Original Article

Correlation of degree of dysplasia in potentially malignant disorders with tobacco use: A cross-sectional study

Monika Aroquiadasse, Mariappan Jonathan Daniel, Subramanian Vasudevan Srinivasan, Vannathan Kumaran Jimsha

Department of Oral Medicine and Radiology, Mahatma Gandhi Postgraduate Institute of Dental Sciences, Puducherry, Puducherry UT, India

ABSTRACT

Background: Oropharyngeal malignancies are the sixth leading cause of cancer worldwide. However, in India, oral and pharyngeal cancers are the most common cancer among men. It has been well established that virtually all oral cancer are preceded by a visible oral precursor lesions. Furthermore, the incidence of oral malignancies is higher among persons who use tobacco. We aimed to study the association between the degree of dysplasia in potentially malignant disorders (PMDs) with the type and duration of tobacco use. **Materials and Methods:** A record based cross-sectional study was conducted during February 2015. We included all the PMDs diagnosed and biopsied in our institute between 2006 and 2013. The study variables such as sex, age, type, and duration of tobacco habit were retrieved from the registers maintained in the Department of Oral Medicine and Radiology, and the histopathological diagnosis was retrieved from the biopsy reports of the PMDs documented in the Department of Oral Pathology. Lesions were classified as high-risk lesions (HRLs) or low-risk lesions (LRLs) based on the grade of cellular atypia and architectural features. The data were analyzed using EpiData software. **Results:** Out of total 112 cases, 80 (71%) were males and majority were older than 45 years (58%). About 64 (57%) reported use of any form of tobacco product. Of the tobacco users, 39 (65%) patients had reported tobacco use for 10 or more years. About one-fifth had HRL, and the remaining had LRL. Increasing age, any form of tobacco use (chewable or smoke form), tobacco smoking and longer duration of tobacco use were significantly associated with the development of HRLs ($P < 0.05$). **Conclusion:** By this retrospective study, we concluded that HRLs were more common among people who use any form of tobacco, either chewable or smoke form. Clearly, there is an increasing proportion of HRL with advancement in age and the duration of tobacco use.

Key words: Dysplasia, epidemiology, high-risk lesion, low-risk lesion, oral cancer, tobacco

INTRODUCTION

Oral and pharyngeal cancer, grouped together, is the sixth most common cancer in the world.[1] In the Indian subcontinent, the incidence of oral cancer is the highest among all cancers in men.[2] It is well known that oral cancer is preceded by visible oral precursors. The following disorders are regarded as being potentially malignant disorders (PMDs): Leukoplakia, erythroplakia, oral submucous fibrosis (OSMF), palatal lesions in reverse smokers, oral lichen planus, and discoid lupus erythematosus. In addition, there is an increased risk of oral cancer in patients suffering from rare inherited syndromes such as Cowden syndrome, Xeroderma pigmentosum, and Fanconi's anemia, cases of prolonged immunodeficiency due to prolonged use of immunosuppressive drugs or an

Address for correspondence: Dr. Monika Aroquiadass,
Department of Oral Medicine and Radiology,
Mahatma Gandhi Postgraduate Institute of Dental Sciences,
Gorimedu, Puducherry, India.
E-mail: monikadasse@gmail.com

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.197870

Cite this article as: Aroquiadasse M, Daniel MJ, Srinivasan SV, Jimsha VK. Correlation of degree of dysplasia in potentially malignant disorders with tobacco use: A cross-sectional study. Clin Cancer Investig J 2016;5:398-402.

underlying HIV infection and in chronic graft versus host disease after stem cell transplantation.[3] The prevalence of OSMF ranged from 0.4% to 1.2%[4] and the malignant transformation rate varies from 7.6% to 40%.[5,6] The prevalence of leukoplakia varied from 0.2% to 4.9%[7] while Petti *et al*. reported the global prevalence to be 2.6%.[8] The malignant transformation of leukoplakia ranges from 3.6% to 17.5%.[9-11]

Erythroplakia is rare and has an incidence of 0.02%–0.83%.[12] Villa *et al*. reported the global mean prevalence of oral erythroplakia to be 0.11%.[13] All cases of erythroplakia show some degree of epithelial dysplasia. Of which nearly half are invasive squamous cell carcinoma, two-fifths are carcinoma *in situ* or severe epithelial dysplasia and mild-to-moderate dysplasia accounted for <10%.[14] A malignant transformation rate of 14.3%–66.7% was reported by Villa *et al*.[13] Palatal lesions were reported in 9.5% of reverse smokers and has been associated with significant risk of malignant transformation.[15]

It is well-established that tobacco smoking and alcohol consumption are important independent risk factors for squamous cell carcinoma of the oral cavity and pharynx.[16,17]

Aims

Through this study, we aim to study the correlation between the degree of dysplasia in PMDs with the type and the duration of tobacco use.

