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Gastroesophageal Reflux Frequency, Severity, Age of Onset, Family History and Acid Suppressive Therapy Predict Barrett's Esophagus in a Large Population

Omar Bakr, MD, MPH¹, Wei Zhao, MPH², and Douglas Corley, MD, PhD²

¹UCLA Department of Medicine

²Kaiser Permanente Division of Research, 2000 Broadway Oakland, CA 94612, Tele: 510-891-3811, Fax: 510-891-3606

Abstract

Goals—To identify risk factors associated with BE for potential improved surveillance and risk reduction.

Background—Gastroesophageal reflux disease (GERD) is a known risk factor for esophageal adenocarcinoma, but the ability of GERD symptom frequency and severity to predict presence of its putative precursor lesion, Barrett's esophagus (BE), is less well-defined in large, community-based populations.

Study—We conducted a case-control study within the Kaiser Permanente Northern California population. Cases had new diagnoses of BE. To identify risk factors in the general population, we contrasted cases with population controls; to identify risk factors only among patients with GERD, we contrasted cases with GERD patients who lacked BE.

Results—We interviewed 953 patients; 320 patients with BE, 316 patients with GERD who lacked BE and 317 population controls. Compared to population controls, BE risk was highest among patients with the most frequent and severe GERD symptoms (OR 27.00 [95% confidence interval 14.52-50.21]), nocturnal symptoms (OR 5.40 [3.81-7.72]), and family history of GERD (OR 2.55 [1.80-3.62]) or BE (OR 10.08 [2.83-35.84]). Although at least weekly proton pump inhibitor (PPI) use was a risk factor for BE (OR 9.85 [95% CI 6.54-14.84]), among PPI users in the general population, GERD symptoms were not strongly associated with the risk of BE. Compared with GERD controls, cases were more likely to have onset of GERD symptoms before 30 years of age (OR 1.93 [1.15–3.22]) and a family history of BE (OR 3.64 [1.50-8.83]).

Conclusions—Severe and frequent GERD symptoms are strongly associated with increased risk of BE in the general population, especially in the absence of frequent PPI use. Among people with GERD, family history of BE and early age of symptom onset were stronger predictors of BE. These findings may improve identification of patients at highest risk for BE.

Conflicts of Interest

The authors declare that they have no competing interests

Keywords

Barrett's esophagus; Esophagus; GERD; Proton pump inhibitors; Acid suppressive therapy

Introduction

Esophageal adenocarcinoma (EAC) is a leading cause of cancer-related deaths in the world and one of the few cancers in the United States increasing in incidence, with a seven fold increase over the last four decades^{1,2}. Barrett's esophagus (BE) is a metaplastic transformation of the normal squamous mucosa of the esophagus to a columnar lining that, when present, confers a predisposition to the development of EAC³. Given that Barrett's esophagus is associated with an estimated 30-125 increased risk of cancer and has a prevalence of 5.6% in the United States, reducing the burden of Barrett's esophagus could potentially lead to a decrease of deaths from EAC^{4,5}.

Studies have suggested that gastroesophageal reflux disease (GERD) serves as a risk factor for Barrett's esophagus, and is on the casual pathway of EAC⁶⁻⁸. Ambulatory pH monitoring demonstrates increased acid reflux in the distal esophagus in nearly all patients with Barrett's esophagus. This excessive acid reflux is primarily due to a deficient lower esophageal sphincter, which is present in more than 90% of patients with Barrett's esophagus⁹. It has been proposed that GERD causes chronic esophageal injury to the normal mucosa, which might induce a change in the expression of developmental transcription factors that causes mature esophageal cells to transdifferentiate into columnar cells or induce immature esophageal progenitor cells to differentiate into columnar cells rather than squamous cells⁸. It is largely unknown, however, why Barrett's esophagus only develops in approximately 8-10% of patients with GERD¹⁰.

