Laryngopharyngeal Reflux Symptoms Better Predict the Presence of Esophageal Adenocarcinoma Than Typical Gastroesophageal Reflux Symptoms

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Objective: To determine whether the presence of laryngopharyngeal reflux symptoms is associated with the presence of esophageal adenocarcinoma (EAC).

Background: Most patients diagnosed with EAC have incurable disease at the time of detection. The majority of these patients are unaware of the presence of Barrett's esophagus prior to cancer diagnosis and many do not report typical symptoms of gastroesophageal reflux disease (GERD). This suggests that the current GERD symptom-based screening paradigm may be inadequate. Data support a causal relation between complicated GERD and laryngopharyngeal reflux symptoms. We theorize that laryngopharyngeal reflux symptoms are not recognized expeditiously, resulting in chronic esophageal injury and an unrecognized progression of Barrett's esophagus to EAC.

Methods: This is a case-comparison (control) study. Cases were patients diagnosed with EAC (n = 63) between 1997 and 2002. Three comparison groups were selected: 1) Barrett's esophagus patients without dysplasia (n = 50), 2) GERD patients without Barrett's esophagus (n = 50), and 3) patients with no history of GERD symptoms or antisecretory medication use (n = 56). The risk factors evaluated included demographics, medical history, lifestyle variables, and laryngopharyngeal reflux symptoms. Typical GERD symptoms and antisecretory medication use were recorded. Multivariate analysis of demographics, comorbid risk factors, and symptoms was performed with logistic regression to provide odds ratios for the probability of EAC diagnosis.

Results: The prevalence of patients with laryngopharyngeal reflux symptoms was significantly greater in the cases than comparison groups ($P = 0.0005$). The prevalence of laryngopharyngeal reflux symptoms increased as disease severity progressed from the non-GERD comparison group (19.6%) to GERD (26%), Barrett's esophagus (40%), and EAC patients (54%). Symptoms of GERD were less prevalent in cases (43%) when compared with Barrett's esophagus (66%) and GERD (86%) control groups ($P < 0.001$). Twenty-seven percent (17 of 63) of EAC patients never had GERD or laryngopharyngeal reflux symptoms. Fifty-seven percent of EAC patients presented without ever having typical GERD symptoms. Chronic cough, diabetes, and age emerged as independent risk factors for the development of EAC.

Conclusions: Symptoms of laryngopharyngeal reflux are more prevalent in patients with EAC than typical GERD symptoms and may represent the only sign of disease. Chronic cough is an independent risk factor associated with the presence of EAC. Addition of laryngopharyngeal reflux symptoms to the current Barrett's screening guidelines is warranted.

(*Ann Surg* 2004;239: 849–858)

The incidence of esophageal adenocarcinoma (EAC) arising from Barrett's esophagus has increased by 350% since 1970.[1] The prognosis for EAC is poor and the overall 5-year survival rate is less than 10%.[1] At the time of presentation, at least half of all patients have advanced disease with no chance for cure.[2]

Endoscopic screening for Barrett's esophagus and EAC has been recommended for patients with classic and chronic symptoms of gastroesophageal reflux disease (GERD). Several retrospective studies have demonstrated an earlier stage of diagnosis and a marked improvement in survival of patients with cancers detected by routine endoscopic surveillance of Barrett's esophagus.[3–8] Despite these efforts, the majority of patients who develop EAC are unaware of the presence of Barrett's esophagus prior to cancer diagnosis.[3] In addition, a large proportion of these patients have never experienced symptoms of GERD.[4] This finding reflects the inadequacy of using typical reflux symptoms as the "trigger" for screening endoscopy and highlights the need for improved

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This work was supported in part by National Institutes of Health grants K23 DK066165-01 and RO3 CA105959-01.

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ISSN: 0003-4932/04/23906-0849
DOI: 10.1097/01.sla.0000128303.05898.ee

screening criteria for Barrett's esophagus and EAC.[9] Some investigators have suggested that patients who develop Barrett's esophagus may not have typical GERD symptoms and therefore are not selected for endoscopic screening.[10] As a result, occult disease progression occurs and advanced cancer is present at the time of diagnosis.

Substantial published data support a causal relation between documented GERD and laryngopharyngeal reflux (LPR) symptoms.[11–21] However, the prevalence of GERD-related esophageal injury in patients with laryngopharyngeal symptoms is unknown. The aim of this investigation was to determine whether the presence of laryngopharyngeal symptoms is associated with an increased risk for the presence of EAC. This may provide insight required to improve risk stratification for EAC and potentially modify the inclusion criteria for routine Barrett's esophagus screening.

METHODS

Following institutional review board approval, this case-comparison study examined the prevalence of LPR symptoms in veterans seen at the Portland VA Medical Center. Cases (n = 63) were identified by ICD code and included all patients who had been diagnosed with EAC between 1997 and 2002. The diagnosis of EAC was confirmed by reviewing the pathology report for each case. There were 3 groups selected for comparison: 1) Barrett's esophagus patients without dysplasia (n = 50), 2) GERD patients without Barrett's esophagus (n = 50), and 3) non-GERD "normals" as defined by the absence of heartburn, regurgitation, and antisecretory medication use (n = 56).

