Laryngeal Cancer and Gastroesophageal Reflux Disease: A Case-Control Study

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ABSTRACT

PURPOSE: Gastroesophageal reflux disease (GERD) is common in patients with laryngeal cancer. However, the role of GERD in laryngeal cancer remains controversial because of poor matching and selection of inappropriate control groups in prior studies. We aimed to better understand this relationship by conducting a matched case-control study.

METHODS: This study was based in a single tertiary care center over a 2-year period. Cases included all patients with a diagnosis of new laryngeal cancer presenting to the otolaryngology clinics. Two controls, derived from the internal medicine clinics, were matched to the cases on an individual basis for age (within 1 year), gender, ethnicity, and time of first visit to the institution (within 1 month). Data were extracted by chart review. Conditional logistic regression was used to assess the relationship between laryngeal cancer and GERD, tobacco, and alcohol consumption.

RESULTS: A total of 96 cases were matched to 192 controls. On univariable analysis, the significant risk factors were current smoking, odds ratio (OR) 5.46 (95% confidence interval [CI], 2.59-11.50); alcohol, OR 1.97 (CI, 1.19-3.26); and GERD, OR 1.79 (CI, 1.03-3.11). On multivariable analysis, only smoking and GERD continued to be significantly associated with laryngeal cancer, OR 6.08 (CI, 2.82-13.10) and OR 2.11 (CI, 1.16-3.85), respectively.

CONCLUSIONS: Smoking and GERD are significant risk factors for laryngeal cancer and may have an independent incremental risk for laryngeal carcinogenesis. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Laryngeal cancer; GERD; Smoking

Laryngeal cancer is the most common head and neck cancer in the United States with an annual incidence of approximately 10,000 new cases.1-6 The 5-year mortality from this cancer is reported to be 40%.7 Identification and reduction of the risk factors might decrease the incidence of this cancer. However, although some causal factors are well established, the role of others is still controversial. Among the former group are smoking1-6 and, to a certain extent, alcohol use, whereas the latter group include genetic,8 environmental,9 certain occupations,10,11 viral infections,12 and dietary factors.13 Gastroesophageal reflux disease (GERD), because of its high prevalence in patients with laryngeal cancer, has attracted attention as a possible etiologic factor.14-20 In a meta-analysis of the effect of GERD on laryngeal cancer, we recently reported a pooled odds ratio (OR) of 2.37 (95% confidence interval [CI], 1.38-4.08) for GERD in patients with cancer.21 However, prior studies assessing the role of GERD in laryngeal cancer suffer from potential bias and confounding. For example, despite published data on age, gender, and ethnic predilection in patients with laryngeal cancer,3,22,23 no study has matched the subjects on these variables. Matching may be especially important in this disease because the same demographic variables (age, gender, and ethnicity) also may have an effect on GERD diagnosis.24 In addition, prior controlled studies have been criticized for the choice of controls not being representative of the general population, possibly decreasing the reliability and generalizability of the study results.
Thus, we aimed to perform a case-control study evaluating the risks of smoking, alcohol, and GERD in the development of laryngeal cancer and overcome these limitations by matching cases and controls for the 3 significant demographic variables (age, gender, and ethnicity) and selecting appropriate controls for each subject with laryngeal cancer.

METHODS

The study design was reviewed and approved by the institutional review board of The Cleveland Clinic Foundation, Cleveland, Ohio.

Study Population

This study was conducted in a single tertiary care center with a large referral base from northeast Ohio. The cases in this study included all the adult patients (age ≥21 years) who presented to our Head and Neck Institute and were first diagnosed with laryngeal cancer between January 1, 2002, and December 31, 2003. They were identified from the database of the department medical records by using International Classification of Diseases, 9th Revision (ICD-9) codes (161.0-161.9). The diagnosis of cancer required pathologic confirmation. Patients presenting with recurrent cancers were excluded.

Controls were selected from the large database of internal medicine clinics. Two controls were matched to a single case on an individual basis as follows: The first step was to identify a group of potential controls who were matched to the case by age, within 1 year. Gender, ethnicity, and time of first clinic visit (within 1 month) also were matched to cases. The time of the first visit to the institution in controls was determined on the basis of the unique institutional identifying number for each patient. The institutional identifying numbers of the controls were first placed in the ascending order, and then two controls with institutional identifying numbers closest to the case after matching for age, gender, and ethnicity were selected (Figure 1).

CLINICAL SIGNIFICANCE

- The role of GERD in laryngeal cancer is uncertain due to disparate studies.
- Age, gender, and ethnicity are the three important determinants for GERD, which were controlled in our study but not in previous studies.
- We found that the risk of laryngeal cancer was highest among patients who smoked and had GERD.