GERD symptoms, such as heartburn and regurgitation, have been associated with Barrett's esophagus and have been suggested as a risk stratification tool for identifying patients with Barrett's esophagus¹¹. Few community-based studies with population controls exist and most included only patients with GERD whom are already undergoing endoscopy. The few studies with population controls show a positive association between GERD symptom severity/frequency/duration and Barrett's esophagus¹²⁻¹⁴, while those using patients with GERD as controls find results ranging from positive to inverse associations¹⁵⁻¹⁹. Furthermore, prior studies did not typically assess the effect of acid suppressive therapy on the association between GERD symptoms and Barrett's esophagus, or explore other factors such as family history of GERD or Barrett's esophagus, nocturnal GERD symptoms, asthma or frequency of physician visits. Here, we present a case-control study within a large community-based population with both population and GERD control groups, allowing us to investigate the above factors in a single community-based population, potentially providing improved ability to predict and risk stratify patients for their risk of Barrett's esophagus.

Materials and Methods

Study Population

We conducted a case-control study within the Kaiser Permanent Northern California (KPNC) population. KPNC is an integrated health services delivery organization with approximately 3.3 million members whose demographic characteristics closely approximate the population of northern California²⁰. All potential study subjects were adult (ages 18-79 years), English-speaking KPNC members enrolled for at least two years prior to their index date who met the case and control definitions. This study population has previously been examined to determine relationships between waist circumferences, *Helicobacter pylori* and dietary intake with Barrett's esophagus²¹⁻²⁴

Case Definition

Eligible cases were all KPNC members newly diagnosed with Barrett's esophagus between October 2002 and September 2005. They were identified using the International Classification of Disease, Ninth Revision (ICD-9) code 530.2. At KPNC, this is uniquely coded on reporting sheets as "Barrett's esophagitis." Each potential case's endoscopic and pathology reports were then reviewed by a single board-certified gastroenterologist (DAC). A case was included if: (1) the endoscopist described a visible length of columnar-type epithelium proximal to the gastro-esophageal junction, (2) a biopsy was performed and (3) the biopsy showed specialized intestinal epithelium. The index date for cases was defined as the date of diagnosis of Barrett's esophagus.

Population Controls

Population controls were KPNC members without a diagnosis of Barrett's esophagus during the case selection period. Subjects were randomly selected from the at-risk population of the entire KPNC membership using risk set sampling, frequency matched to cases by sex, age at index date and home medical facility. The index date for controls was the midpoint of each three month selection interval for the cases.

GERD Comparison Group

GERD comparison controls were chosen from KPNC members with the following characteristics: (1) GERD-related ICD-9 code (530.11, reflux esophagitis or 530.81, gastroesophageal reflux), (2) a 90-day or more prescription for a histamine-2 receptor antagonist or a proton pump inhibitor, (3) no prior diagnosis of Barrett's esophagus and (4) an esophagogastroduodenoscopy that did not show esophageal columnar metaplasia of any type. The index date for GERD comparison controls was the midpoint of each three month selection interval for the cases.

Exposure Measurements

All subjects completed an in-person interview reviewing GERD symptoms, medication use, medical history and tobacco use. Demographic characteristics and prescription drug use were collected from electronic databases of Kaiser Permanente. Both population control and GERD comparison control groups have the condition of interest, GERD symptoms and

severity. This allows us to utilize the case-control method of analysis, comparing the frequency of this condition between each group to estimate odds ratio (OR).

GERD symptoms were assessed using a validated symptom questionnaire²⁵. GERD was defined as present when the patient had heartburn (a burning pain or discomfort behind the breast bone in your chest) or acid reflux (a sour tasting fluid coming up into the throat or mouth). These symptoms were classified as mild (could be ignored if you did not think about it), moderate (could not be ignored, but did not affect your life-style), severe (affected your life-style) or very severe (markedly affected your life-style). These questions were asked about the time period before the subject's index date; subjects were also asked to assess symptoms separately for time periods where they were on and off medications used to treat GERD.

