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Research Paper

Association of gastroesophageal reflux disease and laryngeal cancer☆

Mursalin M. Anis [a,*], Mir-Muhammad Razavi [b], Xiao Xiao [c], Ahmed M.S. Soliman [d]

[a] *Coastal Ear, Nose and Throat, Jersey Shore University Medical Center, Neptune, NJ, USA*
[b] *Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA*
[c] *Department of Statistics, Fox School of Business, Temple University, Philadelphia, PA, USA*
[d] *Department of Otolaryngology – Head and Neck Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA*

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Abstract *Objective:* Studies examining the association of reflux disease with the risk of developing laryngeal cancer have both proven and disproven the null hypothesis.
Methods: This retrospective case–control study examines the association of reflux in two populations exposed to similar risk factors, including tobacco, to the extent that end-organ malignant transformation has occurred. After IRB approval was obtained, a search of our hospital's cancer center's database was performed from 2000 to 2013. A retrospective chart review was then performed and the prevalence of gastroesophageal reflux disease among patients with laryngeal cancer ($n = 290$) was determined. It was then compared to the prevalence of gastroesophageal reflux disease among patients presenting with lung cancer ($n = 2440$) during the same time period. A multivariate logistic regression was performed to determine the association of reflux with laryngeal cancer.
Results: Taking into consideration tobacco use, there was a strong association between male gender and occurrence of laryngeal cancer as opposed to lung cancer ($OR = 3.30$; 95% CI 2.53–4.36, $P < 0.001$). There was a modest association between reflux and laryngeal cancer ($OR = 1.65$; 95% CI 1.19–2.25, $P = 0.003$). However, there was no association between reflux

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* Corresponding author. Department of Otolaryngology – Head & Neck Surgery, Lewis Katz School of Medicine at Temple University, 3440 North Broad Street Kresge West, Suite 309, Philadelphia, PA, 19140, USA. Fax: +1 215 707 7523.
E-mail address: mursalinanis@gmail.com (M.M. Anis).

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and the propensity for carcinoma in specific laryngeal subsites ($P = 0.47$).
Conclusions: In this study examining a heterogeneous population with end-organ malignancy there was a modest association between reflux and laryngeal cancer. Further research is necessary to determine the biologic relevance of this finding.

Introduction

In 2017, there are estimated 13,360 new cases of laryngeal cancer in the United States with an estimated 3660 individuals who would die from the disease.[1] Nearly 100,000 people with laryngeal cancer currently reside in the United States.[1] The two primary risk factors for the development of laryngeal cancer are smoking and alcohol use.[1] Gastric reflux as a risk factor has been suggested, but conflicting results found in different studies all of which have shortcomings.[2,3] The effect of extraesophageal reflux disease on the larynx has been well characterized.[4] The laryngeal mucosa is susceptible to injury from gastric refluxate containing acid and activated pepsin. However the association between chronic laryngeal injury secondary to laryngopharyngeal reflux and development of laryngeal cancer has not been well defined.[2] Laryngopharyngeal reflux (LPR) and gastroesophageal reflux disease (GERD) are two distinct clinical entities with a shared mechanism of gastric refluxate—induced mucosal injury.[4,5] GERD affects approximately 20% of North Americans and given this high prevalence, it is pertinent to elucidate the possible association between reflux disease and laryngeal cancer.[6] Both smoking and alcohol increase reflux through their effect upon the lower esophageal sphincter.[2]

A significant challenge to overcome in any case—control study examining reflux disease and laryngeal cancer is the confounding variables of coexisting tobacco and alcohol use. Ideally, a control population of patients without laryngeal cancer should have the same prevalence of tobacco and alcohol use as patients with laryngeal cancer. Due to the infrequent reporting of tobacco and alcohol use, previous case—control studies have struggled with matching of cases and controls.[7]

The current retrospective study addresses this challenge by including controls who share the same risk factors as laryngeal cancer patients but have different end-organ malignant transformation. For this study, lung cancer patients served as controls. As there are no diagnostic codes for LPR, we examined the prevalence of GERD among the matched laryngeal cancer and lung cancer patients.

Patients and methods

Patients

After Institutional Review Board approval was obtained, a retrospective chart review was performed. The Temple University Health System electronic medical record was searched to identify all patients who met the selection criteria during the study period, January 2000 to December 2013. Inclusion criteria were patients with diagnoses of laryngeal cancer (Cases) and lung cancer (Controls). The following International Classification of Diseases 9th Edition (ICD-9) diagnostic codes were queried against the electronic medical record: 161 to 161.9 for laryngeal cancer and 162 to 162.9 for lung cancer. Exclusion criteria were patients who had additional head and neck malignancies and those with both laryngeal cancer and lung cancer.