MATERIALS AND METHODS

Study design, setting, and population

A record-based cross-sectional study was conducted during February 2015 in a teaching Dental College Hospital in Puducherry. This Institution caters to the needs of patients not only from Puducherry but also from the neighboring districts of Villupuram, Cuddalore, and Thiruvannamalai. On an average, around 150 new patients visit the out-patient Department of Oral Medicine and Radiology every day. Patient who is clinically diagnosed to have premalignant lesions in the oral cavity was subjected to biopsy and histopathological examination of the biopsied tissue. We included all the PMDs diagnosed and biopsied in our hospital between 2006 and 2013.

Study variables and procedure

The study variables including the demographic data sex, age, type, and duration of tobacco and areca nut use were retrieved from the register maintained in the Department of Oral Medicine and Radiology. Moreover, the histopathological diagnosis was retrieved from the biopsy reports of the PMDs documented in the Department of Oral Pathology. Histopathological reports with the diagnosis of leukoplakia, erythroplakia, lichen planus, and OSMF were included in the study. Invasive carcinomas and other malignancies were excluded from this study. The histopathological diagnoses were later classified according to the WHO 2005 classification.[18,19] Based on the presence and the grading of cellular atypia and architectural (thickness of dysplastic layers compared with the total epithelial height), the lesions were classified into the following categories: squamous hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma *in situ*. Histopathological diagnosis was then classified according to the binary system of grading dysplasia as, low-risk lesion (LRL) (no/questionable/mild dysplasia) and high-risk lesion (HRL) (moderate/severe dysplasia/carcinoma *in situ*).[20]

Statistical analysis

The data were single entered and analyzed using EpiData software (version 3.1 for data entry and version 2.2.2.182 for analysis, EpiData Association, Odense, Denmark). Categorical variables such as gender, age group, type of tobacco, duration of tobacco use, and provisional diagnosis were expressed as a proportion. Chi-square test was used to find the association between age, type of tobacco and the duration of tobacco use with the occurrence of HRL. Odds ratio with 95% confidence interval was calculated for the risk of development of HRL. The level of statistical significance was set as 0.05.

RESULTS

The sociodemographic characteristics of the study participants are shown in Table 1. A total of 112 patients with PMDs included in our analysis 80 (71%) were male and the remaining 32 (29%) were female. We divided the age of the patients into three categories as follows: <45 years, 45–60 years, and >60 years. Of the total 112, 42% (n = 47) of the patients were <45 years and about 16% (n = 18) were aged >60 years. About 64 patients had reported the use of any form of tobacco product in the past. The majority of the tobacco users were smokers (n = 41). Of the total 112, chewing tobacco and chewing areca nut was reported by 29 (25.9%) and 27 (24.1%), respectively. About six patients reported use of both smoke form as well as chewable form of tobacco. The types of the chewable tobacco varied from the traditional betel quid consisting of the leaf of the betel vine wrapped around areca or betel nut (nut of *Areca catechu*), slaked lime, catechu (extract of *Acacia*), and tobacco. Other variants were Gutkha, Hans, Pan Parag and other commercially available tobacco products. All patients who reported tobacco smoking used either beedi or cigarette. Nearly, two-third of the patients had

been using tobacco for >10 years. The most common provisional diagnosis was leukoplakia (38.4%), followed by lichen planus (30.4%), and erythroleukoplakia (16.1%).

