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Gender Differences in Smoking and Risk for Oral Cancer

Joshua E. Muscat, John P. Richie, Jr., Seth Thompson, and Ernst L. Wynder

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ABSTRACT

Based on studies that show gender differences in cigarette smoking and lung cancer risk, we hypothesized that sex differences also exist in the risk for cancer of the oral cavity and pharynx. A hospital-based study of 1009 patients with oral neoplasia and 923 age-matched controls was conducted from 1981–1990. All subjects were interviewed directly with an extensive questionnaire containing items on tobacco smoking, alcohol consumption, and occupational exposures. Using a cumulative lifetime measure of exposure to cigarette tar, the adjusted odds ratio for men, according to increasing quartile of tar consumption and relative to never smokers, was 1.0 (95% confidence interval (CI), 0.6–1.6) for the lowest category, 0.9 (95% CI, 0.6–1.6) for the second category, 1.6 (95% CI, 1.0–2.5) for the third category, and 2.1 (95% CI, 1.4–3.2) for the highest category. Among nonsmokers, there was a significantly higher proportion of women than men in the age group of 50 years. This was consistent for all subsites within the oral cavity. These findings support the hypothesis that there are gender differences in the smoking-related risks for oral cancer and in the risk for nonsmoking-related oral cancer as well. The role of nutrition in relation to these findings is discussed.

INTRODUCTION

Cigarette smoking is the predominant cause of cancer of the lung, oral cavity, and pharynx. The risk of lung cancer is higher in women than men per cumulative dose of cigarette smoking (1–8), and there is limited evidence that women have a higher susceptibility to tobacco smoke carcinogens than men (9, 10). These observations, and a previous analysis of risk factors for oral cancer by our group showing higher ORs3 for current smokers in women than in men (11), led us to hypothesize that female smokers are at higher risk for oral cancer than male smokers. In the current paper, we examine the association of smoking by gender on the development of oral cancer. Because alcohol consumption is a cofactor in oral carcinogenesis (12, 13), the risk estimates were adjusted for levels of alcohol intake. Subjects (men) who smoked pipes or cigars were excluded from the analysis. In addition, we examine the epidemiology of oral cancers in nonsmokers.

MATERIALS AND METHODS

A hospital-based study of oral cancer was conducted between 1981 and 1990 (see “Acknowledgments”). Case patients were men and women between the ages of 21 and 80 years with newly diagnosed histologically confirmed cancer of the oral cavity and pharynx (ICD, 9th Revision, codes 141, 143–146, 148, and 149). Patients with cancer of the salivary gland (ICD 142) and nasopharynx (ICD 147) were excluded. Controls were hospital patients admitted for conditions unrelated to tobacco use. Controls were matched to cases by sex, age (± five years), race, and date of admission (± three months). Eligible patients were identified from daily hospital admission logs. Ninety-one percent of cases and 97% of controls who were approached agreed to be interviewed by a trained interviewer and signed consent forms. Within each hospital, cases and controls were interviewed by the same interviewer.

The most detailed section of the questionnaire contained data on lifetime smoking history. Subjects were asked to provide information for each brand of cigarette smoked, the age they started smoking, and the duration and frequency of smoking. Never smokers were those who never smoked cigarettes regularly. Current smokers were defined as subjects who had smoked at least one cigarette/day during the past year. Ex-smokers were quitters who had not smoked within the past year. The tar content of the brand of cigarette was obtained from the 1977 and 1988 Federal Trade Commission reports (14). A cumulative tar yield was divided into quartiles based on the distribution of smokers in the entire control group (e.g., men and women combined), and subjects were compared to never smokers when calculating ORs. Likewise, a pack-year measure was calculated by multiplying the years of smoking by the number of packs smoked/day for each brand of cigarette. Detailed questions were asked on current alcohol consumption including beer, wine, and hard liquor. Alcohol consumption was divided into several categories. Nondrinkers were classified as subjects who never consumed alcohol or drank less than one drink/week. Occasional drinkers include subjects who drank >1 drink/week and <1 drink/day. Subjects were asked to give a detailed employment history including job title and type of occupation. For each job, subjects were asked whether they had been exposed to one or more of 45 occupational exposures including hydrocarbon emissions and fumes, solvents, metals, chemicals, dyes, dusts, and fibers for at least 8 h/week for one year or more.

