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Squamous Cell Carcinoma in Upper Aerodigestive Tract: Comparative Study In between Smoking Tobacco and Smokeless Tobacco Products

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Abstract

Background: Squamous cell carcinoma in upper aerodigestive tract is most often caused by smoking. Smokers get laryngeal cancer, while chewers get mouth cancer. With the surge in smokeless tobacco use, it's important to determine if this differentiation influences clinical and pathological characteristics beyond site distribution. **Objective:** The purpose of the present study was to assess any relation between tobacco smoking, oral intake of tobacco with betel leaf or tobacco powder and squamous cell carcinoma in upper aerodigestive tract. **Methodology:** This cross-sectional study was conducted in a single Diagnostic center at Dhaka, Bangladesh for a period of one year from July 2022 to June 2023 on patients presented with histopathologically established upper aerodigestive tract malignancies. Patients age, gender and involved site was taken from the patients report. **Results:** Males were predominant than females. Male to female ratio was 3.3:1. Mean age of the patients was 59.26 ± 12.55 years of the male and 56.11 ± 13.13 years of the female. Cancer was more in female at 5th and 6th decade whereas cancer was found more in male at 6th and 7th decade. Most common location of the lesions was sub-glottis (27.6%) and tongue (20.0%). The most common causes of Upper Aerodigestive Tract cancer were smoking (76.2%) and smokeless tobacco using (54.1%). There was no association between smoke and smokeless tobacco with severity of carcinoma. Maximum cases of carcinoma were grade II but there was no significant difference in grade of carcinoma between tobacco smoker and tobacco non-smoker. There was no significant difference in grade of malignancy between tobacco user and non-user. **Conclusion:** Smoke and/or smokeless tobacco user have increased risk of development squamous cell carcinoma in upper aerodigestive tract. However, there is no significant difference between incidence and grade of tumor among only smoker, smokeless tobacco user or both. *[Journal of National Institute of Neurosciences Bangladesh, January 2024;10(1):52-56]*

Keywords: Tobacco; Squamous cell carcinoma; upper aerodigestive tract

Introduction

Smoking tobacco has close relation with squamous cell carcinoma in upper aerodigestive tract. Tobacco smoke contains more than 7000 chemicals, at least 70 of which known to cause cancer[1]. The World Health Organization (WHO) has labeled smokeless tobacco (SLT) as a carcinogenic agent. Nicotine, the most common known product of cigarette smoking[2]. Its metabolites 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N′-nitrosonornicotine (NNN) have carcinogenic properties[3-5]. NNK and NNN bind to the nicotinic acetylcholine receptor to promote cell proliferation and create a microenvironment for tumor growth. Again, components of cigarette smoke, particularly tar, polycyclic aromatic hydrocarbons, benzopyrine and nitrosamine are potent carcinogen for human. Smoking increases DNA methylation and DNA damage acts as a vital cause of tumor development[6]. Some, scientific studies suggest cigarette smoke begins to cause DNA damage within minutes- not years or months, called – "a stark warning"[7].

Oral squamous cell carcinoma (OSCC) is a pathological

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type of oral cancer, accounting for over 90% of oral cancers[8]. A vast quantity of scientific, clinical and epidemiological data shows that tobacco is associated with the development of oral squamous cell carcinoma[9]. Tobacco as an important risk factor can cause epigenetic alteration of oral epithelial cells, inhibit multiple systemic immune functions of the host, and its toxic metabolites can cause oxidative stress on tissues and induce OSCC[9].

Esophageal cancer (EC) is the sixth leading cause of cancer mortality in the world[10]. Esophageal squamous-cell carcinoma (ESCC) and esophageal adenocarcinoma (EA) are the two main histological subtypes of esophagus cancer. Within recent decades, in North America and Europe, the incidence and mortality rate of ESCC have decreased. But in Asia, particularly in China, ESCC still occupies the vast majority of EC[11]. Laryngeal cancers represent one-third of all head and neck cancers and maybe a significant source of morbidity and mortality. They are most often diagnosed in patients with significant smoking history, who are also at risk for cancers in the remainder of the aerodigestive tract[12].