The GERD and Barrett's esophagus comparison groups were identified and selected from the Portland VA Medical Center endoscopic registry (Clinical Outcomes Research Initiative). The results of all endoscopic procedures performed at the Portland VA are entered into the registry. The GERD and Barrett's esophagus patients were identified by their indication for endoscopic examination, which included either chronic GERD symptoms or Barrett's esophagus surveillance. Incident cases of Barrett's esophagus were included in the Barrett's esophagus comparison group. Comparison patients were selected over the study time interval but were not chosen consecutively. Pathology reports were reviewed to confirm the presence of intestinalized epithelium without dysplasia in the Barrett's esophagus patients, and esophagitis without Barrett's esophagus in the GERD patients. If a biopsy was not performed in a GERD comparison group patient, endoscopic evidence of esophagitis was required for inclusion. Patients with nonerosive reflux disease were excluded from the GERD comparison group. Per institutional protocol, endoscopic biopsies were obtained if the squamocolumnar junction was located proximal to the anatomic gastroesophageal junction. Four quadrant "jumbo" biopsies were obtained at each 2-cm interval of suspected Barrett's esophagus. If the squamocolumnar junction was sharp, circular, and located at the level of the gastroesophageal junction, a biopsy was not obtained and the patient was considered free of Barrett's esophagus. Barrett's esophagus was defined as the presence of intestinal metaplasia within the tubular esophagus as determined by histologic examination by an experienced gastrointestinal pathologist.

The non-GERD "normal" comparison group was selected from the Dental Clinic roster over the study time period. Similarly, these patients were not selected consecutively. The entire patient chart was reviewed, and the absence of heartburn, regurgitation, and antisecretory medication use was required for inclusion. Thirty-six percent (20 of 56) of this group had undergone a prior upper endoscopy for non-GERD–related problems (eg, iron deficiency anemia) and the absence of esophagitis, Barrett's esophagus, stricture, or hiatal hernia was confirmed.

Once the cases and comparison groups were identified, patient electronic charts were reviewed beginning from the first recorded encounter. All data were recorded onto a specific form created for data ascertainment. The risk factors evaluated included demographics (age, race, gender), past medical history, LPR and GERD symptoms, lifestyle variables, and medication use. The presence of comorbid diseases, including congestive heart failure, diabetes, hypertension, and coronary artery disease, was recorded. The diseases were considered present if listed within the medical record. Smoking was defined as the routine use of tobacco for greater than 10 years and the number of pack-years was calculated. LPR symptoms were defined as chronic cough, asthma, aspiration, hoarseness, globus, sore throat, and sinusitis (Table 1). Classic GERD symptoms were considered present if the patient had either heartburn or regurgitation. A symptom was considered present if documented at any time in the patient chart. In cases, symptoms were evaluated up to the date of cancer diagnosis. Antisecretory medication use was defined as antacid, histamine$_2$ blocker, and proton pump inhibitor therapy documented at any time point in the chart. Each of these risk factors was obtained from provider notes by a single abstractor.

Statistical Analysis

Univariate comparisons of demographic and comorbid risk factors between groups was performed. Continuous variables (age and pack-years of smoking) were evaluated with analysis of variance. Nominal variables (history of smoking, gender, ethnic identity, and comorbid risk factors) were evaluated with χ^2 tests. Univariate analysis with χ^2 tests was also performed to determine which LPR symptoms were significantly associated with a group. A Bonferroni correction for multiple comparisons was used in the pairwise comparisons between the EAC group and each comparison group. χ^2 test was used to compare cough and dysphagia by T stage in

TABLE 1. Laryngopharyngeal Reflux Symptom Definitions

Symptom	Symptom Definition
Chronic cough	Presence of cough > 2 weeks; patients on ACE inhibitor therapy were excluded
Asthma	Symptom of wheezing treated with bronchodilators, steroids, or other asthma medications
Globus	Sensation of food feeling stuck/caught or post swallow "lump in throat" for >2 weeks' duration
Sore throat	Report of chronic or progressive pain in throat >2 weeks' duration
Aspiration	Treatment for aspiration pneumonia; unexplained aspiration events involving food/drink resulting in recurrent coughing spells
Sinusitis	Sinusitis diagnosed and treated empirically or radiographic evidence of sinusitis in a patient undergoing formal evaluation
Hoarseness	Progressive loss or change in voice >2 weeks' duration not attributable to obvious causes such as voice abuse

ACE, angiotensin converting enzyme.

EAC patients. Multivariate analysis of demographic variables, comorbid risk factors, and LPR symptoms was performed with logistic regression to provide odds ratios and 95% confidence intervals for the probability of EAC diagnosis. An alpha value of 0.05 was used to designate statistical significance.

RESULTS

Patient groups were similar with regards to race, gender, and tobacco use. However, EAC patients were, on average, 10 years older than subjects in the comparison groups. Although there was a trend toward a higher prevalence of comorbid disease in EAC patients, there was no statistical difference between groups (Table 2).