Gender specific ORs and 95% CIs for tar quartiles were calculated. Unconditional multiple logistic regression analysis was performed to obtain maximum likelihood estimates of ORs, adjusted for the continuous covariates age (five ordinal levels) and education (four ordinal levels). Additional terms for religion, marital status, race, and body mass index were tested by the likelihood ratio statistic. In models that evaluated trends and interactions, T was treated as continuous by assigning the median cumulative tar yield value for each of the four categories. The confounding or interaction effects of alcohol consumption were also modeled as a continuous variable by assigning median values to each category of consumption. To determine whether the effects of smoking were significantly greater for women than for men, a model that combined all subjects was evaluated, and an interaction term for gender and tar was tested. The fit of the final model was evaluated by plotting the changes in the Pearson χ² against the estimated logistical probabilities (15).

RESULTS

Partial or complete information on brands of cigarettes smoked was missing for 56 cases and 60 controls. This left a final sample of 1009 cases (687 men and 322 women) and 923 controls (619 men and 304 women). The subsite distribution among cases was similar for men...
Among women, 61% of cases and 21% of controls were current smokers. There were some differences in the prevalence of smoking when the case subjects were stratified by subsite. Male cases with cancer of the tongue had the lowest prevalence of current smoking (57%), and cases with cancer of the mouth floor had the highest prevalence (74%). Among women, the smoking prevalence was also lowest for the buccal mucosa (2 of 10 cases) and tongue (53%) and highest for the floor of mouth (75%). The case-control differences in alcohol consumption were even more marked than those for cigarette consumption. Among men, 83% of cases and 70% of controls consumed at least one alcoholic drink/day, and 45% of cases and 16% of controls took seven or more drinks/day. Among women, the corresponding figures were 47 and 20% for at least one drink/day and 14 and 1% for seven or more drinks/day.

Table 2 provides the adjusted ORs associated with cumulative tar intake by quartiles relative to never smokers. Comparing men to women, the OR was 1.0 (95% CI, 0.6—1.6) versus 1.8 (95% CI, 1.1—3.0) for the lowest quartile, 0.9 (95% CI, 0.6—1.6) versus 2.8 (95% CI, 1.6—4.9) for the second quartile, 1.6 (95% CI, 1.0—2.5) versus 3.2 (95% CI, 1.9—5.6) for the third quartile, and 2.1 (95% CI, 1.4—3.2) versus 4.6 (95% CI, 2.5—8.7) for the upper quartile. A linear increase in risk was statistically significant for both men and women (P < 0.01). When smoking-risk estimates were calculated according to pack-years, similar results were found (Table 2). Combining men and women together, the effect of cumulative tar intake and of pack-years, as modeled by a gender × smoking interaction term, was significantly higher for women than for men (β = 0.11; P < 0.01). In contrast, there was no significant gender × alcohol interaction after adjusting for tar.

The stratified analysis (Table 3) shows that for almost every smoking/alcohol category, the risks are higher for women than for men. In men, there was no increased risk associated with smoking in never drinkers. Elevated risks were observed only for high levels of lifetime tar intake (>3.5 kg) and daily or greater alcohol consumption. Among women, increased risks were observed for all levels of smoking and alcohol intake. The one category where equivalent or higher ORs were observed for men than women was the heaviest alcohol drinkers (>4 drinks/day). However, the ORs for women in this category were highly unstable because there were only two female cases and one female control who never smoked cigarettes. Further modeling of this data revealed a significant interaction between smoking (ever versus never) and alcohol consumption for both men and women. A separate model revealed that each tar quartile × alcohol term was statistically significant, although the β coefficients slopes did not vary. Regression diagnostic plots did not reveal any large values that indicated a poor fit.

