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Age at Onset of GERD Symptoms Predicts Risk of Barrett's Esophagus

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Abstract

OBJECTIVES—Symptoms of gastroesophageal reflux disease (GERD) are the primary risk factor for Barrett's esophagus (BE). However, the significance of age at symptom onset is unknown. We examined the effects of multiple dimensions of GERD exposure on BE risk and whether these associations are modified by other risk factors for BE.

METHODS—Data were from a cross-sectional study of 683 Veterans Affairs patients undergoing an elective esophagogastroduodenoscopy (EGD) or a study EGD concurrently with colonoscopy from primary care clinics. We compared 236 patients with both endoscopically suspected and histologically confirmed BE to 447 primary-care patients ("primary-care controls") without endoscopically suspected BE on their study EGD. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariate logistic regression.

RESULTS—Age at onset <30 years of frequent (at least weekly) GERD symptoms was associated with highest risk of BE (OR = 15.1, 95% CI 7.91–28.8), and risk increased linearly with earlier age at onset of symptoms (*P*-trend = 0.001). This association was independent of cumulative GERD symptom duration. People with early onset GERD symptoms who reported ever using proton pump inhibitors were at especially high risk of BE (OR = 31.1, 95% CI 13.9–69.7). In people with frequent GERD symptoms, BE risk was almost 80% lower among

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CONFLICT OF INTEREST

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Helicobacter pylori-positive patients (OR = 2.60, 95% CI 1.26–5.40) than those negative for *H. pylori* (OR = 8.24, 95% CI 5.00–13.6).

CONCLUSIONS—Risk of BE increased linearly with earlier age at onset of frequent GERD symptoms. Age at symptom onset may help practitioners decide which patients with GERD symptoms to refer for endoscopic screening for BE.

INTRODUCTION

Adenocarcinoma of the esophagus is a rapidly fatal disease that is becoming more common in the United States, Western Europe, Australia, and other industrialized nations (1–3). Almost all cases of esophageal adenocarcinoma are thought to arise within areas of Barrett's esophagus (BE), a metaplastic change in the mucosal lining of the lower esophagus. The rates of BE have increased rapidly during the past several decades (4–6).

Gastroesophageal reflux disease (GERD) has been strongly implicated as the primary causal factor for BE, and is a very common condition among Western populations (7). Epidemiological studies have reported >10-fold relative risks for BE associated with frequent GERD symptoms (8,9). However, presence of GERD is a poor predictor of BE as only 5–13% of people with symptoms of GERD will develop BE over their lifetime (10–13). Thus, the various dimensions of GERD exposure such as frequency, duration, severity, and age at onset of symptoms are likely to have an impact on risk.

Epidemiological studies have found that the risk of BE may increase linearly with increasing frequency, severity, and duration of GERD symptoms (8,9). Although it has been shown that people who develop GERD symptoms at an earlier age are at highest risk for esophageal adenocarcinoma (14), it is unclear whether the magnitude of risk for BE associated with GERD symptoms independent of duration is mediated by age at onset. Similarly, although it has been shown that the risk of esophageal adenocarcinoma associated with GERD symptoms is greater among smokers and people who are obese, the role of these potential effect modifiers is less clear in BE. Thus, there may be other cofactors that further modulate the effect of GERD on the risk of BE.

We therefore analyzed in this study the effects of multiple dimensions of GERD exposure on the risk of BE. Specifically, we sought to quantify the effects of frequency and severity of GERD that develops at an earlier age on the risk of BE, and to identify potential effect modifiers of the association between GERD symptoms and BE.

