Familiality in Barrett's Esophagus, Adenocarcinoma of the Esophagus, and Adenocarcinoma of the Gastroesophageal Junction

Amitabh Chak,[1] Heather Ochs-Balcom,[4] Gary Falk,[6] William M. Grady,[8] Margaret Kinnard,[5] Joseph E. Willis,[2] Robert Elston,[4] and Charis Eng[3,7,9]

[1]Division of Gastroenterology and [2]Department of Pathology, University Hospitals of Cleveland and Ireland Cancer Center, [3]Department of Genetics, CASE Comprehensive Cancer Center, Case Western Reserve University School of Medicine; [4]Department of Epidemiology and Biostatistics, Case Western Reserve University School of Medicine; [5]Division of Gastroenterology, Wade Park VA Medical Center, Case Western Reserve University School of Medicine; [6]Center for Swallowing and Esophageal Disorders, Department of Gastroenterology and Hepatology, Cleveland Clinic Foundation; [7]Genomic Medicine Institute and Taussig Cancer Center, Cleveland Clinic Foundation, Cleveland, Ohio; [8]Vanderbilt University, Nashville, Tennessee; and [9]Division of Human Genetics, The Ohio State University, Columbus, Ohio

Abstract

Background and Aim: **The familial aggregation of Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction, jointly termed familial Barrett's esophagus, may represent a complex genetic trait. The aim of this study was to determine the proportion of patients with these diseases who have familial Barrett's esophagus.**

Methods: **Information on gastroesophageal reflux symptoms, known risk factors for Barrett's esophagus, and family history of Barrett's esophagus and cancers, was collected at six hospitals using a structured questionnaire from probands with either long-segment Barrett's esophagus, adenocarcinoma of the esophagus, or adenocarcinoma of the gastroesophageal junction. Family history of Barrett's esophagus or esophageal cancer in a first- or second-degree relative was determined by reviewing medical records of all relatives reported to be affected.**

Results: **Seventy one of 411 (17.3%) probands reported an affected first- and/or second-degree relative. Upon review of medical records of the reportedly affected relatives, familial Barrett's esophagus was definitively determined in the case of 30 (7.3%) probands comprising 17 of 276 (6.2%) with Barrett's esophagus, 11 of 116 (9.5%) with adenocarcinoma of the esophagus, and 2 of 21 (9.5%) with adenocarcinoma of the gastroesophageal junction. The diagnosis in the relative reported by the proband to be affected was found not to be Barrett's esophagus or adenocarcinoma in 15 (3.6%) cases. The diagnosis could not be determined in 26 (6.3%) cases in which the proband reported an affected relative. There were no significant differences in age of disease onset, gender, race, or gastroesophageal reflux symptoms between definitive familial Barrett's esophagus probands and nonfamilial probands.**

Conclusion: **Familial Barrett's esophagus can be confirmed in 7.3% of persons presenting with Barrett's esophagus, adenocarcinoma of the esophagus, or adenocarcinoma of the gastroesophageal junction.** (Cancer Epidemiol Biomarkers Prev 2006;15(9):1668–73)

Introduction

During the past three decades, there has been an alarming increase in the incidence of adenocarcinoma of the esophagus in the U.S. (1-3). The prognosis for these patients remains poor, with the majority dying of cancer-related causes (4). Most cases of adenocarcinoma of the esophagus originate in Barrett's epithelium (5-12), a premalignant condition in which normal squamous epithelium is replaced by metaplastic specialized intestinal-type columnar epithelium (13). The majority of population studies, including a recent study of a large multi-institutional volunteer adult American population (14), and a randomly surveyed Swedish population (15), report an overall prevalence of 1.6% or less in adult patients and up to 12% in the subset with chronic gastroesophageal reflux disease (GERD; refs. 13-17).

