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# Prevalence of Non-Habit-Associated Oral Squamous Cell Carcinoma and its Site Predilection - A Retrospective Institution Based Study

Krishnapriya Umashankar<sup>1</sup>, Gheena S<sup>2</sup>, Hannah R<sup>3</sup>, Pratibha Ramani<sup>4</sup>, Abhilasha R<sup>5</sup>

<sup>1</sup>Department of Oral Pathology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai-600077, India; <sup>2</sup>Associate Professor, Department of Oral Pathology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai-600077, India; <sup>3</sup>Senior Lecturer, Department of Oral Pathology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai-600077, India; <sup>4</sup>Professor and Head of the Department, Department of Oral Pathology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai-600077, India; <sup>5</sup>Reader, Department of Oral Pathology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai-600077, India.

## ABSTRACT

**Background:** Worldwide Oral Squamous Cell Carcinoma (OSCC) is one of the most frequent malignancies, and it carries a bad prognosis with a global mortality rate of 1.9 deaths per 100,000 per year. Most cases of OSCC are preceded by asymptomatic clinical lesions collectively referred to as Oral Potentially Malignant Disorders (OPMDs).

**Objectives:** The objective of the study was to describe the prevalence of Non-habit-associated OSCC and site predilection among patients visiting our institution.

**Methods:** Of 50 oral squamous cell carcinoma, 15 cases were treated between July 2019 to February 2020 in our institution were identified as not having the habit of tobacco use during their lifetime. These cases were reviewed to gather data on multiple clinical-pathological variables.

**Results:** The mean age of non-habit associated OSCC of the oral cavity was 59.9 years and 60% were males. The tumour was more commonly seen on the tongue followed by buccal mucosa.

**Conclusion:** The Non-habit-associated OSCC is seen more commonly in the elderly with a male predilection.

**Key Words:** Oral Squamous Cell Carcinoma, Non-smoker, Non-habit, Oral Cancer, Human papilloma virus, Carcinoma

## INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the eighth most common cancer worldwide and ranks among the top three cancers in India. OSCC primarily occurs in males in their 5th to 8th decade of life.<sup>1</sup> However, based on the recent study in Europe an increase in the evidence of OSCC has been observed in younger adults with no history of tobacco and alcohol.<sup>2,3</sup> There is also an increase in the incidence among females.<sup>24</sup> While tobacco and smoking are well-established etiological factors for the development of OSCC, non-smoking, and non-drinking patients with OSCC have been identified in the literature as a unique and growing subgroup.<sup>5,6</sup> In contrast to the general predilection for males in OSCC, the Non-habit-associated OSCC has a female preponderance,

young mean age, and the carcinoma is more likely to be in the oral cavity than in the other site.<sup>5,7,8</sup> The Non-habit-associated OSCC population currently represents about 13 to 35% of the OSCC population, although this may increase as tobacco use decreases.<sup>9</sup>

The Human Papilloma Virus (HPV) in particular HPV-16 has been implicated in oropharyngeal OSCC in young non-habit-associated patients.<sup>10,11</sup> The clinical behavior of OSCC associated with HPV is uncertain.<sup>11,12</sup> Various studies have shown oral cancer in elderly patients with no use of tobacco or alcohol.<sup>11,13,14</sup> The proportion of elderly patients is increasing alongside life expectancy, with as many as 24% of Head and Neck Squamous Cell Carcinoma (HNSCC) found in patients over 70 years of age.<sup>11,15</sup> The etiology of Non-habit-associated OSCC in the elderly population is unknown.<sup>11,16</sup>

### Corresponding Author:

**Dr. Gheena S**, Associate Professor, Department of Oral Pathology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai-600077, India; Phone: +91- 9884033777; Email: [gheena@saveetha.com](mailto:gheena@saveetha.com)

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The absence of any known potential risk factors suggests that specific molecular and genetic mechanisms may be involved in tumorigenesis of head and neck.<sup>17</sup> Sorenson et al found no p53 mutation in non-habit-associated with OSCC.<sup>18</sup> Koch et al. found a lower p53 mutation and a higher HPV infection rate in non-smoking head and neck squamous cell carcinoma population.<sup>19</sup> There is also evidence that non-smokers were likely to have less of loss of heterozygosity at chromosome 3p, 4q, 11q13, and the lower overall percentage of microsatellite alterations.<sup>19,20</sup>

Thus, the analysis of a new distinct group of Non-habit-associated OSCC may shed light on several issues such as specific clinical-pathological features, additional risk factors of these patients. In the present study, we retrospectively described the clinical-pathological characteristics of 15 Non-habit-associated OSCC along with its prevalence and its site predilection in patients visiting Saveetha dental College and hospitals.

