The Risk of Barrett's Esophagus in Patients with Mild Gastroesophageal Reflux Disease Symptoms in the Context of Proton-Pump Inhibitor Use

by

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a thesis

Presented to the Department of Public Health & Preventive Medicine

and the Oregon Health & Science University

School of Medicine

in partial fulfillment of the requirements for the degree of

Master of Public Health

May 2007

School of Medicine
Oregon Health & Science University

CERTIFICATE OF APPROVAL

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ACKNOWLEDGMENTS

Thesis committee members and mentors:
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Peggy Cook
Jennifer Holub
LeAnn Michaels
Kris Weymann

MD-MPH program:
John Stull
Maureen Schau Baldwin

This study was supported by the following grants: 1UL1RR024140 Oregon Clinical and Translational Research Institute; K23 DK066165-01 (Jobe) NIH, NIDDK, Screening for Barrett's in Otolaryngology Patients; and 1 U01 DK57132 Clinical Outcomes Research: An Endoscopic Database.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common chronic medical condition defined by the American College of Gastroenterology as "symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus."[1] Heartburn and regurgitation are considered typical and highly specific symptoms of GERD, especially when they occur after large or fatty meals.[2] However, GERD can also have extraesophageal manifestations namely cough, laryngitis, asthma, and non-cardiac chest pain.[3] The majority of patients with GERD have macroscopically normal esophageal mucosa,[4] but some develop complications of GERD such as erosive esophagitis,[5, 6] esophageal stricture,[7] and Barrett's esophagus,[8] a metaplastic change of the esophageal lining that is a precursor to esophageal adenocarcinoma.[9, 10]

GERD is a major public health problem given its prevalence, the associated use of health care resources, and its role in population-level cancer prevention strategies. Estimates of its prevalence range from 25 to 57 percent in the Western world.[11, 12] A recent systematic review—defining GERD as heartburn and/or regurgitation occurring at least once per week—found the prevalence of GERD to be about 10 to 20 percent of Western populations, with an incidence of 5 per 1000 person-years.[13] Studies specific to the United States estimate that 25 to 35% of the population experience GERD.[14]

The impact of GERD extends into the health care system and country's economy at large. The annual cost of treating GERD in the United States was about $500 per patient in the late 1990s.[15] In the United Kingdom, the cost of GERD to the UK National Health

Service was about £750 million in 2004 (about US$1.3 billion).[16] In some European countries, the annual cost incurred by GERD per patient has been estimated to be €382 (about US$350 at the time of the study), 90% of which were direct costs and 10% indirect. These estimates did not include the cost of diagnostic endoscopy, so they are most likely underestimating the actual cost of the disease, but of the costs that were calculated, medications accounted for 64% of the total costs. [17] The usage and cost of GERD medications, particularly proton pump inhibitors, are not insignificant: in 2001 among noninstitutionalized Medicare beneficiaries alone, 5 million patients were using $3 billion worth of proton pump inhibitors.[18]

The current initial management of GERD is empirical medical treatment of patients with symptoms consistent with GERD. Patients who respond to appropriate therapy are considered to have GERD. "Appropriate therapy" usually consists of gastric acid suppression with proton pump inhibitors (PPI), which are prescribed to relieve GERD symptoms and to heal esophagitis.[1] PPI therapy has been shown to normalize the impaired quality of life caused by GERD, given that it decreases the severity and frequency of GERD symptoms.[19] Further diagnostic testing, particularly with endoscopy, is reserved for patients who do not respond symptomatically to therapy or who have symptoms that suggest complicated disease. These symptoms may be so-called alarm symptoms such as dysphagia, odynophagia, bleeding, weight loss, and anemia. More commonly, they may be merely GERD symptoms of sufficient duration to put a patient at risk for Barrett's esophagus[14] and consequently also for esophageal adenocarcinoma.[20]

Barrett's esophagus is the only known major risk factor for esophageal adenocarcinoma,[21] a cancer whose incidence has increased by 350% since 1970[22] and whose diagnosis most often occurs at a stage late enough to produce an overall five year survival of less than 10%.[23,24] Persons with Barrett's esophagus have a 40 to 125 times higher probability of developing esophageal adenocarcinoma compared to the general population. Although Barrett's esophagus is prevalent (0.4%-1% of patients undergoing upper endoscopy for all clinical indications),[25, 26] most patients with Barrett's do not develop invasive adenocarcinoma.[27, 28] Currently it is not possible to identify the Barrett's patients most at risk for developing dysplasia or carcinoma, so esophageal adenocarcinoma prevention strategies have focused on screening high-risk groups and following patients with known Barrett's. This practice is supported by several retrospective studies that have revealed an earlier stage of diagnosis and a reduction in mortality from esophageal adenocarcinoma endoscopic surveillance compared to no surveillance.[20, 29-33] However, despite this evidence in support of screening and surveillance, no prospective trials have demonstrated a reduction in cancer-related mortality, most likely due to the low incidence of esophageal adenocarcinoma (7800 cases anticipated in 2007) in the face of the high prevalence of GERD (about 100 million people in the United States).

Barrett's esophagus is a known complication of severe GERD, with 8-20% of persons with chronic GERD thought to develop Barrett's.[34, 35] In GERD, the reflux of gastric juice into the esophagus or oropharynx causes symptoms and tissue injury such as ulceration, fibrosis, and esophageal stricture formation. The ulcerated squamous

epithelium of the distal esophagus can be replaced by metaplastic, intestinal-type mucosa known as Barrett's esophagus. Consequently, GERD itself is a strong risk factor for esophageal adenocarcinoma[20] as well as for its dysplastic precursor Barrett's esophagus. Because up to 20% of the population of the United States experiences weekly symptomatic reflux,[11] the population eligible for endoscopic screening for esophageal adenocarcinoma and Barrett's esophagus is enormous. EGD has not been adopted for screening all patients with symptoms of GERD because of the cost, complexity and risks.[21] Therefore, the American College of Gastroenterology currently recommends that only patients who have "chronic GERD symptoms" be screened for Barrett's screening.[36]

Barrett's esophagus,[10] symptomatic gastroesophageal reflux,[20] white ethnicity and male sex[37] are known risk factors for esophageal adenocarcinoma. However, the populations most at risk for esophageal adenocarcinoma remain ill-defined: the majority of patients (>90%) who develop esophageal adenocarcinoma are unaware of the presence of Barrett's esophagus prior to cancer diagnosis.[29] This suggests that the majority of patients who are at highest risk for the development of esophageal adenocarcinoma were never screened for Barrett's esophagus. That is, the current screening paradigm has not been adequate in identifying the population most at risk for Barrett's esophagus and esophageal adenocarcinoma. Not only is there still active debate regarding the proper indications for Barrett's screening,[38-40] but the increasing use of proton pump inhibitors[18] and the growing recognition of atypical GERD symptoms[41] suggests that a better understanding of the Barrett's esophagus in the context of mild GERD could help better define the population of GERD patients to screen.

