Sites of Origin of Oral Cavity Cancer in Nonsmokers vs Smokers
Possible Evidence of Dental Trauma Carcinogenesis and Its Importance Compared With Human Papillomavirus

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**IMPORTANCE** The relatively high and possibly rising incidence of mouth squamous cell carcinoma in nonsmokers, especially women, without obvious cause has been noted by previous authors. Is chronic dental trauma and irritation a carcinogen, and what is its importance compared with human papillomavirus (HPV) oropharyngeal cancer in nonsmokers?

**OBJECTIVE** To determine whether oral cavity cancers occurred more commonly at sites of dental trauma and how the position of these cancers varied between nonsmokers lacking major identified carcinogens and smokers. If these cancers occurred more frequently at sites of chronic trauma, especially in nonsmokers, it would suggest chronic dental trauma as a possible carcinogen.

**DESIGN, SETTING, AND PARTICIPANTS** A retrospective analysis of 881 patients with oral cavity or oropharyngeal cancers seen through a tertiary referral hospital between 2001 and 2011 was performed.

**MAIN OUTCOMES AND MEASURES** Patient medical records were analyzed to determine the location of the tumor within the oral cavity and oropharynx and how it relates to patient demographics, smoking and alcohol histories, and comorbidities. Dental histories were also sought, including use of dentures.

**RESULTS** Nonsmokers comprised 87 of 390 patients with mouth cancer (22%) and 48 of 334 patients with oropharyngeal cancer (14%). Female nonsmoking patients included 53 with oral cancer (61%) but only 12 with oropharyngeal squamous cell carcinoma (25%). Oral cancers occurred on the lateral tongue, a potential site of chronic dental trauma, in 57 nonsmokers (66%) compared with 107 smokers/ex-smokers (33%) (P < .001). Gingival and floor of mouth lesions occurred in older patients, possibly from chronic denture rubbing. Twenty-six patients had dental abnormalities recorded in close proximity to where their tumor developed.

**CONCLUSIONS AND RELEVANCE** Oral cavity cancers occur predominantly at sites of potential dental and denture trauma, especially in nonsmokers without other risk factors. Recognizing teeth irritation as a potential carcinogen would have an impact on prevention and treatment strategies.
The oral cavity is the most common site of origin of head and neck mucosal malignant neoplasms. Traditionally, head and neck squamous cell carcinoma (HNSCC) has been associated with the 5 “Ss” of smoking, spirits, syphilis, spices, and sharp (or septic) teeth. The role of smoking and alcohol consumption as causative factors are unquestionable and accepted. The role of syphilis and spices, including betel nut, in Western societies appears to be minor. However, spices and untreated syphilis may be factors in the much higher incidence of oral cavity squamous cell carcinoma (SCC) in developing countries such as India and Pakistan, compared with Europe and North America. Other risk factors include immunosuppression and diet. The role of human papillomavirus (HPV) in head and neck malignancy is accepted in oropharyngeal SCC, but its role elsewhere is uncertain. Previously, there have been a few limited studies that have suggested that chronic irritation from poor dentition or ill-fitting dentures had a role in developing mouth cancer. However, recurrent dental trauma is not widely accepted as a carcinogen. Head and neck oncology generally gives little emphasis to chronic teeth or denture irritation. If dental or denture irritation is a potent carcinogen, clinician rarely recognize, and even less frequently document, whether dental trauma was present before the development of cancer symptoms. This study sought to elucidate the carcinogenicity of dental trauma retrospectively by studying the sites of origin of mouth SCC in patients with respect to the more established risk factors. If chronic dental trauma is a cocarcinogen, compounding the effects of smoking and alcohol, there would be a relatively higher incidence of cancer occurring in smokers at the sites of trauma than at other sites in the mouth. Sites of chronic dental trauma include the tongue edge and the buccal mucosa within the range of sharp teeth or a rough dental edge. The gingiva, floor of mouth, and buccal mucosa are the key sites of trauma from chronic denture rubbing. If dental or denture irritation is a potent carcinogen in its own right, oral mucosa malignant neoplasms would be more likely to develop at sites of trauma in nonsmokers without other known risk factors.