## MATERIALS AND METHODS

A cross-sectional, observational, retrospective study was conducted. The study was approved by the ethical committee of Saveetha Dental College and Hospital, Chennai (Ethical number: SDC/SIHEC/2020/DIASDATA/0619-0320). The clinical data of the 86000 patients visiting the institution were reviewed and analyzed from June 2019 to March 2020. The samples consisted of patients who were diagnosed with OSCC without the habit of tobacco use. The following details were obtained – Age, gender, symptoms, clinical presentation, tumor size, histopathological diagnosis, and site along with treatment.

### Statistical Analysis

Statistical analysis was performed to directly compare the Non-habit-associated OSCC with the OSCC with the habits group using IBM SPSS statistics 20. Chi-square test was employed for site predilection and demographics.

## RESULTS

A total of 50 patients were identified with OSCC in which 15 patients (30%) did not have the habit of tobacco (Figure 1). Nearly 53.3% of the non-habit-associated OSCC population reported between the age of 40 to 50 years (Figure 2); The mean age for the presentation of the non-habit OSCC patients was 59.9 years there with no regular use of smokeless tobacco (snuff, pan) or other carcinogens such as areca nut. 40% of the patients with non-habit-associated OSCC were noted to be females (Figure 3). Male to female predilection was noted to be 3:2. The most common involved site was

the tongue (40%) followed by buccal mucosa (26.7%) (Figure 4). The tumor size ranges from 2-4 cm in 66.7% of the Non-habit-associated OSCC (Figure 5). Histopathologically non-habit-associated OSCC was mostly graded as well-differentiated squamous cell carcinoma (86.7%). Figure 6, 7, 8 compares the age, gender, and site data of habit and Non-habit-associated OSCC. The Chi-square test for Non-habit-associated OSCC with its histopathological diagnosis and site was noted to be statistically significant with  $p < 0.05$ .

### Discussion

Worldwide OSCC is one of the most frequent malignancies, and it carries a bad prognosis with a global mortality rate of 1.9 deaths per 100,000 per year.<sup>2,7</sup> Most cases of OSCC are preceded by asymptomatic clinical lesions collectively referred to as oral potentially malignant disorders.<sup>2,7</sup> Numerous aetiological factors such as tobacco, alcohol, betel nut chewing which may or may not be associated with genetic factors play a crucial role in the development of OSCC.<sup>2,7</sup> The non-habit-associated OSCC patients represented 30% of all the patients with OSCC treated at our centre the non-habit-associated OSCC seems to be a clinically distinct group this group is defined by bimodal age distribution and is more likely to present with a maxillary alveolar or oral tongue lesion, whereas tobacco-associated OSCC patients are more likely to have tumors in the retromolar trigone mandibular alveolus.<sup>2,7,35</sup> None of the non-habit-associated OSCC patients had a second primary tumor outside the oral cavity.<sup>21,22,23–26</sup> It has been stated in the literature that Non-habit-associated OSCC does have the worst outcomes especially among elderly females.<sup>2,7</sup>

Our study outcome was inconsistent with the previously existing literature, although only relatively few studies have evaluated Non-habit-associated OSCC. Males were more affected than this in our study. Weismann et al. conducted a series of investigation of 40 non-habit-associated patients with head and neck squamous cell carcinoma with a higher percentage of older women (75%, mean age 60).<sup>27</sup> Constantinides et al. describe a cohort of 10 patients, their mean age was 75 years and 9 of them were women.<sup>17</sup> Boer et al. in his study found 125 Non-habit-associated OSCC in women older than 40 years.<sup>28</sup>