![Figure 1](Image) Flowchart depicting the process of patient selection.
Data Collection

Data collected from the computerized archives of patients included demographics (date of birth, gender, and ethnicity), date of cancer diagnosis, GERD-related symptoms, presence of other gastrointestinal disorders, use of acid-suppressive medications, and smoking and alcohol history. The presence of other factors, including exposure to radiation and family history of laryngeal cancers also was noted. The results of investigations performed for GERD, such as esophagoscopy, barium swallow, and pH monitoring were noted.

Definition of Variables

For evaluation of smoking, all of the subjects were assigned to one of three mutually exclusive groups: current smokers, ex-smokers, and lifetime nonsmokers. For current smokers, information was obtained regarding the intensity (packs per day) and duration (in years) of smoking. For ex-smokers, time since smoking cessation also was recorded. Alcohol use was divided into 2 groups: consumers (including both current and former consumers) and nonconsumers (lifetime nonconsumers). As with smoking, information about the intensity (drinks per day) and duration of consumption, and time since cessation (if former drinker) also were recorded.

Diagnosis of GERD was established by ICD-9 codes and presence of symptoms (heartburn or acid regurgitation), esophagitis ± Barrett’s epithelium, abnormal pH monitoring, hiatal hernia, reflux on barium swallow, or presence of long-term acid-suppressive medications (in the absence of

| Table 1 | Univariable Associations with Laryngeal Cancer |
| --- | --- | --- |
| Characteristics | Cases (n = 96) | Controls (n = 192) | Odds Ratio (95% CI) |
| Age (y) median (25th, 75th percentiles) | 61.0 (53.9-71.3) | 61.5 (54.0-70.8) | 0.94 (0.36-2.67) |
| Females | 21 (21.9%) | 42 (21.9%) | 1.00 (0.56-1.83) |
| Ethnicity |  |  |  |
| Whites | 86 (89.6%) | 172 (89.6%) | 1.00 (0.29-3.08) |
| Blacks | 7 (7.3%) | 14 (7.3%) | 0.99 (0.09-4.15) |
| Others | 3 (3.1%) | 6 (3.1%) | 4.66 (2.59-11.50) |
| Alcohol |  |  |  |
| Never | 60 (62.5%) | 85 (45.3%) | 1.97 (1.19-3.26) |
| Ex-smokers | 34 (35.4%) | 70 (36.7%) | 2.03 (1.12-3.14) |
| Current | 44 (45.8%) | 41 (21.5%) | 5.46 (2.59-11.50) |
| Years of smoking | 30.0 (15.0-40.0) | 0.0 (0.0-30.0) | 1.23 (1.12-1.34) |
| GERD (Any criteria) | 37 (38.5%) | 52 (27.1%) | 1.79 (1.03-3.11) |
| Symptomatic GERD† | 13 (13.5%) | 11 (5.7%) | 2.58 (1.11-6.10) |
| GERD diagnosis by ICD-9 codes | 12 (12.5%) | 39 (20.3%) | 0.52 (0.24-1.09) |
| Long-term acid-suppressive therapy‡ | 27 (28.1%) | 36 (18.8%) | 1.81 (0.97-3.36) |

GERD = gastroesophageal reflux disease; CI = confidence interval; n = number of patients with this variable; ICD-9 = International Classification of Diseases, 9th Revision.

*Number of patients in whom the data from the corresponding variable were available.
†Symptomatic GERD included heartburn or acid regurgitation.
‡In the absence of other known gastrointestinal disorders.

| Table 2 | Conditional Logistic Regression Model for the Association of Gastroesophageal Reflux Disease and Smoking with Laryngeal Cancer |
| --- | --- | --- | --- | --- |
| Factor | Level | Odds Ratios | 95% Lower Limit | 95% Upper Limit |
| GERD | No | 1.00 | — | — |
| Yes | 2.11 | 1.16 | 3.85 |
| Smoking | Never | 1.00 | — | — |
| Quitter | 2.02 | 0.98 | 4.18 |
| Current smoker | 6.08 | 2.82 | 13.10 |

GERD = gastroesophageal reflux disease.
other known gastrointestinal disorders). The presence of any one of these findings established the diagnosis of GERD.

Statistical Analysis

Bivariable analysis was performed on all variables (demographics, GERD symptoms, tobacco, and alcohol use). Frequencies of laryngeal cancer for each level were calculated, and ORs were estimated. Multivariable analysis using conditional logistic regression was next performed to estimate the odds of disease as a function of presence of GERD, tobacco, and alcohol consumption, and the interaction terms between them (GERD*smoking, GERD*alcohol, and smoking*alcohol). Conditional logistic regression was used because the data were matched. Final models were chosen with a backward elimination method. This method started with a model containing all of the factors mentioned above and eliminated the least significant terms among the included factors one at a time until all variables remaining in the model had a significance level lesser than .05. A type I error rate of 0.05 was used for all analyses. SAS 9.1 software (SAS Institute, Cary, NC) was used to carry out all analyses.