Methods

Study Design

This study was approved by the Princess Alexandra Hospital Ethics Committee. This retrospective medical record review identified 881 patients presenting with oral and oropharyngeal malignant neoplasms to the Princess Alexandra Hospital’s Head and Neck Cancer Multi-Disciplinary Clinic between 2001 and 2011. Data were obtained to compare nonsmoking oral cancer rates with the better-known and widely studied HPV-associated nonsmoking oropharynx malignant neoplasms. With assistance from medical epidemiologists at the University of Queensland School of Population Health, a data pro forma was constructed. Information sought from the medical records included patient demographics, age at presentation, site of origin, and TNM staging of the malignant neoplasms and the treatment modalities used to manage them. Smoking histories were ascertained, including number of pack-years smoked, as well as current smoking status. Ex-smokers were defined as having ceased smoking for more than 1 year prior to the diagnosis of their malignancy, and lifelong nonsmokers were defined as having a less than 2 pack-year history of smoking. Alcohol intake was also quantified by grams of ethanol intake per day. Information was sought for evidence of immunosuppression from long-term immunosuppression, steroid use, organ transplants, or autoimmune disorders, as well as previous malignant conditions. We also sought specific information regarding the state of the patient’s dentition at the time of presentation. This included irritation of the tongue or buccal mucosa from teeth or dentures, as well as rough or loose dentures abrading the alveolar arch or floor of mouth.

Statistical Analysis

For statistical analysis, we used STATA v11.2 software (StataCorp), with \( P \leq .05 \) considered statistically significant. Cases were excluded from analysis if they were not categorized in the oral cavity or oropharynx groups or if the tumor was too large at time of presentation to determine with accuracy the exact site of origin of the cancer. Cases were also excluded if they were not SCCs, since most head and neck mucosal tumors are histologically SCCs. Other tumor types, such as salivary carcinomas, sarcomas, and metastases from distal sites such as the kidney, were excluded because they have different etiologies. We primarily used \( \chi^2 \) tests to examine oral cavity cancer according to sex and smoking status, as well as the association between smoking status and location of tumor (edge of tongue vs other locations) in the oral cavity. To estimate the relative risk of edge of tongue tumors, relative to other locations according to smoking status, we used logistic regression to obtain the odds ratio and 95% CI.

Results

Of the 881 oral and oropharyngeal tumors seen over 10 years (2001-2011), 157 cases were excluded from the study. Of these exclusions, 61 cases were large cancers with an indeterminate exact site of origin, 5 cases were not cancers, 5 cases were not squamous cell carcinomas, and 2 cases were recurrent neoplasms; a further 84 patients were excluded because of insufficient information in the patients’ medical record, including 25 without a close numerical description of the patient’s smoking history. Of the remaining 724 patients, 334 had oropharyngeal and 390 had oral cavity malignant neoplasms. Both cancers were more common among men (265 of 334 oropharyngeal SCCs and 255 of 390 mouth SCCs). The mean age at diagnosis of oropharyngeal cancer was 60.20 years, which was slightly younger than the mean age at diagnosis of oral cavity (61.73 years) \( (P = .09) \). From the 334 patients with oropharyngeal lesions, 48 were lifelong nonsmokers, 266 were current smokers, and 20 were ex-smokers. Of the 390 patients with mouth cancer, 87 were lifelong nonsmokers, 276 were current smokers, and 27 were ex-smokers.
The prevalence of oral and oropharyngeal SCC varied by sex (Table 1). Among women, there were 69 oropharyngeal and 135 oral cavity SCCs. Thus in the 10 years studied, women had almost twice the incidence of oral cavity SCC compared with oropharyngeal cancer. In men, the number of cancers were very similar between the 2 locations, with 265 oropharyngeal and 255 oral cavity SCCs. The difference in incidence between oral cavity SCC and oropharyngeal SCC (19%), as shown in Figure 1, simply reflects the difference in incidence in the female population alone.

