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DIFFERENT TUMOUR GRADING IN SMOKELESS TOBACCO (NASWAR) USER AND NON-USER IN SQUAMOUS CELL CARCINOMA.

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ABSTRACT… Objectives: To determine the relationship of Naswar with different tumour grading in squamous cell carcinoma. **Study Design:** Comparative cross-sectional study using non-probability, consecutive sampling. **Setting:** Department of Oral Pathology, Rehman College of Dentistry, Peshawar, Khyber Pakhtunkhwa, Pakistan. **Period:** January 2017 till June 2017. **Material & Methods:** 60 cases of oral squamous cell carcinoma were included. Half the cases (30) had a history of Naswar use while the other half (30) had no history of Naswar use. Data was analysed using SPSS v 22. **Results:** This study included 60% male and 40% female cases, ranging from 40 years to 80 years (mean = 57.6 + 11 years). Majority of patients 80% had well differentiated squamous cell carcinoma, while the rest (20%) had poorly differentiated. Distribution of male and female across both groups was equal (p 0.598). Both the groups were comparable in terms of grade of tumour (p 0.519). **Conclusion:** Naswar use was not associated with any particular histological grade of oral squamous cell carcinoma in our study. However, further research is needed to explore this association.

Key words: Angiogenesis, Grading, Naswar, Oral Squamous Cell Carcinoma, Smokeless Tobacco, Squamous Cell Carcinoma.

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the commonest malignant tumour of oral cavity which accounts for more than 90% of head and neck malignancies.[1] Pakistan has high incidence rates of OSCC.[2] OSCC is commonest cancer among men and the second most common cancer in women.[3] Tobacco use along with alcohol is considered as the leading modifiable risk factors for OSCC and account for over 70% of the population attributable fraction for OSCC.[4]

Naswar is a smokeless tobacco composed of slaked lime, crushed tobacco leaves and burned ash. It is consumed in two ways, sniffing which is done nasally and dipping where a pinch of it is placed between lip and the gum.[5,6] Naswar is easily accessible in Afghanistan, Pakistan, Iran and South Africa. In Northern Pakistan, the most commonly used form of smokeless tobacco is Naswar. The nicotine effects can occur within 5 minutes after its intake producing a slight burning sensation on the inner mucosa and tongue. According to a recent study (2012) in Peshawar, the use of Naswar is quite high among cooks (31.5%), followed by sweepers (30.3%), prisoners (28.3%), dairy workers (22.42%) and teachers (7.32%).[7] Naswar has a high PH value and contains unionized nicotine as well as tobacco in the form of N-nitrosamines (TSNAs); with a carcinogenic property and have a bad influence on oral and general health.[8]

Naswar is one of the important risk factor related with many of oral and systemic disease in particularOSSC.[9] Tobacco is composed of more than 3000 carcinogens and commonest among them is nicotine and N-nitrosamines. Tobacco chewing habit for 5-15 years cause an increase frequency of mutation in codons 12,13,61 of

H-ras, K-ras and N-rasoncogene and also causes keratosis of oral mucosa leading ultimately to carcinoma.

The prognosis of OSCC depends upon its clinical staging as well as histopathological grading. Poorly differentiated tumours are considered high grade and have a worse prognosis compared to well differentiated tumors.[10] To the best of our knowledge, there have been no studies on the association of Naswar use and histopathological grading. We hypothesize that Naswar use is associated with poorly differentiated OSCC. Therefore, the aim of this study is to determine the relationship of Naswar with different tumour grading in OSCC.

MATERIAL & METHODS

This is comparative cross-sectional study, carried out at the Department of Oral Pathology, Rehman College, Peshawar, *Khyber Pakhtunkhwa*, Pakistan from January 2017 till June 2017. Non-probability, consecutive sampling was used. Total 60 cases of oral squamous cell carcinoma were included in this study. Out of these 60 cases, 30 cases had a history of using Naswar whereas, the other 30 cases didn't have Naswar history. Patients of both genders, clinically diagnosed with OSCC were included. Patients without the history of Naswar were taken as controls. Patient with inappropriate history and clinical records were excluded. Patients with other systemic diseases were also excluded from the study. The study protocol and ethical aspects were approved by the ethics committee of the Rehman College of Dentistry (RCD).

Surgical specimens after the removal were placed in adequate 10% formalin. The containers were labelled with the patient's name and Patient Registration Numbers (PRN), detailed history and the site of biopsy. Specimens were then sent to the histopathology laboratory. Biopsies of clinically diagnosed OSCC were received from Oral and Maxillofacial department of RCD and after staining with Hematoxylin-eosin, the H & E slides were reviewed in order to classify the cases according to the World Health Organization International Histological Classification of Tumors.[11] Those cases which fulfilled the inclusion criteria were selected for the study.