Besides smoking other risk factors include smokeless tobacco and alcohol, chronic inflammation, ultra violet (UV) radiation (for lip cancer), human papilloma virus (HPV), Candida infections, immunosuppression, genetic predisposition, and diet. But, among these, tobacco is the most potential one, specially SLT for oral cancer. However, unfortunately the prevalence of smoking is increasing in young people, particularly women[13]. The purpose of the present study was to assess any relation between tobacco smoking, oral intake of tobacco with betel leaf or tobacco powder and squamous cell carcinoma in upper aerodigestive tract.

Methodology

Study Settings and Population: This study was carried out in a single Diagnostic Center from July 2022 to June 2023 over a period of one year. The laboratory received samples from patients suspected to have squamous cell carcinoma in the upper aerodigestive tract.

Study Procedure: These samples were sent from various hospitals for histopathology testing. For this study, a total of 185 patients who were confirmed to have squamous cell carcinoma in the upper aerodigestive tract through histopathology were enrolled. The histopathological grading of the tumor was done according to Modified Broadmann's method as Grade I: well differentiated carcinoma, Grade II: moderately differentiated carcinoma, Grade III: poorly differentiated carcinoma, and Grade IV: undifferentiated carcinoma.

Statistical Analysis: Data were analyzed using Statistical Package for Social Science (SPSS)-22. Qualitative data were presented as frequency with percentage whereas numerical data were presented as mean with standard deviation. Statistical analysis was done by Chi-Square test.

Ethical Implications: Written informed consent was obtained from from each of the patient or from legal guardian. Patient confidentiality was strictly maintained. No name, address or contact details of the patient was divulged.

Results

Males were predominant than females. Male to female ratio was 3.3:1. Mean age of the patients was 59.26 ± 12.55 years of the male and 56.11 ± 13.13 years of the female. Cancer was more in female at 5th and 6th decade whereas cancer was found more in male at 6th and 7th decade (Table 1).

Table 1: Demographic Profile of the Study Subjects (n=185)

Age Group	Male	Female	Total
≤40 Years	14 (9.9%)	2 (4.7%)	16 (8.6%)
41 to 50 Years	21 (14.8%)	17 (39.5%)	38 (20.5%)
51 to 60 Years	48 (33.8%)	14 (32.6%)	62 (33.5%)
61 to 70 Years	39 (27.5%)	7 (16.3%)	46 (24.9%)
>70 Years	20 (14.1%)	3 (7.0%)	23 (12.4%)
Total	**142(76.8%)**	**43(23.2%)**	**185(100%)**
Mean ± SD	59.3±12.55	56.1±13.13	58.5±12.72

Most common location of the lesions was sub glottis (27.6%) and tongue (20.0%). Highest number of lesion was found in sub glottis area among the smokers only as well as smoker and smokeless tobacco users whereas tongue cancer was observed among the smokeless tobacco users as well as both smoker and smokeless tobacco users (Table 2).

As per figure I, most common cause of upper aerodigestive tract cancer was tobacco smoking (76.2%) and smokeless tobacco using (54.1%). 6.5% of cases did not have any addiction of smoking or tobacco chewing.

Maximum cases of carcinoma were grade II carcinoma but there was no significant difference in grade of carcinoma between tobacco smoker and tobacco non-smoker (Table 3).

Table 2: Association between use of smokeless tobacco and tobacco smoking with classified diagnosis (n=185)