Differences were found when analyzing by smoking status for these patients. Of the oral cavity lesions in the non-smoking population, 34 (39%) were in men compared with 53 (61%) in women. This contrasts with the smoking population, where male cases (n = 221 [72%]) outnumbered female cases (n = 82 [28%]). Oropharyngeal and oral cavity SCC in nonsmoking men had a near equal incidence (36 cases compared with 34); however, nonsmoking women had more than 4 times the rate of oral than oropharyngeal SCC (53 vs 12 cases) and 50% more than male nonsmokers (53 vs 34 cases). Logistic regression shows that the risk of oral cavity cancer compared with oropharyngeal cancer in nonsmoking men is almost half that of nonsmoking women (odds ratio, 0.49; 95% CI, 0.35-0.69).

Mouth SCC cases were also analyzed regarding the site of tumor origin. These tumors were then subdivided by the patient’s smoking status (Table 2 and Figure 2), and their mean ages at presentation were calculated.

Current and ex-smokers had tumors arising predominantly on the edge of the tongue (107 of 303 cases), followed by floor of mouth (82 cases) and retromolar trigone (38 cases). By comparison, in nonsmokers, 66% of tumors occurred on the edge of the tongue (57 of 87). Edge of tongue tumors were thus proportionately much more common in nonsmokers (57 of 87 [66%]) than in those who currently smoked or who had smoked previously (107 of 303 [35%]). This difference in oral cavity cancer position was statistically significant (P < .001).

Larger tumors involving the floor of mouth and extending onto the surrounding tissues were also seen much less commonly in nonsmokers (1 case [1%]) compared with those who had smoked (31 cases [10%]). This probably reflects less attention to health concerns and later presentation to health professionals by smokers. The 1 case of very advanced oral cavity cancer in a nonsmoker occurred in a woman aged 86 years.

Further analysis was performed on the location of the tumor when subdivided by a patient’s sex. There were significant differences in sites of origin of mouth cancer between men and women. However, this difference in location was negligible when a patient’s smoking status was taken into account, and thus the difference in sex can be attributed to a patient’s smoking status.

Nonsmoking patients with lateral tongue malignant neoplasms had a mean age of 61.8 years. The nonsmoking patients with alveolar ridge, buccal mucosa, and floor of mouth were older with mean ages 72.7, 75.4, and 67.5 years, respectively (Table 2).

Our data on drinking alcohol were difficult to interpret because many patients were recorded as social drinkers. However, none of our nonsmoking patients were recorded as heavy drinkers.

### Discussion

Overall our data are consistent with other published epidemiologic studies of oral cavity cancer. However, this is the first large study looking specifically at the possible importance of dental trauma in oral cavity carcinogenesis. We acknowledge that this study does not prove that chronic dental trauma causes cancer. However we believe that the data and discussion provided herein suggest that it may be a more important and common carcinogen than is currently perceived, especially in cases involving nonsmoking female patients.
Currently, 18% of Australians smoke, compared with 19.5% in 2001 and 40% to 50% in the 1940s through the 1970s. In most Organization for Economic Cooperation and Development countries, men smoke more often than women by a factor between 2 and 9, but this difference in magnitude is declining. When the average age of presentation of oral cavity cancer is 60 years, there will be a high percentage of ex-smokers, assuming that most 60-year-old smokers started smoking in their teenage years in or before the 1970s, when 40% to 50% smoked. Maru et al demonstrated than HNSCC has been falling in incidence from 1973 to 2006, probably because of declining tobacco use.

The key finding of this study is that the location where oral cavity cancers arise is different in smokers and nonsmokers (Figure 2 and Table 2). There were marked differences in location distribution. Most mouth cancers occurred on the edge of the tongue. Nonsmokers, however, had a significantly higher proportion occurring on the edge of the tongue (66%) compared with 33% in smokers. This result was significant (P < .001). Thus, we can confidently conclude that there is some carcinogen in nonsmokers that is preferentially affecting the edge of the tongue. In ex-smokers and current smokers there was a 20% higher incidence of cancer in the edge of tongue than in the floor of mouth. In nonsmokers there was a nearly 6-fold higher incidence of cancer in the edge of tongue (57 patients) than in the floor of mouth (10 patients).