In never smokers, there was no increased risk associated with

Table 1 Characteristics of oral cancer patients and controls, 1980–1990

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 322) %</th>
<th>Controls (n = 619) %</th>
<th>OR 95% CI</th>
<th>Cases (n = 304) %</th>
<th>Controls (n = 619) %</th>
<th>OR 95% CI</th>
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</tr>
<tr>
<td>&lt;50</td>
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<td>1.0</td>
<td>24.0</td>
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<td>50–59</td>
<td>35.4</td>
<td>35.1</td>
<td>1.0</td>
<td>36.0</td>
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<tr>
<td>60–69</td>
<td>31.3</td>
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<td>33.0</td>
<td>31.3</td>
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<tr>
<td>≥70</td>
<td>9.9</td>
<td>10.3</td>
<td>1.0</td>
<td>11.2</td>
<td>10.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Education (yr)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≤12</td>
<td>29.8</td>
<td>26.3</td>
<td>1.0</td>
<td>29.7</td>
<td>27.1</td>
<td>1.0</td>
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<tr>
<td>13–15</td>
<td>14.7</td>
<td>20.2</td>
<td>1.0</td>
<td>16.0</td>
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<td>≥16</td>
<td>22.3</td>
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<td>1.0</td>
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<tr>
<td>Never</td>
<td>10.2</td>
<td>22.3</td>
<td>1.0</td>
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<tr>
<td>Current</td>
<td>66.8</td>
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<td>66.8</td>
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<tr>
<td>Former</td>
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<td>42.3</td>
<td>1.0</td>
<td>23.0</td>
<td>42.3</td>
<td>1.0</td>
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<tr>
<td>Alcohol (%)</td>
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<tr>
<td>0–1/day</td>
<td>8.5</td>
<td>28.6</td>
<td>1.0</td>
<td>8.5</td>
<td>28.6</td>
<td>1.0</td>
</tr>
<tr>
<td>1–4/day</td>
<td>23.6</td>
<td>26.8</td>
<td>1.0</td>
<td>23.6</td>
<td>26.8</td>
<td>1.0</td>
</tr>
<tr>
<td>≥7/day</td>
<td>44.9</td>
<td>16.4</td>
<td>1.0</td>
<td>44.9</td>
<td>16.4</td>
<td>1.0</td>
</tr>
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<td>Protestant</td>
<td>39.9</td>
<td>32.5</td>
<td>1.0</td>
<td>39.9</td>
<td>32.5</td>
<td>1.0</td>
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<tr>
<td>Catholic</td>
<td>50.7</td>
<td>48.5</td>
<td>1.0</td>
<td>50.7</td>
<td>48.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Jewish</td>
<td>5.2</td>
<td>13.9</td>
<td>1.0</td>
<td>5.2</td>
<td>13.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Other/none</td>
<td>4.1</td>
<td>5.2</td>
<td>1.0</td>
<td>4.1</td>
<td>5.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* For men, χ² = 17.9; P < 0.01.
* For men, χ² = 33.1; P < 0.01; for women, χ² = 28.1; P < 0.01.
* Excludes pipe and cigar smokers.
* Current smokers.
* Occasional drinkers include >1 drink/week and <1 drink/day.

and women (tongue, 34.0 and 35.1%; floor of mouth, 27.5 and 27%; palate, 11.5 and 11.2%; pharynx, 9.9 and 10.6%; tonsil, 10.8 and 8.1%; buccal mucosa, 2.3 and 3.1%; and retromolar trigone, 3.9 and 5.0%). Ninety-two percent of cases had a histological designation of squamous cell carcinoma. Controls were patients with cancer (large bowel, breast, prostate, skin, or lymphoma), 44.3%; benign neoplastic disease, 7.3%; and a variety of nonneoplastic conditions, 48.4% (e.g., injuries, fractures, spinal disc problems, hernia, gall bladder disorders, genitourinary disorders, cataract, osteoarthritis, and so forth).

Table 1 shows that cases and controls were similar in age. Male cases were less educated than their controls (P < 0.01). Eighty-nine percent of cases were more likely to have smoked cigarettes than controls. Among women, 61% of cases and 21% of controls were current smokers.
drinking. The adjusted OR for men, relative to never drinkers, was 1.2 (95% CI, 0.6—1.2) for occasional drinkers, 1.4 (95% CI, 0.7—3.1) for 1—4 drinks/day, and 1.6 (95% CI, 0.6—4.2) for >4 drinks/day. In women, corresponding ORs were 0.9 (95% CI, 0.4—2.1), 0.6 (95% CI, 0.4—2.1), and 4.6 (95% CI, 0.4—52.2).