Our findings and the current literature showed a contradiction in the gender affected and the median age group affected. Nearly 46.7% of patients reported ulceration in our study. The most common affected site was the tongue which was nearly 40% of all the non-habit-associated squamous cell carcinoma cases that reported to our institution. Ranganathan *et al* stated that nearly 72% of the non-habit-associated OSCC affected the tongue.<sup>1,29,30,31</sup> The factors that could contribute to the site predilection of non-habit-associated OSCC could be attributed to HPV and constant trauma to that site (sharp tooth).<sup>1,29,32</sup> Increasing incidence

of non-habit-associated OSCC in the tongue has also been documented in various studies from several countries.<sup>2,7,23,24</sup> Such studies have suggested that HPV could be the probable reason for the shift of pattern among oropharyngeal squamous cell carcinoma.<sup>33,34</sup>

HPV has been implicated in the development of oropharyngeal localized neoplastic lesions. GERD and chronic voice abuse have suggested being possible aetiological factors for laryngeal squamous cell carcinoma, but not for OSCC as in the cases of our patients.<sup>33,34</sup>

Though HPV could be considered as an important risk factor in Non-Habit-Associated OSCC, absence or less of p53 mutation, loss of heterozygosity at chromosome 3p, 4q, and 11q13 with lower overall percentage of microsatellite alterations were also considered and proved by various authors for the development of OSCC in non-habit patients.<sup>18,19,20</sup>

Not much of studies are done in the Indian population to assist the prevalence of non-habit-associated or else, cell carcinoma. This is the first of its kind study done at an institutional level to assess the prevalence of non-habit-associated OSCC for a period of ten months. This study was done to assess the site predilection of these lesions.

The major limitations of the study included the time period which was only eight months with the sample size of only 15 cases of non-habit-associated OSCC among the 50 total OSCC cases reported to our institution. This study could be conducted for a period of two years and also at multicentric level to assess for the prevalence and other findings in the Indian population.

## CONCLUSION

To conclude our study demonstrated Non-habit-associated OSCC to be prevalent among the male population of older age with T2 tumor size which was more commonly seen in the tongue. Histopathologically the non-habit-associated OSCC was mostly diagnosed as well differentiated OSCC. More knowledge about the epidemiology and ascertaining the possible etiology of Non-habit-associated OSCC of the oral cavity is required to throw light on the multifarious aspects of this particular group which is in the throes of explosive growth.

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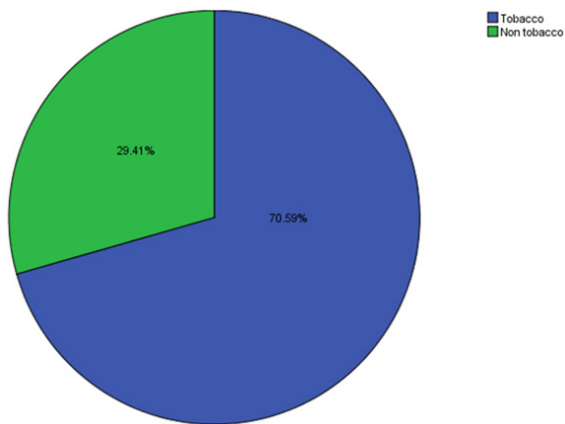
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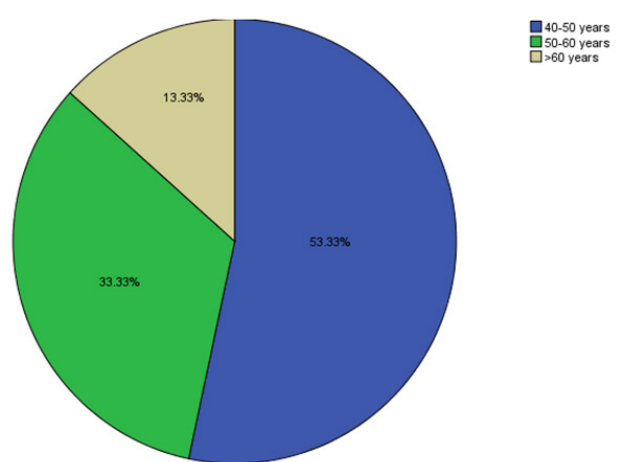
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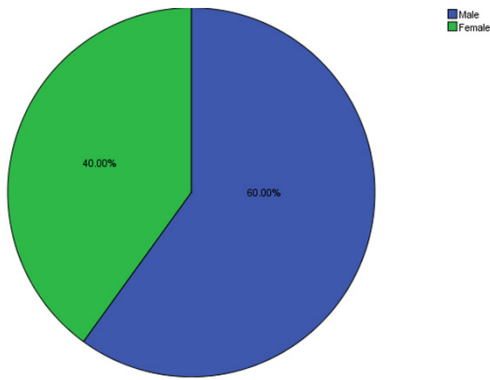