METHODS

Study design and participants

We used data from a cross-sectional case–control study of BE performed at the Michael E. DeBakey Veterans Affairs Medical Center in Houston, Texas (15). The study was approved by the Institutional Review Boards for the Michael E. DeBakey Veterans Affairs Medical Center and the Baylor College of Medicine. Patients aged 40–80 years undergoing an elective esophagogastroduodenoscopy ("elective EGD group") between 15 February 2008 and 31 December 2011, and patients scheduled for outpatient clinic visits in primary care (at one of seven selected clinics in the Houston VA) between 1 September 2008 and 31 December 2010, who were also eligible for screening endoscopy ("primary-care group"), were prospectively enrolled into the study (Supplementary Figure 1 online). The lower age limit in the primary-care group was 50 as this is the age when screening colonoscopy is recommended to commence. The purpose of enrolling patients seen in primary care was to obtain controls without endoscopically suspected BE from the source population for BE

cases at the Houston VA. These controls represent patients, who, if they had BE, would be diagnosed with BE at the Houston VA. None of the primary-care patients were primarily referred for EGD and, if they agreed to participate in the study, underwent the study EGD at the same time as their colonoscopy. The same eligibility criteria were used for both groups. Patients with a previous history of gastroesophageal surgery, previous diagnosis of cancer (esophageal, lung, liver, colon, breast, or stomach), currently taking anticoagulants, with significant liver disease (as indicated by platelet count <70,000, ascites, or known gastroesophageal varices), or a history of major stroke or mental disorder were ineligible for the study. Among eligible patients in the elective EGD group, 70% completed the study (underwent the study EGD and completed the study questionnaire). In the primary-care group, 43% of eligible patients completed the study; however, among patients who actually underwent their colonoscopy, 85% completed the study.

We compared BE cases with a primary-care control group without endoscopically suspected BE on their study EGD. Eligible BE cases included patients from the elective EGD group or the primary-care group with incident or prevalent BE. BE was defined as the presence of specialized small intestinal epithelium in the histopathological examination of at least one biopsy obtained from endoscopically suspected BE areas using Jumbo biopsy forceps. We excluded endoscopically suspected BE patients without specialized intestinal metaplasia and controls recruited from the elective EGD group from this analysis.

Presence and length of BE was recorded at the study EGD according to the Prague C & M classification (16), and two pathologists reviewed all slides for endoscopically suspected BE to determine the presence of specialized intestinal epithelium. Two investigators (HES and ZQ) reviewed the study data-collection forms as well as the clinical reports for the study EGD and biopsy results for all patients with endoscopically suspected BE, as well as a randomly selected sample of 300 patients without endoscopically suspected BE. Overall, an agreement on case–control status of approximately 90% was found; inconsistencies were resolved by discussion with the study pathologists.

Measurement of exposure to GERD

All study participants completed an RA-administered computer-assisted survey before the study EGD. We ascertained a history of GERD symptoms using a slightly modified version of the validated Gastroesophageal Reflux Questionnaire (17). We asked participants about experience of heartburn (“a burning pain or discomfort behind the breastbone in your chest”) or acid regurgitation (“a bitter or sour-tasting fluid coming up into your throat or mouth”); positive responses to these initial screening questions elicited further questions about age at onset of symptoms and frequency of symptoms at ages 10–19, 20–29, 30–49, and 50–79 years, as applicable, on a five-point ordinal scale. See the questionnaire in the Appendix for full details. We defined participants as never having had GERD symptoms if they reported no symptoms of heartburn and acid regurgitation at all age periods; for all other participants, frequency and severity of GERD symptoms were equal to their highest reported frequency (and severity) of either heartburn or acid regurgitation. We defined “frequent symptoms” as those occurring at least weekly. Cumulative GERD symptom duration (years) was defined as the total number of years from age 10 to age at study recruitment in which a participant had frequent GERD symptoms, and was calculated by summing all age intervals where at least weekly GERD symptoms were reported.

Measurement of potential confounders

The survey asked participants about their education, history of tobacco smoking and alcohol intake, medical history, ever use of H_2-receptor antagonists and proton pump inhibitors (PPIs), and use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) in the last

year. We calculated body mass index (BMI) by dividing weight (in pounds) by height (in inches) squared and multiplying by 703, and we used the World Health Organization categories (healthy weight: <25.0, overweight: 25.0–29.9, obese: ≥30). Never smokers were defined as those who had smoked <100 cigarettes over their whole life, and we derived cumulative packyears of smoking history. Participants were classified as positive for *Helicobacter pylori* infection if organisms were seen on histopathological examination of any of the study's gastric biopsies, or if review of medical records revealed previously positive biopsy or serum antibodies or treatment for *H. pylori* received.