Oral snuff use and chewing tobacco were unrelated to oral cancer risk. Among men, 9 cases (1.3%) and 10 controls (1.6%) reported using snuff at least once a week for one or more years. Among women, the corresponding ORs were 0.9 (95% CI, 0.4—2.1), 0.6 (95% CI, 0.4—2.1), and 4.6 (95% CI, 0.4—52.2).

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case-control study of oral cavity cancer in Italy, Franceschi et al. (21) observed similar alcohol-related risks for men and women. We did observe a significant interaction between ever smoking and alcohol in both men and women, although this effect did not vary by levels of lifetime tar consumption.

The main limitations of this study are its hospital-based nature and lack of information on nutritional factors. Possible biases that could account for the current findings include a greater underreporting of smoking consumption in women than in men. However, Wagenknecht et al. (22) found no gender differences in the misclassification rates (under 3% for white subjects) in a study of 3445 healthy reported nonsmokers when validated against serum cotinine. Previous studies of the reproducibility of questions on smoking and hard liquor consumption in this data found very high intraclass correlation coefficients in men and in women (23). Still, the validity of reported alcohol consumption in heavy drinkers may be problematic. Women may tend to underreport heavy alcohol consumption as social drinking, although this may occur among men as well. Some studies have demonstrated the unreliability of self-reported alcohol consumption among problem drinkers (24). Because relatively few women drink heavily, misclassification of heavy drinkers as moderate drinkers would result in a slightly spurious effect associated with moderate levels of alcohol consumption but would result in a substantial underestimation of risk in the heavy alcohol consumption category.

When interpreting gender-specific risks in case-control data, it is necessary to consider the absolute rates of cancer in nonsmokers. In a pooled analysis, Risch et al. (25) calculated that the female: male ratio of age-adjusted lung cancer rates was 0.7. This difference, which may reflect a greater exposure to occupational carcinogens (26, 27), does not account for the 2–3-fold higher relative risks of lung cancer among female smokers than male nonsmokers (25). However, there is little population-based data of oral cancer rates in nonsmokers. In a 1960 study of one million men and women, Hammond (28) calculated a oropharyngeal mortality rate of 7 per 100,000 in nonsmoking men ages 65–79. This was based on five deaths after three years of follow-up. The rate for women in this age group was also seven, although this number included larynx and esophagus deaths as well. Some data indirectly suggest that men do not have a higher baseline risk of oral cancer than women. For example, several studies have found little evidence for occupational oral carcinogens (29–36). Occupation and occupational exposures were unrelated to oral cancer risk in this study. The use of oral snuff may be associated with increased rates of oral cancer in men (37), although combined data from the Mortality Followback Survey and National Health Interview Survey show no increased risk of oral cancer from any form of smokeless tobacco. There has been an increase in the incidence of snuff use among young men (38) and an increase in the incidence of tongue cancers in men under age 40 since the 1950s in the United States (39, 40) and Scotland (41). In our data, snuff use was unrelated to oral cancer risk. This did not seem to reflect the low prevalence of snuff use in controls (1.6%). There was 80% statistical power to detect an OR of 2.8 given this level of exposure in controls. Among the nonsmoking cases, there was a slightly higher percentage of men than women under the age of 40 (26% versus 18%), although this difference was not statistically significant. If the age differences between nonsmoking male and female cases do reflect a male-specific risk factor besides snuff, it would not seem to account for the differences in smoking-related risks between men and women in this study.

Possible biological explanations for the higher risks of oral cancer in women than in men include nutritional deficiencies. There was a higher proportion of nonsmoking female cases than nonsmoking male cases (24% versus 10%). In nonsmoking cases over age 50, there was a significantly greater percentage of women than men (Table 4). Ahlbom was among the first investigators to relate the occurrence of Plummer-Vinson syndrome in Sweden (42), a precancerous condition resulting from chronic iron deficiency and associated anemia during the menstrual years, to an increased risk of oral and other cancers in almost exclusively older women. Riboflavin deficiency is also characteristic of Plummer-Vinson disease. In a study of 810 mostly nonsmoking patients with a variety of alimentary tract cancers in Sweden, Wynder et al. (43) found a higher percentage of women with oral cancer in older age groups than men with oral cancer and a significant association with Plummer-Vinson symptoms in these women. The similar findings with respect to the higher prevalence of older women than men in the current data could reflect a subclinical condition, similar to Plummer-Vinson syndrome, associated with iron depletion and low intake of vitamins and minerals. Iron and riboflavin deficiency in mice leads to cell atrophy in upper alimentary tract epithelium, conditions similar to patients with Plummer-Vinson disease (44–46). Subsequent hyperplasia has been observed with riboflavin deficiency (42). Rats fed diets deficient in zinc also have similar morphological changes in the buccal mucosa (47).