The presence of Barrett's esophagus in a limited subset of the population with chronic GERD and its predominance in White males suggests that selected patients are susceptible to the development of intestinal metaplasia in their esophageal mucosa. Familial aggregation of Barrett's esophagus and associated cancers has been reported and is termed familial Barrett's esophagus (18-24). In these reports, the prevalence of Barrett's esophagus in relatives has been >20% and the prevalence of GERD has been ~40%. A previous study showed increased aggregation of Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction in the families of patients with these diseases compared with families of GERD controls (25). We have postulated that Barrett's esophagus and its associated cancer are complex genetic diseases. Familial Barrett's esophagus is proposed to be the phenotypic expression of undiscovered susceptibility gene(s) that predispose individuals to the development of intestinal metaplasia in the esophagus. The purpose of this study was to determine the proportion of patients with Barrett's esophagus, adenocarcinoma of the esophagus, and/or adenocarcinoma of the gastroesophageal junction that have a positive family history of these diseases.

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Note: Current address for W.M. Grady: Clinical Research Division, Fred Hutchinson Cancer Research Center, Division of Gastroenterology, University of Washington Medical School, Seattle, Washington.

Requests for reprints: Amitabh Chak, University Hospitals of Cleveland, Case School of Medicine, 11100 Euclid Avenue, Cleveland, OH 44106. Phone: 216-844-5385; Fax: 216-983-0347. E-mail: Amitabh.chak@case.edu

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Materials and Methods

Study Design. The Institutional Review Board for human investigation approved the protocol at each study center. The study population was recruited from patients undergoing endoscopy at four tertiary care hospitals and two Veterans Affairs hospitals. All eligible patients with Barrett's esophagus, adenocarcinoma of the esophagus, or adenocarcinoma of the gastroesophageal junction seen during the active enrollment period were invited to participate. Enrollment periods, depending on available study personnel and Institutional Review Board approval, differed at the participating institutions and ranged from 1 to 4 years. Study subjects were given a Familial Barrett's Esophagus Questionnaire (see following sections), encouraged to take the questionnaire home, discuss family history with relatives, and then return the questionnaire by mail. Permission was obtained from all subjects to contact their relatives. All subjects who did not return their questionnaires within a month were contacted once by telephone or mail. Attempts were then made to confirm the histologic diagnosis for all family members reported to have a history of Barrett's esophagus or esophageal cancer. Attempts were also made to confirm diagnoses when relatives were reported to have cancer of the ''stomach'' or cancer of the ''throat'' because patients may not understand the medical distinction between these terms and the esophagus.

Study Group. The probands were recruited from patients with a known diagnosis of long-segment Barrett's esophagus undergoing surveillance endoscopy, patients with a recent diagnosis of long-segment Barrett's esophagus, patients with a known diagnosis of adenocarcinoma of the esophagus or gastroesophageal junction undergoing a palliative or staging endoscopic procedure, and patients with a new diagnosis of adenocarcinoma of the esophagus or gastroesophageal junction seen in the endoscopy suites of the participating hospitals during the active recruitment period. Men or women ages 18 years or older with a histologic diagnosis of Barrett's esophagus, adenocarcinoma of the esophagus, or adenocarcinoma of the gastroesophageal junction were eligible for study. Patients with short-segment Barrett's esophagus were not included in this study. A gastrointestinal pathologist reviewed the histology slides to confirm the diagnosis.

Study Definitions. Barrett's esophagus was defined as a 3 cm or longer segment of salmon-colored mucosa in the esophagus at endoscopy with biopsies demonstrating intestinal metaplasia. No documentation of length, or length <3 cm, on the endoscopy report was considered short-segment Barrett's esophagus and excluded from the study. If the endoscopy report simply stated that biopsies were obtained at the gastroesophageal junction and the histology showed intestinal metaplasia, the diagnosis was categorized as intestinal metaplasia of the gastric cardia and these patients were also excluded. Adenocarcinoma of the esophagus was defined as tumor mass arising predominantly in the esophagus. Adenocarcinoma of the gastroesophageal junction was defined as a tumor mass that was centered within 2 cm of the presumptive gastroesophageal junction and involved the gastric cardia.