Statistical analysis

Our primary aim was to quantify the associations between key measures of exposure to GERD (age at onset, frequency, severity, and duration) and the risks of BE. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional multivariate logistic regression models. Any covariate that produced a change in the OR for symptoms of GERD by ≥10% was included in the final model. Multivariate analyses are shown adjusted for age at study recruitment (in years; continuous), sex, highest level of education ("school only", "technical college/ diploma", and "university"), cumulative smoking history ("Never smoker", "<30 pack-years", and "≥30 pack-years"), BMI (continuous), alcohol intake (in standard drinks/week; continuous), and use of aspirin or NSAIDs in the last year ("No", "Yes"). We examined potential statistical interactions between GERD variables and other risk factors by including a multiplicative term in the multivariate model. To assess potential biological interactions between GERD symptoms and other exposures in relation to the risk of BE, we created new variables that reclassified participants according to their combined exposure (see Supplementary Tables 4–6 online for full details) and tested for departure from additivity using the Synergy Index (SI). A SI >1 indicates that the joint effect of two risk factors on the risk of BE is greater than the sum of their independent effects and suggests the presence of biological interaction.

Statistical significance was determined at $\alpha = 0.05$, and all tests for statistical significance were two-sided. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

In total 245, BE cases and 455 primary-care controls completed the study, of whom 236 BE cases (195 elective EGD patients and 41 primary-care patients) and 447 primary-care controls had complete data on frequency and duration of GERD symptoms and were included in the analyses. The BE case group included 185 patients with incident BE and 51 patients with prevalent BE. We present here the results for the combined case group (incident + prevalent cases). The results from the analysis of incident BE cases only were similar to those reported here for the combined group, and are provided as **Supplementary Material** online only (Supplementary Tables 1–3 online).

Table 1 presents descriptive characteristics of the study participants. Mean age of study participants was 62 years, and 97% of participants were male. BE cases were significantly more likely to be white and have ever used PPIs, and significantly less likely to have *H. pylori* infection compared with the primary-care controls. We found no differences in the distributions of education, BMI, smoking, alcohol consumption, and use of aspirin or NSAIDs between cases and controls.

Approximately 83% of BE cases reported ever experiencing GERD symptoms, with 19% experiencing frequent GERD symptoms before the age of 30 years and 40% ever experiencing severe symptoms. Compared with primary-care controls, BE cases were

significantly more likely to report either ever using PPIs or ever experiencing GERD symptoms (88.1% vs. 49.0%, $P < 0.001$).

Frequency of GERD symptoms, age at onset, and risk of BE

BE cases were significantly more likely than primary-care controls to have ever experienced GERD symptoms (OR = 5.70, 95% CI 3.86–8.42), and the risk of BE increased with frequency of GERD symptoms (Table 2). When we examined the association between age at onset of GERD symptoms and risk of BE (unadjusted for cumulative duration of GERD symptoms; Table 2), the highest risks were observed among people reporting GERD symptoms at earlier ages, and risk increased linearly with earlier age at onset (*P*-trend = 0.001). Compared with those with never GERD symptoms, people who developed frequent symptoms of GERD before the age of 30 years (≥weekly GERD symptoms, OR = 15.1, 95% CI 7.91–28.8) had higher risks for BE than those with first symptoms between ages 30 and 49 years (OR = 6.87, 95% CI 4.22–11.2) and 50 to 79 years (OR = 4.73, 95% CI 2.91–7.67). We performed separate analyses for associations between age at onset of heartburn symptoms or acid regurgitation symptoms and risk of BE, and found similar magnitudes and patterns of risk for BE to that observed for the combined GERD exposure variable (data not shown).