This study examines the relationship between the severity of patients' GERD symptoms and the presence of the esophageal lesions targeted by endoscopic screening: Barrett's esophagus, esophageal dysplasia, and esophageal adenocarcinoma. The nature of their association can offer some insight into these diseases' natural histories and into the subpopulations most at risk for esophageal adenocarcinoma. The study also explores the effect that proton pump inhibitors have on the relationship between GERD symptom severity and Barrett's esophagus or worse, and it considers the risk of Barrett's esophagus or worse associated with esophageal or "typical" versus extraesophageal or "atypical" GERD symptoms.

METHODS

Overview

This study is a cross-sectional analysis of gastroesophageal reflux disease (GERD) symptoms and endoscopic findings in patients at Oregon Health & Science University (OHSU) and the Portland Veterans Administration Medical Center (PVAMC) in Portland, Oregon. At the time of their endoscopic evaluations, all study participants completed validated GERD symptom questionnaires: the GERD Health-Related Quality of Life Questionnaire and the Reflux Symptom Index. The risk of esophageal injury—specifically, Barrett's esophagus, esophageal dysplasia, or esophageal adenocarcinoma—was estimated with the odds ratio calculated by logistic regression.

Study Population

Three cohorts were combined to create the study population: Cohort A consisted of adult patients referred for esophagogastroduodenoscopy (EGD) November 2002 through July 2004. Data on these patients were collected for the purposes of quality assurance: each patient was given two GERD symptom questionnaires (discussed below) to be completed and given to the endoscopist performing the procedure. Per their usual clinical practice, the endoscopists evaluated each patient's esophagus, took biopsies as they judged necessary, and entered their EGD findings into a central electronic database. Of the 3748 patients who had an EGD during the quality assurance time period, 415 completed at least half of the questionnaire questions and were included in the study analysis.

The second cohort (Cohort B) consisted of patients referred for EGD, May 2004 through February 2005, who consented to an additional small-caliber research endoscopy. Patients with typical GERD symptoms (heartburn, regurgitation, or dysphagia) undergoing their first EGD or undergoing Barrett's esophagus surveillance were recruited for a randomized controlled trial comparing the feasibility, accuracy, and patient acceptance of unsedated small-caliber endoscopy compared to conventional sedated endoscopy.[42] Patients with conditions that increased the risk associated with the research endoscopy—specifically, prior anti-reflux surgery, esophageal diverticulum, pregnancy, anti-coagulation therapy, esophageal varices, otolaryngological malignancy, recurrent epistaxis, prior nose injury, prior laryngeal surgery, trauma to the larynx, or other contraindication to EGD—were excluded from participation. Of 274 eligible patients, 101 completed both the research and conventional EGD per the randomized crossover study design as well as the GERD symptom questionnaires. Data collected via the conventional EGD were used in this study.

The third cohort (Cohort C) was composed of patients being treated in outpatient otolaryngology (ENT) clinics. Patients with laryngopharyngeal symptoms of GERD such as hoarseness, throat-clearing, excess mucus, or cough were recruited from February 2005 through March 2007 to participate in a research small-caliber EGD procedure with endoscopic follow-up after proton-pump inhibitor therapy. As in Cohort B, those patients with conditions that increased the risk of a research endoscopy were excluded (specific criteria as listed above). Of 423 eligible patients, 253 completed the initial research EGD

and at least half of the GERD symptom questionnaire questions and were included in the analysis of this study.

Data Collection and Variable Definition

Independent Variables: GERD Symptom Evaluation

The severity of study participants' typical GERD symptoms was quantified using the modified GERD Health Related Quality of Life Questionnaire (GERD QoL), [43] a disease-specific instrument whose validity and reliability have been assessed in comparison to generic quality-of-life scales (SF-36)[44] and to physiologic parameters of GERD.[45] The Reflux Symptom Index (RSI) was used to assess the severity of *atypical* symptoms of GERD, specifically laryngopharyngeal symptoms such as hoarseness and cough (Table 1). Its validity and reliability have been evaluated in patients with laryngopharyngeal reflux who were treated with proton-pump inhibitors.[46]

Table 1: Gastroesophageal Reflux Disease Symptom Questionnaires

GERD Health-Related Quality of Life (GERD QoL)	
1. How bad is your heartburn? 2. Do you have heartburn when lying down? 3. Do you have heartburn when standing up? 4. Do you have heartburn after meals? 5. Does heartburn change your diet? 6. Does heartburn wake you from sleep? 7. Do you have difficulty swallowing? 8. Do you have pain with swallowing? 9. Do you have bloating or gassy feelings?	☐ no symptoms ☐ symptoms noticeable, but not bothersome ☐ symptoms bothersome every day ☐ symptoms affect daily activities ☐ symptoms are incapacitating—unable to do daily activities
Reflux Symptom Index (RSI)	
Within the last month, how did the following problems affect you? Please circle the number that describes how you felt: 1. Hoarseness or a problem with your voice 2. Clearing your throat 3. Excess throat mucus or postnasal drip 4. Difficulty swallowing food, liquids, or pills† 5. Coughing after you eat or after lying down 6. Breathing difficulties or choking episodes 7. Troublesome or annoying cough 8. Sensations of something sticking in your throat or a lump in your throat	no problem→severe problem 0 1 2 3 4 5

†= not used when responses from GERD QoL and RSI were combined to avoid duplication of dysphagia data

The questionnaire responses were categorized into one of three severity categories (Table 2): no, mild, and severe symptoms.

Table 2: Categorization of Gastroesophageal Reflux Disease Symptom Severity

GERD Health-Related Quality of Life	Reflux Symptom Index	Symptom Severity (value)
o No symptoms	0	No symptoms (0)
o Symptoms noticeable, but not bothersome	1 2	Mild symptoms (1)
o Symptoms bothersome every day o Symptoms affect daily activities o Symptoms are incapacitating—unable to do daily activities	3 4 5	Severe symptoms (2)

Four GERD symptom severity measures—two global measures and two measures specific to the symptom type (typical or atypical)—were created for each study participant. The first measure was the sum of GERD symptom severity scores from both the GERD QoL and RSI subscales. "No symptoms" had a value of 0, "mild symptoms" a

value of 1, and "severe symptoms" a value of 2. The other measures were simple counts of the number of "severe" symptoms from the GERD QoL, from the RSI, and from both questionnaires. All four measures were analyzed as continuous variables (Table 3).

Table 3: Gastroesophageal Reflux Disease (GERD) Symptom Severity Variables

Global Measures (both typical and atypical GERD symptoms)	**Range of Values**
summed GERD symptom severity score	0 to 32
total number of severe GERD symptoms	0 to 16
Typical vs Atypical Symptom Measures	
Number of severe typical symptoms (GERD Qol)	0 to 9
Number of severe *atypical* symptoms (RSI)	0 to 8

"typical" GERD symptoms measured by GERD Health-Related Quality of Life Questionnaire (QoL);
"atypical" GERD symptoms measured by Reflux Symptom Index (RSI)

Study Outcome: Endoscopic and Histologic Evaluation of the Esophagus

As mentioned in the description of the study cohorts, conventional sedated EGD was performed on Cohorts A and B by clinic endoscopists per their usual clinical practice. That is, an unstandardized protocol was used to make endoscopic diagnoses and to take esophageal biopsies for histologic diagnosis. The endoscopic findings were entered into a structured electronic database managed by the Clinical Outcomes Research Initiative (CORI).

