Tobacco Smoking History and Presentation of Oral Squamous Cell Carcinoma

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Purpose: The association between tobacco smoking and oral squamous cell carcinoma is well established. However, few studies have evaluated the smoking history based on a smoking versus never-smoking history or analyzed the relationship between smoking history and site and stage of presentation. The purpose of this study was to examine the relationship between smoking versus never-smoking history and the stage and site of presentation of oral squamous cell carcinoma.

Patients and Methods: The design of this study was a retrospective review of all patients presented at the Legacy Emanuel Hospital Head and Neck Tumor Board in Portland, Oregon, with a biopsy-proven oral squamous cell carcinoma between 1998 and 2000. Data collected included age, gender, smoking history (smoker versus never smoker), pack-years of tobacco, site, and stage (T, N, and group stage) at presentation.

Results: A total of 67 patients were reviewed; 33% of patients were never smokers and 67% of patients had a history of smoking with an average of 49.4 pack-years. The floor of mouth and gingiva were the most commonly affected sites. There was a statistically significant difference between site of presentation and a history of smoking ($P = .0007$). The 2 sites that showed a significant association with smoking were posterolateral tongue and floor of mouth.

Conclusions: The findings of this study demonstrate that approximately one third of patients with oral squamous cell carcinoma will report that they have never smoked. There was a strong association between a history of smoking and carcinoma involving the posterolateral tongue and floor of mouth.

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The role of tobacco has been clearly established in the pathogenesis of carcinoma arising from oral epithelium.[1-4] Large epidemiologic studies continue to confirm the role of tobacco in cancers of the head and neck. Despite the heterogeneity of the anatomic sites comprising the head and neck region, almost all large-scale studies evaluating the etiologic role of tobacco have treated cancers within the head and neck region as a single anatomic group. Although 95% of cancers in the head and neck region are squamous cell carcinomas (SCCs) and have identical histologic features, the clinical behavior of oral cavity SCC is distinct, relative to the other head and neck sites. Oral cavity SCC is known for early metastasis and high rates of locoregional recurrence.[5-8] Few studies have evaluated the oral cavity as a single site or looked at oral cavity site-specific differences relative to the risk of tobacco smoking, nor have the available studies evaluated smoking history based on a smoking versus never-smoking history or analyzed the relationship between smoking history and site and stage of presentation.[9,10] The purpose of the present study was to examine the relationship between smoking tobacco

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history (smoker versus never smoker) and the site and stage of SCC at the different oral cavity sites.

Patients and Methods

The design of this study was a retrospective review. All patients who presented at the Legacy Emanuel Hospital Head and Neck Tumor Board in Portland, Oregon, with a biopsy-proven oral SCC between 1998 and 2000 were reviewed. Patient information was obtained from hospital and clinical records. Data collected included age, gender, smoking history (smoking versus never smoking), pack-years of tobacco, site, and stage at presentation. *Never smoking* was defined as no present or previous history of tobacco smoking. Staging was based on the American Joint Committee on Cancer and included primary tumor size (T), regional neck status (N), and group stage.[11] Clinical records without information regarding tobacco smoking history were excluded. Site of presentation was evaluated based on 6 oral cavity sites: anterior tongue, posterior tongue, gingiva, floor of mouth, retromolar trigone, and palate. Using the above clinical information, the following null hypotheses were tested: 1) there is no significant association between smoking history and stage of presentation; 2) there is no significant association between tobacco pack-years and stage of presentation; and 3) there is no significant association between smoking history and site of presentation.

The *t* test was used to evaluate whether there was a difference in stage grouping based on smoking history. The Fisher test was used to evaluate whether there was a difference in T and N staging and site of presentation based on smoking history. The association between tobacco pack-years and stage was also evaluated with the Fisher test.