Severity of GERD symptoms, age at onset, and risk of BE

Risk of BE increased with severity of GERD symptoms (Table 3). Compared with people with never symptoms, those with any history of severe symptoms had 12-fold higher risk of BE (OR = 12.0, 95% CI 7.34–19.6). We found some evidence of higher BE risk in people with younger age at onset severe symptoms (OR = 15.9, 95% CI 3.99–63.3), however, the CIs for all categories were overlapping and the test for trend was not statistically significant (*P*-trend = 0.87).

Cumulative GERD symptom duration, age at onset, and risk of BE

We found a significant linear trend of increasing risk of BE with increased cumulative GERD symptom duration (Table 4; *P*-trend = 0.002). Among those with GERD symptoms, BE risk increased almost 30% per 10 additional years of exposure (OR = 1.27, 95% CI 1.13–1.42). For patients with cumulative GERD symptom duration ≤20 years, those who developed frequent GERD symptoms before the age of 30 years had similar risks of BE to those that developed symptoms later in life. However, when we modeled age at onset as a continuous variable, early age at onset of GERD symptoms was associated with significantly higher BE risk even after adjusting for cumulative GERD symptom duration also modeled as a continuous variable (unadjusted for cumulative GERD symptom duration, OR per 10 year increase in age at onset = 0.75, 95% CI 0.65–0.87; adjusted for cumulative GERD symptom duration, OR = 0.81, 95% CI 0.69–0.95).

Statistical and biological interaction of GERD symptoms and other risk factors for BE

The strength of the associations between GERD symptoms (frequency, duration, and age at onset) and BE were consistent across strata of BMI, smoking history, use of aspirin or NSAIDs, use of PPIs, and *H. pylori* infection, and all multiplicative interaction terms were not statistically significant (data not shown). In analyses of combined exposure (examining additive interaction), we found no evidence for a joint effect of GERD symptoms and BMI, smoking status, or use of aspirin or NSAIDs (Supplementary Tables 4–6 online). However, the risk of BE associated with frequent GERD symptoms was markedly lower among *H. pylori*-positive patients compared with those negative for *H. pylori* (Supplementary Table 4 online). The relative risk for combined exposure was approximately 80% lower than expected under the additive model (SI = 0.23, 95% CI 0.08–0.64). The pattern of effect was

similar for duration of GERD symptoms (SI = 0.12, 95% CI 0.03–0.53). Although not statistically significant, the risk of BE because of the combined effects of GERD symptoms and use of PPIs was approximately twofold higher than expected under simple additive models (frequency of symptoms 10 years before diagnosis, SI = 1.84, 95% CI 0.82–4.14; duration, SI = 1.87, 95% CI 0.84–4.17; age at onset, SI = 2.15, 95% CI 0.77–6.02). Those with early-onset GERD symptoms who reported PPI use had the highest risk of BE (OR = 31.1, 95% CI 13.9–69.7).

DISCUSSION

In this cross-sectional study, we confirmed that the presence, frequency, severity, and duration of GERD symptoms are strong and significant risk factors for BE. Most importantly, we found evidence that age at onset of frequent GERD symptoms may be an indicator of increased risk of BE independent of duration of exposure. People with early onset of frequent GERD symptoms and a history of PPI use were at an especially high risk of BE, whereas risk of BE associated with GERD symptoms was significantly lower among people positive for *H. pylori*. We found no evidence that the observed associations between GERD symptoms and BE were modified by BMI, tobacco smoking, or use of aspirin or NSAIDs.

Epidemiological studies have consistently shown that symptoms of GERD are the main risk factor for BE (10,18–21). Although duration of GERD has been shown to be a risk factor for BE (22,23), this study provides the first strong preliminary evidence that age at onset may modify the effect of GERD on the risk of BE independent of duration of symptoms. We found strong evidence that risk increased linearly with earlier age at onset of frequent GERD symptoms, and some indication (albeit not statistically significant) that severe GERD at an early age may be associated with higher risks of BE than severe GERD that developed later in life. The increased risk of BE with early-onset frequent GERD symptoms is analogous to that obtained for esophageal adenocarcinoma by Pandeya *et al.* (14) who showed that the magnitude of risks was highest for those with frequent GERD symptoms before the age of 20 years. Analyses of data from an Australian case–control study for BE found greatest risk in those with age at onset between 50 and 79 years (20). However, because the reference group in that study included both those reporting no symptoms for all age intervals and those with GERD symptoms present at other age intervals, the risk estimates at younger age intervals may have been attenuated.