Cohort C was evaluated with a small-caliber unsedated EGD by a single endoscopist according to a research protocol: any esophageal squamocolumnar junction (SCJ) with ZAP grades I through III were considered to have the appearance of Barrett's esophagus,[47] in which case four-quadrant esophageal biopsies were obtained at the anatomic esophagogastric junction and extending every 2 cm to the level of the SCJ. Endoscopic findings were entered into a structured electronic database maintained by

study staff. This small-caliber EGD has been shown to be equally accurate in screening for Barrett's esophagus,[42] and so the two methods of endoscopy were considered to be equivalent for the purposes of this study.

All esophageal biopsy specimens were evaluated by the hospital staff pathologist on call. The diagnosis of Barrett's esophagus (intestinal metaplasia) required the unequivocal presence of goblet cells within columnar epithelium. Cardia intestinal metaplasia was not considered Barrett's esophagus. Standard diagnostic criteria were used to identify columnar epithelial dysplasia.[48]

The outcome examined in this study was the diagnosis of Barrett's esophagus, esophageal dysplasia, or esophageal adenocarcinoma (henceforth called "Barrett's") ascertained by histological examination of the esophageal biopsy obtained during the study EGD. Study participants who reported a history of Barrett's esophagus but who did not have a study biopsy diagnostic of Barrett's were considered to be free of Barrett's for the purposes of analysis.

Potential Confounders

Demographic, clinical, and study-specific patient characteristics were analyzed as potential confounders (Table 4).

Table 4: Variable Definitions of Potential Confounders

Variable	Values	Analysis
Age at time of endoscopy	Age in years	Continuous
Sex	Male Female	Categorical
Race/Ethnicity	White (Caucasian, not Hispanic) Not White	Categorical
Use of proton-pump inhibitor	Yes No	Categorical
Presence of hiatal hernia	Yes No	Categorical
Source cohort	Cohort A Cohort B Cohort C	Categorical
Source clinic	Gastroenterology (GI) Otolaryngology (ENT)	Categorical
Source institution	Oregon Health & Science University (OHSU) Portland Veterans Administration Medical Center (PVAMC)	Categorical

Due to sample size constraints, race and ethnicity were analyzed as White (i.e., Caucasian and not Hispanic) or not White. Source cohort, clinic, and institution reflected the methods of study recruitment. Recruitment from a gastroenterology clinic was interpreted as patients' presenting with predominantly typical GERD symptoms; recruitment from a otolaryngology clinic was interpreted as predominantly *atypical* GERD symptom presentation.

Statistical Analysis

Descriptive statistics and logistic regression models were used to explore the relationship between GERD symptom severity and Barrett's. Odds ratios were used as the primary measure of association.

Statistical analyses were performed with SPSS 14.0 for Windows Graduate Student Version (SPSS Inc., Chicago, Illinois), SPSS 15.0 for Windows (SPSS Inc., Chicago,

Illinois), SAS 9.1 TS Level 1M2 (SAS Institute Inc., Cary, North Carolina), and Microsoft Office Excel 97 (Microsoft Corporation, Bellevue, Washington).

Treatment of Missing Data

The value of 80 missing questionnaire responses for 62 subjects was estimated using the mean (rounded to the nearest integer) of each case's actual responses for that specific questionnaire (GERD QoL or RSI). This imputation allowed for the creation of summary GERD symptom severity measures although it underestimated the variability of each subject's experience.

Descriptive Statistics

Means, standard deviations, and ranges were presented for continuous variables. Proportions were presented for categorical variables.

Univariate Analysis

The presence of an association between the symptom severity variables and Barrett's was assessed using simple logistic regression models. The relationships between the outcome and the categorical covariates were assessed with the Pearson chi-square test for independence and simple logistic regression (referent cell method of coding). Ordinal covariates were examined using the Mantel Haenszel Chi-Square Test of Trend to assess the presence of a linear trend in symptom severity with respect to the outcome. Patient age was analyzed with an independent t-test and simple logistic regression. Associations with a p-value of less than 0.05 were considered statistically significant.

Assessment of Confounding

Univariate models of the GERD symptom severity variables and Barrett's were assessed for confounding by age, gender, race/ethnicity, use of proton-pump inhibitor, presence of hiatal hernia, and study sub-population (Cohorts A, B, and C). The first five factors are known to be associated with both GERD symptoms[49, 50] and with Barrett's esophagus.[51-53] A difference of at least 10% in the odds ratios of the GERD symptom severity variable in bivariate and full models, with and without these adjustment covariates was considered evidence of confounding by the covariate being assessed.[54]

Construction of a Main-Effects Multiple Logistic Regression Model

Using the variable selection methods described by Hosmer and Lemeshow,[55] a multiple logistic regression model was created to model the relationship between the GERD symptom severity variables and the study's outcome, the diagnosis of Barrett's esophagus or worse.

Variables that were significant in univariate analysis with $p<0.25$ and those that had known biological importance (specifically, age, gender, race/ethnicity, presence of hiatal hernia, use of proton-pump inhibitor) were selected for the multiple logistic regression model. Pearson two-tailed correlation statistics were calculated for all potential confounders. Of pairs that had at least moderate correlation ($r>0.70$), only one variable was included in the preliminary model. Backward step-wise selection was used to derive the preliminary effects model. A Wald statistic with $p> 0.10$ was the criterion for a variable's removal. The variable with the largest p-value was removed sequentially until

all variables had a p-value of less than 0.10 or were uncovered as confounders as defined above. The following variables were included regardless of significance for their importance in understanding the association: age, gender, presence of hiatal hernia, and use of proton-pump inhibitor. A score statistic with $p<0.05$ was the criterion for a variable's entry into the model. A separate logistic model was created for each measure of GERD symptom severity for a total of four separate main effects models. Categorical variables were coded by the referent cell method.

Exploration of Non-Linear or Interaction terms to Include in Final Model

Proper scaling of the continuous variable (age) was assessed visually with Lowess Smoothing curve, scatter plots, and histograms, as well as in tertiles, quartiles, and dichotomous splitting (using the referent cell and polynomial contrasts methods). The most statistically significant categorization scheme of age in the main effects model was used.

Possible interactions between each GERD symptom severity variable and age, gender, and the current use of proton-pump inhibitor were assessed. Interaction terms that were significant when added individually to the main effects logistic regression model were added simultaneously to the main effects model, and interactions terms significant at Wald statistic $p<0.05$ were retained in the final model.

Assessment of the Final Model

The final model's goodness-of-fit was assessed with the Hosmer and Lemeshow test. These model diagnostics were analyzed to assess the fit of the model: change in Pearson' chi-square versus predicted probabilities, change in model deviance versus predicted probabilities, and Cook's distance versus predicted probabilities. Potential outliers were identified visually, and any case that changed parameter estimates by at least 10% was removed. One case met these criteria and was deleted from the final dataset used for analysis.