Statistical Analysis

Unconditional logistical regression was used to determine the association between GERD symptom severity and Barrett's esophagus, with the assumption that the odds ratio approximates the risk ratio. All results are presented as odds ratios with confidence intervals set at the 95% level; all tests of statistical significance are two-sided.

We tested the following variables for confounding of the association between GERD symptoms and Barrett's esophagus: sex, age, race (white vs non-white), *Helicobacter pylori* status, smoking, education (<college vs. some college), waist circumference, total fat intake, statin use (prescription year before reference date vs. none), total fruit and vegetable servings, a comorbidity index (the DxCG score)^{26,27}, body mass index, alcohol use, height, serum iron, total iron-binding capacity, ferritin and C-reactive protein. None of the potential confounders listed above changed the OR more than 10%. Based on this testing, our main model only included GERD symptoms and variables with previously demonstrated strong associations with Barrett's esophagus in the KPNC population (race, tobacco use) and the frequency-matched variables (sex and age)^{28–30}.

Effect modification was assessed by examining stratum specific ORs and by checking cross-products for significance. To assess the effect modification of proton pump inhibitor (PPI) use on the relationship between GERD symptom severity, with at least weekly symptoms, and risk of Barrett's esophagus, we constructed a model with a binary variable for at least weekly PPI use versus none, and GERD symptom severity, split into three groups, none or less than weekly, mild to moderate severity (at least weekly), and severe to very severe (at least weekly). The study and the analyses were approved by the institutional review board of Kaiser Permanente Northern California; Stata was used for all statistical analyses (version 10; Stata Corp, College Station, TX).

Results

Study Population

Baseline characteristics of the subjects are displayed in Table 1. Cases were more likely to smoke than either the GERD or population controls, and both cases and GERD controls had more GERD symptoms than the population controls. Questionnaire and electronic data

elements were available for all 953 interviewed subjects: 320 cases, 316 GERD controls and 317 population controls. For additional details of the study design please see prior descriptions²¹.

GERD Symptom Frequency or Severity: Barrett's Esophagus vs. Population Controls

Compared with the population control group, the risk of Barrett's esophagus was statistically significantly increased with any increase of GERD symptom severity or frequency (Figures 1 & 2). Cases were more likely than population controls to have GERD symptoms weekly to monthly (OR 5.84 [3.60-9.46]) and more than once a week (OR 16.28 [10.24-25.87]), compared with persons with less than monthly symptoms. Cases were more likely than population controls to describe their GERD symptom severity as moderate (OR 3.84 [2.41-6.15]), severe (OR 8.77 [5.35-14.38]) or very severe (OR 16.01 [8.99-28.50]), than none-mild.

In a model with both symptom frequency and severity, the OR for Barrett's esophagus was highest in patients with very severe, daily to weekly GERD symptoms (OR 27.00 [14.52-50.21]) (Figure 3).

Proton Pump Inhibitor Effect Modification: Barrett's Esophagus vs. Population Controls

The strength of the association between GERD symptom severity and Barrett's esophagus was stronger among those who did not take PPIs at least weekly than among those with at least weekly use (p-value interaction= 0.03).

Among those with at least weekly PPI use, cases were similarly likely to have GERD of mild to moderate severity (OR 2.08 [0.66-6.56]), but were somewhat more likely to have severe to very severe GERD symptoms (OR 2.65 [1.18-6.23]). In contrast, among cases that did not use PPIs, GERD of both mild to moderate severity (OR 6.77 [3.76-12.14]) and severe to very severe conferred a significantly higher risk of Barrett's esophagus (OR 9.93 [5.63-17.53]), reference group was symptom frequency less than weekly (Figure 4).

