

Clinicopathological Correlation in Dysplastic and Malignant Lesions of The Oral Cavity and Oropharynx in Tertiary Care Center in Central India

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ABSTRACT

Background: Late detection and diagnosis of oral and oropharyngeal carcinomas are responsible for the related increased morbidity and mortality. Understanding the risk factors and patterns of malignancy can help early identification and prompt treatment of patients with oral cancers. In the current study, we aimed to study the pattern of oral dysplastic and neoplastic lesions in tertiary care centre in central India and study its association with various risk factors.

Methods: The oral biopsy tissues received in the Department of Pathology, GMC, Bhopal for histopathological evaluation during the duration of one and a half years were included in the study. The data was analysed by appropriate statistical tests (software SPSS).

Result: A total of 334 cases presented for oral neoplastic lesions during the study period with mean age of presentation of malignant lesions and premalignant lesions being 51 years and 46 years respectively. 78.3% cases were reported as malignant lesions with majority being Well Differentiated Squamous Cell carcinomas (57%) among oral cavity lesions and Moderately Differentiated Squamous Cell Carcinoma (41%) among oropharyngeal lesions. 87% of patients reported use of tobacco chewing smoking and alcohol, either alone or in combination.

Conclusion: High risk individuals included males more than 35 years of age indulging in tobacco chewing, smoking and alcohol with exclusive tobacco chewing associated more with oral malignant lesions whereas the smoking and alcohol along with tobacco chewing associated more with oropharyngeal lesions. Substance abuse awareness programs and screening early lesions in high risk individuals are recommended to curtail oral malignancies.

Keywords: Oral Squamous Cell Carcinoma, Oropharyngeal Squamous Cell Carcinoma, Dysplasia, Tobacco Chewing

Introduction

Cancers of oral cavity and oropharynx collectively come among top three cancers in India with Bhopal region in central India showing one of the highest incidence rates according to the recent National Cancer Registry Programme report.^[1,2] Majority of the oral cancers are diagnosed in the advanced stages and this delay in diagnosis and treatment leads directly to increased morbidity and mortality. Early institution of therapy warrants early diagnosis of oral cancer translating to a better prognosis. Understanding the risk factors and patterns of degree of dysplasia and malignancy can help early identification and prompt treatment of patients with oral cancers.

Oral and oropharyngeal cancers have a multifactorial carcinogenesis with a plethora of lifestyle and environmental factors acting as risk factors. Severe alcoholism, use of tobacco like cigarettes, smokeless tobacco, betel nut chewing and human papilloma virus (HPV), syphilis, oral sepsis, iron deficiency, oral candidiasis, Fanconi anemia, poor dental care and poor diet are the most common risk factors for oral cancer.^[3-5] Due to wide range of cultural

and regional differences, it is important to identify specific risk factors in a particular population.

In the current study, we aimed to study the pattern of oral and oropharyngeal dysplastic and neoplastic lesions in a tertiary care center located in Bhopal region in central India and study its association with various risk factors.

Materials and Methods

This study was a cross-sectional observational study conducted in the Department of Pathology, Gandhi Medical College and Hamidia Hospital Bhopal, Madhya Pradesh between the duration 1st March 2017 to 1st July 2018. All the oral biopsy tissues (for neoplastic lesions) received in the Department of Pathology, GMC, Bhopal for histopathological evaluation during the study duration were included in the study. Biopsies with tissue insufficient for histopathological evaluation and autolyzed samples were excluded from the study. The study was approved by institutional Ethics Committee of Gandhi Medical College, Bhopal (M.P.). A thorough history information was taken from requisition forms received in department of pathology. History was also taken through interview

and case files. Biopsy samples were processed for H&E staining. Sections were fixed in 10% formalin overnight at room temperature, processed and embedded in paraffin wax. Four μm sections were cut, deparaffinized and stained with H&E stains.^[6]

The data was analyzed using appropriate statistical tests using software SPSS. The qualitative data was expressed in terms of percentages. Comparison of the qualitative variables between groups was done using the chi-square test as well as Z test and for quantitative data student t test was applied. P value was considered significant if $p < 0.05$, and highly significant if $p < 0.01$. Z score > 1.96 was considered significant.