Table 5 Types of cigarette smoked among ever-smoking cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Fema</th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR</td>
<td>Cases</td>
<td>Controls</td>
<td>OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Filter</td>
<td>37.1</td>
<td>44.0</td>
<td>1.0</td>
<td>49.8</td>
<td>60.2</td>
<td>1.0</td>
<td></td>
<td></td>
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<tr>
<td>SW 20+</td>
<td>28.7</td>
<td>22.8</td>
<td>1.5</td>
<td>27.9</td>
<td>20.3</td>
<td>1.7</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SW 1–19'</td>
<td>12.4</td>
<td>17.2</td>
<td>0.9</td>
<td>13.1</td>
<td>9.8</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfilter</td>
<td>21.8</td>
<td>16.1</td>
<td>1.6</td>
<td>9.3</td>
<td>9.8</td>
<td>1.1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

a SW, switched from smoking nonfilter to filter.
b Switched from smoking nonfilter to filter 20 years before diagnosis.
c Switched from smoking nonfilter to filter 10 years before diagnosis.

Populations that consume low amounts of fruits experience elevated rates of oral cancer. Decreased blood nutrients of vitamins A and B12 and β-carotene have been detected in patients with oral cancer (48). Similarly, vitamin A-deficient animals are more susceptible to tobacco smoke polycyclic aromatic hydrocarbons (49). Nutritional deficiencies associated with oral cancer may also arise indirectly through excessive alcohol consumption because a large percentage of daily calorie intake in alcoholics comes from alcohol (50). Intake of fruits and vegetables is likely to be low in persons with excessive alcohol consumption. Alcohol consumption can also directly inhibit the absorption of nutrients and vitamins (51).

The effects of a higher absolute risk of oral cancer in nonsmoking older women resulting from menstrual-associated nutritional deficiencies during the reproductive years would result in an underestimate of the smoking effects in women by increasing the numbers of nonsmoking female cases relative to nonsmoking male cases. However, although nutritional deficiencies may be a risk factor for oral cancer, the etiology of nonsmoking-related oral tumors remains largely unknown.
Only beer consumption in men and low body weight in women have also been identified as possible causes (52). It has been hypothesized that human papilloma virus may cause oral cancer in nonsmokers (53, 54). We did not find any differences in educational levels between postmenopausal nonsmoking cases and controls. There may be other unidentified risk factors that are gender-specific and thus could have confounded our results.

Another possible interpretation of this data is that there is a greater exposure to tobacco juice among female smokers than male smokers. Filter cigarettes reduce the contact with tobacco juice relative to nonfilter cigarettes and reduce the risk for oral cancer. In the previous report by Kabat et al. (11), the independent effects of filter use compared to nonfilter use on the risk of oral cancer were similar for men and women. Table 5 shows that few women have smoked nonfilter cigarettes exclusively, whereas more men have smoked nonfilter cigarettes exclusively. Thus, the current findings are unlikely to be due to a greater oral contact with tobacco juice among women.

Estrogens may be involved in the promotion of oral cancer. Using the Surveillance, Epidemiology, and End Results (SEER) Program data, Begg et al. (55) found that women also had a higher risk than men of developing second primaries of the head and neck, as well as lung, esophagus, urinary bladder, and kidney cancers.

We noted that the higher proportion of postmenopausal cases, compared to male cases over age 50, was reported as early as 1957 (16) and have suggested that possible risk factors more specific to women include iron, vitamin, and mineral deficiency. In addition, glutathione, an active antioxidant, is found to be depleted in the elderly (56) and associated with age-related morbidity (57). Low blood glutathione levels and low dietary glutathione intake may also play a role in oral cancer risk (58). Further investigations should consider the effects of age in nonsmokers by sub-site. Cancer of the tonsil in nonsmokers occurs almost exclusively in older individuals, and this may provide further clues to the origins of mouth cancer.

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