Before going for the data collection process, authorization letter was obtained from the relevant authorities for collection of samples. Written consents were taken from every participant and before starting the data collection from patients, study objectives were clearly explained to the participants. Confidentiality of scoring/rating to individuals was ensured.

Data was recorded and analyzed in SPSS v 20. Continuous data was displayed as the mean ± standard deviation (SD), while the categorical and nominal data was presented as frequencies and percentages. Chi-square test was applied and a p-value of <0.05 was considered statistically significant with a confidence level of 95%.

RESULTS

Out of 60, 36(60%) were male and 24(40%) were female patients. Mean age of the patients was 57.6 + 11 years with a range of 40-80 years. Majority of patients 48(80%) had well differentiated OSCC, while the rest had poorly differentiated OSCC (Table-I).

Variables	f(%)
Gender	
Male	36(60%)
female	24(40%)
Age group	
40- 60 years	42(70%)
61 – 80 years	18(30%)
Grade of tumour	
Well differentiated	48(80%)
Poorly differentiated	12(20%)

Table-I. Demographic characteristics of patients. (n=60)

Gender distribution of male and female across both groups was equal (p 0.598).In addition, there was no significant difference in the age between the two groups. Most of the patients in both the groups were in well differentiated grade. *Although the proportion of poorly differentiated OSCC was higher in the Naswar users group, there was no*

statistically significant difference (p 0.519). (Table-II).

	Naswar User	Non-Naswar User	P-Value
Gender			
Male	17(56.7%)	19 (63.3%)	0.598
Female	13 (43.3%)	11(36.7%)	
Age Group			
40 – 60 years	20(66.7%)	22(73.3%)	0.573
61-80 years	10(33.3%)	8(26.7%)	
Grade of Tumour			
Well differentiated	23(76.7%)	25(83.3%)	0.519
Poorly differentiated	7(23.3%)	5(16.7%)	

Table-II. Comparison of age categories between Naswar and Non- Naswar users.

DISCUSSION

Smokeless tobacco is believed as a risk factor for oral cancer and its use is on a rise worldwide and specifically in South Asian countries.[9] Previous studies have mainly investigated the association of smokeless tobacco with OSCC. However, *Naswar* has not been investigated greatly in the context of cancer risk and its relationship with the grade of tumour. One study from the KPK showed increase biochemical risk linked with the constituents of *Naswar.*[12]

Majority (80%) of OSCC *were well differentiated in the current study.* As previously demonstrated by others[13], OSCC has a male predilection. This was also shown in our study for both Naswar users and nonusers. A higher percentage of males were seen with Naswar users but this was not statistically significant.

Lu et al.[14] reported that improper oral habits such as tobacco, smokeless tobacco and alcohol consumption may induce chronic inflammation of the oral mucosa, which in turn results in an increased macrophage density (IMD) in these oral lesions. The elevated number of M1-macrophages can help to promote the formation of oral pre-cancers and cancers. However, in the present study, majority of the patients using Naswar (smokeless tobacco) presented with well differentiated OSCC.

Merne et al. in 2002[15] stated that snuff (smokeless tobacco) does not induce epithelial cell proliferation but indeed increases the life span and differentiation of epithelial cells leading to hyperkeratosis and epithelial thickening. Smokeless tobacco has shown effects on cell proliferation, apoptosis and activation of inflammatory mediators.[16] The association of smokeless tobacco with dysplastic changes is well established.[17] Furthermore, the high percentage (90.9%) of dysplasia/carcinoma development at the site of smokeless tobacco placement also demonstrates the association between smokeless tobacco (Naswar) and oral epithelial dysplasia.[18]

However, another study conducted in past by Younus et al[19] in Pakistan which concluded that most of OSCC patients with habits of gutka, cigarette smoking and pan were associated with poorly differentiated carcinoma.

In the current study, we could not find an association of Naswar use with different histological grades of OSCC in the available patients. Future research should be focused on prospective cohort studies with a larger sample size. Future studies should also take into account other environmental as well as genetic factors besides Naswar use. In addition, the increasing use of Naswar in KPK can be limited by providing awareness campaigns in the local population who believes that Naswar (smokeless tobacco) is a harmless product, providing them education about the myths and hazards of smokeless tobacco.

CONCLUSION

Naswar use was not associated with any particular histological grade of oral squamous cell carcinoma in our study. However, further research is needed to explore this association.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Sahd Rashid	Data collection, Literature reviews.	
3	Muhammad Irshad	Designed research methodology, Manuscript writing, Manuscript final reading, Approval.	
4	Maria Tasneem Khattak	Case diagnosis, Literature search, Literature review.	
5	Hina Shabir	Data interpretation, Statistical analysis.	