Result

During the study period of one and a half years, a total of 334 cases were reported for oral neoplastic lesions. The mean age of presentation of lesions was 50.5 years \pm 14.9 years (SD). Majority of cases belonged to an age-group of 51-65 year (35.4%) and 36-50 years (32.8%). However, around 20 % of cases corresponded to a younger age group, 20-35 years. Out of the studied 334 cases, 259 were males (77.4%) and 75 were females (22.6%). Male:Female ratio was 3.4:1. M:F ratio for oral cavity lesions was 2.8:1 and for oropharyngeal lesions 1:0.

The cases were histologically divided into Benign, Pre-malignant and Malignant categories (Table 1). Out of 334 cases, 78.3% cases were reported as malignant lesions with majority being Well Differentiated Squamous Cell carcinomas (51.5%). 15% of cases were reported as benign lesions and 5.7% of cases were diagnosed as pre-malignant conditions.

The mean age of presentation of pre-malignant lesions was 46 years which is significantly lower than the mean age of presentation of malignant lesions, i.e. 51 years (**T-test; p value = 0.046**). Proportion of malignant cases in the age groups 20-35 yrs, 36-50 yrs, 51-65 yrs and above 65 years was 64 %, 82 %, 82 % and 84 % respectively. However, this difference was not found to be statistically significant (Chi square; p value= 0.2). The distribution of benign, malignant and pre-malignant lesions did not differ significantly between males and females (p value > 0.05). Irrespective of gender, malignant lesions were the predominant category of lesions with proportion increasing as the age increases (Table 2).

In our study, we included the neoplastic cases of oral cavity and oropharynx. Majority of the cases presented with oral cavity lesions (82%). Oral and oropharyngeal lesions were further segregated into subcategories according to the exact site involved. In oral cavity lesions, buccal mucosa

was most common site involved (55%) followed by tongue (lateral border and tip) (25 %), gingiva (12%), lip (6%) and hard palate (1%) (Figure 1). Most of the malignant lesions in oral cavity were reported in buccal mucosa (40%), followed by lateral borders of tongue (20%) and gingiva (11%). In oropharynx, most of the malignant lesions were reported in supraglottis (49%) followed by base of tongue (28.6%) and tonsillar pillars (18.4%) (Figure 2).

Malignant lesions were the predominant histological category in both oral cavity and oropharyngeal sites followed by benign lesions and premalignant lesions. The proportion of premalignant lesions in oral cavity (6.6%) was higher than that reported in oropharyngeal lesions, however, the difference was not statistically significant (p-value = > 0.05). The distribution of specific neoplastic lesions in oral cavity and oropharynx were distinct (Figure 2). WDSCC cases form the major bulk (57%) in oral cavity lesions which was significantly higher than proportion of WDSCC in oropharyngeal lesions (27%) (*Z-Score = 3.72; p-value = 0.0001*). In oropharynx, majority of lesions were reported as MDSCC (41%) which was significantly higher than proportion of MDSCC reported in oral cavity lesions (17%) (*Z-Score = 3.27; p-value = 0.001*). The proportion of PDSCC cases in oropharyngeal lesions was also significantly higher in oropharyngeal lesions (9.8%) than in oral cavity lesions (3%) (*Z-Score = 2.04; p-value = 0.02*).

Lesions presented as ulcer, growth, leucoplakia, or difficulty swallowing. Most of the lesions presenting as ulcer and growth were malignant (86% and 74% respectively). However, lesions presenting as leucoplakia were reported as malignant only in 44% of cases with 33% cases being diagnosed pre-malignant and 22 % cases benign.

Besides the non-modifiable risk factors like age and gender, the well documented modifiable lifestyle risk factors were also studied. History of substance abuse was taken along with the duration of abuse. Tobacco chewing was the most common reported lifestyle risk factor in the studied cases being present alone in 53% of cases. Around 13% of cases denied any substance use (Figure 3).