RESULTS

A total of 96 patients with newly diagnosed laryngeal cancer were identified over the 2-year study period. Some 192 matched controls from a total of 88,508 patients visiting the internal medicine outpatient clinics were randomly selected. Matching was successful for age, gender, and ethnicity (Table 1). The median age of cases was 61.0 years (25th and 75th percentiles: 53.9-71.3) compared with 61.5 years (25th and 75th percentiles: 54.0-70.8) in controls. Females constituted 21.9% of cases and controls, 89.6% of subjects were white, 7.3% were black, and 3.1% were of other ethnicity.

Laryngeal Cancer and Smoking

Smoking tobacco was significantly associated with laryngeal cancer; 45.8% of patients with laryngeal cancer were current smokers compared with 21.5% of controls ($P < .0001$) (Table 1). By using nonsmokers as the reference, the odds of developing cancer in current smokers were 5.46 (95% CI, 2.59-11.50) (Table 1). The multivariable model also suggested a significant ($P < .001$) association between smoking and laryngeal cancer (OR 6.08; 95% CI, 2.82-13.10) (Table 2).

The risk of developing laryngeal cancer in smokers seemed to be incremental and a function of the duration of smoking as it increased by 23% for every 5 years of smok-
ing (OR 1.23; CI, 1.12-1.34) (Figure 2). The cancer risk was also related to the intensity of smoking increasing by approximately 4 times for every additional pack of smoking (OR 3.86; 95% CI, 2.26-6.57) (Figure 3). Furthermore, both duration and intensity of smoking had an additive effect on laryngeal cancer development (Figure 4). Smoking cessation diminishes the likelihood of developing laryngeal cancer. The risk of developing cancer decreases by approximately 23% with every 5 years of smoking cessation (OR 0.77; 95% CI, 0.65-0.92) (Figure 5). The maximum risk reduction was noted in the first 15 years of smoking cessation, but the risk did not disappear completely (Figure 5).

### Laryngeal Cancer and Alcohol Consumption

History regarding alcohol consumption was not consistently detailed in patients’ medical records. Nonetheless, the effect of alcohol was more modest compared with smoking (Table 1). The univariable model suggested an increased risk for laryngeal cancer with an OR of 1.97 (95% CI, 1.19-3.26). The intensity (volume) of drinking also was an associated risk factor (OR 1.17; CI, 1.01-1.35) with approximately a 17% increased risk of laryngeal cancer with one additional drink of alcohol per day (Figure 6). However, the multivariable model did not identify alcohol use as a significant risk factor for laryngeal cancer (OR 1.22; 95% CI, 0.67-2.20).

### Laryngeal Cancer and Gastroesophageal Reflux Disease

GERD was significantly associated with laryngeal cancer in both the univariable and multivariable models: OR 1.79 (95% CI, 1.03-3.11) and OR 2.11 (95% CI, 1.16-3.85), respectively (Tables 1 and 2). Significantly more cases (38.5%) than controls (27.1%) had GERD. Furthermore, symptomatic GERD also was significantly higher in patients with cancer compared with controls, 13.5% versus 5.7%, respectively (OR 2.58; 95% CI, 1.11-6.10). However, the numeric superiority of long-term acid suppression did not reach statistical significance in cases compared with controls (OR 2.58; 95% CI, 1.14-5.82). For any given level of smoking, the presence of GERD increased the probability of developing laryngeal cancer (Figure 7). There was no interaction between smoking and GERD ($P = .4$), alcohol and GERD ($P = .2$), and smoking and alcohol ($P = .1$).

### DISCUSSION

In this study, we found that the risk of laryngeal cancer was highest in patients who smoked and had GERD. Tobacco use was the single most important risk factor in developing laryngeal cancer. Presence of GERD alone also increased the risk for laryngeal cancer significantly.
irrespective of smoking. Alcohol use, although significant in the univariable model, was not significantly associated with laryngeal cancer when adjusting for GERD and tobacco consumption. Thus, our data suggest that tobacco and GERD may have independent associations with laryngeal cancer development.

Several prior studies have suggested an association between smoking and laryngeal cancer, which is also confirmed in our matched case-control study. We also confirmed prior observations on the longitudinal effect of smoking on laryngeal cancer. Our data also suggest that the intensity of smoking may carry a far greater risk than duration of smoking. However, unlike other studies finding a decline in the cancer risk for the general population after 15 years of cessation, we found that the risk reduction might be much slower. Increased risk might last up to 40 to 45 years.