We can only speculate on the apparent increased risk of BE associated with younger age at onset of GERD. This may represent mechanical disruption of the anti-reflux mechanism at the gastroesophageal junction by the formation of a hiatus hernia, and/or genetic factors that predispose to increased risk of BE. Family and twin studies have identified an inherited tendency toward developing GERD, and a locus common to multiple families with severe GERD has been found on 13q14 (24,25). Our finding may also reflect the presence of additional risk factors (e.g., diet, medications, and childhood obesity) that promote the development of early onset as well as severe GERD. Lastly, factors that have a dual but independent effect on GERD as well as BE development such as abdominal obesity in young age may also contribute to our finding of an association between younger age at onset of GERD and increased BE risk.

Our data suggest that patients with BE were significantly more likely than primary-care controls to have ever used PPIs, and among those with a history of PPI use, patients who reported no GERD symptoms had eightfold increased risk of BE. Furthermore, like others (9), we observed highest risk of BE in people with frequent or severe GERD symptoms who have ever used PPIs, and some evidence of an additive interaction. Some have speculated

that PPIs may increase BE risk by altering the stomach chemistry and promoting asymptomatic episodes of bile reflux (26), and that acid and bile reflux may act synergistically when present together (27). However, a more likely explanation is confounding by indication, with severity of GERD symptoms acting as the underlying risk factor associated with PPI use and BE. Increased risk of BE in patients with no GERD who have ever used PPIs may be due to other conditions such as dyspepsia. Larger studies of frequent, long-term PPI use are required to clarify these issues. On the other hand, we found strong evidence of interaction between *H. pylori* and GERD symptoms. Our data suggest that the possible protective effects of *H pylori* on BE should be greatest in those with more frequent, early and long-lasting GERD symptoms.

Consistent with some previous epidemiological studies (9), but not all (28,29), we found no association between smoking and BE in this study. Although a recent pooled analysis found that BE risk among ever smokers approached twofold (30), given the high-level of heterogeneity between studies, the results should be interpreted with caution. Like other single-institution studies (9,28), we found no evidence of a synergistic effect between smoking and GERD with regard to BE. Although GERD has been found to act synergistically with obesity and use of aspirin or NSAIDs in studies of esophageal adenocarcinoma (14,31), we in this study, and others previously (9), have found no evidence that these factors interact with GERD with regards to risk of BE. However, these nonsignificant findings may be because of a lack of power and warrant further investigation.

The major advantages of this study include the large sample size (largely white males, who are most commonly affected by BE) and prospective enrollment of study participants, the standardized histological definition used to diagnose BE, and the use of a comprehensive survey to capture multiple dimensions of GERD exposure at different age intervals and detailed data on many potential confounders. There are several limitations to our study. Although we collected survey data before the study EGD to minimize potential recall and interviewer bias, our case group included patients with incident and prevalent BE. Biased recall among prevalent BE cases is possible; however, exclusion of these patients from the analyses did not appreciably alter our results (Supplementary Tables 1–3 online). The moderate participation rate in our study may have led to selection bias; however, as primary-care controls had similar prevalence of frequent (weekly) GERD symptoms to the general population (7), our results are unlikely to be explained by biased selection of the control group. Although the cases had a lower limit of age compared with the controls, a series of sensitivity analyses showed that the inclusion of all BE cases (aged 40–80 years) did not appreciably bias the risk estimates for GERD symptoms in our study (data not shown). Although we attempted to control for known confounders, we cannot completely rule out residual confounding from unmeasured or poorly measured variables. Finally, because we studied predominantly male veterans, our results may not be generalizable to women and nonveterans.