Proportion of cases using tobacco chewing alone was significantly higher in malignant oral cavity lesions (52.8%) than in malignant oropharyngeal lesions (20%) (*Z-Score is 2.99. The p-value is 0.003*). However, proportion of cases indulged in smoking along with tobacco chewing was higher for malignant oropharyngeal lesions (40%) than malignant oral lesions (15.7 %) (*The Z-Score is 3.29. The p-value is 0.001*). Similarly, combined use of tobacco chewing, smoking and alcohol was more associated with

oropharyngeal lesions (40%) than oral lesions (5.3%) (*Z-Score is 2.55. The p-value is 0.01*) (Table 3).

A subset of study subjects which comprised 13.5% of our studied sample population did not give an account of any substance abuse habit (Table 3). These nonusers of tobacco and alcohol belonged predominantly to age group 51-65 yrs (47.6%) and had a female predominance (57.9%)

as compared to substance use indulged group where the majority were males (81%) (*Chi-square -12.7; p-value – 0.002*). The lesions affected oral cavity mostly (90.5%) similar to user group. The lesions were largely malignant lesions (66.77%); however, the proportion of benign lesions was higher (28.6%) than substance use indulged group (15%).

Table 1: Distribution of oral neoplastic lesions among the cases studied.

	Histological types and grades	Frequency of cases	Percent (%)
BENIGN (52)	CI	45	12.8
	SQ	7	2.1
PREMALIGNANT (19)	OIN I	6	1.8
	OIN II	4	1.2
	OIN III	9	2.6
MALIGNANT (263)	VC	7	2.1
	WDSCC	173	51.5
	MDSCC	68	20.2
	PDSCC	13	3.9
	Mucoepi ca	2	0.6

CI: Chronic Inflammation; SQ: Squamous papilloma; WDAC: Well differentiated adenocarcinoma; MDAC: Moderately differentiated adenocarcinoma; PDAC: Poorly differentiated adenocarcinoma; VC: Verrucous carcinoma; Mucoepi ca: Mucoepidermoid Carcinoma; OIN: Oral Intraepithelial Neoplasia

Table 2: A comparison of patient characteristics across benign, premalignant and malignant lesions of oral cavity and oropharynx.

Characteristics	Frequency		
	Benign Lesions n(%)	Premalignant Lesions n(%)	Malignant Lesions n(%)
No. of patients in age group 20-35 years	17 (33.3%)	6 (31.6%)	43 (16.5%)
36-50 years	13 (25.5%)	6 (31.6%)	89 (34.2%)
51-65 years	17 (33.3%)	5 (26.3%)	96 (37%)
Above 65 years	4 (7.8%)	2 (10.5%)	32 (12.3%)
Mean age	45 yrs	46 yrs	51 yrs
Gender Females	12 (23%)	2 (10.5%)	58 (22%)
Males	40 (77%)	17 (89.4%)	205 (78%)

Table 3: Distribution of substance use habits in relation to benign, premalignant and malignant lesions localized to oral cavity and oropharynx.

Substance Use	Benign Lesions		Malignant Lesions		Premalignant Lesions	
	oral	Oro- pharynx	oral	Oro- pharynx	oral	Oro-pharynx
None	15	0	38	2	3	0
Chewing	17	2	117	8	14	0
Chewing & Smoking	10	5	35	18	0	1
Chewing & Alcohol	0	0	3	0	0	0
Chewing, Smoking & Alcohol	0	0	12	8	1	0
Smoking	0	3	18	5	0	0
Smoking & Alcohol	0	0	0	0	0	0
Total	42	10	223	41	18	1

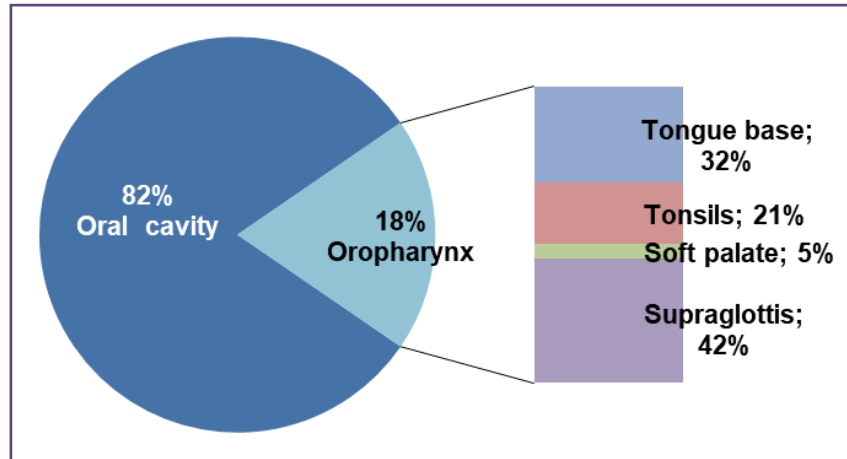


Fig. 1: Localization of overall lesions.