Familial Barrett's Esophagus Questionnaire. The Familial Barrett's Esophagus Questionnaire, which has been used in previous studies, is a structured instrument that collects data on GERD symptoms, risk factors for Barrett's esophagus and adenocarcinoma of the esophagus, and family history of Barrett's esophagus and cancer (25, 26). Reflux symptoms are defined with a modified version of the standardized Mayo reflux symptom questionnaire developed by Locke et al. (used with permission; ref. 27). The exposure section elicits details on ethnicity, smoking, alcohol consumption, current weight and height, as well as weight and height at 1, 5, 10, and 20 years prior to study enrollment. The family history section asks structured questions regarding family history of Barrett's esophagus, esophageal cancer, and other cancers. A detailed history is elicited for all first-degree relatives and any affected second-degree relatives. Permission to contact relatives and their contact information is also obtained using this questionnaire.

Determination of Familial Status. Familial Barrett's esophagus was defined as having a first- or second-degree relative with long-segment Barrett's esophagus, adenocarcinoma of the esophagus, or adenocarcinoma of the gastroesophageal junction whose diagnosis was confirmed by review of endoscopy and histology reports. Efforts were made to confirm diagnoses for all reported relatives with Barrett's esophagus, esophageal cancer, cancer of the stomach, or cancer of the throat by contacting the reportedly affected relatives (next of kin, if the affected relative was deceased) and obtaining a signed release of medical information. The institution where the affected relative(s) received medical care was contacted for endoscopy reports and pathology reports, as well as histology slides when available. The medical record departments of the institution were contacted by phone at least twice before considering the reports to be unavailable. Death certificates were also examined when medical reports could not be obtained. If the relative reported as having esophageal cancer had squamous cell cancer or a cancer that did not involve the esophagus, the family history was classified as a false positive. Similarly, if there was insufficient documentation on the histology and endoscopy reports to confirm a diagnosis of Barrett's esophagus, the reported family history was considered a false positive.

Statistical Analysis. The proportion of probands with a definitive (diagnosis in reportedly affected relative confirmed by review of medical reports) family history of Barrett's esophagus, adenocarcinoma of the esophagus, or adenocarcinoma of the gastroesophageal junction was determined. Body mass index (BMI) was calculated as (weight in kg) / (height in meters)^2. Differences in GERD symptoms and other risk factors such as age at diagnosis, gender, race, smoking, and BMI (kg/m^2) were compared between the confirmed familial Barrett's esophagus cases and the remainder of the group that had no definite evidence for an affected first- or second-degree relative. Pearson's χ^2 tests, Fisher's exact tests, and t tests were used to investigate differences in the variables mentioned above. $P < 0.05$ were considered statistically significant. For all analyses, we used the Statistical Package for Social Sciences software (SPSS, Inc. for Windows, version 11.0).

Results

Patient Population. The study enrolled 413 of 752 (55%) eligible patients seen at the six participating hospitals. Of these 413 probands, 276 had long-segment Barrett's esophagus, 116 had adenocarcinoma of the esophagus, and 21 had adenocarcinoma of the gastroesophageal junction. Three hundred and ninety-five (96%) of the probands were White and 338 (82%) were men. Patients with esophageal adenocarcinoma in the study population (n = 116) included a similar proportion of men (85.3% versus 82.7%; P = 0.449) and a similar proportion of Whites (95.7% versus 93.9%; P = 0.415) but were significantly younger [mean age at diagnosis, 62.6 years (SD 12.3) versus 67.4 years (SD 12.5); P = 0.001] compared with patients with esophageal adenocarcinoma enrolled in the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute between 1999 and 2003. Similarly, patients with gastroesophageal junction adenocarcinoma included in the study population (n = 21) were not significantly different in gender (85.7% versus 78.3% men; P = 0.597), race

(95.2% versus 88.9% White; $P = 0.723$), or age [mean age, 60.1 years (SD 19.0) versus 67.4 years (SD 12.9); $P = 0.102$] from the Surveillance, Epidemiology, and End Results sample.