Other Risk Factors: Barrett's Esophagus vs. Population Controls

Compared with population controls, BE patients were also more likely to have GERD symptom onset before 30 years old (OR 2.93 [95% CI 1.67-5.15]), a stuck feeling in throat (OR 3.00 [95% CI 2.13-4.24]), nocturnal GERD symptoms (OR 5.40 [95% CI 3.81-7.72]), PPI use at least weekly (OR 9.85 [95% CI 6.54-14.84]), and a family history of GERD (OR 2.55 [95% CI 1.80-3.62]) or BE (OR 10.08 [95% CI 2.83-35.84]). No significant associations were found for adult asthma or for GERD symptoms in a spouse. BE patients were also significantly more likely than population controls to have visited a health care provider for GERD or for any reason in the prior year (Table 2).

GERD Symptom Frequency or Severity: Barrett's Esophagus vs. GERD Controls

Cases reported mostly similar GERD symptom severity and frequency as GERD controls undergoing endoscopy who lacked Barrett's esophagus. Cases were similarly likely to GERD controls to have GERD symptoms weekly to monthly (OR 1.22 [0.72-2.05]), but more likely to experience symptoms more than once a week (OR 1.63 [1.01-2.63]),

reference group was less than monthly symptoms. Cases were similarly likely as GERD controls to describe their GERD symptom severity as moderate (OR 0.95 [0.55-1.63]), severe (OR 0.96 [0.57-1.61]) and very severe (OR 1.36 [0.73-2.54]), compared to a reference group with no-mild symptoms (Figure 2).

Other Risk Factors: Barrett's Esophagus vs. GERD Controls

Cases were more likely than GERD controls who lacked Barrett's esophagus to have had an onset of GERD symptoms under 30 years of age (OR 1.93 [1.15-3.22]) and a family history of Barrett's esophagus (OR 3.64 [1.50-8.83]) (Table 2).

Supplemental Analysis

Data was collected on heartburn and acid reflux symptoms separately and on/off medications separately, as explained in methods. When analyzing the associations between the presence of each of these symptoms and Barrett's esophagus, we found similar results for acid reflux symptoms, for heartburn symptoms and regardless if the patient reported their overall symptom severity or their symptom severity when they are not taking any medications to relieve symptoms. On constructing the model that included PPI use as an effect modifier, it is of note that PPI use itself was a risk factor for Barrett's esophagus, as a marker of GERD, but upon stratified analysis presented above, among PPI users GERD severity is not a risk factor for Barrett's esophagus.

Conclusions

There has been substantial interest in identifying patients at risk of Barrett's esophagus for possible surveillance or chemoprevention of esophageal adenocarcinoma; although prior evaluations have found GERD to be a risk factor, there have been very inconsistent results in determining whether increased symptom frequency and severity is positively, inversely or not related to risk of Barrett's esophagus, particularly among GERD patients. In addition, there are minimal such data from large, community-based populations within which most cases of Barrett's esophagus are diagnosed. In the current study, we found that GERD symptoms of acid regurgitation and heartburn are more frequent and severe among Barrett's esophagus patients than among population controls. In the population studied, patients with at least weekly, very severe symptoms are over 25 times more likely to have Barrett's esophagus than patients with no or rare GERD symptoms. In contrast, while these symptoms may be an excellent method to identify high risk patients in the general population, these symptoms are not as useful in patients already taking PPIs at least weekly, among whom the association decreases by 73%. Similar to patients with at least weekly PPI use, patients with clinically diagnosed GERD (without Barrett's esophagus) who undergo endoscopy do not have a strong association between their GERD symptoms and Barrett's esophagus. In this GERD population, severity of symptoms does not reliably predict Barrett's esophagus and frequency is only associated in the most frequent group and at a risk that is 90% lower than in the general population. However, among such GERD patients, those with Barrett's esophagus are much more likely to have a family history of Barrett's esophagus and to have GERD symptoms before the age of 30 years. Barrett's esophagus patients are also more

likely to visit a physician for any reason and visit a physician for GERD treatment than population controls, but less likely to visit compared to GERD patients.