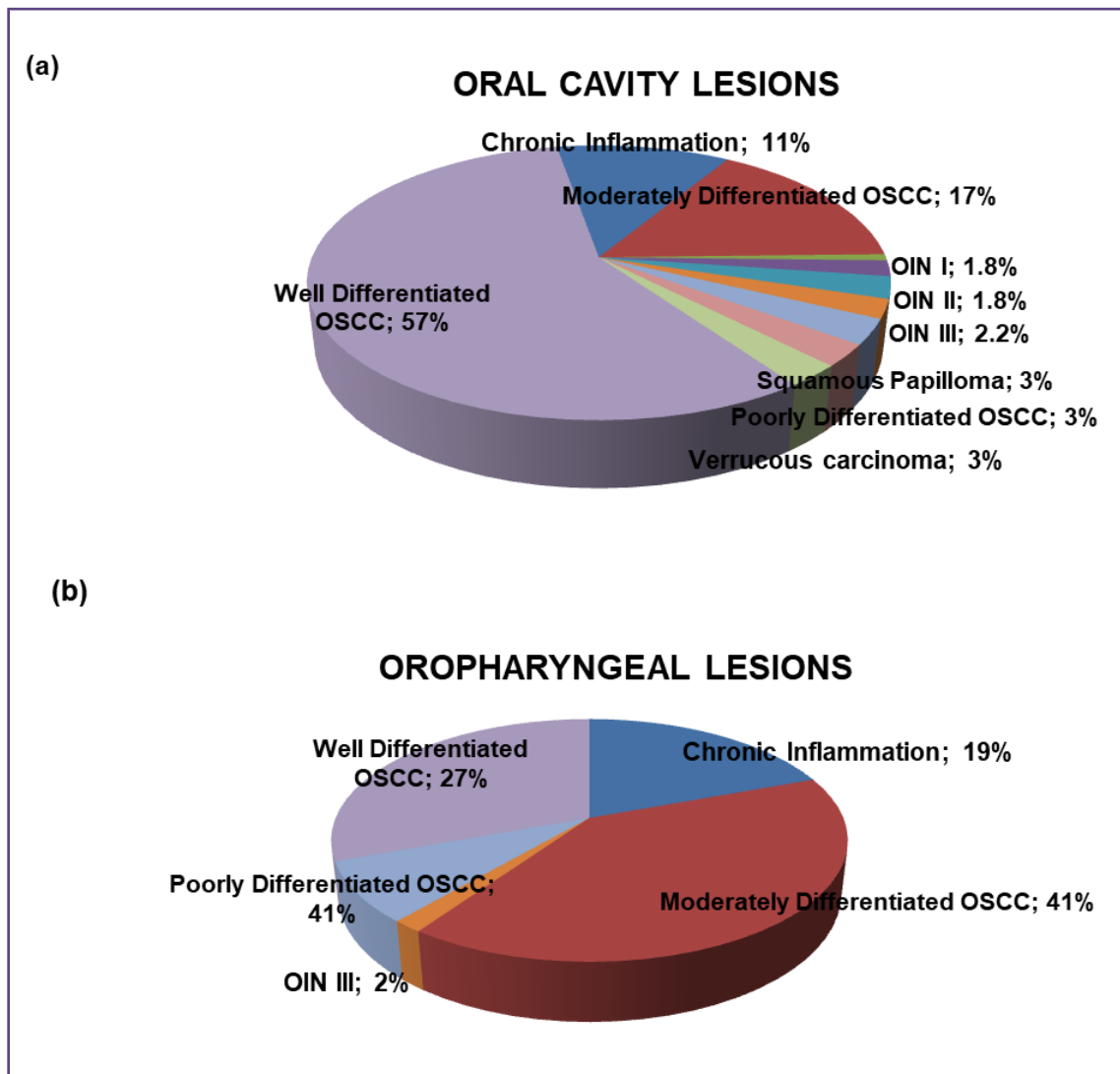


Fig. 2: Distribution of occurrence of various histological types in (a) oral cavity and (b) oropharynx.