RESULTS

Study Population Characteristics

The study analysis included 769 subjects, of whom the majority were male (65.4%), Caucasian (94.3%), and not Hispanic (97.8%). Most presented with typical GERD symptoms (67.1%) and were using a proton-pump inhibitor (57.2%). Their GERD symptom severity scores spanned the full possible range of values; however the average number of severe symptoms was low: 5.8 (±4.3) severe GERD symptoms out of 16 possible. One hundred twenty two (15.9%) of the subjects had the study outcome, Barrett's esophagus or worse (Table 5).

Univariate Analysis

GERD symptom severity—analyzed both as number of severe symptoms (OR 0.94; 95% CI: 0.89, 0.98) and as a symptom score (OR 0.97; 95% CI: 0.95, 0.99)—was significantly associated with Barrett's esophagus or worse, with lower symptom severity being a risk factor of the study outcome. When typical and *atypical* GERD symptoms were analyzed separately, both types were still significantly and negatively associated with the study outcome (OR 0.92; 95% CI: 0.86, 0.99; and OR 0.91; 95% CI: 0.84, 0.99, respectively) (Table 6).

The symptoms of GERD independently and negatively associated with the study outcome were the severity of heartburn, whether heartburn changed subjects' diet, difficulty swallowing, pain with swallowing, feelings of bloating, and voice hoarseness (Tables 7 and 8).

Table 5: Study Population Characteristics

		total (n=769)	Barrett's	no Barrett's	unadjusted OR	95% CI	p-value
Demographics							
age	years (mean±std dev)	57.1±13.7	61.6±11.6	56.3±13.9	1.03	1.02, 1.05	<0.001
gender	male	503 (65.4%)	111 (22.1%)	392 (77.9%)	6.56	3.46, 12.44	<0.001
	female	266 (34.6%)	11 (4.1%)	255 (95.9%)			
race/ethnicity*	White	708 (92.1%)	115 (16.2%)	593 (83.8%)	3.36	1.03, 10.95	0.017
	not White	55 (7.2%)	3 (5.5%)	52 (94.5%)			
use of proton-pump inhibitor#	yes	440 (57.2%)	89 (20.2%)	351 (79.8%)	2.41	1.55, 3.72	<0.001
	no	325 (42.2%)	31 (9.5%)	294 (90.5%)			
hiatal hernia	yes	365 (47.5%)	89 (24.4%)	276 (75.6%)	3.63	2.36, 5.57	<0.001
	no	404 (52.5%)	33 (8.2%)	371 (91.8%)			
Recruitment Sources							
source clinic	otolaryngology (ENT)	253 (32.9%)	31 (12.3%)	222 (87.7%)	0.65	0.42, 1.01	0.051
	gastroenterology (GI)	516 (67.1%)	91 (17.6%)	425 (82.4%)			
source institution	PVAMC	365 (47.5%)	94 (25.8%)	271 (74.2%)	4.66	2.97, 7.31	<0.001
	OHSU	404 (52.5%)	28 (6.9%)	376 (93.1%)			
source study cohort							<0.001
	GI pts unscreened (A)	415 (54.0%)	46 (11.1%)	369 (88.9%)	referent		
	GI pts w/GERD (B)	101 (13.1%)	45 (44.6%)	56 (55.4%)	6.45	3.92, 10.61	
	ENT pts w/LPR (C)	253 (32.9%)	31 (12.3%)	222 (87.7%)	1.12	0.69, 1.82	

Study Outcomes

Barrett's esophagus	104 (13.5%)
esophageal dysplasia	17 (2.2%)
esophageal adenocarcinoma	6 (0.8%)
Barrett's esophagus or worse	**122 (15.9%)**

"Barrett's" and "Barrett's esophagus or worse" = Barrett's esophagus, esophageal dysplasia, or esophageal adenocarcinoma

PVAMC = Portland Veterans Administration Medical Center; OHSU = Oregon Health & Science University Hospital; OR = odds ratio; CI = confidence interval; GERD = gastroesophageal reflux disease; GI = gastroenterology; ENT = otolaryngology; LPR = laryngopharyngeal reflux symptoms

* 6 subjects were missing data on race and ethnicity

4 subjects were missing data on proton-pump inhibitor use

Table 6: Risk of Barrett's Esophagus or Worse by Gastroesophageal Reflux Disease (GERD) Symptom Severity and Proton-Pump Inhibitor (PPI) Use

	range	mean (SD)	unadjusted OR	95% CI	p-value		range	mean (SD)	adjusted OR	95% CI	p-value
total # severe GERD symptoms	0-16	5.77 (4.30)	0.937	(0.892, 0.983)	0.007	**PPI-user**	0-16	6.33 ±4.33	0.897	(0.838, 0.960)	0.002
						PPI-non-user	0-16	4.99 ±4.15	1.063	(0.961, 1.176)	0.237
GERD symptom severity score	0-32	15.80 (8.24)	0.97	(0.947, 0.993)	0.011	**PPI-user**	0-32	16.93 ±8.06	0.947	(0.915, 0.980)	0.002
						PPI-non-user	0-32	14.27 ±8.27	1.036	(0.984, 1.091)	0.175
# severe typical GERD symptoms	0-9	2.79 (2.97)	0.92	(0.857, 0.987)	0.017				0.904	(0.831, 0.985)	0.020
# severe *atypical* GERD symptoms	0-8	3.33 (2.53)	0.913	(0.844, 0.989)	0.023	**PPI-user**	0-8	3.60 ±2.56	0.808	(0.717, 0.911)	<0.001
						PPI-non-user	0-8	2.97 ±2.46	1.293	(1.089, 1.535)	0.003

Multivariate logistic regression model adjusted for age (categorized with cut-offs at ages 58 and 68), gender, race/ethnicity (White vs. not White), use of proton-pump inhibitor, presence of hiatal hernia, clinic of recruitment (gastroenterology versus otolaryngology), and institution of recruitment (Oregon Health & Science University versus Portland Veterans Administration Medical Center). Three multivariate models included an interaction term between the GERD symptom severity variable and the use of proton-pump inhibitor (PPI) and so were reported stratified by PPI-use.

OR = odds ratio calculated by logistic regression, CI = confidence interval, SD = standard deviation; p-value of Wald statistic