Results

A total of 96 patients (51 men and 45 women) were reviewed. The average age of the 96 patients was 63.3 years (age range, 20 to 89 years) (Table 1). The average age of the smokers was 63.7 years (range, 42 to 81 years), and the average age of the never smokers was 71.4 years (range, 29 to 89 years). There was no statistically significant difference in age between the smokers and never smokers. Thirty of 96 (31%) of patients were never smokers, and 66 of 96 (69%) of patients had a history of smoking with an average of 47.1 pack-years (Table 1). The site of presentation relative to smoking history is presented in Figure 1. The number of patients with a history of smoking in whom SCC developed at the 6 different sites were for anterior tongue, 5; posterior tongue, 16; gingiva, 9; floor of mouth, 25; retromolar trigone, 10; and palate, 1 (Fig 1). The number of patients with a history of never smoking in whom SCC developed at the 6 different sites were for anterior tongue, 6; posterior tongue, 2; gingiva, 15; floor of mouth, 2; retromolar trigone, 3; and palate, 2 (Fig 1). The sites of presentation for all patients (smokers and never smokers) (in decreasing order) were floor of mouth, gingiva, posterior tongue, retromolar trigone, anterior tongue, and palate. There was a statistically significant difference between site of presentation and a history of smoking ($P = .0007$). Floor of mouth and posterior tongue showed a significant association with tobacco smoking.

Stage (T, N, and group stage) at presentation for all patients is presented in Table 2. The most common T stage was 1 (n = 44), and the most common N stage was 0 (n = 72). Forty percent of patients had a group stage of 1 at presentation. There was no statistically significant difference in T, N, or group stage in the smokers versus never smokers. Among the smokers, there was no statistically significant association be-

Table 1. SUMMARY OF PATIENT INFORMATION

96 Patients
51 Men
45 Women
Mean age, 63.3 ± 14.7 yr
Smoking history
66 Smokers (tobacco pack-years, 47.1 ± 32.4)
30 Never smokers

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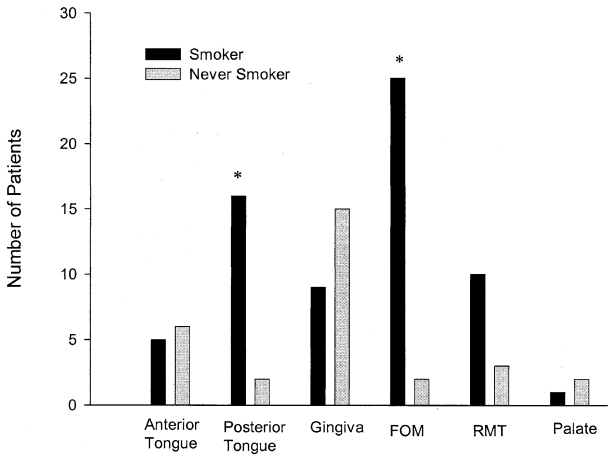

FIGURE 1. Site of presentation of oral SCC and smoking history. There was a statistically significant difference between site of presentation and a history of cigarette smoking. Floor of mouth and posterior tongue showed a significant association with tobacco smoking (*). FOM = floor of mouth, RMT = retromolar trigone.

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Table 2. STAGE AT PRESENTATION FOR ALL PATIENTS

	0	1	2	3	4
Group stage		38	21	10	27
T		44	27	7	18
N	72	11	13		

NOTE. Stage is based on primary tumor size (T), regional neck status (N), and group stage. Number of patients with a particular stage is listed.

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tween pack-years of smoking and stage of presentation.

Discussion

In this study we found that approximately one third of patients with oral SCC have never smoked tobacco. Our finding that 33% of patients with oral cancer are never smokers is in contrast to many previous studies evaluating the role of tobacco in oral cancer. In previous studies, tobacco smoking was found to be an independent risk factor in 80% to 90% of patients, and the relative risk of developing oral cancer was 6 to 8 times that of the risk in nonsmokers.[3,9,12,13] The etiology of oral SCC in never smokers is unclear. A viral etiology, particularly human papilloma virus (HPV), has been implicated in the pathogenesis of oral SCC. However, the current studies regarding the role of HPV and oral SCC are conflicting. HPV-16 is 5 times as likely to be present in oral SCC than in normal mucosa.[14,15] However, more recently, quantitative real-time polymerase chain reaction, which is considered the most sensitive and specific analytical method for identifying HPV, was used to evaluate the role of HPV-16 in oral SCC.[16] The authors found that HPV infection is seldom found in invasive oral carcinoma and, therefore, rarely contributes to oral SCC development.[16] Although the oral carcinogenic process remains unknown in never smokers, the results of the present study show the importance of evaluating all patients, regardless of tobacco exposure for oral cancer.