Table 1: Demographic and disease characteristics of the study population (*n*=112)

Demographic and disease characteristics (*n*=112)	Frequency (%)
Gender	
Male	80 (71.4)
Female	32 (28.6)
Age group (years)	
<45	47 (42.0)
46-60	47 (42.0)
>60	18 (16.0)
History of tobacco and areca nut use	
Any form of tobacco	64 (57.1)
Tobacco chewing	29 (25.9)
Tobacco smoking	41 (36.6)
Areca nut chewing	27 (24.1)
Tobacco use with areca nut	20 (17.9)
Duration of tobacco use (*n*=64), years	
<5	8 (12.5)
5-10	14 (21.8)
11-20	24 (37.5)
>20	18 (28.2)
Provisional diagnosis	
Leukoplakia	43 (38.4)
Lichen planus	34 (30.4)
Erythroleukoplakia	18 (16.1)
Oral submucous fibrosis	10 (8.9)
Erythroplakia	1 (0.9)
Others	6 (5.4)
Category of lesion	
HRL	25 (22.3)
LRL	87 (77.7)

Others include lichenoid reaction, erythematous candidiasis, and allergic stomatitis. LRL: Low-risk lesion, HRL: High-risk lesion

The association between the different risk factors and the occurrence of HRL is shown in Table 2. Of the total, about 25 (22.3%) had HRL, and the remaining 87 (77.7%) had LRL according to the binary system of grading dysplasia. There is a significant correlation between tobacco use in any form and the occurrence of HRL with odds ratio (95% confidence interval) of 3.8 (1.3–12.4). Smokers had higher odds of having high-risk dysplastic lesions than nonsmokers with an odds ratio of 2.8. Chewable tobacco users had 1.9 times more risk of having HRL than persons who did not use chewable form of tobacco, but the association was not statistically significant. However, there was no significant association between areca nut chewing or tobacco use with areca nut with the development of premalignant lesions. There was clearly an increasing proportion of HRL in the age group 46–60 years. There was a linear dose-response relationship between the duration of tobacco use, and the occurrence of high-grade dysplastic lesions and the association was statistically significant ($P = 0.023$).

DISCUSSION

Two-third of oral squamous cell carcinoma (OSCC) occurs in the developing countries.[2] An age-adjusted rate of oral cancer in India is high that is, 20/100,000 population and accounts for over 30% of all cancers in the country.[21] It is well known that OSCC could be preceded by clinically evident PMDs and oral leukoplakia is the most common PMD clinically.[22,23]

Table 2: Correlation of age and history of tobacco use with the degree of lesions: High-risk lesions include moderate and severe dysplasia and carcinoma-*in situ*; low-risk lesions include lesions with mild or questionable dysplasia

Risk factors	HRL (*n*=25)	LRL (*n*=87)	Total (*n*=112)	OR (95% CI)	*P*
Age group (years)					
<45	5 (10.6)	42 (89.4)	47 (100)	Reference	
46-60	16 (34.0)	31 (66.0)	47 (100)	4.3 (1.4-14.3)	0.006
>60	4 (22.2)	14 (77.8)	18 (100)	2.4 (0.5-10.6)	0.226
Any form of tobacco use					
Yes	20 (31.2)	44 (68.8)	64 (100)	3.8 (1.3-12.4)	0.008
No	5 (10.4)	43 (89.6)	48 (100)	Reference	
Tobacco smoking					
Yes	14 (34.1)	27 (65.9)	41 (100)	2.8 (1.2-7.2)	0.022
No	11 (15.5)	60 (84.5)	71 (100)	Reference	
Tobacco chewing					
Yes	9 (31.0)	20 (69.0)	29 (100)	1.8 (0.7-4.9)	0.191
No	16 (19.3)	67 (80.7)	83 (100)	Reference	
Chewing arecanut					
Yes	5 (18.5)	22 (81.5)	27 (100)	0.7 (0.2-2.1)	0.586
No	20 (23.5)	65 (76.5)	85 (100)	Reference	
Tobacco use with arecanut					
Yes	4 (20.0)	16 (80.0)	20 (100)	0.8 (0.2-2.7)	0.783
No	21 (22.8)	71 (77.2)	92 (100)	Reference	
Duration of tobacco use (years)[#]					
<5	1 (12.5)	7 (87.5)	8 (100)	1	0.023
6-10	2 (14.3)	12 (85.7)	14 (100)	1.2	
11-20	9 (37.5)	15 (62.5)	24 (100)	4.2	
>20	9 (50.0)	9 (50.0)	18 (100)	7.0	