Table 7: Risk of Barrett's Esophagus or Worse By Typical Gastroesophageal Reflux Disease (GERD) Symptoms as Measured by the GERD Health-Related Quality of Life Questionnaire (QoL)

	total (n=769)	Barrett's	no Barrett's	unadjusted OR	95% CI	p-value
How bad is your heartburn? (QoL 1)						0.028
no symptoms	241	41 (17.0%)	200 (83.0%)	referent		
mild symptoms	236	47 (19.9%)	189 (80.1%)	1.21	0.76, 1.93	
severe symptoms	292	34 (11.6%)	258 (88.4%)	0.64	0.39, 1.05	
Do you have heartburn when lying down? (QoL 2)						0.261
no symptoms	277	46 (16.6%)	231 (83.4%)	referent		
mild symptoms	218	40 (18.3%)	178 (81.7%)	1.13	0.71, 1.80	
severe symptoms	274	36 (13.1%)	238 (86.9%)	0.76	0.47, 1.22	
Do you have heartburn when standing up? (QoL 3)						0.235
no symptoms	305	54 (17.7%)	251 (82.3%)	referent		
mild symptoms	233	39 (16.7%)	194 (83.3%)	0.93	0.59, 1.47	
severe symptoms	231	29 (12.6%)	202 (87.4%)	0.67	0.41, 1.09	
Do you have heartburn after meals? (QoL 4)						0.062
no symptoms	277	50 (18.1%)	227 (81.9%)	referent		
mild symptoms	268	47 (17.5%)	221 (82.5%)	0.97	0.62, 1.50	
severe symptoms	224	25 (11.2%)	199 (88.8%)	0.57	0.34, 0.96	
Does heartburn change your diet? (QoL 5)						0.029
no symptoms	349	58 (16.6%)	291 (83.4%)	referent		
mild symptoms	193	39 (20.2%)	154 (79.8%)	1.27	0.81, 1.99	
severe symptoms	227	25 (11.0%)	202 (89.0%)	0.62	0.38, 1.03	
Does heartburn wake you from sleep? (QoL 6)						0.518
no symptoms	356	51 (14.3%)	305 (85.7%)	referent		
mild symptoms	178	32 (18.0%)	146 (82.0%)	1.31	0.81, 2.13	
severe symptoms	235	39 (16.6%)	196 (83.4%)	1.19	0.76, 1.87	
Do you have difficulty swallowing? (QoL 7)						0.014
no symptoms	303	61 (20.1%)	242 (79.9%)	referent		
mild symptoms	230	35 (15.2%)	195 (84.8%)	0.71	0.45, 1.12	
severe symptoms	236	26 (11.0%)	210 (89.0%)	0.49	0.30, 0.81	
Do you have pain with swallowing? (QoL 8)						<0.001
no symptoms	483	91 (18.8%)	392 (81.2%)	referent		
mild symptoms	162	11 (6.8%)	151 (93.2%)	0.31	0.16, 0.60	
severe symptoms	124	20 (16.1%)	104 (83.9%)	0.83	0.49, 1.41	
Do you have bloating or gassy feelings? (QoL 9)						0.019
no symptoms	201	43 (21.4%)	158 (78.6%)	referent		
mild symptoms	267	43 (16.1%)	224 (83.9%)	0.71	0.44, 1.13	
severe symptoms	301	36 (12.0%)	265 (88.0%)	0.50	0.31, 0.81	

Barrett's = Barrett's esophagus, esophageal dysplasia, or esophageal adenocarcinoma; OR = odds ratio calculated by logistic regression; p-value of Wald statistic

Table 8: Risk of Barrett's Esophagus or Worse by *Atypical* GERD Symptoms As Measured By the Reflux Symptom Index (RSI)

	total (n=769)	Barrett's	no Barrett's	unadjusted OR	95% CI	p-value
hoarseness or a problem with your voice (RSI 1)						0.031
no symptoms	317	62 (19.6%)	255 (80.4%)	referent		
mild symptoms	178	28 (15.7%)	150 (84.3%)	0.77	0.47, 1.25	
severe symptoms	274	32 (11.7%)	242 (88.3%)	0.54	0.34, 0.86	
clearing your throat (RSI 2)						0.240
no symptoms	168	33 (19.6%)	135 (80.4%)	referent		
mild symptoms	207	34 (16.4%)	173 (83.6%)	0.80	0.47, 1.37	
severe symptoms	394	55 (14.0%)	339 (86.0%)	0.66	0.41, 1.07	
excess throat mucus or postnasal drip (RSI 3)						0.113
no symptoms	172	34 (19.8%)	138 (80.2%)	referent		
mild symptoms	179	32 (17.9%)	147 (82.1%)	0.88	0.52, 1.51	
severe symptoms	418	56 (13.4%)	362 (86.6%)	0.63	0.39, 1.00	
difficulty swallowing food, liquid, or pills (RSI 4)						0.014
no symptoms	318	64 (20.1%)	254 (79.9%)	referent		
mild symptoms	179	27 (15.1%)	152 (84.9%)	0.71	0.43, 1.15	
severe symptoms	272	31 (11.4%)	241 (88.6%)	0.51	0.32, 0.81	
coughing after you eat or after lying down (RSI 5)						0.747
no symptoms	295	48 (16.3%)	247 (83.7%)	referent		
mild symptoms	187	32 (17.1%)	155 (82.9%)	1.06	0.65, 1.74	
severe symptoms	287	42 (14.6%)	245 (85.4%)	0.88	0.56, 1.38	
breathing difficulties or choking episodes (RSI 6)						0.353
no symptoms	318	57 (17.9%)	261 (82.1%)	referent		
mild symptoms	189	25 (13.2%)	164 (86.8%)	0.70	0.42, 1.16	
severe symptoms	262	40 (15.3%)	222 (84.7%)	0.83	0.53, 1.28	
troublesome or annoying cough (RSI 7)						0.249
no symptoms	302	53 (17.5%)	249 (82.5%)	referent		
mild symptoms	183	32 (17.5%)	151 (82.5%)	1.00	0.61, 1.61	
severe symptoms	284	37 (13.0%)	247 (87.0%)	0.70	0.45, 1.11	
sensations of something sticking in your throat or a lump in your throat (RSI 8)						0.358
no symptoms	224	42 (18.8%)	182 (81.3%)	referent		
mild symptoms	173	24 (13.9%)	149 (86.1%)	0.70	0.40, 1.21	
severe symptoms	372	56 (15.1%)	316 (84.9%)	0.77	0.50, 1.19	

Barrett's = Barrett's esophagus, esophageal dysplasia, or esophageal adenocarcinoma; OR = odds ratio calculated by logistic regression; p-value of Wald statistic

As expected, male gender, non-Hispanic Caucasian race/ethnicity, and older age were significantly associated with Barrett's esophagus or worse, as was the use of a proton-pump inhibitor and the presence of a hiatal hernia. There was a trend towards patients' having the study outcome if they were recruited from a GI clinic rather than an ENT clinic; however, the association ($p= 0.051$) did not meet the pre-determined level of statistical significance ($p<0.05$) (Table 5).

Assessment of Confounding and Associations among Covariates

Absence of Confounding

Neither age, gender, race/ethnicity, use of proton-pump inhibitor, the presence of a hiatal hernia, nor referent study cohort confounded the relationship between the GERD symptom severity variables and the study outcome.

Associations With Proton-Pump Inhibitor Use

The use of proton-pump inhibitors was significantly associated with more severe GERD symptoms (all four measures, $p\leq 0.01$). Use of a proton-pump inhibitor was not independently associated with patients' age, gender, race/ethnicity, presence of hiatal hernia, or institution (OHSU or PVAMC).

The association between GERD symptom severity and Barrett's esophagus or worse differed by proton-pump inhibitor use (interaction with number of severe GERD symptoms, $p=0.006$; interaction with GERD symptom score, $p=0.004$). Among PPI-users, lower GERD symptom severity was independently associated with Barrett's

esophagus or worse. Among subjects who were *not* using a PPI, there was no association between GERD symptom severity and the study outcome.