The study population was also compared with esophageal adenocarcinoma cases who did not participate in the study ($n = 70$), but for whom limited data were available. The enrolled study population ($n = 116$) with esophageal adenocarcinoma contained a similar proportion of men (85.3% versus 77.1%; $P = 0.156$) with a similar age [mean age at diagnosis, 62.6 years (SD 12.3) versus 62.3 years (SD 24.5); $P = 0.854$] but a greater proportion of Whites (95.7% versus 75.7%; $P = 0.001$) than patients not enrolled in the study. Enrolled patients with gastroesophageal junction adenocarcinoma were not significantly different in gender (85.7% versus 100%; $P = 0.27$) or race (88.9% versus 84.6%) but were slightly younger in age [60.1 years (SD 19.0) versus 69.9 years (SD 6.85); $P = 0.025$] from the gastroesophageal junction adenocarcinoma patients who did not participate ($n = 13$).

Determining Familial Barrett's Esophagus. A family history of Barrett's esophagus or cancer of the esophagus was initially reported on the questionnaire by 71 of 411 (17.3%) probands—46 (16.7%) probands with Barrett's esophagus, 22 (19.0%) probands with adenocarcinoma of the esophagus, and 3 (13.6%) probands with adenocarcinoma of the gastroesophageal junction. Upon review of the available medical records of affected relatives, familial Barrett's esophagus was definitive in 30 (7.3%) probands—17 of 276 (6.2%) probands with Barrett's esophagus, 11 of 116 (9.5%) probands with adenocarcinoma of the esophagus, and 2 of 21 (9.5%) probands with adenocarcinoma of the gastroesophageal junction.

The demographics and age at diagnosis for each group are listed in Table 1. There was no significant discernible difference in age of diagnosis of Barrett's esophagus or adenocarcinoma of the esophagus between probands with familial Barrett's esophagus and the remainder of the probands. Twenty-three of the 30 probands with familial Barrett's esophagus had an affected first-degree relative and 7 had an affected second-degree relative.

After verification efforts, the family history was classified as false positive for 15 of 411 (3.6%) probands—11 of 276 (4.0%) Barrett's esophagus probands, 3 of 116 (2.6%) adenocarcinoma of the esophagus probands, and 1 (4.8%) adenocarcinoma of the gastroesophageal junction proband. Despite repeated efforts to obtain medical records for the reportedly affected relatives, the family history could not be confirmed in 26 (6.3%) probands. The diagnosis in the reported affected family member could not be determined in 18 of 276 (6.5%) probands with Barrett's esophagus and 8 of 116 (6.9%) probands with adenocarcinoma of the esophagus. Of these 26 family histories that could not be verified, 12 could not be verified because the affected family member or nearest living relative refused study participation or the proband did not provide valid contact information. The other 14 could not be verified because medical records were not available for the relative who was reported to be affected.

GERD Symptoms and Risk Factors. The duration and severity of heartburn, acid regurgitation, and difficulty of swallowing (dysphagia) were measured using the study questionnaire. The results are shown in Table 2. There were no significant differences in the duration or severity of GERD symptoms between familial Barrett's esophagus probands and the remainder of the probands.

Differences in smoking status, coffee intake, alcohol usage, and self-reported current and past weight and height were also assessed by the study questionnaire. The responses are shown in Table 3. There were no significant differences in smoking, coffee, and alcohol intake between familial Barrett's esophagus probands and the remainder of the probands. When individuals were classified as having a BMI >30 kg/m^2 (obese) or not, ~38% of Barrett's cases were obese within the year prior to study entry (or diagnosis). For the cancer cases, ~30% reported a BMI >30 kg/m^2 (obese) in the 1 to 10 years prior to diagnosis. Familial Barrett's esophagus probands with cancer had a significantly lower BMI than nonfamilial probands with cancer, and there was a tendency for familial Barrett's esophagus probands with adenocarcinoma to have a lower BMI 1 year prior to diagnosis and 5 years prior to diagnosis. However, this difference was not present at 10 and 20 years prior to diagnosis.

