitis and OPMD after controlling for confounders. The findings of the study were consistent with the findings observed by Tezal et al., (2005) who indicated a possible relationship between periodontitis and oral precancer such as leukoplakia, erythroplakia and non-specific ulcer. Jornet and Alonso found that CPITN scores were worse in people with oral lichen planus (López-Jornet and Camacho-Alonso, 2012). The findings from a health study conducted in Pomerania showed that gingivitis characterised by bleeding on probing and periodontitis (as measured by CAL) was associated with an increase probability for the occurrence of oral leukoplakia in a dose-dependent pattern (Meisel et al., 2012). However, the dose-dependent association was attenuated for CAL when smoking was adjusted in the model. The present study showed association between periodontitis and OPMD persisted despite adjusting for smoking, tobacco-chewing, alcohol, age and gender.

The prevalence of OPMD in the present study was 5% that was higher compared to studies done in Germany, U.S. and India (Gupta et al., 1998; Reichart and Kohn, 1996; Scheifele et al., 2003) but lesser than that in Taiwan (Yang et al., 2001). However, the prevalence of OPMD in the present study was much lower compared to a study conducted amongst rural workers in Brazil (Ferreira et al., 2016).

It is important to note that factors such as periodontitis emerged to be significant risk indicators for OPMD after adjusting for the confounders. The findings suggest inflammatory pathway for the development of OPMD. In the study, while nearly 1.5% of them with none/mild

periodontitis had OPMD, 9% of them with moderate/severe periodontitis were found to have OPMD. Though the prevalence of periodontitis is high, OPMD is relatively rare compared to periodontitis. It is clear that periodontal inflammation per-se could rarely induce OPMD development (Grivennikov et al., 2010; Mantovani, 2010). Use of tobacco, alcohol and betelquid/arecanut are known causes for leukoplakia, erythroplakia, OSF and periodontitis observed in the study population. It is speculated that the tobacco, betelquid and alcohol could lead to activation of specific transcription factors that cause alteration in the expression of genes in turn leading to enhanced production of inflammatory mediators as well as creating areas of genetically modified precancerous keratinocytes (Feller et al., 2013). It is well known that inflammation is associated with infection. Chronic periodontitis may be associated with oral premalignant or malignant lesion through toxic effects of oral microbiota and their by-products or from chronic inflammation. OPMD could develop as a cumulative effect of chronic exposure to carcinogenic metabolites of periodontal pathogens (Meisel et al., 2012). A few researchers have also found association between inflammation and OPMD/oral squamous cell carcinoma (Chang et al., 2013; Sahingur and Yeudall, 2015). However, the exact mechanism of action needs further exploration.

Tobacco chewing was associated with OPMD in the present study. Low education and its relationship with chewing habits have been observed in other studies (Hashibe et al., 2003). Poor literacy and low education status have been associated with habits such as smoking and tobacco chewing which have shown association with OPMD (Lee et al., 2003). The participants of the study were from rural background from farming and fishing communities having lower levels of education. Furthermore, it was a cultural norm in these communities to chew tobacco.

In the present study, diagnoses of leukoplakia, erythroplakia, OSF and suspicious malignant lesions were based on clinical diagnosis. Confirmation through histopathology was not available as the rural people did not agree to undergo biopsy at the time of interview and examination. However, they were referred to nearby hospitals but could not be followed-up. The periodontal status of the participants were measured using the CDC-AAP case definition and provides clinically assessed information compared to studies which have used self-reported status of periodontal health (Hughes et al., 2017).

The present study is one of the few studies, which has examined the association of periodontitis and other associated factors with OPMD in a rural Indian population. The present study used a robust study design and followed the guidelines of National Survey for Adult Oral health Protocol Australia and measured periodontitis using the CDC-AAP case definition. Unlike other studies, we have included only moderate and severe periodontitis cases to avoid any misclassification. From the available evidence, we could suggest that rigorous screening and diagnosis for OPMD should be followed in patients/participants with chronic periodontitis and habits of tobacco, alcohol and betel-quid use.

In conclusion, periodontitis and tobacco-chewing were independently associated with OPMD in the present study. Further longitudinal studies are needed to provide evidence of the temporal relationship of the association.

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Statement conflict of Interest

Authors declare no conflict of interest.

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