From this patient data set the following demographic parameters were extracted: age, gender, and ethnicity. The following ICD-9 codes were used to identify patients with tobacco and alcohol dependence: 305.1, V15.82, 305.0, and V11.3. Similar to prior retrospective studies, the prevalence of reflux disease was determined by identifying cases and controls with the ICD-9 code 530.81 that defines GERD, as extraesophageal reflux and laryngopharyngeal reflux do not have separate ICD-9 codes.[7,8]

Statistical analysis

To investigate the potential relationship of exposures (smoking, reflux) with laryngeal cancer, a logistic regression model was used. The outcome in the statistical analysis was the presence or absence of laryngeal cancer. Patients who had lung cancer served as controls (absence of laryngeal cancer). The data was analyzed using multivariate logistic regression with demographics, tobacco dependence and GERD as determinants of outcomes. Comparisons between cases and controls with respect to patient characteristics were done with the Chi-squared test using deviance.

To analyze the association of reflux disease with a particular laryngeal cancer subsite, a multivariate logistic regression was done using the Wald test. Transglottic, subglottic, and cancers with unknown laryngeal subsites were grouped together into the category, "Other". The 3 groups of laryngeal cancer for analytical purposes were: Glottic, Supraglottic, and Other. Glottic cancer was treated as the reference group against which the other groups were compared. Statistical significance was defined as $P < 0.05$. The statistical software R, version 2.15.3 (http://www.r-project.org/) and SAS (SAS Institute Inc., Cary, NC) were used to perform statistical analysis.

Results

Search of the electronic medical record at Temple University Health System identified 290 laryngeal cancer patients treated between 2000 and 2013. During this same time

period 2440 lung cancer patients were identified who received treatment at Temple University Health System hospitals. Patient characteristics of cases and controls are compared in Table 1. The mean age of laryngeal cancer patients and lung cancer patients was similar, 68.9 and 69.5 years of age. Compared to lung cancer patients, the majority of laryngeal cancer patients were male patients, 72% vs. 45%. Reflux disease was more prevalent among laryngeal cancer patients than lung cancer patients, 20% vs. 14% ($P = 0.01$). The ethnic composition of the two populations was heterogeneous and significantly different as shown in Table 1. The distribution of tobacco smoking was equal between laryngeal cancer and lung cancer patients ($P = 0.77$). Alcohol dependence was less frequently coded in ICD-9 and as such was not included for data analysis.

A multivariate logistic regression was performed to determine the adjusted odds ratio (*OR*) of the association of demographics and exposures to laryngeal cancer, Table 2. Male gender was significantly associated with development of laryngeal cancer over lung cancer with an *OR* of 3.30 ($P < 0.001$). Lastly, reflux was found to be associated with laryngeal cancer over lung cancer with an odds ratio of 1.65 ($P = 0.003$).

Among the 290 laryngeal cancer patients, there were 124 glottic, 83 supraglottic, 6 transglottic, 1 subglottic, and 76 cancer patients without designation of laryngeal subsite. Since we were primarily interested in the association of reflux with supraglottic and glottic cancers, we grouped the rest, including cancers of undesignated laryngeal subsites, into the category "Other". We performed a multivariate logistic regression. There was no significant association between reflux and the odds of developing supraglottic cancer over glottic cancer (glottic cancer was arbitrarily set as reference) $OR = 1.31$, $P = 0.47$. However, both age and male gender were associated with increased odds of developing glottic cancer over supraglottic cancer, $OR = 1.47$, $P < 0.0001$ for age; and $OR = 2.56$, $P = 0.004$ for male gender, respectively.

Discussion

The association of reflux disease and laryngeal cancer has long been surmised and sought but not well delineated. The challenge has been the coexistence of alcohol and tobacco use. Both of these habits are well known risk factors for laryngeal malignancy. In addition, both have been reported to increase reflux disease, and as such confound any analysis of an association between reflux and laryngeal cancer.[2,3] Comparing newly diagnosed laryngeal cancer patients with controls matched with respect to age, gender, and ethnicity, Vaezi et al[8] had demonstrated that GERD, as defined by ICD-9 designation and symptoms, was associated with laryngeal cancer. Unfortunately, the 96 cases were not matched with the 192 control patients with regards to smoking. Despite this, multivariate analysis between GERD and smoking revealed that for any given amount of tobacco use, patients with GERD had increased likelihood for developing laryngeal cancer.[8] Bacciu et al[9] demonstrated that even among lifetime non-smokers and non-drinkers, there was a significant association between GERD and laryngeal cancer, although the number of laryngeal cancer patients was small at 36. A retrospective study of the U.S. Department of Veterans Affairs patient database found an association between GERD and laryngeal and pharyngeal cancers in a predominantly Caucasian male population.[10] Their control groups were cancer-free and noted to have less documentation of tobacco and alcohol use.[10] Finally, in a pilot prospective study Lewin et al[11] have shown an 85% incidence of laryngopharyngeal reflux, as measured by dual-probe pH monitoring in patients with premalignant laryngeal lesions but there were no matched controls who were tested.