The prevalence of patients with one or more LPR symptom was significantly greater in the cases than in comparison groups ($P = 0.0005$; Table 3). The prevalence of LPR symptoms increased as disease severity progressed from the non-GERD comparison group (19.6%) to GERD (26%), Barrett's esophagus (40%), and to EAC patients (54%). Considering the comparison groups only, LPR symptoms were more prevalent in Barrett's esophagus patients when compared with GERD and non-GERD patients ($P = 0.003$; Table 3). In EAC patients, chronic cough (38.1%) was the most common laryngopharyngeal symptom followed by asthma (15.9%), sore throat (15.9%), and aspiration (9.5%). Sinusitis was more common in Barrett's esophagus patients (12%) than in cancer patients (6.4%; Table 3). Isolated LPR symptoms (ie, without GERD symptoms) were significantly more prevalent in cases than in Barrett's esophagus and GERD patients (Fig. 1).

Typical symptoms of GERD were less prevalent in EAC patients (43%) than in Barrett's esophagus (66%) and GERD (86%) groups ($P < 0.001$). Isolated typical GERD symptoms (ie, without laryngopharyngeal symptoms) were also less prevalent in EAC patients than in the comparison groups ($P < 0.0001$; Fig. 2). No patients in the non-GERD comparison group had isolated typical GERD symptoms, by exclusion.

Twenty-seven percent (17 of 63) of EAC patients never had GERD or LPR symptoms at any point in their medical history (Fig. 3). Of EAC and Barrett's esophagus patients, 57% (36 of 63) and 34% (17 of 50), respectively presented without ever having had a typical GERD symptom recorded

TABLE 2. Demographics, Smoking History, and Comorbidities by Group: Mean ± SD (Number of Subjects)

	EAC (n = 63)	BE (n = 50)	GERD (n = 50)	Normal (n = 56)	*P*
Age (yr)	69.6 ± 9.3	63.7 ± 11.2	64.7 ± 13.4	58.9 ± 13.7	<0.0001
Tobacco abuse	65.1% (41)	50.0% (25)	56.0% (28)	60.7% (34)	0.4150
Pack-years	21.0 ± 25.0	15.2 ± 21.0	21.2 ± 26.6	24.1 ± 25.4	0.3177
Gender (male)	98.4% (62)	98.0% (49)	98.0% (49)	92.9% (52)	0.2829
Race (white)	100.0% (63)	98.0% (49)	96.0% (48)	94.6% (53)	0.3061
Comorbidities					
Diabetes	36.5% (23)	20.0% (10)	20.0% (10)	19.6% (11)	0.0825
CAD	28.6% (18)	24.0% (12)	20.0% (10)	19.6% (11)	0.6330
HTN	60.3% (38)	44.0% (22)	50.0% (25)	39.3% (22)	0.1185
CHF	17.5% (11)	8.0% (4)	6.0% (3)	10.7% (6)	0.2176

CAD, coronary artery disease; HTN, hypertension; CHF, congestive heart failure; BE, Barrett's esophagus.

TABLE 3. LPR Symptoms Among Groups

	% With Symptom (*P* value from comparison to EAC group*)				
	EAC (n = 63)	BE (n = 50)	GERD (n = 50)	Normal (n = 56)	Overall *P* Value†
Chronic cough	38.1	16.0 (0.0096)	12.0 (0.0018)	12.5 (0.0015)	0.0007
Asthma	15.9	10.0 (0.3608)	14.0 (0.7821)	8.9 (0.2546)	0.6344
Aspiration	9.5	4.0 (0.2555)	0.0 (0.0249)	1.8 (0.0733)	0.0551
Hoarseness	4.8	4.0 (0.8449)	2.0 (0.4300)	0.0 (0.0981)	0.4002
Globus	6.4	2.0 (0.2642)	2.0 (0.2642)	0.0 (0.0551)	0.1821
Sore throat	15.9	14.0 (0.7821)	8.0 (0.2071)	1.8 (0.0081)	0.0528
Sinusitis	6.4	12.0 (0.2935)	8.0 (0.7340)	1.8 (0.2155)	0.2161
≥1 LPR symptom	54.0	40.0 (0.1398)	26.0 (0.0027)	19.6 (0.0001)	0.0005

*Bonferroni correction for multiple comparisons of 24 tests (8 × 3) with an overall alpha level of 0.05 lowers the alpha level of individual tests to 0.0021.

†Univariate analysis using χ^2 test with an alpha of 0.05.

in their chart (ie, absence of LPR and GERD symptoms or presence of only LPR symptoms) (Figs. 1 and 3).

Multivariate analysis of demographics, comorbid risk factors, and symptoms was performed to explore potential contributions to esophageal carcinogenesis. Smoking history and pack-years were similar among groups and did not contribute to the logistic regression model. Chronic cough, diabetes, and age emerged as independent risk factors for the presence of EAC (Fig. 4). While the prevalence of dysphagia increased with increasing T-stage in patients with EAC, there was no correlation between the presence of cough and T stage ($P = 0.62$; Table 4).

Seventy-three percent (46 of 63) of esophageal cancer patients were unaware of the presence of Barrett's esophagus prior to the diagnosis of EAC. Following diagnosis, EAC patient survival for all stages and treatment regimens declined precipitously with a 90% 30-day survival, 64% 6-month survival, 43% 1-year survival, and 14% 3.5-year survival.