Discussion

Aggregation of Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction in families, termed familial Barrett's esophagus, could theoretically be due either to shared environmental factors or to inheritance of common susceptibility gene(s). The significantly increased aggregation of these diseases in families (25) and the pedigree structures of reported families suggest that familial Barrett's esophagus is a complex genetic disease (18-24, 26). Furthermore, investigators propose that the trait inheritance in families is consistent with a major Mendelian autosomal dominant gene with relatively high penetrance (20-24, 26). Our consortium of investigators has also reported previously on the pedigree structure of 70 familial Barrett's esophagus families (28). Assuming that familial Barrett's esophagus is mainly an inherited phenomenon, this study shows that the putative inherited susceptibility gene(s) plays a role in the development of Barrett's esophagus and its associated cancers in at least 7% of patients with these conditions.

An estimation of the prevalence of familial Barrett's esophagus is important for gaining some understanding of what proportion of Barrett's esophagus and its associated cancers may have a genetic basis, and for designing future

Table 1. Demographics by diagnosis and familiality, *n* (%) or mean (SD)

	Barrett's esophagus ($n = 276$)			Adenocarcinoma of esophagus ($n = 116$)			Adenocarcinoma of gastroesophageal junction ($n = 21$)		
	Familial ($n = 17$)	Nonfamilial ($n = 259$)	P	Familial ($n = 11$)	Nonfamilial ($n = 105$)	P	Familial ($n = 2$)	Nonfamilial ($n = 19$)	P
Men	14 (82.4%)	207 (79.9%)	0.999	10 (90.9%)	89 (84.8%)	0.999	2 (100%)	16 (84.2%)	0.999
White race	17 (100%)	247 (95.4%)	0.999	11 (100%)	100 (95.2%)	0.999	2 (100%)	18 (94.7%)	0.999
Education									
<High school	0 (0%)	31 (12.0%)	0.037	1 (9.1%)	10 (9.5%)	0.729	—	2 (10.5%)	0.171
High school	6 (35.3%)	132 (51.0%)		6 (54.5%)	65 (61.9%)		—	10 (52.6%)	
College graduate	6 (35.3%)	45 (17.4%)		1 (9.1%)	18 (17.1%)		1 (50%)	3 (15.8%)	
Beyond college	5 (29.4%)	51 (19.7%)		3 (27.3%)	12 (11.4%)		1 (50%)	4 (21.1%)	
Age at diagnosis	55.4 (11.7)	52.5 (14.3)	0.418	60.9 (13.2)	62.8 (12.3)	0.642	76.0 (0.0)	55.9 (16.8)	0.001

NOTE: χ^2 tests or t tests for differences by familial status. Fisher's exact tests when there are cells with $n < 5$.

Table 2. Symptoms by diagnosis and familiality, *n* (%)

	Barrett's esophagus (n = 276)			Adenocarcinoma of esophagus and gastroesophageal junction (n = 137)		
	Familial (n = 17)	Nonfamilial (n = 259)	P	Familial (n = 13)	Nonfamilial (n = 124)	P
Heartburn (yes/no)						
Present	14 (82.4%)	191 (73.7%)	0.573	8 (61.5%)	78 (62.9%)	0.923
More than 10 years	12 (80.0%)	138 (70.0%)	0.561	6 (75.0%)	53 (67.1%)	0.999
Moderate/severe	12 (80.0%)	143 (71.9%)	0.765	5 (62.5%)	56 (73.7%)	0.678
Acid regurgitation (yes/no)						
Present	12 (70.6%)	177 (68.3%)	0.847	9 (69.2%)	76 (61.8%)	0.766
More than 10 years	9 (69.2%)	107 (56.6%)	0.564	5 (55.6%)	24 (30.8%)	0.153
Moderate/severe	12 (92.3%)	144 (77.4%)	0.306	6 (66.7%)	55 (72.4%)	0.708
Dysphagia (yes/no)						
Present	8 (50.0%)	89 (34.4%)	0.204	9 (69.2%)	78 (63.4%)	0.770
More than 10 years	3 (37.5%)	23 (25.3%)	0.429	—	8 (9.8%)	0.999
Moderate/severe	4 (50.0%)	66 (72.5%)	0.228	8 (88.9%)	68 (86.1%)	0.999