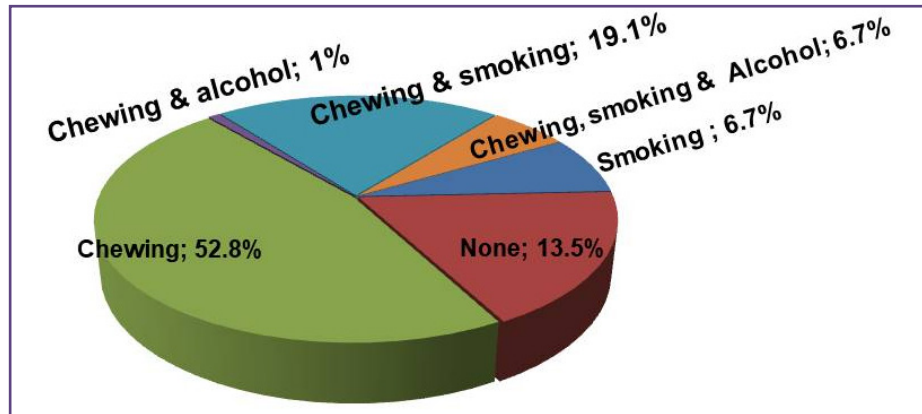


Fig. 3: Distribution of substance use habits across overall cases.

Discussion

The study was done to assess the pattern of oral cavity and oropharyngeal carcinomas in our tertiary care center and study its association with various modifiable and non-modifiable risk factors.

A total of 334 cases presented for oral neoplastic lesions in Hamidia hospital, Bhopal during the period of 1st March 2017-30th June 2018. The mean age of presentation of pre-malignant lesions was around five years lower than the mean age of presentation of malignant lesion. This implicates that there is a prospect of early intervention by early diagnosis and treatment to halt the progression to malignant lesions.

Majority of cases belonged to an age-group of 51-65 years and second peak in 35-50 years. This is consistent with other studies where prevalent age-group was 50-70 years [7-9] and studies showing an increasing trend of incidence in young males.^[10,11] The prevalence in older age-group represents the time taken for carcinogenesis by multifaceted etiology. Male: Female ratio was 3.4:1. Considering the gender in all the age groups, males are more affected than females. This is in accordance with epidemiological statistics from other similar studies where men are two to four times more affected than women. [7,12,13] The higher incidence of oral cancer amongst males may be attributed to the easy acceptance of habits by males. Heavy indulgence in both tobacco and alcohol by males is a scenario commonly encountered in most countries. In India, consumption of alcohol and tobacco is considered a taboo amongst the female population. This may be the reason for lower female preponderance. Additionally, oropharyngeal lesions were seen exclusively in males. This is perhaps due to higher exposure to tobacco smoking and alcohol drinking required to induce oropharyngeal than oral cancer.

Majority of cases were reported as malignant cases. Well differentiated squamous cell carcinoma was the predominant malignancy reported in oral lesions whereas moderately differentiated carcinomas was the predominant malignancy reported in oropharyngeal lesions. Hence, mostly the patients are being diagnosed at later stages with oropharyngeal lesions carrying a worse prognosis than oral carcinomas. Most of the patients coming to our tertiary treatment centre are of rural background. Many of the patients cannot afford the treatment. In rural areas, patients have inadequate access to trained providers with very limited health services. Also, they revert initially to local non-allopathic treatments which further cause delay leading to presentation with advanced disease.

Majority of cases were of oral cavity lesions (82%) with buccal mucosa was most common site involved followed by tongue (lateral border and tip), gingiva, lip and hard palate. This may be attributed to the habit of the practice of holding smokeless tobacco in the form of gutka, paan, or zarda in buccal pockets for long time with intermittent chewing.