DISCUSSION

Several investigations have demonstrated that the current GERD symptom-based screening paradigm is ineffective in detecting the majority of EAC patients prior to esophageal obstruction and the development of dysphagia.[3] The implication is that the use of typical GERD symptoms (heartburn and regurgitation) as the "trigger" for Barrett's esophagus and cancer screening lacks the sensitivity and specificity required to impact the natural history of this disease.[4] We wished to determine whether LPR symptoms were valuable predictors for the presence of esophageal cancer. Our secondary aim was to evaluate whether typical GERD symptoms represent a useful indicator for the development or presence of Barrett's esophagus and EAC.

Our results demonstrate an increasing frequency of LPR symptoms from unaffected controls to GERD, Barrett's esophagus, and EAC patients. This suggests that as one progresses along the metaplasia, dysplasia, carcinoma se-

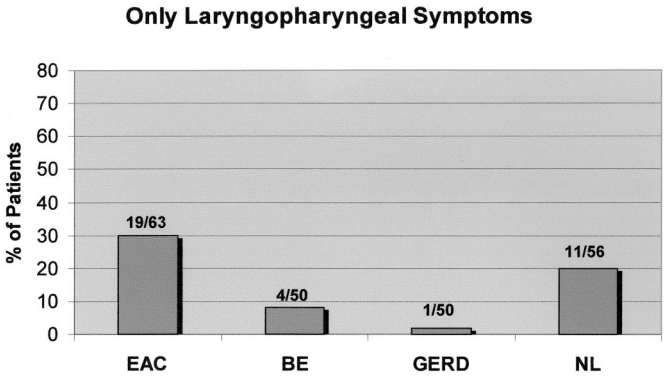

FIGURE 1. The prevalence of isolated laryngopharyngeal reflux symptoms (no GERD symptoms) by group.

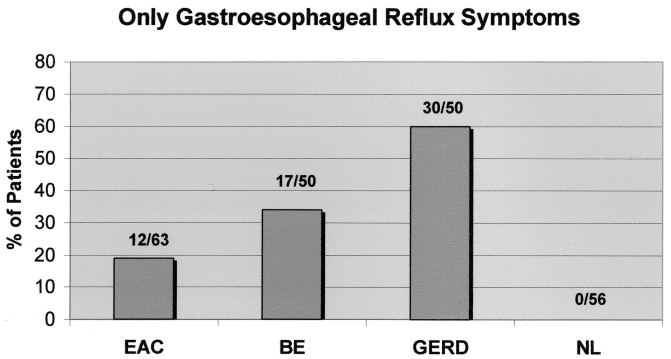

FIGURE 2. The prevalence of isolated gastroesophageal reflux symptoms (no laryngopharyngeal reflux symptoms) by group.

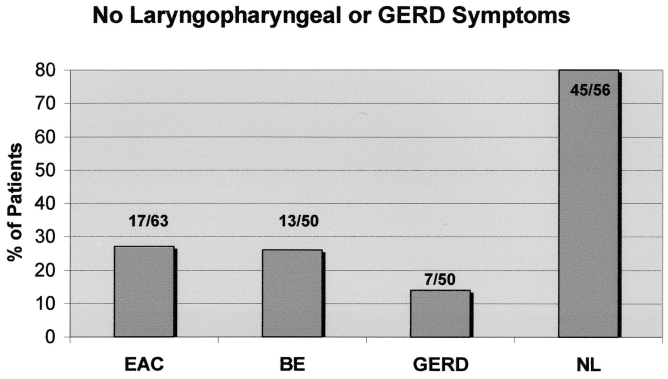

FIGURE 3. The prevalence of patients without laryngopharyngeal reflux or GERD symptoms by group.

quence, proximal reflux episodes become more prevalent. Patients with objective evidence of proximal esophageal acid exposure have been established to have longer duration reflux episodes with a resultant increase in esophageal mucosal injury when compared with patients without proximal reflux.[21,22]

Thirty percent of EAC patients in this study had LPR symptoms without GERD symptoms, whereas only 19% of patients had GERD symptoms without LPR symptoms. It is possible that patients with only LPR symptoms are not identified for endoscopic screening and occult disease progression occurs until alarm symptoms are manifested. The prevalence of isolated laryngopharyngeal symptoms in EAC patients was several times higher than that observed for Barrett's esophagus and GERD comparison groups. This suggests that LPR symptoms may represent a useful marker of cancer presence with or without typical GERD symptoms.

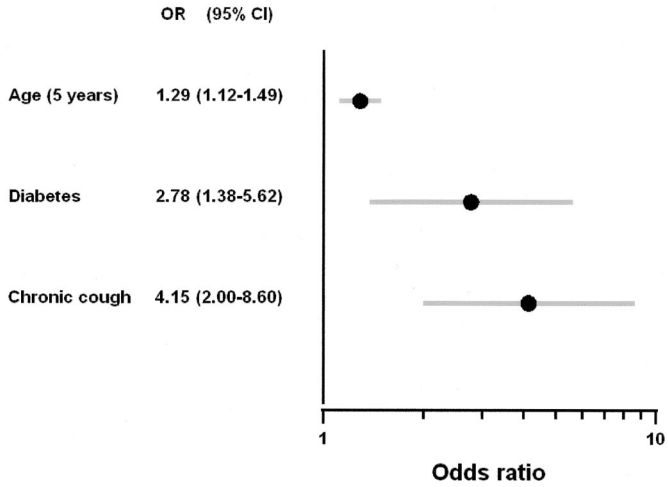

FIGURE 4. Plot of odds ratios from multivariate logistic regression model estimating probability of EAC diagnosis ($\log_{10}$ scale).