Associations Between GERD Symptom Severity and Esophagitis

GERD symptom severity was significantly related to the presence of esophagitis. This relationship persisted when only typical GERD symptoms were considered, but there was no significant association between the severity of *atypical* GERD symptoms and esophagitis. In the subpopulation of PPI-users, the severity of typical GERD symptoms was significantly associated with esophagitis, but the comprehensive measures of GERD symptom severity were *not*(Table 9).

Table 9: Association of Esophagitis and Gastroesophageal Reflux Disease (GERD) Symptom Severity

	OR	95% CI	p-value		OR	95% CI	p-value
total # severe GERD symptoms	1.05	(1.01, 1.09)	0.015	**PPI-user**	1.05	(1.00, 1.11)	0.065
				PPI-non-user	1.07	(1.01, 1.13)	0.024
GERD symptom severity score	1.03	(1.01, 1.05)	0.005	**PPI-user**	1.03	(1.00, 1.06)	0.076
				PPI-non-user	1.05	(1.02, 1.08)	0.003
# severe typical GERD symptoms	1.08	(1.02, 1.14)	0.006	**PPI-user**	1.09	(1.01, 1.18)	0.023
				PPI-non-user	1.09	(1.01, 1.19)	0.035
# severe *atypical* GERD symptoms	1.04	(0.97, 1.11)	0.244	**PPI-user**	1.03	(0.94, 1.13)	0.485
				PPI-non-user	1.08	(0.98, 1.19)	0.129

"typical" GERD symptoms measured with GERD Health-Related Quality of Life Questionnaire; "atypical" GERD symptoms measured with Reflux Symptom Index; OR = odds ratio calculated by logistic regression; CI = confidence interval; p-value of Wald statistic

Final Multiple Logistic Regression Models

The final multiple logistic regression model for Barrett's esophagus or worse included these covariates: GERD symptom severity (as number of severe GERD symptoms, number of severe typical GERD symptoms, number of severe *atypical* GERD symptoms,

or overall GERD symptom severity score), age (categorized with cut-offs at ages 58 and 68), gender, race/ethnicity (White vs. not White), use of proton-pump inhibitor, presence of hiatal hernia, clinic of recruitment (gastroenterology versus otolaryngology), and institution of recruitment (OHSU vs. PVAMC). All the models, except the one for number of severe typical GERD symptoms, included an interaction term between GERD symptom severity and use of proton-pump inhibitor (Table 6).

Interpretation of the Final Models

Global GERD Symptom Severity Measures

After adjusting for patient age, gender, race/ethnicity, presence of hiatal hernia, clinic and institution of recruitment, GERD symptom severity was significantly associated with Barrett's esophagus or worse among patients using a proton-pump inhibitor. Each fewer severe GERD symptom was associated with a 10.3% increase in the odds of Barrett's esophagus or worse (p=0.002). Each fewer point of the GERD symptom severity score was associated with a 5.3% increase in the odds of Barrett's esophagus or worse (p=0.002). That is, among patients using a proton-pump inhibitor, a lower number of severe GERD symptoms was significantly associated with an increased odds of Barrett's esophagus or worse. Among patients *not* using a proton-pump inhibitor, GERD symptom severity was *not* significantly associated with the study outcome (p=0.237 and p=0.175, respectively).

Typical and *Atypical* GERD Symptom Severity

Each fewer severe typical GERD symptom was associated with a 9.6% increase in the odds of Barrett's esophagus or worse ($p=0.020$) for both users and non-users of PPI's.

Among PPI-users, each fewer severe *atypical* GERD symptom was associated with a 19.2% increase in the odds of Barrett's esophagus or worse ($p<0.001$). Among patients *not* using a PPI, each fewer severe *atypical* GERD symptom was associated with a 29.3% *decrease* in the odds of Barrett's esophagus or worse ($p=0.003$).

Discussion

The incidence of esophageal adenocarcinoma has been increasing dramatically over the past few decades for reasons that are not yet entirely clear. Better understanding of its risk factors and natural history could provide the foundation for effective prevention and treatment of this disease. This study offers insight into which patients with gastroesophageal reflux symptoms are most at risk for Barrett's esophagus, esophageal dysplasia, and esophageal adenocarcinoma in terms of GERD symptom severity, esophageal versus extraesophageal manifestations of GERD, and use of proton pump inhibitors.

Lagergren *et al* established symptomatic GERD as a risk factor for esophageal adenocarcinoma in their population-based case-control study of all Swedish esophageal adenocarcinoma cases diagnosed in the late 1990s.[20] They identified symptomatic GERD as recurrent heartburn or regurgitation and found that subjects with the most severe GERD had a risk of esophageal adenocarcinoma 20 times as high as those without symptoms. They also found that persons with both long-standing and severe GERD symptoms has an adjusted odds ratio for esophageal adenocarcinoma of 43.5 compared to asymptomatic persons. These strong findings form the scientific basis on which patients are identified for endoscopic screening.

Barrett's esophagus is the most definitive risk factor for esophageal adenocarcinoma.[9] Treatment of Barrett's esophagus reduces the incidence of esophageal dysplasia,[56] and identification of Barrett's esophagus is the purpose of endoscopic screening for patients

with long-standing GERD.[1] Given the risks and yield of endoscopic screening, many studies have tried to identify the subset of GERD patients most at risk for Barrett's esophagus. While cross-sectional and matched case-control studies of patients referred for EGD have shown that the age of onset and duration of symptoms of GERD are associated with Barrett's esophagus,[14, 35, 57] the relationship between the severity of GERD symptoms and Barrett's esophagus has been less well understood. Gerson *et al* demonstrated that, in GERD patients referred for esophageal diagnostic testing, more severe heartburn, nocturnal pain, and odynophagia as well as less severe dysphagia are associated with Barrett's esophagus.[35] However, Locke *et al* found no association between the presence of Barrett's esophagus and GERD symptom severity in a large community-based population referred for EGD.[58] Eloubeidi *et al* even found that veterans with Barrett's esophagus were more likely to report *less severe* symptoms (adjusted OR 0.125, 95% CI 0.04-0.42) than veterans with clinical GERD and no Barrett's esophagus.[59]

This study evaluated patients with and without esophageal symptoms of GERD referred for EGD as well as patients manifesting extraesophageal symptoms of GERD in otolaryngology clinics. The study population represents a wider spectrum of clinical GERD patients in terms of symptom severity and type than previously studied. The study analysis found that GERD symptom severity was inversely related to the presence of Barrett's esophagus, particularly in patients using proton pump inhibitors. That is, persons with less severe GERD were *more* likely to have Barrett's or worse than persons with more severe GERD. This finding challenges the understanding of GERD's natural

course implied by the targeted screening of symptomatic patients. The different manifestations of GERD may lie on a continuous spectrum of disease with severity increasing over time,[60, 61] but patients' symptom severity may not progress in parallel. When identifying GERD symptom severity as a strong risk factor for esophageal adenocarcinoma, Lagergren *et al* asked study participants to report symptoms of heartburn and regurgitation that had occurred at least 5 years before their cancer diagnosis.[20] Studies of the relationship between Barrett's esophagus and GERD symptom severity, including this study, have asked study participants to report on symptoms around the time of endoscopic evaluation. It could be that the severity of GERD symptoms increases over time until the esophagus develops pre-cancerous lesions not sensitive to gastric reflux. If this is the true natural history of GERD, patients whose GERD symptoms have resolved over time may be the subset of patients at greatest risk for Barrett's esophagus.