Lifelong nonsmokers were more prevalent in our study (19%) than in prior reports (5%-10%). The reason for this discrepancy is not entirely clear. Differences in patient population may be one reason. It also may be the result of declining smoking prevalence in the U.S. population. With the decreasing tobacco consumption, increasing laryngeal cancer prevalence in the US population may need to be explained by other causes. Our study suggests that GERD may be an important possible cause. Although smoking prevalence has decreased, the prevalence of GERD has increased over the past 3 decades.

The association of GERD with laryngeal cancer was first suggested in 1983 by Olson, who identified laryngeal cancers in a series of patients with GERD. Since then, several studies have reported a high prevalence of GERD in patients with laryngeal cancer. However, these studies were not well matched and were criticized for selection of inappropriate control population. African Americans are more likely to have laryngeal cancer than whites, females are more susceptible to this cancer than males, and patients aged more than 60 years are more likely to acquire this cancer. GERD symptoms, diagnosis, and treatment also have ethnic and gender predilection. Thus, demographic variability may have played an important confounding role in prior studies of GERD and laryngeal cancer. Our matched case-control study, however, continues to support an association between GERD and laryngeal cancer.

Selection of inappropriate control groups in the past has resulted in conflicting reports regarding association of GERD with laryngeal cancer. For example, in a study by Chen et al., who chose cases and controls from the ear, nose, and throat clinics, concluded no association between GERD and laryngeal cancer. However, El-Serag et al.
reported a significant association based on a Veterans Affairs patient population. Because laryngeal cancer develops in the general population, the appropriate control group would also need to be selected from this population. We chose controls from the internal medicine clinics because this group of patients most closely resemble the general population than those presenting to specialty clinics. As a verification of this contention, GERD prevalence of 27% in our control group closely resembles the GERD prevalence previously reported in the general population (20%-40%).

Important shortcomings of our study may include the presence of misclassification bias and inability to address the issue of reverse causality. The misclassification bias becomes evident because of non-uniformity of the GERD diagnosis. For example, GERD diagnosis in the patients with laryngeal cancer was more commonly established on the basis of the presence of GERD symptoms. Thus, GERD classification in this group could have been overestimated if symptoms were not attributable to GERD and if acid suppression was administered for non-GERD reasons. Such a misclassification would increase the likelihood of finding an association between GERD and laryngeal cancer. In addition, more of the control group were diagnosed with GERD by ICD-9 codes. Because ICD-9 codes are not indicative of the severity and current activity of the disease, it is possible that patients with occasional heartburn in the past could have been coded as having GERD. Such a misclassification would have decreased the likelihood of GERD association with cancer. The differing practices of diagnosing GERD between the otolaryngology and internal medicine physicians may also be a cause for potential misclassification in our study. These misclassification biases assume added importance because the 95% CI for GERD barely crossed significance. However, the increased significance of GERD on inclusion of smoking in the logistic regression model suggests that there might be an interaction between the two risk factors, which was not detected because of the study sample size.

Another deficiency of our study was a failure to assess the effect of reverse causality. Given the limited data on the duration of GERD in cases and controls, evaluation of this phenomenon was not possible. Thus, it is possible that laryngeal cancer may increase the prevalence of GERD, and our current observation of increased GERD prevalence in laryngeal cancer may be a case of reverse causality. There are currently no data suggesting that laryngeal cancer can induce GERD; however, this possibility will need to be addressed in future clinical studies. Other potential biases, which could not have been controlled for may include Berkson’s bias, referral bias, and length bias. Berkson’s bias

Figure 5  Smoking cessation and the likelihood of developing laryngeal cancer. LL = lower limit of 95% confidence interval; OR = odds ratio; UL = upper limit of 95% confidence interval.
would have not been substantial in this study because both the cases and controls were evaluated and diagnosed as outpatients. Referral bias was unavoidable given the fact that the study was conducted in a tertiary referral center. However, both cases and controls were from the same institution. Length bias may have existed if the patients with more severe laryngeal cancer died before being evaluated.

CONCLUSION
In this matched case-control study, smoking and GERD were independent risk factors for laryngeal cancer development. To reduce the risk of laryngeal cancer, physicians should educate patients on complete cessation of smoking and treat GERD in symptomatic patients. Future studies are needed to assess the role of reverse causality and prospective assessment of GERD in controls and in patients with laryngeal cancer.

References
Figure 7  Estimated probability of laryngeal cancer based on tobacco consumption and GERD status. GERD = gastroesophageal reflux disease.