**Figure 1:** Pie chart depicting the frequency of distribution of tobacco associated and non tobacco associated OSCC. Green represents non tobacco associated OSCC (29.41%) and blue represents tobacco associated OSCC (70.59%)

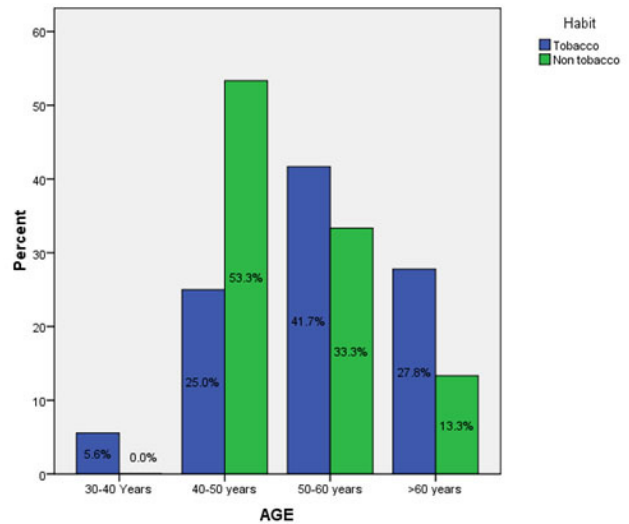


**Figure 2:** Pie chart depicting the age distribution of Non-habit-associated OSCC. 53.3% in 40-50 years, Blue represents 40-50 years (53.33%), green represents 50-60 years (33.33%) and grey represents >60 years (13.33%)

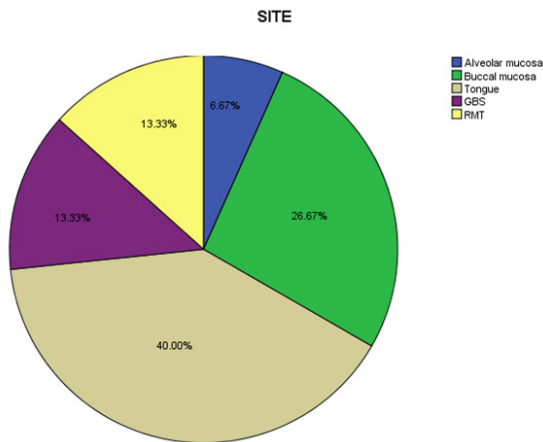




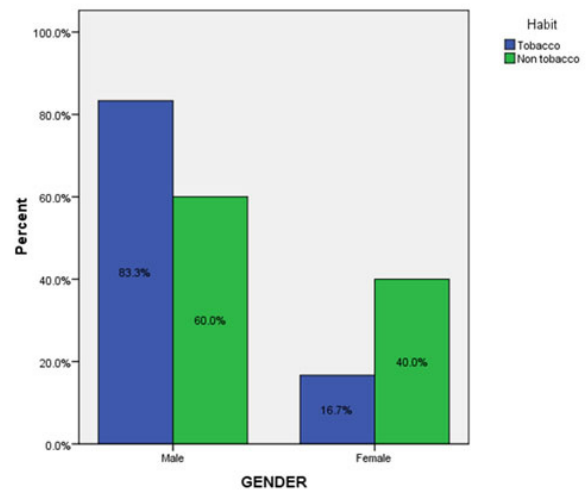
**Figure 3:** Pie chart showing the gender distribution of Non-habit-associated OSCC, Green represents females (40%), and Blue represents males (60%).