Dahlstrom et al had similar data in their study of 172 never smoker/never drinker (NSND) patients in a total group of 1303 patients with HNSCC. Their NSND patients were more likely to be female. They were commonly young women with oral tongue cancer and older women with gingival or buccal cancers. The authors said that no single known factor is responsible for the majority of HNSCC in NSND patients. We suggest that the younger women in their cohort were more likely to have had their own teeth causing irritation than the elderly patients who wore dentures, which would predominately affect their gingiva and lower buccal mucosa.

It is surmised that the dose of carcinogen applied and the absorption of the myriad topical carcinogens in cigarette smoke and alcohol would vary in different parts of the mouth owing to confounding factors. These factors include the sump effect of the pooling of the carcinogen in saliva, local rubbing, mucosal thickness, and how tightly bound down the mucosa is to the underlying bone and soft tissue. This sump effect may explain why smokers have a propensity for forming floor of mouth tumors (90 patients) compared with nonsmokers (10 patients). The edge of tongue was the most common site of tumor occurrence in both smokers and nonsmokers, though it was proportionally much more common in nonsmokers by a factor of 2. The edge of the tongue would not normally be considered a sump for salivary carcinogens. One explanation for this high incidence of edge of tongue cancers is chronic dental trauma. If chronic dental trauma is a carcinogen, it would be expected that a high incidence of oral cavity malignant neoplasms would occur near teeth, especially on the edge of the tongue or the buccal mucosa if there was lateral dental irritation. This irritant effect may explain why lifelong nonsmokers, in the absence of other major risk factors, develop oral cavity cancers most commonly on the lateral edge of their tongue. Edge of tongue tumors were also the most common site for cancer to occur in smokers. This could be explained if chronic dental trauma enhances the absorption of other known oral cavity carcinogens, especially cigarette smoke and alcohol. These topical carcinogens would have increased absorption through broken and ulcerated mucosa compared with absorption through intact lining. However, with the ubiquitous application of tobacco carcinogens throughout the oral cavity in smokers and drinkers, tumor location in smokers is considerably more diverse compared with nonsmokers.

One explanation why cancer is more likely to occur on the tongue from dental trauma than on the buccal mucosa is because teeth are more often turned inwards toward the tongue than outwards. Also, the tongue, through chewing and talking, has more movement against the teeth than the buccal mucosa.

Previous articles have specifically supported the role of chronic dental trauma in the causation of mouth cancer, but they are generally articles with small sample sizes or with relatively unconvincing evidence. Thumfart et al examined 86 oral cavity SCCs, of which 71 (83%) were in smokers and 42 (49%) were in heavy alcohol consumers. This article suggested that 44% of these patients showed a correlation be-
between the site of cancer development and the site of some form of chronic dental irritation. This chronic irritation included sharp teeth, damaged or poorly formed fillings, and poorly fitting dentures. Lockhart et al\textsuperscript{13} examined a series of 28 intraoral malignant neoplasms and found that all those neoplasms occurred in areas in contact with teeth and/or dental appliances, with all 10 tongue tumors occurring on the lateral border and all 6 floor of mouth tumors occurring at the flange extension of the lower denture. A Brazilian-Canadian study by Velly et al\textsuperscript{12} of 717 oral cavity and oropharyngeal SCCs showed that oral cavity cancers were not associated with well-fitting dentures but rather with a history of what they described as “oral sores,” ulcerations secondary to ill-fitting dentures. They also found that infrequent tooth brushing was associated with oral cavity malignant neoplasms. However, these studies, which are not recent publications, were in smaller study populations or did not separate the smoking population from the nonsmoking population. Our study was of a large patient cohort and separated patients based on smoking status.