[#]*P* value obtained by extended Mantel-Haenszel Chi-square for linear trend. OR: Odds ratio, CI: Confidence interval, LRL: Low-risk lesions, HRL: High-risk lesions

The diagnosis and grading of oral epithelial dysplasia are subjective and has considerable inter- and intra-observer variations in grading.[24] More recently, there has been an attempt to more clearly define the criteria for grading epithelial dysplasia. We have used a new scheme based on the same morphological criteria used by the WHO classification 2005 (architecture and cytology changes) that grades the lesions into either "Low risk" (no/questionable/mild) and "High risk" (moderate/severe/carcinoma *in situ*) based on scoring the features.[18-20]

In this study, leukoplakia (38.4%) was the most common presentation as reported in the literature.[23] More than half of the patients with dysplastic lesions reported tobacco use. Among tobacco users, smoke form of tobacco was the most common form of tobacco used (64%), and smokeless form was used by 29 (45%) patients. This finding is similar to the data from GATS 2009 to 2010, where tobacco smoking (9.1%) was more common than tobacco chewing (4.8%) in Puducherry.[25]

The proportion of LRL (77.7%) was found to be higher than that of HRLs (22.3%). In our study, people who used any form of tobacco (either chewable or smoke form) had a greater risk of developing HRL s, compared to those who did not use tobacco. This finding reinforces the fact tobacco serves as an important risk factor for developing oral cancer as it contains >7000 different chemicals of which >60 chemicals are known carcinogens.[26]

On assessing the type of tobacco, we found that greater proportion of patients developing HRL were tobacco smokers than tobacco chewers. This finding is similar to the other study from India.[27] This could be because of the synergistic effect of localized elevation in the temperature of the oral cavity, which may make the epithelium more susceptible to genotoxic effect of tobacco products. Benzopyrene and other polycyclic aromatic carcinogenic agents in tobacco smoke are considered to increase the prevalence and spectrum of TP53 mutations and smokers have more p53 mutations than nonsmokers.[28,29]

The high incidence of oral cancer in India has been attributed to the widespread tobacco usage among the population either in chewable or smoke form. Tobacco has traditionally been chewed in India as an ingredient of betel quid or pan, which is a combination of betel leaf, areca nut, and lime; however, in recent time, there is an increase in consumption of commercial forms such as Gutkha, Khaini, and Mawa. Smoking in the form of cigarettes is usually restricted to the urban and higher socioeconomic strata, whereas in the rural population and low socioeconomic groups, tobacco is most commonly smoked in the form of beedi.[27]

In our study, it was also found that a steady increase in the development of HRL was observed with increase in duration which may be because tobacco use increases with age and initiation of tobacco usage usually take place much earlier in life. There exists a dose-response relationship between the duration of tobacco use and occurrence of HRL. The limitation of this study was the absence of a control group and also that frequency of tobacco usage could not be included due to inadequate documentation.

CONCLUSION

The results of our study are supportive of the fact that tobacco consumption is one of the major etiological factors in the development of HRLs (PMDs with moderate, severe dysplasia, and carcinoma *in situ*). Premalignant lesions developing in individuals with tobacco habit show a greater tendency for structural and morphological changes in the oral epithelium and hence may be at a higher risk of malignant transformation. HRLs occur more commonly among elderly. Although not statistically significant, there is an increased risk of HRLs among people with longer duration of tobacco use. Early detection and intervention have the potential for decreasing the incidence and considerably reduces the mortality and morbidity of oral cancer, improving the overall survival of the patient. It is obligatory for the health professional to be knowledgeable about the risk factors, clinical presentation, and pathogenesis of these PMDs. The clinicians including dentists and physicians play a vital role not only in early detection and management of these conditions but also in creating awareness among the public about the deleterious effects of tobacco and the vicious relationship of tobacco use with the development of oral cancer.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45:309-16.
2. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin 2002;52:195-215.
3. van der Waal I. Oral potentially malignant disorders: Is malignant transformation predictable and preventable? Med Oral Patol Oral Cir Bucal 2014;19:e386-90.
4. Pindborg JJ, Mehta FS, Gupta PC, Daftary DK. Prevalence of oral submucous fibrosis among 50,915 Indian villagers. Br J Cancer 1968;22:646-54.
5. Murti PR, Bhonsle RB, Pindborg JJ, Daftary DK, Gupta PC, Mehta FS. Malignant transformation rate in oral submucous