Consideration of patients' GERD symptom characteristics—namely esophageal or extraesophageal—can further define the patient population most at risk of Barrett's esophagus and esophageal adenocarcinoma. Most previous studies limit their definitions of clinical GERD to heartburn and acid regurgitation, although patients with extraesophageal manifestations of GERD have been shown to be as likely to have Barrett's esophagus as patients with heartburn.[62] In fact extraesophageal GERD symptoms, particularly a chronic cough, have been associated with more severe esophageal disease. In a case-control study of patients with esophageal adenocarcinoma, Reavis *et al* found that 54% of cases had at least one extraesophageal GERD symptom

compared to 40% of controls with Barrett's esophagus, 26% of controls with GERD, and 19.6% of controls with no GERD symptoms. The same study also found a decreasing frequency of typical GERD symptoms from unaffected controls to GERD (86%), Barrett's esophagus (66%), and esophageal adenocarcinoma (43%) groups.[41] Our study also found a difference in the relationships between typical and extraesophageal symptoms of GERD with respect to patients' risk of Barrett's esophagus or worse: Barrett's esophagus or worse was associated with less severe typical GERD symptoms but *more severe* extraesophageal GERD symptoms, at least among patients not treated with a proton pump inhibitor.

In this study, the use of proton pump inhibitors (PPI) was a strong effect modifier of the relationship between GERD symptom severity and Barrett's esophagus or worse, suggesting that patients' use of this medication must be considered by clinicians deciding whether or not to screen them endoscopically. In patients not using a PPI, GERD symptom severity was not significantly associated with Barrett's esophagus or worse; in patients using a PPI, less severe GERD was associated with Barrett's esophagus or worse, which is consistent with the findings of previous studies. Only 18% of Locke *et al*'s study population used PPI's, and that study found no association between the severity of typical GERD symptom and Barrett's esophagus.[58] In another study population with 62.5% of study participants using a PPI, patients with Barrett's esophagus were less likely to report severe typical GERD symptoms.[59] In contrast to the current practice of sending to endoscopy the patients whose symptoms are *not* responsive to PPI's,[1] these study results suggest that patients whose symptoms resolve with PPI's are

the high-risk patients who *should* be evaluated by endoscopy. The severity of symptoms induced by esophageal acid exposure has been shown to be less in patients with Barrett's esophagus compared to GERD patients without Barrett's esophagus. In fact, patients with the most severe esophageal injury—namely Barrett's esophagus, esophageal dysplasia, and esophageal adenocarcinoma—may have very mild GERD symptoms.[63] PPI's may relieve patients GERD symptoms and heal esophagitis, but even high-dose PPI therapy nearly eliminating esophageal acid exposure does not usually result in healing Barrett's esophagus.[64-66] At least one study has even shown that PPI-use reveals the Barrett's esophagus hidden by active esophagitis.[67] Other studies show that PPI-use may be masking the progression of esophageal injury and may be diverting the patients most at risk for Barrett's esophagus and esophageal adenocarcinoma from endoscopic evaluation. Alternatively, PPI-use could be masking the natural resolution of GERD symptoms in the face of continued acid reflux.[68] This phenomenon would also divert the most high-risk patients away from endoscopic screening.

Strengths of the Study

This study draws its observations from patients with the full spectrum of GERD symptom severity and from patients who are not currently being targeted for screening, thus offering a more accurate description of GERD symptoms' association with esophageal injury than previous studies limited to those patients already being screened.[35] It also offers a comparison of Barrett's prevalence in patients with different GERD symptom profiles, thus identifying a sub-population of GERD patients who are elevated risk of Barrett's and who should be targeted for screening. Thirdly, it elucidated and

demonstrated the strong modifying effect PPI-use has on GERD symptom severity in the context of selecting patients for endoscopic screening.

Limitations of the Study

The study also has some limitations with respect to its design, its study population, and the variables used.

As a cross-sectional study, this study reports only correlations at a single point in time among the variables of interest. It cannot demonstrate causation. Given these limitations, the cross-sectional design *does* simulate the patient population encountered clinically in that the patients present with a wide range of GERD symptom severity and are at various stages of esophageal injury and reflects prevalent disease.

Although this study uses a population closer in symptom composition to the general population, it is still not entirely representative of the general primary care population to whom screening criteria are applied. It includes only persons who were motivated and able to access specialty medical care at two tertiary medical centers in Portland, Oregon. The three groups of patients included in this study were considered collectively to represent patients who have come to medical attention and who have a range of GERD symptoms and esophageal pathology, but they are not a clinically or physiologically coherent population. An ideal study would follow a well-described group of people representative of the general population for many years. Study participants could keep detailed diaries of their GERD symptoms, be randomized to PPI treatment or placebo,

and be evaluated by endoscopy regularly. Future studies could assess the association between GERD symptom severity and Barrett's in other communities and in the primary care patient population.

The results of this study could also have been affected by selection bias. Only 11% of patients eligible to be included in cohort A, i.e. patients who had an EGD during the data collection period, were included in the study analysis. The majority (88%) of patients that were not included never completed any of part of the GERD symptom questionnaire, which most likely reflects the way the questionnaires were distributed to patients. GI clinic reception desk staff were asked to give the questionnaires to all patients scheduled for EGD, which was not always done due to personnel changes and the staff's competing responsibilities. The completed paper questionnaires were then retrieved by a research assistant. Given the magnitude of non-response, it appears that the majority of non-responders were never asked to complete the questionnaire. Assuming that a patient's chance of receiving a questionnaire was not affected by his/her GERD symptomatology or his/her EGD findings, this particular cause of "non-response" should not bias the study results. However, of patients who received the questionnaire, one might expect those patients with more severe GERD and those with known esophageal damage to be more likely to complete the questionnaire. So, inclusion of cohort A should bias the study results towards the null, meaning that the magnitude of association between mild GERD symptoms and severe esophageal damage is actually greater than found in this study.

This study used as its outcome the diagnosis of Barrett's esophagus, esophageal dysplasia, or esophageal adenocarcinoma. The few cases of esophageal dysplasia (17 of the 769 study participants) and of esophageal adenocarcinoma (6 out of 769) were added to the more numerous cases of Barrett's esophagus (104 out of 769) in order to capture all study participants with advanced esophageal injury. Given the variable participation exclusion criteria applied to potential study participants, the prevalence of disease in this study population is not representative of the prevalence in any naturally occurring patient population. However, this outcome variable still represents more severe esophageal injury in a manner that allows the study analysis to be valid.