The suggestion that chronic irritation and inflammation can lead to the development of cancer elsewhere in the body is not a new concept. Multiple cancers in different sites have been shown to be a result of chronic trauma, irritation, or inflammation. Among otolaryngology–head and neck clinicians, it is known that textile workers have a higher risk of laryngeal malignancy owing to chronic irritation from textile fibers,\textsuperscript{22} and cancers can occur in chronically infected mastoid cavities. Esophageal carcinoma and posterior laryngeal cancer have been shown to develop with chronic gastroesophageal reflux disease,\textsuperscript{23,24} and inflammatory bowel disease has been implicated in the development of carcinoma of the colon.\textsuperscript{25} Asbestos is a potent carcinogen of the lung. One of the theories of asbestos carcinogenesis is chronic irritation from their sharp fibers embedding in the constantly moving pleural surfaces.\textsuperscript{26}

Men are much more likely to develop oral cavity cancer than women by a factor of 2.88:1 in developed countries and 1.77:1 in less developed areas.\textsuperscript{27} This is frequently attributed to the higher incidence of smoking in men.\textsuperscript{28} There was indeed a sex difference in oral and oropharyngeal tumor incidence in our smoking group. In our study the incidence of oropharyngeal SCC in nonsmokers was not significantly different between men and women (P = .42). However, oral SCCs were overall 19% more common than oropharyngeal SCC in our cohort, which is consistent with the findings of other studies.\textsuperscript{28}

There was a higher incidence of mouth cancer in female nonsmokers compared with male nonsmokers (53 of 87 cases were female). That is a 50% higher rate in women than in men. This result was significant (P < .001). This finding correlates with other studies by Wiseman et al,\textsuperscript{14} Dahlstrom et al,\textsuperscript{18} and Kruse et al.\textsuperscript{29} Wiseman et al\textsuperscript{14} found that 78% of HNSCCs in lifelong NSND patients occurred in women. Interestingly, 75% of these cancers were in the oral cavity, and there was a very high incidence of second (25%), third (10%), and even fourth metachronous primary tumors, all occurring within the oral cavity. Is the high rate of secondary primary tumors the result of nonrecognition of the actual dental trauma carcinogen? Kruse et al\textsuperscript{29} similarly found that mouth SCC in nonsmokers was twice as likely to be in women than in men (45 women compared with 22 men).

The study by Dahlstrom et al\textsuperscript{18} also found a high incidence of oral cavity cancer in nonsmoking women. The authors found a bimodal distribution of age at presentation among NSND women, peaking in the fifth decade with tongue cancers and the eighth decade when “gingivo-buccal” lesions were more common. In our study, the mean ages of nonsmoking patients with alveolar arch and floor of mouth tumors were 75.4 and 67.5 years, respectively. The mean age of patients with lateral tongue cancer was 61.8 years. This confirms a similar age discrepancy between the young tongue and the older alveolar arch and floor of mouth tumors observed by Dahlstrom et al.\textsuperscript{18} Presumably, the younger women were more likely to have their own teeth. Those teeth were possibly broken, in-turned, or rough medially. Patients in their 80s would be more likely to have full dentures. Generally, the acrylic or porcelain dental crowns on dentures are smooth surfaced and well aligned so that the individual false teeth do not rub the tongue. However, the undersurface of full dentures can rub, especially in those patients with long-standing dentures where alveolar bone shrinkage secondary to tooth loss will leave those dentures loose and rubbing, particularly traumatizing the alveolus, floor of mouth, and lower buccal mucosa. We contend that this is the factor in oral cavity cancer that Dahlstrom and colleagues\textsuperscript{18} were looking for but did not recognize after they discounted other factors such as marijuana use, passive smoking, and occupational exposures.

Overall, the literature reports that 30% to 35% of all head and neck mucosal malignant neoplasms arise in the oral cavity, with other high incidence areas being the larynx and oropharynx.\textsuperscript{28} However, in the nonsmoking population, the cancers in the head and neck mucosa appear to be predominantly within the oral cavity, up to 75% in the cohort of Wiseman et al.\textsuperscript{14} This further enhances our argument for the role of dental trauma in the development of nonsmoking head and neck cancers and that dental trauma is a potential cocarcinogen with tobacco of oral cancer.