We found a strong association between a history of smoking and SCC involving the floor of mouth and posterolateral tongue. Previous studies have shown that the floor of mouth and tongue are particularly sensitive to the carcinogenic effects of tobacco.[17] Wynder et al[17] evaluated 543 patients with oral cancer and found that for patients smoking more than 35 cigarettes per day, the rate of floor of mouth cancer was significantly greater than expected relative to other oral sites. Keller and Terris[18] found a statistically significant excess of patients who smoked 40 or more cigarettes per day among cases of tongue and floor of mouth cancer but not among cases of oral cancer from other sites. Similar to our findings, it has been shown that the percentage of smokers is significantly lower for SCC of the gingiva relative to SCC of the floor of mouth and tongue.[4,19,20] These findings suggest that the posterolateral tongue and floor of mouth are particularly sensitive to the local carcinogenic effects of tobacco. The pooling of saliva containing carcinogens, such as benzopyrene and nitrosamine, in gravity-dependent regions has been proposed to explain the frequent location of oral SCC along the lateral and ventral surfaces of the tongue and in the floor of the mouth.[4,21] These sites might also be at risk because they receive the highest concentration of carcinogenic-containing tobacco smoke on inhalation.[19] The combustion mainstream of 1 cigarette contains approximately 500 mg of gas and particulate matter, which contain the major carcinogenic activity of cigarette smoke. "Tars" or aromatic hydrocarbons range from 1 to 35 mg and contain the highest concentration of carcinogens. Furthermore, the floor of mouth and posterior tongue might be sensitized to the carcinogens by the heat of the inhaled gas stream. The combination of heat and carcinogens has also been proposed to explain the development of lip cancer in pipe smokers who develop a habitual position for the pipe stem and develop lip carcinoma at that site. The absence of keratin at the floor of mouth and ventral tongue might further contribute to the vulnerability of these sites to carcinogens. In contrast, the presence of keratin has been suggested to protect the gingiva from the carcinogenic effects of tobacco smoke and explain the lower rates of smoking-related cancers at this site.[4]

One limitation of our study was the lack of information on alcohol consumption. We were therefore unable to adjust for the potentially confounding effects that alcohol might have on site and stage of presentation. We did not evaluate the role of alcohol consumption because it is extremely difficult to quantify alcohol consumption using medical and dental records. A second limitation of our study relates to the information obtained regarding smoking history. This information was obtained from clinical and hospital records. We did not evaluate for the potential confounding effect of smoking cessation because not only are the temporal effects of exposure to tobacco smoke and the oral carcinogenic process unknown but also it is unclear how long a smoker must have stopped smoking before the risk of oral cancer is reduced to that of a never smoker. It has been proposed that in heavy smokers, approximately 15 years must pass before the risk for head and neck cancer approaches that of people who never smoked.[22] Also, obtaining accurate smoking information regarding amount smoked and time since smoking cessation

from clinical records is notoriously problematic. Therefore, even with accurate information regarding pack-years and time since last cigarette, the relationship between smoking and oral cancer would be unclear. To limit the effects of this misinformation, we classified patients into smoker and never-smoker groups.

We have found that a significant proportion of patients with oral cancer report no history of smoking. There is no difference in the stage of presentation in never smokers versus smokers. Smokers are clearly more likely to develop cancer of the posterior tongue and floor of mouth. Elucidation of the oral carcinogenic process in never smokers will add significantly to our current understanding of the genetic and epigenetic events underlying oral epithelial malignant progression. Such an understanding of these events will likely provide diagnostic biomarkers and possibly therapeutic targets.

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