Recent literature has highlighted the limitations of our ability to accurately identify patients with Barrett's esophagus, which is thought to be due to excessive focus on solely GERD symptoms for patient selection¹¹. With previous literature showing increasing severity or frequency of GERD symptoms to be positively, inversely or not associated with Barrett's esophagus, it is clear that a more careful application of GERD symptoms is needed. The current study suggests that it may be most strategic, in the general population, to utilize GERD symptom severity and frequency as a risk factor for Barrett's esophagus in patients who do not take PPI's weekly. In contrast, among patients with GERD symptoms, the severity and frequency of such symptoms are not markedly increased in patients with Barrett's esophagus; in such patients the age of GERD symptom onset and family history have stronger predictive value. This is supported further with the findings of a previous cross sectional study showing that, particularly in patients with PPI use, severe GERD symptoms were inversely associated with the risk of Barrett's esophagus¹⁸. Additionally, in multiple studies utilizing patients with GERD undergoing EGD as controls, increased GERD symptom severity and frequency were not reliable as risk factors for Barrett's esophagus^{16,17,19}. In these patients, other risk factors such as family history of Barrett's esophagus and GERD symptom age of onset before 30 may have more utility; with early age of onset or long term GERD being shown to be associated with Barrett's esophagus previously^{16,31}, although these studies were largely limited to populations of military veterans.

This study has several strengths. The symptoms of GERD were assessed with validated questionnaires that separately assessed the symptoms of acid reflux and heartburn, allowing us to show that the presence of either symptom was strongly associated with risk of Barrett's esophagus. We also were able to ask about symptom severity both when taking and not taking medication to treat the symptoms, symptom duration, and family history. Given that the GERD comparison group has all undergone upper endoscopy, we can be confident this group is classified correctly, minimizing misclassification bias. We also were able to assess relationships with two different comparison groups (population controls and GERD controls) within the same population, elucidating the most effective patients to utilize symptom severity and frequency in assessing risk of Barrett's esophagus. Finally, the Kaiser Permanente Northern California population is diverse and community-based, with very similar characteristics to the general population of the region, compared with census demographics, increasing the generalizability of our results²⁰.

Limitations of this study include an inability to determine causality between increasing GERD symptom severity and frequency and Barrett's esophagus. It is possible that an increased frequency and severity of GERD symptoms in the population simply increases the likelihood of having clinically relevant GERD and once this threshold is met, there is a static rate of increased risk of Barrett's esophagus or of referral to endoscopy for diagnosis. This may be supported by the loss of the association in patients with clinically diagnosed GERD who also underwent EGD and in patients who take PPI's weekly, both of which likely represents a significant burden of GERD symptoms. This is further supported by our finding

that at least weekly PPI use increases risk of Barrett's esophagus 10 fold, likely serving as a marker for severe GERD. Thus, GERD symptom severity and frequency may be a less effective screening tool to risk stratify patients who are already involved in frequent care of their GERD symptoms^{12,14}.

In conclusion, there were strong, increasing associations between increasing GERD symptom frequency and severity and Barrett's esophagus. In the general population, very severe and frequent symptoms, of either regurgitation or heartburn, were effective predictive factors for Barrett's esophagus, especially in the absence of frequent PPI use. In the population of patients with GERD who have already received an endoscopy, family history and early age of onset become much more reliable predictors than symptom frequency or severity. Carefully choosing risk factors relevant to the patient of interest will enhance our ability to discriminate whom is at highest risk of Barrett's esophagus.

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Figure 1.

Association between gastroesophageal reflux disease (GERD) symptom frequency and severity and risk of Barrett's esophagus: comparison of cases versus population controls. Estimates adjusted for age, sex, race and smoking; cases vs. population controls.