Kruse et al\textsuperscript{29} found that 67% of oral cavity tumors were in female patients and that the majority of mouth cancers in a nonsmoking population were on the mandibular or maxillary alveolar arch. Only 24% occurred on the lateral tongue in their cohort, compared with 66% in our cohort. This difference in cancer position in nonsmokers is confounding to our study and that of Dahlstrom et al\textsuperscript{18} but could be explained by the differences in dental care access, dental tradition, and affordability of dentistry between Australia and the United States and the dentistry practiced in Switzerland. Perhaps this reflects a higher rate of partial or full denture use in Switzerland.

One of the key limitations of this study was that the data were collected retrospectively. This particularly hindered the gathering of information regarding the state of dentition for our patients. There were many different clinicians recording clinical information into our medical records over the past 10 years, and not all our clinicians were cognizant of the potential role of chronic dental irritation in the carcinogenesis of oral cavity cancer. Likewise, data were rarely recorded regarding the presence of ill-fitting dentures in the patients with oral cav-
ity cancer, especially alveolus and floor of mouth. We believe that the number of our patients with a recorded history of dental trauma significantly underestimates their true numbers. However, there were a number of cases where the site of den- tition and trauma was commented on. In cancers of the lateral tongue, 18 of the 57 tumors in nonsmokers had notes specifically detailing dental abnormalities causing ulceration or irritation. Of these 18 cases, 16 were reported on in the last half of the collection period (2006-2011), correlating with a development of a general consensus among clinic members regarding dental irritation and carcinogenesis. There were 2 of 7 buccal mucosa malignant neoplasms in nonsmokers where dental trauma to the cheek was recorded. Six floor of mouth tumors in smokers were also mentioned in clinical notes to be at sites of trauma from ill-fitting dentures. While this information is largely subjective in its interpretation, it further strengthens the argument that chronic dental trauma is a carcinogen in the mouth.

Human papilloma virus (HPV) is a known, potent carcinogen within the oropharynx; however, its role in mouth cancer is not as clearly elucidated. Epithelial warts, caused by HPV, are known to implant at sites of trauma. Therefore, HPV could be a cocarcinogen with dental trauma. There is a wide recognition of the importance of HPV in the causation of oropharyngeal cancer and in Australia the upward trend of the worldwide incidence of HPV-associated cancers is acknowledged. The Australian government was the first government to subsidize HPV vaccines in teenage boys to try to minimize HPV-associated cancers in the future. In the 10-year period of this study, however, lifelong nonsmoking men had equal incidence of oral and oropharyngeal malignant neoplasms, but nonsmoking women had more than 4 times the incidence of oral cavity cancer compared with oropharyngeal malignant neoplasms. For the nonsmoking woman, dental trauma per se may be a more important carcinogen than HPV in the upper airway mucosa.

Conclusions

Cigarette smoking and alcohol are the most recognized factors in the causation of cancers of the oral cavity. However, in our study, nonsmokers accounted for a notable proportion (22%) of oral SCC cases. Currently, in Queensland, Australia, a lifelong nonsmoker is 50% more likely to develop an oral cavity cancer than an oropharyngeal cancer, but for women that figure is 400%. The majority of oral cavity cancers in the nonsmoker occur where teeth or dentures can rub. Our data support the limited evidence from the small number of previous studies that recognized a potential role of chronic dental irritation in carcinogenesis. Our study demonstrated a statistically significant correlation between smoking status and site of origin of the cancer. Nonsmokers develop mouth cancer on the edge of the tongue at twice the rate of smokers. Given that chronic irritation is a key factor in the development of tumors elsewhere in the body, this study provides further evidence that dental trauma could be a significant cause of oral cavity SCC, possibly the major cause in lifelong nonsmokers. This study supports other studies showing that women are particularly prone to mouth cancer, even when they do not smoke, and that cancers occur more often on the lateral tongue in young people and where dentures rub in elderly people. We argue for an increasing recognition of the potential carcinogenicity of dental trauma in its own right and its cocarcinogenicity with smoking. Therefore, patients presenting to medical and dental services with evidence of dental irritation or premalignant changes to oral mucosa should have appropriate dental care to help prevent cancer development. Our study also suggests that appropriate dental advice and management of early malignant lesions could reduce the progression of carcinogenesis and prevent new primary lesions from arising in the future, which unfortunately occur fairly commonly in oral cavity cancer.

REFERENCES