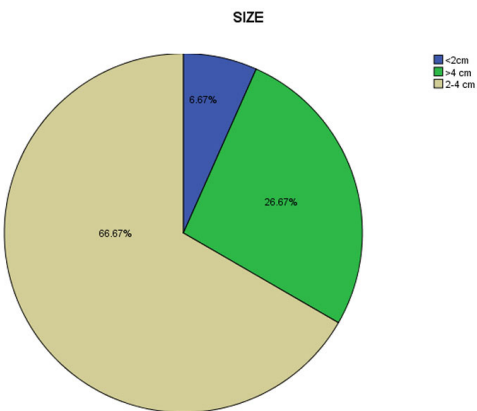
**Figure 6:** Bar graph depicting the correlation of Age with habit and non-habit-associated OSCC. Blue represents habit-associated and green represents non-habit-associated OSCC. Maximum of 53.3% of non-habit-associated OSCC patients belonged to 40-50 years of age. Chi-square analysis (Chi-square value=4.510) did not show statistical significance with  $P=0.211$  ( $P>0.05$ ).



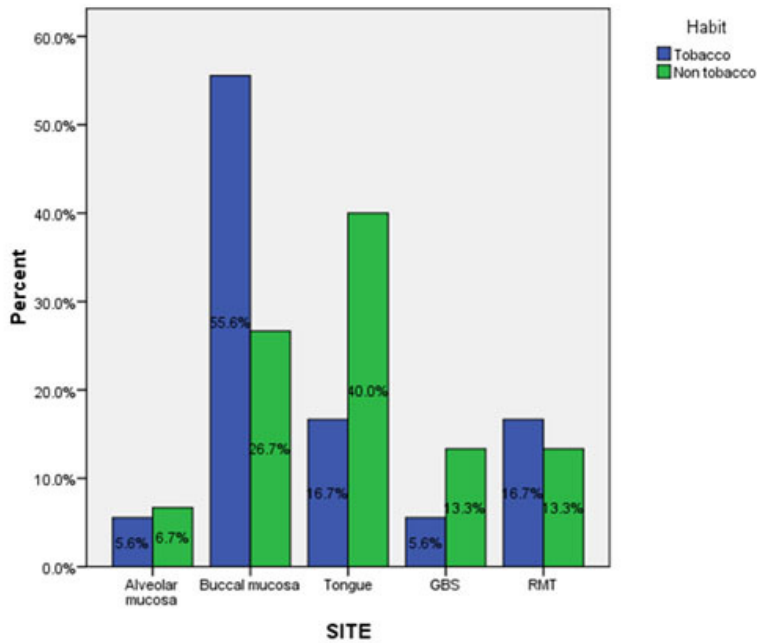
**Figure 4:** Pie chart depicting the common site of involvement in Non-Habit-Associated OSCC. 40% involving the tongue (Grey), 26.67% involving the buccal mucosa (Green), 13.33% involving the gingivobuccal sulcus (Purple), 13.33% involving the retromolar trigone (Yellow) and 6.67% involving the alveolar mucosa (Blue).



**Figure 7:** Bar graph depicting the comparison of prevalence of tobacco and Non-tobacco associated OSCC between gender. Blue represents habit-associated and green represents non-habit-associated OSCC. X-axis depicts the gender and Y-axis depicts the percentage of cases. Maximum of 83.3% of habit-associated OSCC were found in males, whereas non-habit-associated OSCC was more common among females (40%). Chi-square analysis (Chi-square value=3.204) did not show statistical significance with  $P=0.073$  ( $P>0.05$ ).



**Figure 5:** Pie chart representing the tumor size in Non-habit-associated OSCC patients, 66.7% were between 2-4 cm (grey), 26.6% were >4cm and 6.67% were <2cm in size.



**Figure 8:** Bar chart depicting the Correlation of site of involvement of OSCC with habit. X-axis depicts the site of lesion and Y-axis the percentage of cases. Blue represents habit-associated and green represents non-habit-associated OSCC. Maximum of 55.6% of habit-associated OSCC was found in the buccal mucosa, whereas among non-habit-associated OSCC maximum (40%) were found in the tongue. Chi-square analysis (Chi-square value = 5.242) did not show statistical significance with  $P=0.263$  ( $P>0.05$ ). Non-habit-associated OSCC is more common in the tongue.