fibrosis over a 17-year period. Community Dent Oral Epidemiol 1985;13:340-1.
6. Wahi PN, Kapur VL, Luthra UK, Srivastava MC. Submucous fibrosis of the oral cavity 1. Clinical features. Bull World Health Organ 1966;35:789-92.
7. Mehta FS, Pindborg JJ, Gupta PC, Daftary DK. Epidemiologic and histologic study of oral cancer and leukoplakia among 50,915 villagers in India. Cancer 1969;24:832-49.
8. Petti S. Pooled estimate of world leukoplakia prevalence: A systematic review. Oral Oncol 2003;39:770-80.
9. Pindborg JJ, Jolst O, Renstrup G, Roed-Petersen B. Studies in oral leukoplakia: A preliminary report on the period pervalence of malignant transformation in leukoplakia based on a follow-up study of 248 patients. J Am Dent Assoc 1968;76:767-71.
10. Roed Petersen B. Cancer development in oral leukoplakia: Follow up of 331 patients. J Dent Res 1971;50:711.
11. Silverman S Jr., Gorsky M, Lozada F. Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. Cancer 1984;53:563-8.
12. Reichart PA, Philipsen HP. Oral erythroplakia – A review. Oral Oncol 2005;41:551-61.
13. Villa A, Villa C, Abati S. Oral cancer and oral erythroplakia: An update and implication for clinicians. Aust Dent J 2011;56:253-6.
14. Shafer WG, Waldron CA. Erythroplakia of the oral cavity. Cancer 1975;36:1021-8.
15. Pindborg JJ, Mehta FS, Gupta PC, Daftary DK, Smith CJ. Reverse smoking in Andhra Pradesh, India: A study of palatal lesions among 10,169 villagers. Br J Cancer 1971;25:10-20.
16. IARC. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans: Alcohol Drinking. Vol. 44. Lyon, France: World Health Organization; 1988. p. 35.
17. IARC. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans: Tabacco Smoking and Involuntary Smoking. Lyon, France: World Health Organization; 2004. p. 83.
18. Barnes L, Eveson JW, Reichart P, Sidransky D, editors. World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours. Lyon, France: IARC Press; 2005.
19. Bouquot J, Speight PM, Farthing PM. Epithelial dysplasia of the oral mucosa diagnostic problems and prognostic features. Curr Diagn Pathol 2006;12:11-22.
20. Kujan O, Oliver RJ, Khattab A, Roberts SA, Thakker N, Sloan P. Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. Oral Oncol 2006;42:987-8.
21. Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, *et al*. Effect of screening on oral cancer mortality in Kerala, India: A cluster-randomised controlled trial. Lancet 2005;365:1927-33.
22. Warnakulasuriya S, Mak V, Möller H. Oral cancer survival in young people in South East England. Oral Oncol 2007;43:982-6.
23. van der Waal I, Schepman KP, van der Meij EH, Smeele LE. Oral leukoplakia: A clinicopathological review. Oral Oncol 1997;33:291-301.
24. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med 2007;36:575-80.
25. International Institute for Population Sciences, Ministry of Health and Family Welfare, Government of India. Global Adult Tobacco Survey India (GATS India), 2009-10. New Delhi: Ministry of Health and Family Welfare; Mumbai: International Institute for Population Sciences; 2010. Available from: http://mohfw.nic.in/WriteReadData/l892s/1455618937GATS%20India.pdf [Last accessed on 2016 Nov 12].
26. Preeti S, Raut DK. Prevalence and pattern of tobacco consumption in India. Int Res J Soc Sci 2012;1:36-43.
27. Garg KN, Raj V, Chandra S. Trends in frequency and duration of tobacco habit in relation to potentially malignant lesion: A 3 years retrospective study. J Oral Maxillofac Pathol 2013;17:201-6.
28. Cogliano V, Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F; WHO International Agency for Research on Cancer. Smokeless tobacco and tobacco-related nitrosamines. Lancet Oncol 2004;5:708.
29. He QQ, Wong TW, Du L, Jiang ZQ, Yu TS, Qiu H, *et al*. Environmental tobacco smoke exposure and Chinese schoolchildren's respiratory health: A prospective cohort study. Am J Prev Med 2011;41:487-93.