TABLE 4. Dysphagia Versus Cough by T Stage in EAC Group

Symptom	T1	T2	T3	T4	*P**
Dysphagia (%)	6/9 (67)	2/8 (25)	22/24 (92)	21/22 (95)	<0.001
Chronic cough (%)	5/9 (56)	2/8 (25)	9/24 (38)	8/22 (36)	0.62

*Univariate analysis using χ^2 test with an alpha of 0.05.

Ye et al evaluated asthma as a risk factor for the development of EAC in Sweden over a 30-year period.[23] More than 92,000 patients were observed for a mean of 8.5 years. Asthmatics proved to be at increased risk for the development of EAC when compared with the population as a whole. In our study, asthma was not an independent risk factor for EAC, but associated with cough, it became predictive of an increased prevalence of EAC (Table 3).

The prevalence of *isolated* LPR symptoms in the non-GERD comparison group was 20%, which was not statistically different from the EAC group (Fig. 1). By nature of the inclusion criteria for non-GERD patients, the only symptoms observed in this group were laryngopharyngeal. This accounts for the proportionally high prevalence of isolated symptoms observed in these patients. The prevalence of *any* LPR symptoms, whether isolated or in conjunction with GERD symptoms, increased as disease severity progressed from the non-GERD comparison group to EAC patients (Table 3).

Based on the findings of this study, that chronic LPR symptoms (especially cough) are more commonly associated with EAC than typical GERD symptoms, we believe that patients with isolated laryngopharyngeal symptoms should be investigated with traditional or thin caliber esophageal endoscopy. In addition, these data suggest that the traditional triggers for endoscopic screening for Barrett's esophagus and cancer (ie, moderate to severe heartburn for $>$ 5 years) be lower in patients with heartburn and LPR symptoms.

A substantial decrease in the prevalence of typical GERD symptoms was observed from the GERD patients to Barrett's esophagus and EAC patients. Over half of the EAC patients never had had documentation of typical GERD symptoms in their chart. This suggests that the majority of EAC patients (57%) were never identified for screening based on the current recommendations put forth by the American College of Gastroenterology.[24,25] In support of this, 73% of the EAC group was not aware of the presence of Barrett's esophagus prior to cancer diagnosis. The lack of typical GERD symptoms in this group of patients may indicate an attenuation of vagal afferent sensory input secondary to the transmural esophageal injury caused by severe reflux or tumor infiltration.[26,27] Although the widespread use of proton pump inhibitors (PPIs) has all but eliminated strictures and

severe erosive esophagitis, the incidence of EAC continues to rise, presumably from Barrett's esophagus.[28] It has been theorized that PPI therapy may mask typical GERD symptoms and enable continued distal esophageal injury and disease progression.[29] Excluding the non-GERD comparison groups, the majority of subjects in this study, cases and comparison groups, were on PPI therapy. Because of this, the only symptoms predicting severe reflux (and a need for screening) may be laryngopharyngeal. In addition, patients with LPR symptoms have more proximal reflux, and the development of long-segment Barrett's esophagus has been associated with long duration, severe reflux involving the entire esophageal body.[30] Long-segment Barrett's esophagus has a threefold higher prevalence of dysplasia than short-segment disease (23% vs. 9%).[31]

Nearly 30% of both EAC and Barrett's esophagus patients did not have a history of LPR or GERD symptoms in their chart. Barrett's esophagus in the absence of typical reflux symptoms may be more prevalent than previously thought. We hypothesize that patients without typical GERD symptoms are the primary group that develop Barrett's esophagus and EAC. Because the true prevalence of Barrett's esophagus is unknown, it is difficult to determine its potency as a risk factor.[32] Additionally, merely relying on GERD symptoms to identify patients at risk for the development of Barrett's esophagus may be misguided. Gerson et al reported that in a population of veterans without typical GERD symptoms or antisecretory medication use, the prevalence of biopsy proven Barrett's esophagus was 25%.[10] This was a predominately white, male population, $\geq$ 50 years of age, and patients were not queried for LPR symptoms. Although unlikely, it is possible that the complete absence of symptoms observed in our investigation is secondary to the effect of PPI therapy.

It is appropriate to question whether the increased prevalence of LPR symptoms, particularly cough, in cancer patients is caused by the obstructing tumor. Perhaps fluid and food matter are retained within the esophagus and chronic regurgitation and microaspiration ensue. Esophageal fluid retention may also cause esophagitis and stimulation of the vagal-mediated esophagobronchial reflex, which results in cough.[33] Alternatively, tumor infiltration may trigger the esophagobronchial reflex. Conversely, that cough was significantly increased in patients with Barrett's esophagus (no obstruction or infiltration of the neural plexus) compared with GERD and non-GERD patients, supports LPR rather than cancer as the factor responsible for cough. In addition, the symptoms recorded within this population were often chronic and present several years prior to cancer diagnosis, suggesting that the symptoms were present before the cancer. Finally, there was no correlation between T stage and cough, which suggests that this symptom occurs independent of the degree of obstruction. Irrespective of cause and effect, cough may prove to be a useful marker for the presence of Barrett's esophagus and EAC prior to the onset of dysphagia, and thus may provide an opportunity to detect cancer at a curable stage.