NOTE: χ^2 tests or t tests for differences by familial status.

linkage studies to identify this putative gene(s). The prevalence of familial Barrett's esophagus clearly depends on how the trait is defined. A narrower definition of the trait such as three or more individuals with adenocarcinoma of the esophagus in the family would assure an underlying genetic etiology in all families but the identification of such families for a genetic linkage analysis would be prohibitive. On the other hand, a broader definition of the trait that included GERD in affected family members would likely lead to the identification of many families in whom the aggregation of the diseases had a nongenetic basis. The inclusion of Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction as part of the same complex trait is justified because there is strong evidence that nearly all adenocarcinomas of the esophagus and a substantial proportion of adenocarcinomas of the gastroesophageal junction arise in Barrett's epithelium (7-12). Short-segment Barrett's esophagus was deliberately not included in the definition of familial Barrett's esophagus because it can be difficult to distinguish between short-segment Barrett's esophagus and intestinal metaplasia of the gastric cardia (29). Documentation and compliance with recommended guidelines for diagnosing Barrett's esophagus is poor among practicing endoscopists and pathologists (30). Therefore, the inclusion of short-segment Barrett's esophagus within the familial Barrett's esophagus trait would make it especially problematic to ascertain the phenotype of relatives whose endoscopy was not done at one of the participating institutions and would result in large misclassification biases.

This study found no significant differences in the major risk factors (older age, male gender, White race, GERD, and smoking) for Barrett's esophagus (31, 32) between familial probands and nonfamilial probands. A younger age of disease incidence is often considered a surrogate marker for a genetic predisposition, however, there were no statistically significant differences in this sample. The age of incidence of Barrett's esophagus cannot be defined, so it is not surprising that there were no differences in mean age of diagnosis of Barrett's esophagus. The study may have failed to identify a difference in the age of cancer incidence because of insufficient power. We estimate that a sample which includes 80 familial probands with adenocarcinoma of the esophagus would be required to detect an age difference of 5 years at $\alpha = 0.05$ and $\beta = 0.2$.

The study did find that familial Barrett's esophagus probands with cancer had a significantly lower BMI at diagnosis than nonfamilial probands with cancer, as well as a tendency towards a lower BMI at 1 and 5 years prior to diagnosis. This finding is intriguing. One possible explanation could be that a genetic predisposition increases the risk of

Table 3. Risk factors by diagnosis and familiality, *n* (%) or mean (SD)

	Barrett's esophagus (n = 276)			Adenocarcinoma of esophagus and gastroesophageal junction (n = 137)		
	Familial (n = 17)	Nonfamilial (n = 259)	P	Familial (n = 13)	Nonfamilial (n = 124)	P
Smoking						
Ever smoke (yes/no)	12 (70.6%)	157 (60.9%)	0.424	10 (76.9%)	99 (79.8%)	0.729
Heaviest packs per day	1.29 (1.16)	1.06 (1.10)	0.402	1.46 (1.13)	1.37 (1.15)	0.775
Coffee						
Drink coffee (yes/no)	14 (82.4%)	195 (75.3%)	0.511	11 (84.6%)	99 (79.8%)	0.999
Average cups per day	2.41 (1.77)	2.27 (2.42)	0.818	1.85 (1.86)	2.47 (2.83)	0.438
Alcoholic drinks per week						
None	3 (17.6%)	53 (20.7%)		3 (23.1%)	17 (13.7%)	
Less than 1 drink per week	7 (41.2%)	126 (49.2%)		5 (38.5%)	59 (47.6%)	
1-5 drinks per week	3 (17.6%)	42 (16.4%)	0.316	2 (15.4%)	27 (21.8%)	0.796
5-10 drinks per week	1 (5.9%)	22 (8.6%)		2 (15.4%)	11 (8.9%)	
More than 10 drinks per week	3 (17.6%)	13 (5.1%)		1 (7.7%)	10 (8.1%)	
BMI (kg/m^2)						
Current	29.7 (6.5)	29.0 (5.2)	0.628	23.1 (3.3)	26.4 (5.0)	0.019
1 year ago	29.9 (7.0)	29.0 (5.4)	0.511	25.7 (4.9)	28.8 (6.0)	0.072
5 years ago	29.0 (6.4)	28.4 (5.0)	0.682	26.4 (5.1)	29.5 (5.8)	0.070
10 years ago	27.3 (6.3)	27.5 (5.0)	0.892	27.6 (4.0)	28.5 (5.3)	0.555
20 years ago	25.9 (4.2)	25.9 (4.5)	0.964	27.3 (4.3)	27.1 (4.6)	0.895