Figure 2. Association between gastroesophageal reflux disease (GERD) symptom frequency and severity and risk of Barrett's esophagus: comparison of cases versus patients with GERD. Estimates adjusted for age, sex, race and smoking; cases vs. GERD controls.

Figure 3.

Association between gastroesophageal reflux disease (GERD) symptom frequency and severity and risk of Barrett's esophagus: comparison of cases versus population control. Estimates adjusted for age, sex, race and smoking; cases vs. population controls.

Figure 4.

Association between gastroesophageal reflux disease (GERD) symptom severity, among those with at least weekly symptoms, and Barrett's esophagus among patients who do not take proton pump inhibitors (PPI's) weekly (left) and those who take PPI's weekly (right). Estimates adjusted for age, sex, race and smoking; cases vs. population controls.

Table 1**Patient Demographics**

	Cases (n = 320)	GERD control (n = 316)	Population control (n = 317)
Age (y), mean (SD)	62 (11)	61 (11)	62 (10)
20-39	9 (3%)	12 (4%)	9 (3%)
40-59	120 (38%)	116 (37%)	105 (33%)
60-79	191 (60%)	187 (59%)	203 (64%)
Race, n (%)			
White	277 (87%)	253 (80%)	268 (85%)
Hispanic	25 (8%)	20 (6%)	13 (4%)
Black	5 (2%)	21 (7%)	17 (5%)
Asian or Pacific Islander	3 (1%)	7 (2%)	8 (3%)
Other	8 (2%)	13 (4%)	10 (3%)
Unknown	2 (1%)	2 (1%)	1 (0%)
Sex, n (%)			
Male	234 (73%)	218 (69%)	214 (68%)
Smoking (≥ 20 packs), n (%)	212 (66%)	187 (59%)	176 (56%)
BMI (kg/m ²), mean (SD)	29.5 (6.1)	28.9 (5.3)	29.5 (5.8)
PPI use (≥ weekly), n (%)	184 (58%)	227 (72%)	39 (12%)
GERD, n (%)			
Any	298 (93%)	297 (94%)	193 (61%)
At least weekly	256 (80%)	233 (74%)	93 (29%)

BMI – Body Mass Index, PPI – Proton pump inhibitor, GERD - Gastroesophageal reflux disease

Table 2

Risk factors associated with Barrett's esophagus

	No. of subjects (population/case/GERD)	Cases vs Population		Cases vs patients with GERD	
		OR	95% CI	OR	95% CI
Age of first GERD symptom <30 years old?	22/54/36	2.93	1.67-5.15	1.93	1.15-3.22
GERD awoken you at night?	125/250/245	5.40	3.81-7.72	1.03	0.70-1.50
Feeling of food stuck in throat?	77/153/179	3.00	2.13-4.24	0.70	0.51-0.97
Adult Asthma	43/58/59	1.47	0.95-2.29	0.99	0.66-1.50
Spouse Heart Burn	79/76/68	0.89	0.61-1.28	1.12	0.77-1.63
Family history of GERD	105/173/158	2.55	1.80-3.62	1.22	0.86-1.72
Family history of BE	3/18/8	10.08	2.83-35.84	3.64	1.50-8.83
Visit doctor for GERD?					
0 times (within last year)	253/123/81	Referent		Referent	
1-2 times (within last year)	42/141/132	7.13	4.71-10.81	0.72	0.49-1.04
3+ times (within last year)	22/56/103	5.12	2.96-8.83	0.37	0.24-0.58
Visit doctor for any reason?					
0-2 times (within last year)	133/81/71	Referent		Referent	
3-5 times (within last year)	107/126/117	2.06	1.40-3.03	0.98	0.65-1.48
6-10 times (within last year)	42/66/72	2.69	1.65-4.37	0.82	0.52-1.31
10+ times (within last year)	35/47/56	2.25	1.33-3.83	0.78	0.47-1.30

Adjusted for age, sex, race and smoking, GERD - Gastroesophageal reflux disease, BE - Barrett's esophagus