In summary, in this cross-sectional study, there was a significant increase in the risk of BE with earlier age at onset of frequent GERD symptoms. This knowledge may aid practitioners in the selection of GERD patients for targeted screening for BE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Gastroesophageal reflux disease (GERD) is a very common condition among Western populations and is the primary risk factor for Barrett ' s esophagus (BE).

WHAT IS NEW HERE

- ✓ Patients with an early onset of frequent GERD symptoms and a history of PPI use are at the highest risk of BE.
- ✓ Age at onset of GERD symptoms may modify the effect of GERD on the risk of BE independent of duration of symptoms.
- ✓ Age at symptom onset may aid practitioners in selecting patients with GERD symptoms for endoscopic screening for BE.

Table 1

Distributions of characteristics of cases and controls

Variable	BE cases (n = 236)	Primary-care controls (n = 447)	P value[a]
	n (%)	n (%)	
Demographics			
Mean age, year (s.d.)	61.8 (7.1)	62.1 (6.7)	0.58
Male	229 (97.0)	431 (96.4)	0.67
White	205 (86.9)	247 (55.3)	<0.001
Education			
School only	105 (44.5)	203 (45.4)	0.83
Technical college/diploma	82 (34.7)	156 (34.9)	
University	47 (19.9)	81 (18.1)	
Missing	2 (0.9)	7 (1.6)	
BMI			
Mean (s.d.)	30.3 (5.5)	30.8 (6.3)	0.99
<25.0	37 (15.7)	71 (15.9)	
25.0–29.9	82 (34.7)	155 (34.7)	
≥30	117 (49.6)	221 (49.4)	
Cumulative smoking exposure			
Never smoker	54 (22.9)	111 (24.8)	0.26
0–29.9 pack-years	89 (37.7)	188 (42.1)	
≥30 pack-years	93 (39.4)	148 (33.1)	
Alcohol-drinking status			
Nondrinker	18 (7.6)	29 (6.5)	0.70
Ex-drinker	88 (37.3)	163 (36.5)	
Current drinker	130 (55.1)	253 (56.6)	
Missing	0 (0.0)	2 (0.4)	
Helicobacter pylori status			
Negative	189 (80.1)	283 (63.3)	<0.001
Positive	41 (17.4)	151 (33.8)	
Missing	6 (2.5)	13 (2.9)	
Medications			
Ever used PPIs	171 (72.5)	99 (22.2)	<0.001
Ever used H2RA	22 (9.3)	26 (5.8)	0.09
Aspirin or NSAIDs in the last year	145 (61.4)	280 (62.6)	0.76

BE, Barrett's esophagus; BMI, body mass index; H2RA, H2-receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; s.d., standard deviation.

[a] P values were for the comparison between cases and controls and were obtained using Student's t-test for continuous variables and χ^2-tests for categorical variables.

Table 2

Multivariate analyses of the associations between frequency of GERD[a] symptoms and BE