Tobacco chewing was associated with oral malignant lesions more than oropharyngeal lesions, whereas, the use of bidi along with tobacco chewing and combined use of tobacco, bidi and alcohol was associated more with oropharyngeal lesions than the oral lesions. Tobacco and alcohol are well researched carcinogens. Many constituents of tobacco, in particular, Tobacco-specific nitrosamines are being labelled as human carcinogenic compounds by the World Health Organization.^[14] In addition, for smokeless tobacco, the production of reactive oxygen species such as hydrogen peroxide and superoxide anion radicals, which damage the normal DNA and RNA, have been implicated for genotoxic and carcinogenic effects.^[15,16] Boffeta et al., 1992 ^[17] found that stronger association of tobacco smoking in oropharyngeal lesions than oral cavity lesions.

Few studies have documented a sharp decline in risk of oropharyngeal cancer following cessation of smoking.^[18,19] Such drop in risk in a relatively short time suggests that smoking primarily impacts the late stages of oral carcinogenesis.

The association of alcohol with cancers of oral and oropharyngeal sites has also been documented by other studies.^[17,20] Several direct and indirect mechanisms are involved. The direct causal role is through overexpressing certain oncogenes that play a role in the initiation and progression of oral cancer and by impairing DNA damage repair mechanisms.^[21] The indirect effects are due to the dehydrating effect of alcohol on cell walls which enhances permeation of tobacco carcinogens into the oral tissues and the nutritional deficiencies associated with heavy drinking which degrade body's antioxidant production capacity.^[21]

Around 13.5% of cases in our study group were nonusers of tobacco/smoking/alcohol. This subset of patients was different from the substance user group in that nonuser group comprised primarily of adult females (58% vs 19.9%) with higher proportion of benign lesions (28.6% vs 15%) than the user group. Wey et al., 1987^[22] and Kruse et al., 2010^[23] found 13% and 24 % respectively of nonuser group proportion in their study group with majority being women in older age group of more than 65 years. The possible mechanisms suggested for carcinogenesis in the nonuser group are HPV 16/18 infections or different characteristics like mutations in the p53 and K-ras genes.^[24,25] Further studies for comparison of user and nonuser group by immunohistochemical evaluation are warranted to delineate the risk factors in non-user group.

Conclusion

To conclude, high risk individuals included middle aged males indulging in usage of tobacco chewing, and/or smoking and alcohol with exclusive tobacco chewing associated more with oral malignant lesions whereas the smoking and alcohol along with tobacco chewing associated more with oropharyngeal lesions. Majority of cases were malignant suggesting late clinical presentation and a delay in the diagnosis in the studied population. Awareness programs regarding risk factors and clinical signs and symptoms as well as screening for early lesions in high risk individuals are warranted to curtail oral malignancies. In additions, markers to predict progression of dysplastic to malignant lesions as well as predictive markers should be sought.

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Reference

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015 Mar 1;136(5):E359-386.
2. Sharma S, Satyanarayana L, Asthana S, Shivalingesh K, Goutham BS, Ramachandra S. Oral cancer statistics in India on the basis of first report of 29 population-based cancer registries. *J Oral Maxillofac Pathol [Internet]*. 2018 ;22(1):18–26.
3. Rosai, J., Ackerman, L. V., & Rosai, J. Rosai and Ackerman's Surgical Pathology -. In: Rosai and Ackerman's Surgical Pathology [Internet]. 11th ed. Edinburgh: Mosby; 2011.
4. Lin W-J, Jiang R-S, Wu S-H, Chen F-J, Liu S-A. Smoking, alcohol, and betel quid and oral cancer: a prospective cohort study. *J Oncol*. 2011;2011:525976.
5. Jorner PL, Garcia FJG, Berdugo ML, Perez FP, Lopez AP-F. Mouth self-examination in a population at risk of oral cancer. *Aust Dent J*. 2015 Mar;60(1):59–64.
6. Kim S, Christopher L, John B. The Hematoxylin and eosin & Immunohistochemical techniques. In: Bancroft's Theory and Practice of Histological Techniques [Internet]. 7th Edition. Churchill Livingstone; 2012.
7. Sheno R, Devrukhkar V, Chaudhuri, Sharma BK, Sapre SB, Chikhale A. Demographic and clinical profile of oral squamous cell carcinoma patients: a retrospective study. *Indian J Cancer*. 2012 Mar;49(1):21–6.
8. Takeda T, Sugihara K, Hirayama Y, Hirano M, Tanuma J-I, Semba I. Immunohistological evaluation of Ki-67, p63, CK19 and p53 expression in oral epithelial dysplasias. *J Oral Pathol Med*. 2006 Jul;35(6):369–75.
9. Elango JK, Gangadharan P, Sumithra S, Kuriakose MA. Trends of head and neck cancers in urban and rural India. *Asian Pac J Cancer Prev*. 2006 Mar;7(1):108–12.
10. Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for squamous cell carcinoma of the oral cavity in young people--a comprehensive literature review. *Oral Oncol*. 2001 Jul;37(5):401–18.
11. Clinicopathological analysis of oral squamous cell carcinoma among the younger age group in coastal Karnataka, India: A retrospective study Abdulla R, Adyanthaya S, Kini P, Mohanty V, D'Souza N, Subbannayya Y - *J Oral Maxillofac Pathol*
12. Angiero F, Berenzi A, Benetti A, Rossi E, Del Sordo R, Sidoni A, et al. Expression of p16, p53 and Ki-67 proteins