	No tobacco using (n=12)	Only Smoking (n=73)	Only smokeless tobacco using (n=32)	Both (n=68)	Total
Vocal cord	2 (16.7%)	9 (12.3%)	0 (0.0%)	2 (2.9%)	13 (7.0%)
Tonsil	0 (0.0%)	3 (4.1%)	0 (0.0%)	2 (2.9%)	5 (2.7%)
Tongue	1 (8.3%)	8 (11.0%)	11 (34.4%)	17 (25.0%)	37 (20.0%)
Sub glottis	4 (33.3%)	29 (39.7%)	7 (21.9%)	11 (16.2%)	51 (27.6%)
Pyriform fossa	1 (8.3%)	8 (11.0%)	1 (3.1%)	7 (10.3%)	17 (9.2%)
Pharynx	0 (0.0%)	2 (2.7%)	0 (0.0%)	2 (2.9%)	4 (2.2%)
Larynx	0 (0.0%)	1 (1.4%)	0 (0.0%)	2 (2.9%)	3 (1.6%)
Glottis	0 (0.0%)	4 (5.5%)	0 (0.0%)	2 (2.9%)	6 (3.2%)
Esophagus	1 (8.3%)	2 (2.7%)	0 (0.0%)	9 (13.2%)	12 (6.5%)
Epiglottis	0 (0.0%)	0 (0.0%)	2 (6.3%)	2 (2.9%)	4 (2.2%)
Cheek	1 (8.3%)	1 (1.4%)	4 (12.5%)	6 (8.8%)	12 (6.5%)
Buccal mucosa	1 (8.3%)	1 (1.4%)	3 (9.4%)	4 (5.9%)	9 (4.9%)
Others	1 (8.3%)	5 (6.8%)	4 (12.5%)	2 (2.9%)	12 (6.5%)

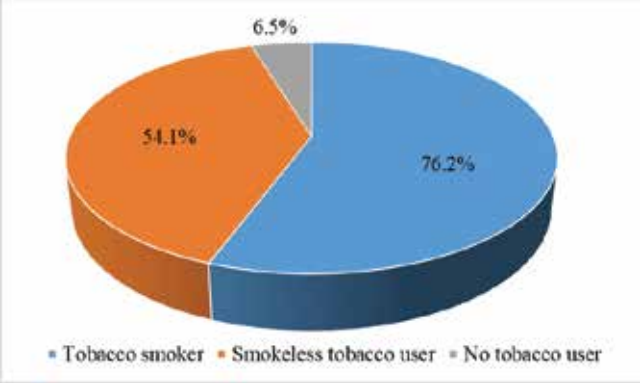

Figure I: Frequency of Tobacco Smoker and Smokeless Tobacco User (n=185)

Table 3: Association of tobacco smoking with severity of squamous cell carcinoma (N=185)

Grade	Tobacco Smoker	Tobacco Non-Smoker	P value
Grade I	21 (14.9)	11 (25.0)	0.260
Grade II	109 (77.3)	31 (70.5)	
Grade III	11 (7.8)	2 (4.5)	
Total	**141(100.0%)**	**44 (100.0%)**	

Chi-Square test was performed to see the level of significance

There was no association between tobacco user and severity of carcinoma (Table 4).

Discussion

Males were more prevalent than females in the study, with a male-to-female ratio of 3.3:1. Similar results were reported by Kumar et al14, who found that upper aerodigestive tract (UADT) tumors were more common in males.

The mean age of male patients was 59.26 ± 12.55 years, and for females, it was 56.11 ± 13.13 years. This trend was consistent with the findings of Kumar et al[14], where the male-to-female ratio was 5:1, and the mean age of presentation was 51.13 ±13.94 years for males and 60.71 ±12.02 years for females.

In this study, carcinoma was more common in the 5th to 6th decade among females and in the 6th to 7th decade among male. Carcinoma was prevalent in the 5th to 7th decade in both males and females. Similar findings were reported in the study by Kumar et al[14], where head and neck cancer were more common in the 4th to 6th decade. Other studies also found a higher incidence in the 5th and 6th decades, with a male-to-female ratio around 4:1[15-17]. Fried et al[18] observed a higher incidence in the 6th and 7th decades, with a male-to-female ratio of 2:1.

From the present study, it can be concluded that malignant cases had male preponderance and the mean

Table 4: Association between Use of Smokeless Tobacco and Tobacco Smoking with Severity of Carcinoma (N=185)

Grade	No tobacco using (n=12)	Only Smoking (n=73)	Only smokeless tobacco using (n=32)	Both (n=68)	p-value
Grade I	3 (25.0)	7 (9.6)	8 (25.0)	14 (20.6)	0.244
Grade II	9 (75.0)	58 (79.5)	22 (68.8)	51 (75.0)	
Grade III	0 (0.0)	8 (11.0)	2 (6.3)	3 (4.4)	
Total	**12(100.0%)**	**73(100.0%)**	**32(100.0%)**	**68(100.0%)**	

Chi-Square test was performed to see the level of significance

age of presentation correlated with findings from other studies. This trend could be explained by increased awareness in the population and the availability of medical facilities, leading to early hospital presentation. Additionally, environmental factors and heightened addiction habits were contributing factors to the observed patterns.