Frequency of GERD symptoms	BE cases, *n* (%)	Primary-care controls, *n* (%)	OR[b] (95% CI)	
Ever				
No	41 (17.4)	241 (53.9)	1.00	(Ref)
Yes	195 (82.6)	206 (46.1)	5.70	(3.86, 8.42)
At age 10–19 years				
Never symptoms	41 (17.4)	241 (53.9)	1.00	(Ref)
≥1 time per month	7 (3.0)	0 (0.0)	—	—
1 time per week	5 (2.1)	0 (0.0)	—	—
>1 time per week	10 (4.2)	3 (0.7)	20.3	(5.28, 78.0)
No symptoms[c]	173 (73.3)	203 (45.4)	5.14	(3.47, 7.61)
At age 20–29 years				
Never symptoms	41 (17.4)	241 (53.9)	1.00	(Ref)
≥1 time per month	9 (3.8)	8 (1.8)	7.07	(2.53, 19.8)
1 time per week	12 (5.1)	8 (1.8)	8.32	(3.19, 21.7)
>1 time per week	30 (12.7)	9 (2.0)	20.7	(9.03, 47.3)
No symptoms[c]	144 (61.0)	181 (40.5)	4.79	(3.20, 7.16)
At age 30–49 years				
Never symptoms	41 (17.4)	241 (53.9)	1.00	(Ref)
≥1 time per month	18 (7.6)	34 (7.6)	3.29	(1.69, 6.42)
1 time per week	25 (10.6)	26 (5.8)	6.17	(3.20, 11.9)
> 1 time per week	94 (39.8)	59 (13.2)	10.4	(6.38, 16.8)
No symptoms[c]	58 (24.6)	87 (19.5)	3.85	(2.39, 6.18)
At age 50–79 years				
Never symptoms	41 (17.4)	241 (53.9)	1.00	(Ref)
≥1 time per month	20 (8.5)	49 (11.0)	2.41	(1.30, 4.48)
1 time per week	29 (12.3)	37 (8.3)	4.79	(2.64, 8.71)
>1 time per week	109 (46.2)	94 (21.0)	7.14	(4.60, 11.1)
No symptoms[c]	37 (15.7)	26 (5.8)	8.82	(4.66, 16.7)
10 years before diagnosis				
Never symptoms	41 (17.4)	241 (53.9)	1.00	(Ref)
≥1 time per month	19 (8.0)	46 (10.3)	2.43	(1.29, 4.57)
1 time per week	30 (12.7)	33 (7.4)	5.54	(3.03, 10.1)
>1 time per week	122 (51.7)	100 (22.4)	7.50	(4.87, 11.6)
No symptoms[c]	24 (10.2)	27 (6.0)	5.44	(2.83, 10.4)
Frequency of GERD and age at onset				
Never symptoms	41 (17.4)	241 (53.9)	1.00	(Ref)

Frequency of GERD symptoms	BE cases, *n* (%)	Primary-care controls, *n* (%)	OR[b] (95% CI)	
≥Weekly age <30 years	45 (19.1)	18 (4.0)	15.1	(7.91, 28.8)
≥Weekly age 30–49 years	74 (31.4)	69 (15.4)	6.87	(4.22, 11.2)
≥Weekly age 50–79 years	58 (24.6)	72 (16.1)	4.73	(2.91, 7.67)
<Weekly age <30 years	5 (2.1)	6 (1.3)	5.17	(1.48, 18.1)
<Weekly age 30–49 years	6 (2.5)	21 (4.7)	1.73	(0.65, 4.58)
<Weekly age 50–79 years	7 (3.0)	20 (4.5)	2.04	(0.80, 5.18)

BE, Barrett's esophagus; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio.

[a] Highest reported symptoms of either heartburn or acid regurgitation.

[b] Adjusted for age, sex, highest level of education, cumulative smoking history, body mass index, alcohol intake, and use of aspirin or nonsteroidal anti-inflammatory drugs.

[c] Symptoms were present at other age intervals.

Table 3

Multivariate analyses of the association between severity of pain from GERD[a] and BE