GERD symptom severity was operationalized by categorizing and summarizing responses to two questionnaires, the GERD Health-Related Quality of Life questionnaire (GERD QoL) and the Reflux Symptom Index (RSI). The original, complete questionnaires are validated, but this study's manipulation of the responses to individual components of the questionnaires is not. The definition of a "severe" GERD symptom was defined with clinical significance in mind, but it is possible that a more restrictive definition of "severe" would have led to different study results such as a statistically significant association between GERD symptom severity and Barrett's among PPI-non-users. Additionally, it is not clear if summed scores from the GERD QoL and the RSI each capture "typical GERD symptoms" and "laryngopharyngeal reflux symptoms," respectively, equally well. The study conclusions are drawn with the assumption that they do. Considering these limitations, this study's operationalization of GERD

symptom severity should be considered as accurate as many other studies'[35, 69] given the lack of a commonly accepted measurement of GERD symptom severity.

A major finding of this study is the strong effect of PPI-use on GERD symptoms, and the finding is based on study participants' questionnaire responses and chart review. Although the questionnaires focus on current and recent GERD symptoms, study participants using PPI's may not have known whether to answer the questions as if they were using or not using the medication. However, if they systematically gave answers of more severe symptoms—presumably describing their untreated symptoms—such a response would have biased the odds ratio towards the null, thus indicating that the "real" risk of Barrett's in less severe GERD is actually greater than that observed in this study. In addition, PPI-use was recorded from either patient report or from medical chart review, but study participants' actual adherence to this medication and their duration of therapy was not measured in this study.

Finally, the analysis did not control for all known risk factors for Barrett's esophagus and esophageal adenocarcinoma, such as obesity[70] and the duration of GERD symptoms.[14, 57] Inclusion of these potential confounders may have demonstrated a different relationship between GERD symptom severity and Barrett's. In particular, knowledge of patients' duration of symptoms might enable us to distinguish asymptomatic patients early in the course of their disease from asymptomatic patients at the end stages of esophageal injury and thus be able to interpret symptom severity more accurately.

Summary and Conclusions

In summary, more mild gastroesophageal reflux symptoms are associated with an elevated risk of Barrett's esophagus, esophageal dysplasia, and esophageal adenocarcinoma among users of proton pump inhibitors, whether those symptoms are esophageal or extraesophageal. In persons not using a PPI, GERD symptom severity in general is not associated with the presence of Barrett's esophagus or worse. However, in this subpopulation, distinguishing between esophageal and extraesophageal GERD symptoms shows that more mild esophageal and more severe extraesophageal GERD symptoms are associated with Barrett's esophagus or worse. Patients with the least severe typical GERD symptoms (like heartburn) are most likely to have pre-malignant or malignant esophageal lesions. Patients' use of a proton-pump inhibitor should be considered in the evaluation of their risk of Barrett's, as the symptomatic relief associated with that medication may falsely reassure the clinician. Clinicians should also be aware that severe laryngopharyngeal reflux symptoms are associated with Barrett's.

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Appendix: Gastroesophageal Reflux Disease Symtpom Questionnaires

GERD Health Related Quality of Life Questionnaire

1853319527

CENTER: ● OHSU ○ VA

Name:_____ Date of Birth:_____

SS # Today's Date:

[ ][ ][ ] - [ ][ ] - [ ][ ][ ][ ] [ ][ ] / [ ][ ] / [ ][ ]

INSTRUCTIONS:
Please answer all of the questions by filling in one circle for each question.

Shade Circles Like This--> ●

Not Like This--> ⊗ ✓

- *** Do not use pencil.**
- *** Use only a blue or black pen.**
- *** Please fill in the circle completely.**

1. How bad is your heartburn?
   - ○ No symptoms
   - ○ Symptoms noticeable, but not bothersome
   - ○ Symptoms bothersome every day
   - ○ Symptoms affect daily activities
   - ○ Symptoms are incapacitating - unable to do daily activities

2. Do you have heartburn when lying down?
   - ○ No symptoms
   - ○ Symptoms noticeable, but not bothersome
   - ○ Symptoms bothersome every day
   - ○ Symptoms affect daily activities
   - ○ Symptoms are incapacitating - unable to do daily activities

3. Do you have heartburn when standing up?
   - ○ No symptoms
   - ○ Symptoms noticeable, but not bothersome
   - ○ Symptoms bothersome every day
   - ○ Symptoms affect daily activities
   - ○ Symptoms are incapacitating - unable to do daily activities

4. Do you have heartburn after meals?
   - ○ No symptoms
   - ○ Symptoms noticeable, but not bothersome
   - ○ Symptoms bothersome every day
   - ○ Symptoms affect daily activities
   - ○ Symptoms are incapacitating - unable to do daily activities

5. Does heartburn change your diet?
   - ○ No symptoms
   - ○ Symptoms noticeable, but not bothersome
   - ○ Symptoms bothersome every day
   - ○ Symptoms affect daily activities
   - ○ Symptoms are incapacitating - unable to do daily activities

Please turn page.

[ ][ ][ ][ ]

6. Does heartburn wake you from sleep?
   - ○ No symptoms
   - ○ Symptoms noticeable, but not bothersome
   - ○ Symptoms bothersome every day
   - ○ Symptoms affect daily activities
   - ○ Symptoms are incapacitating - unable to do daily activities

7. Do you have difficulty swallowing?
   - ○ No symptoms
   - ○ Symptoms noticeable, but not bothersome
   - ○ Symptoms bothersome every day
   - ○ Symptoms affect daily activities
   - ○ Symptoms are incapacitating - unable to do daily activities

8. Do you have pain with swallowing?
   - ○ No symptoms
   - ○ Symptoms noticeable, but not bothersome
   - ○ Symptoms bothersome every day
   - ○ Symptoms affect daily activities
   - ○ Symptoms are incapacitating - unable to do daily activities

9. Do you have bloating or gassy feelings?
   - ○ No symptoms
   - ○ Symptoms noticeable, but not bothersome
   - ○ Symptoms bothersome every day
   - ○ Symptoms affect daily activities
   - ○ Symptoms are incapacitating - unable to do daily activities

10. If you take medication, does this affect your daily life?
    - ○ No symptoms
    - ○ Symptoms noticeable, but not bothersome
    - ○ Symptoms bothersome every day
    - ○ Symptoms affect daily activities
    - ○ Symptoms are incapacitating - unable to do daily activities

11. How satisfied are you with your present condition?
    - ○ Very satisfied
    - ○ Satisfied
    - ○ Neutral
    - ○ Dissatisfied
    - ○ Incapacitated

The Reflux Symptom Index (RSI)

CENTER: ● OHSU ○ VA

Name:_____ Date of Birth:_____

SS # ☐☐☐-☐☐-☐☐☐☐ Date: ☐☐/☐☐/☐☐

Within the last month, how did the following problems affect you? Please circle the number that describes how you felt:

	No problem					*Severe problem*
1. Hoarseness or a problem with your voice	0	1	2	3	4	5
2. Clearing your throat	0	1	2	3	4	5
3. Excess throat mucus or postnasal drip	0	1	2	3	4	5
4. Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
5. Coughing after you eat or after lying down	0	1	2	3	4	5
6. Breathing difficulties or choking episodes	0	1	2	3	4	5
7. Troublesome or annoying cough	0	1	2	3	4	5
8. Sensations of something sticking in your throat or a lump in your throat	0	1	2	3	4	5
9. Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5

8432314825 ☐☐☐☐