Multivariate analysis revealed chronic cough, age, and the presence of diabetes to be independent risk factors for the development of EAC. In Barrett's esophagus, recent data have demonstrated an increase in the prevalence of dysplasia with increasing age[31,34] (Fig. 5). On average, the patients with esophageal cancer were 10 years older than the comparison groups, which may represent an element of bias selection. To date, the relationship between diabetes and EAC has been unexplored. We hypothesize that the relationship between obesity, a known risk factor for the development of EAC,[35] and type II diabetes mellitus may play a principle role in this association.

Because of the study design, the potential for bias exists. We used the medical record as a surrogate for patient symptoms. The abstractor, who was not blinded to the study hypothesis, was expected to interpret the many layers of patient information and accompanying information bias inherent in medical recording. Because of the complexity of chronically ill patients, care providers tend to more thoroughly document symptoms. This may have led to a more thorough inventory of laryngopharyngeal symptoms in cases when compared with Barrett's esophagus, GERD, and non-GERD patients. Care providers tend not to document subtle symptoms in relatively healthy patients. This is problematic in that it may have led to an underrepresentation of all symptoms in the comparison groups.

Because the GERD comparison group was selected based on "chronic GERD symptoms" as an indication for endoscopic screening, the potential for selecting a greater

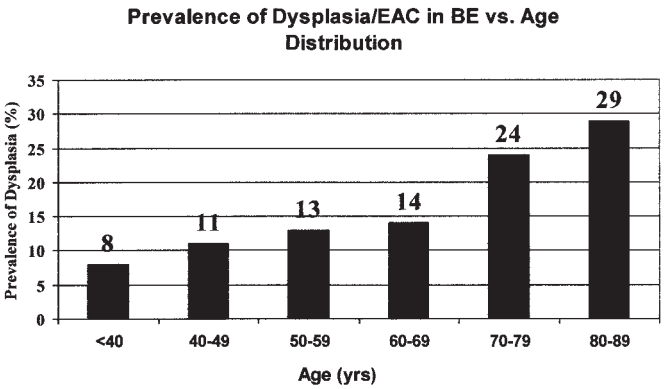

FIGURE 5. The prevalence of dysplasia and EAC arising from Barrett's esophagus increases by age. The risk of dysplasia increases by 3.3% per year. (Adapted with permission from Gopal DV, Lieberman DA, Magaret N, et al. Risk factors for dysplasia in patients with Barrett's esophagus (BE): results from a multicenter consortium. *Dig Dis Sci.* 2003;48:1537–1541.)

number of patients with typical GERD symptoms (ie, less patients with only LPR symptoms) exists. Although this may have introduced some bias into our results, the Barrett's esophagus comparison group had already been enrolled into a surveillance program and was not selected based on symptoms.

EAC patients present with a combination of symptoms that often include dysphagia, chronic cough, heartburn, and regurgitation. Dysphagia is present as an alarm symptom and offers little as an early risk factor. Heartburn, although unmistakable in its presentation, can be masked with the use of antisecretory medications. Typical reflux symptoms are evident at all stages along the path to EAC, yet up to 20% of the population of the United States experiences weekly symptomatic reflux.[36] This investigation has established that LPR symptoms, particularly cough, are very prevalent in patients with Barrett's esophagus and EAC. The presence of laryngopharyngeal symptoms may serve as a more sensitive indicator for the presence of Barrett's esophagus and EAC than typical GERD symptoms. In addition, the presence of these symptoms may better identify patients with existing cancer at an earlier stage. Our results suggest that the majority of EAC patients do not develop typical GERD symptoms and are thus not identified for screening. Incorporation of laryngopharyngeal symptoms within the current guidelines for Barrett's esophagus and cancer screening is warranted.

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Discussions

DR. BRUCE D. SCHIRMER (CHARLOTTESVILLE, VIRGINIA): Dr. Hunter and his colleagues from Portland have just pointed out to us in an excellent presentation that the potential use of larngopharyngeal reflux symptoms is an important parameter to suggest the potential presence of adenocarcinoma of the esophagus. I congratulate them on an excellent study and thank them for sending me a copy of their well-written manuscript.

There seems no doubt, based on these data, that LPR symptoms are valuable and potentially diagnosed in patients with adenocarcinoma. Chronic cough in particular, since it was often present many years prior to the diagnosis, may be particularly helpful.

I agree with the authors' reasoning in the Discussion section of the manuscript that LPR symptoms could have been overrepresented in this study group by a review of the medical records versus patient encounters themselves. Nevertheless, it does appear their conclusion that these symptoms should trigger endoscopic examination is justified. I have 1 observation and 3 questions for Dr. Reavis.

It seems that patients at the Portland VA Hospital are much more likely than the average population to have an upper endoscopy. The control group taken from the Dental Clinic records had a 36% incidence of previous EGD, which obviously ruled out either Barrett's or cancer in this group. Also, one third of the Barrett's patients were described as not having typical symptoms, but they obviously came to diagnosis by endoscopy.