- in the progression of epithelial dysplasia of the oral cavity. *Anticancer Res.* 2008 Oct;28(5A):2535–9.
13. AK E-N, JKC C, JR G, T T, PJ S. WHO Classification of Head and Neck Tumours. 4th ed. Vol. 9. IARC Publications; 2015 .
 14. Tricker AR, Preussmann R. The occurrence of N-nitrosocompounds [corrected] in zarda tobacco. *Cancer Lett.* 1988 Oct;42(1–2):113–8.
 15. Nair J, Ohshima H, Friesen M, Croisy A, Bhide SV, Bartsch H. Tobacco-specific and betel nut-specific N-nitroso compounds: occurrence in saliva and urine of betel quid chewers and formation in vitro by nitrosation of betel quid. *Carcinogenesis.* 1985 Feb;6(2):295–303.
 16. Nair UJ, Floyd RA, Nair J, Bussachini V, Friesen M, Bartsch H. Formation of reactive oxygen species and of 8-hydroxydeoxyguanosine in DNA in vitro with betel quid ingredients. *Chem Biol Interact.* 1987;63(2):157–69.
 17. Boffetta P, Mashberg A, Winkelmann R, Garfinkel L. Carcinogenic effect of tobacco smoking and alcohol drinking on anatomic sites of the oral cavity and oropharynx. *International Journal of Cancer.* 1992 Oct 21;52(4):530–3.
 18. Blot WJ, McLaughlin JK, Winn DM. Smoking and Drinking in Relation to Oral and Pharyngeal Cancer. 1988;7.
 19. Wynder EL, Stellman SD. Comparative epidemiology of tobacco-related cancers. *Cancer Res.* 1977 Dec;37(12):4608–22.
 20. Choi SY, Kahyo H. Effect of cigarette smoking and alcohol consumption in the aetiology of cancer of the oral cavity, pharynx and larynx. *Int J Epidemiol.* 1991 Dec;20(4):878–85.
 21. Znaor A, Brennan P, Gajalakshmi V, Mathew A, Shanta V, Varghese C, et al. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer.* 2003 Jul 10;105(5):681–6.
 22. Wey PD, Lotz MJ, Tiedman LJ. Oral cancer in women nonusers of tobacco and alcohol. *Cancer.* 1987 Oct 1;60(7):1644–50.
 23. Kruse AL, Bredell M, Grätz KW. Oral squamous cell carcinoma in non-smoking and non-drinking patients. *Head Neck Oncol.* 2010 Oct 4;2:24.
 24. Cheng YW, Chiou HL, Sheu GT, Hsieh LL, Chen JT, Chen CY, et al. The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women. *Cancer Res.* 2001 Apr 1;61(7):2799–803.
 25. Gealy R, Zhang L, Siegfried JM, Luketich JD, Keohavong P. Comparison of mutations in the p53 and K-ras genes in lung carcinomas from smoking and nonsmoking women. *Cancer Epidemiol Biomarkers Prev.* 1999 Apr;8(4 Pt 1):297–302.

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