Severity of pain from GERD	BE cases, *n* (%)	Primary-care controls, *n* (%)	OR[b] (95% CI)	
Ever				
Never symptoms	41 (17.5)	241 (53.9)	1.00	(Ref)
Mild	29 (12.3)	67 (15.0)	2.43	(1.40, 4.22)
Moderate	71 (30.2)	89 (19.9)	5.09	(3.20, 8.11)
Severe	94 (40.0)	50 (11.2)	12.0	(7.34, 19.6)
At age 10–19 years				
Never symptoms	41 (29.1)	241 (63.2)	1.00	(Ref)
Mild	10 (7.1)	0 (0.0)	—	—
Moderate	9 (6.4)	3 (0.8)	17.3	(4.44, 67.7)
Severe	4 (2.8)	0 (0.0)	—	—
No symptoms[c]	77 (54.6)	137 (36.0)	3.32	(2.14, 5.16)
At age 20–29 years				
Never symptoms	41 (25.0)	241 (61.3)	1.00	(Ref)
Mild	21 (12.8)	11 (2.8)	11.2	(4.95, 25.2)
Moderate	23 (14.0)	11 (2.8)	12.9	(5.78, 28.8)
Severe	8 (4.9)	3 (0.8)	16.0	(4.02, 64.1)
No symptoms[c]	71 (43.3)	127 (32.3)	3.33	(2.14, 5.20)
At age 30–49 years				
Never symptoms	41 (19.2)	241 (56.6)	1.00	(Ref)
Mild	29 (13.6)	51 (12.0)	3.42	(1.93, 6.05)
Moderate	57 (26.8)	44 (10.3)	8.90	(5.17, 15.3)
Severe	50 (23.5)	23 (5.4)	13.3	(7.19, 24.5)
No symptoms[c]	36 (16.9)	67 (15.7)	3.05	(1.80, 5.19)
At age 50–79 years				
Never symptoms	41 (18.1)	241 (54.8)	1.00	(Ref)
Mild	29 (12.8)	61 (13.9)	2.58	(1.47, 4.52)
Moderate	58 (25.5)	84 (19.1)	4.36	(2.70, 7.06)
Severe	70 (30.8)	33 (7.5)	13.6	(7.89, 23.6)
No symptoms[c]	29 (12.8)	21 (4.8)	9.44	(4.65, 19.2)
Severity of pain from GERD and age at onset				
Never symptoms	41 (17.4)	241 (53.9)	1.00	(Ref)
Severe GERD < 30 years	8 (3.4)	3 (0.7)	15.9	(3.99, 63.3)
Severe GERD 30–49 years	44 (18.7)	21 (4.7)	13.2	(6.97, 24.9)
Severe GERD 50–79 years	42 (17.9)	26 (5.8)	10.6	(5.77, 19.5)
Less-severe GERD < 30 years	25 (10.6)	20 (4.5)	7.94	(3.98, 15.8)
Less-severe GERD 30–49 years	45 (19.2)	65 (14.5)	4.52	(2.68, 7.61)

Severity of pain from GERD	BE cases, *n* (%)	Primary-care controls, *n* (%)	OR[b] (95% CI)
Less-severe GERD 50–79 years	30 (12.8)	71 (15.9)	2.35 (1.36, 4.07)

BE, Barrett's esophagus; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio.

[a] Highest severity of pain from either heartburn or acid regurgitation.

[b] Adjusted for age, sex, highest level of education, cumulative smoking history, body mass index, alcohol intake, and use of aspirin or nonsteroidal anti-inflammatory drugs.

[c] Symptoms were present at other age intervals.

Table 4

Multivariate analyses of the association between cumulative GERD a symptom duration (years) and BE, overall and within strata of age at onset

Age at onset of frequent GERD symptoms	Never symptoms		≥20 years		>20 years		*P*-trend
	Cases/controls	OR[b] (95% CI)	Cases/controls	OR[b] (95% CI)	Cases/controls	OR[b] (95% CI)	
All	41/241	1.00 (Ref)	88/123	4.25 (2.75, 6.54)	107/83	8.13 (5.18, 12.8)	0.002
≥*Weekly symptoms*[c]							
Age at onset <30 years	41/241	1.00 (Ref)	7/10	4.09 (1.43, 11.7)	38/8	31.4 (13.0, 75.8)	0.001
Age at onset 30–49 years	41/241	1.00 (Ref)	34/32	6.93 (3.67, 13.1)	40/37	6.29 (3.48, 11.4)	0.77
Age at onset 50–79 years	41/241	1.00 (Ref)	29/34	4.51 (2.43, 8.37)	29/38	5.03 (2.72, 9.29)	0.58

BE, Barrett's esophagus; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio.

[a] Number of years with at least weekly heartburn or acid regurgitation symptoms.

[b] Adjusted for age, sex, highest level of education, cumulative smoking history, body mass index, alcohol intake, and use of aspirin or non-steroidal anti-inflammatory drugs.

[c] Numbers do not add to total as the group of participants with infrequent (<weekly) GERD symptoms throughout life were excluded from this analysis.