My questions for Dr. Reavis are: Given this high prevalence of EGD in the patient population at the Portland VA, the incidence of adenocarcinoma in asymptomatic patients—that is, those without GERD or LPR symptoms—may be even higher than the 27% given here. Would you care to comment?

Second, this study is done in a white male population. Do you think these findings should be applied to non-Caucasion or female populations, despite their lower incidence of the disease?

Finally, while LPR symptoms are another screening tool to help diagnose adenocarcinoma of the esophagus in its early stages, they still do not seem to be sensitive enough, given the numbers in question 1 that I told you, to serve as a great screening parameter. Do the authors have any thoughts as to how we can otherwise effectively screen for esophageal adenocarcinoma?

DR. DAVID W. MCFADDEN (MORGANTOWN, VEST VIRGINIA): I would like to thank the Association and the authors for the privilege of reading this manuscript. It was very well presented and well researched. I think is an important contribution to the literature.

In brief, I agree with Dr. Schirmer that this paper examines and describes the significant relationship between LPR symptoms and the presence of adenocarcinoma of the esophagus, but only in a select population: white, male, smoking, military veterans over the age of 50 from the Pacific Northwest. This is a statistically robust case-comparison study. And my first question would also be a plea that this should be repeated in a more general population sample.

I also think the authors may have shortchanged themselves a little bit. They report an increase in these LPR symptoms from 20% to 54% in cancer patients. However, it is really only the symptom of chronic cough that individually stands out. In fact, the Barrett's esophagus group is not significantly different in any other symptoms such as asthma or aspiration. Therefore, perhaps the manuscript could be retitled "Laryngopharyngeal reflux symptoms better predict the presence of cancer and Barrett's esophagus than typical gastroesophageal reflux symptoms," making it a more useful and hopefully more appreciated contribution to the literature.

Just a couple of quick questions. Your manuscript mentions the presence of obesity. We all know that this is a risk factor for adenocarcinoma and Barrett's esophagus, and I was wondering if you had looked at this as a separate variable. Also, what about smoking? Anywhere between 50% and 65% of your patients smoke, significantly higher than the general population. How will this bias the results? It may in fact make your test more significant or discriminatory.

DR. ROBERT MARTIN (LOUISVILLE, KENTUCKY): The authors have stated esophageal adenocarcinoma represents one of the most rapidly rising malignancies in the United States, with squamous cell carcinoma truly becoming a rare disease. With this rising incidence, more and more centers are attempting to define a true high-risk patient population. Since gastroesophageal reflux disease affects nearly 7% of the global population and the incidence of esophageal adenocarcinoma is between 30,000 and 40,000 patients annually, this supposed risk factor has lacked true specificity.

I have 4 questions for the authors primarily related to data acquisition. Since this was a retrospective chart review of 4 groups, and, as we know, trying to obtain defined hard data such as weight loss or albumin in a retrospective chart reviews can be significantly difficult, what kind of defined protocol or how reliable were the authors able to obtain a true "LPR review of symptoms" in these 4 groups of patients?

Second, the authors accurately define LPR symptoms; however, as was stated with greater than 60% of the population being long-term smokers, how can this chart review

accurately define these symptoms as LPR versus just a simple chronic VA smoker cough?

Third, with the 3 significant LPR symptoms, what type of sensitivity was obtained in identifying these symptoms? Primarily, how many charts did Dr. Reavis have to essentially exclude because of the inability to accurately define these symptoms completely in these 4 groups?

Lastly, from the data, only 19 of 63 esophageal adenocarcinoma patients, or 30%, had one of these LPR symptoms. Are we proposing that all patients in the VA with a chronic cough should undergo a screening endoscopy?

I want to congratulate the authors on continuing to evaluate but also emphasize the age-old diagnostic modality of the simple history and physical in an attempt to better identify a high-risk patient population.

Dr. Steve Eubanks (Durham, North Carolina): My compliments to Dr. Hunter and his group for this effort and for their ongoing contributions to this body of literature.

Dr. Hunter has accurately applied the aspects of reflux disease that are important to the surgeon, that being the significant complications of gastroesophageal reflux disease. The authors have focused on laryngopharyngeal reflux or proximal reflux and its association with the development of esophageal carcinoma.

LPR usually takes on 1 of 2 patterns, either upright reflux with brief episodic reflux and rapid clearance, as is seen with many pulmonary patients, or a second pattern in which a supine reflux occurs where the esophagus is bathed nocturnally with refluxate and there is prolonged contact between the mucose and the refluxate.

So my questions: Can you comment on your hypothesis regarding which of these 2 patterns of reflux actually occurred in this patient population and its association relative one to the other with the development of esophageal carcinoma? Second, does this study emphasize the need to objectively assess proximal reflux with 24-hour pH studies with a proximal probe as well as a distal probe?

Dr. Kevin M. Reavis (Portland, Oregon): Our study established that laryngopharyngeal reflux symptoms are more common in patients with esophageal adenocarcinoma than in the Barrett's esophagus, GERD, or "normal" comparison groups. In addition, laryngopharyngeal reflux symptoms are more common in cancer patients than typical GERD symptoms, which are the current trigger for screening endoscopy.