In this study, the most significant risk factor for developing laryngeal cancer, tobacco smoking, was accounted for by using a control population of lung cancer patients. Both patient populations had a diverse ethnic composition that share similar risk factors yet develop different end-organ malignancies. Incidence of tobacco smoking was found to be the same between lung cancer patients and laryngeal cancer patients. This represents a better matching of cases and controls with regards to smoking than previous studies.[7,8,10] An association between reflux and laryngeal cancer cannot be made without accounting for the confounding variable of tobacco smoking.[3]

In our study, 20% of laryngeal cancer patients and 14% of lung cancer patients had an ICD-9 designation of GERD. This correlates well with the 18%–28% reported prevalence of GERD in North America.[6] There was a modest association between GERD and laryngeal cancer ($OR = 1.65$) which was

Table 1 Patient Characteristics of Cases (Laryngeal cancer) and Controls (Lung cancer).

Characteristics	Cases	Controls	*P* value
Age (mean ± SE)	68.9 ± 11.0	69.5 ± 10.8	0.39
Male (%)	72.1	44.7	<0.001
Ethnicity (%)			0.003
Caucasian	55.5	60.2	
African American	25.9	22.49	
Hispanic	7.6	3.3	
Asian	1.7	2.2	
Unknown	9.3	11.8	
Reflux (%)	20.3	14.5	0.011
Smoking (%)	11.0	10.3	0.77

Table 2 Multivariate logistic regression analysis.

Characteristics	Odds Ratio	95% *CI*	*P* value[a]
Age Decile	0.94	0.85–1.03	0.19
Male	3.30	2.53–4.36	<0.001
Ethnicity[b]			0.016
H vs B	1.70	0.97–2.90	
O vs B	0.59	0.20–2.41	
U vs B	0.67	0.41–1.07	
W vs B	0.76	0.57–1.03	
Reflux (%)	1.65	1.19–2.25	0.0029
Smoking (%)	0.91	0.60–1.35	0.65

[a] *P* value was obtained with Chi-sq test using deviance.
[b] Ethnicities: H:Hispanic, B:African American, W:Caucasian, O:Asian, U:Unknown.

statistically significant (Table 2). This finding adds to the existing body of literature on the subject. It must be noted that the association between GERD and laryngeal cancer represents a first approximation for several reasons. In this retrospective study, the exact criteria used to assign a patient with GERD in ICD-9 coding was not recorded for the vast majority of patients. In addition, although in the presence of endoscopically proven GERD, the severity of symptoms correlate closely with LPR, patients with GERD may not have coexisting chronic laryngeal injury and inflammation.[4,5,12] Patients with chronic laryngeal inflammation and injury from LPR may not be captured with the ICD-9 designation for GERD if they do not have signs and symptoms of GERD. The lack of ICD-9 designation for LPR prevented a more biologically relevant association study based on diagnostic coding. Not withstanding these shortcomings, there was a statistically significant association in the present study between GERD and laryngeal cancer. Proving or disproving causality from retrospective studies based on ICD-9 diagnostic coding is not possible.

This manuscript focuses on gastroesophageal reflux because the ICD-9 classification does not have a code for laryngopharyngeal reflux (LPR), a distinct disease process compared with GERD. Analyzing the available charted data on the cohort of laryngeal cancer patients, we found that the vast majority of these patients were assigned ICD-9 designation of 530.81 without any objective findings from tests. Future research should focus on prospective cohort studies that enroll patients who meet well-defined objective criteria for LPR and control for confounding variables such as tobacco smoking and alcohol consumption.[3] In addition to determining the incidence of laryngeal cancer in cases versus controls, future research should also determine the incidence of premalignant laryngeal lesions in a controlled fashion.[11] If reflux contributes to the development of laryngeal cancer, then the influence of reflux on the progression towards malignancy should be investigated further.

Conclusions

A modest association was found between GERD and laryngeal cancer over lung cancer with an odds ratio of 1.65. No association was noted between GERD and carcinoma in specific laryngeal subsites. This study's matching was a significant improvement over other studies and attempted to eliminate tobacco use as a confounding factor between cases and controls. Several limitations exist including the retrospective nature of the study and incomplete documentation in the database. Additional research is still required to further delineate the association of laryngopharyngeal reflux disease and laryngeal cancer.

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Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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