The most common causes of upper aerodigestive tract cancer in this study were tobacco smoking (76.2%) and smokeless tobacco using (54.1%). A small percentage (5.9%) did not have any history of smoking or tobacco chewing addiction. In the study conducted by Kumar et al[14], the majority of cases were addicted to tobacco (97%), with 8% having alcohol as an additional addiction, and only 3.0% of cases were completely free from any addiction. This emphasizes the role of tobacco addiction in the carcinogenesis of UADT tumors. These findings align with studies conducted by Rothman[19].

The digestive system begins with the oral (buccal) cavity, which is covered by mucous membranes and contains various structures essential for speech and digestion. Key components of the oral cavity include the palate, uvula, tonsils, salivary glands, teeth, and tongue. In this study, the most common locations for carcinoma were the sub glottis (27.6%) and tongue (20.0%), followed by the pyriform fossa (9.2%), vocal cords (7.0%), cheek (6.5%), esophagus (6.5%), buccal mucosa (4.9%), glottis (3.2%), tonsils (2.7%), pharynx (2.2%), epiglottis (2.2%) and larynx (1.6%). Among smokers, tumors were predominantly found in the sub-glottis, whereas among smokeless tobacco users, tumors were primarily located on the tongue. Patients using both smoked and smokeless tobacco exhibited tumors in areas such as the tongue, sub-glottis, esophagus, pyriform fossa, and cheek. Notably, 12 patients without any addiction exhibited tumors in the sub glottis, vocal cords, tongue, pyriform fossa, cheek, esophagus, and buccal mucosa.

In the series of Kumar et al[14], cases involving tobacco chewing were found to have a higher risk of developing carcinoma in the oral cavity compared to other sites. On the other hand, tobacco smoking was associated with a higher risk of carcinoma in the hypo & oropharynx as well as carcinoma in the larynx when compared to other sites. This observation was consistent with other study findings[20-23]. These studies indirectly indicated a strong correlation between chewing tobacco and carcinoma in the oral cavity, in contrast to tobacco smoking.

The present study aligns with the research conducted by Znaor et al[24] in Chennai and Trivandrum, South India. In this context, tobacco chewing emerged as the most significant risk factor for oral cancer, whereas tobacco smoking was identified as the strongest risk factor for pharyngeal and laryngeal cancers, as reported by Sankaranarayanan et al[23]. Their study demonstrated that 19.0% of cases could be prevented by eliminating smoking alone, 73.0% by eliminating tobacco chewing alone, and 85.0% by eliminating both habits.

Additionally, Nandakumar et al[22] emphasized the importance of distinguishing anatomic subsites when considering risk factors due to the developmental and anatomic differences. The areas of the oral cavity are exposed to a greater degree in tobacco chewing compared to the oro- & hypopharynx. Jayant et al[21] further concluded that the etiologic fraction due to tobacco chewing is high for cancers of the oral cavity and hypopharynx, while the etiologic fraction due to smoking is high for cancers of the oropharynx and larynx but lower for cancers in other sites. The study also revealed that at each of the mentioned sites, tobacco smoking and chewing act synergistically, not independently, as indicated by the studied indices of synergy.

Conclusion

Using tobacco in any form increases the risk of developing squamous cell carcinoma in the upper aerodigestive tract. Tobacco smoking is a known risk factor for squamous cell carcinoma of the lungs and upper aerodigestive tract. However, the use of smokeless tobacco, such as chewing tobacco or snuff, is more closely associated with malignancies of the oral cavity, including the tongue, gums, and neck. The carcinogenic chemicals present in tobacco products increase the risk of acquiring cancer in both cases. . However, there is no significant difference between incidence and grade of tumor among only smoker, smokeless tobacco user or both.

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Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Written informed consent was obtained from each of the patient or from legal guardian. Patient confidentiality was strictly maintained. No name, address or contact details of the patient was divulged.

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