With this in mind, Dr. Schirmer asked if the patients without either laryngopharyngeal reflux or GERD symptoms might have a greater incidence of adenocarcinoma than symptomatic patients. There are a large number of cancer patients who still fly under the radar despite screening for typical GERD symptoms. In fact, the majority of patients who present with esophageal adenocarcinoma are unaware of the presence of Barrett's esophagus prior to cancer diagnosis. This implies that they did not have typical symptoms and therefore were not culled for screening. Based on our study, we cannot conclude that patients without laryngopharyngeal reflux or GERD symptoms are at greater risk for the development of adenocarcinoma. We are currently developing a risk stratification-scoring schema based on factors such as body mass index (BMI), smoking history, age, and symptoms in an attempt to better identify high-risk populations. It does not appear that the currently employed screening paradigm is very effective at all. Some additional screening approaches we foresee include genetic analysis for p53 from biopsy specimens and other types of biochemical assays, which are currently in the investigative phase.

Dr. Schirmer asked about the applicability of our results to populations not represented in our study, such as females and those of non-white descent. These patient populations were not a part of our study so I cannot draw any specific conclusions as to the applicability of our results to other groups. In a recent study from El-Serag and colleagues, whites were affected with esophageal adenocarcinoma 5 times more than blacks, and men were affected 8 times more than women. Symptom histories were not evaluated in this study.

I agree with Dr. McFadden's first thought that our results would hold more weight if incorporated in a prospective study. This study has been initiated. His second question addresses the association of obesity and development of EAC. Cheng et al reported a significant association between elevated BMI in British women and an increased risk for the development of adenocarcinoma. We observed an association between diabetes and the development of EAC. Many patients who are obese have diabetes mellitus type 2 and thus may be at increased risk for adenocarcinoma. Whether this is secondary to immune dysfunction, common to both obese patients and patients with diabetes mellitus, is something that we can only speculate. Most of our patients presented after losing weight as a result of advanced malignancy and many were frankly cachectic, thus losing the validity of BMI as a predictor of cancer risk. Dr. McFadden's third point addresses the fact that cough may be a stronger risk factor than our analysis suggested because our control population had such a high frequency of smoking, thereby diluting the power of the cough analysis. We appreciate Dr. McFadden's observation. We found that both history of smoking for more than 10 years and pack-years not to be statistically different between the cases and the comparison groups.

Dr. Martin first asked about the reliability of the VA charts in terms of acquiring reliable data regarding laryngopharyngeal reflux symptoms. The charts are quite reliable. The VA is thorough in its documentation. It is certainly possible that overreporting or underreporting of symptoms in the chart as a function of case complexity could occur, as Dr.

Hunter pointed out in his presentation. Most patient charts include medication lists and symptom lists in multiple locations, so overall I feel that they are reliable and accurate.

His second question addressed how laryngopharyngeal reflux symptoms differ from that of a good old-fashioned VA smoker's cough. Again, I will note that smoking history and specific pack-years were incorporated into our multivariate analysis. These were not determined to be significant confounders. Cough alone was noted to be an independent risk factor for the presence of adenocarcinoma.

He next asked how many charts needed to be excluded because of inadequate data. Not many charts were excluded because of lack of data. Many charts were excluded while forming the normal comparison group, because, as Dr. Hunter pointed out, it was hard to find patients who were not on antisecretory medication in the VA patient population. Many patients were on these medications for either appropriate treatment, prophylaxis, or they had coughed or complained of abdominal pain once and were subsequently placed on PPI therapy. These charts were excluded from consideration for the normal group.

Lastly, Dr. Martin asked if everyone with a chronic cough should undergo endoscopy. We feel that they should. Twenty percent of all patients (cancer and comparison groups) do have laryngopharyngeal reflux symptoms and 20% of the American population is suffering from weekly reflux. We observed that a history of laryngopharyngeal reflux symptoms were more common than classic GERD symptoms in patients with cancer. This is not to say that screening using only laryngopharyngeal reflux symptoms will be significantly more effective, but this approach is apparently more sensitive than the utilization of classic GERD symptoms alone, the current trigger for screening endoscopy. In combination with GERD symptoms, laryngopharyngeal reflux symptoms will potentially be a much more effective screening tool than what is currently available.

Finally, Dr. Eubanks asked if the cancer patients with only laryngopharyngeal reflux symptoms harbored a specific reflux pattern. We acknowledge the different patterns of reflux including bipositional gastroesophageal and laryngopharyngeal reflux due to a grossly incompetent lower esophageal sphincter and isolated upright reflux, which may occur via a different mechanism. We performed a subgroup analysis of patients with only laryngopharyngeal reflux symptoms to better characterize these patients. We do not know if these patients were bipositional or isolated upright refluxers. The best method to determine the specific reflux pattern would be to utilize 24-hour pH measurement of the hypopharynx as well as multichannel intraluminal impedance measurements of the esophagus.

In conclusion, we are currently enrolling patients in an NIH-sponsored study to define the presence of esophageal injury in patients with laryngopharyngeal reflux symptoms. Our hope is to better define risk factors, improve screening, and detect existing esophageal adenocarcinomas within the curative window.