NOTE: χ^2 tests or t tests for differences by familial status.

disease at a lower BMI or a shorter duration of obesity. However, the difference in BMI was not present at 10 and 20 years prior to diagnosis. Another possible explanation would be that patients with familial cancers have an earlier onset of symptoms resulting in earlier weight loss prior to diagnosis. Given the limited number (13) of probands with cancer in the familial Barrett's esophagus group and because no such difference was found between the familial and nonfamilial probands with Barrett's esophagus, this finding should be interpreted with great caution.

The 7.3% estimate of the proportion of probands with a confirmed family history in patients with Barrett's esophagus and its associated cancers is quite conservative. The number may underestimate the true prevalence because only a proportion of relatives have undergone endoscopy. However, an active endoscopic screening program of first-degree relatives of affected probands at one of the participating institutions has found no new cases of Barrett's esophagus in those who reported no prior family history of disease (26). Another reason that 7.3% may be an underestimate of the prevalence of familial Barrett's esophagus is that it was not possible to confirm the diagnosis in the affected relative in nearly 40% (26) of the probands who reported a positive family history. The major reasons for not confirming the affected status of reportedly affected relatives were either that the medical records were no longer available or the relative (or next of kin) refused to participate in the study. In many cases where the diagnosis in the relative who was reported to be affected could be determined, the relative only had reflux and not Barrett's esophagus. Barrett's esophagus is often misdiagnosed in clinical practice (30), emphasizing the need to use strict criteria for ascertaining familial Barrett's esophagus probands, as in this study.

Although this study is not a strictly population-based study, the large number of patients recruited prospectively at six hospitals in three different cities give us confidence that the prevalence estimates are somewhat reliable. Uncommon diseases like adenocarcinoma of the esophagus are largely referred to tertiary institutions. Thus, the patient population at tertiary institutions for rare diseases may be a reasonable reflection of the regional population. The study population of cancer patients had a race and gender distribution that was not significantly different from the Surveillance, Epidemiology, and End Results population. The study population of esophageal adenocarcinoma patients was younger than the Surveillance, Epidemiology, and End Results population, suggesting some degree of selection bias against the referral of older patients with cancer to tertiary institutions, which consequently may somewhat affect the generalizability of the prevalence estimates. If patients with familial Barrett's esophagus develop cancer at an earlier age than the general population, the selection bias related to referral patterns in our study might have led to an overestimate of the proportion with familial Barrett's esophagus. Non–White patients at our institutions were less likely to participate in the study than White patients. This differential selection likely did not introduce a large bias in our estimates because >80% of adenocarcinoma patients are White. As an example of the reliability of prevalence estimates obtained from studies conducted on rare diseases at tertiary institutions, pheochromocytoma mutation frequencies in one of several genes as well as penetrances were similar in large population-based studies (33, 34) as well as in an international consortium study from tertiary centers (35). These observations may mitigate against some of the selection bias inherently associated with studies done at tertiary academic institutions, and suggest that such studies, given sufficient sample sizes, are an acceptable substitute for population-based studies. The present study may have additional referral bias because two of the participating hospitals were Veterans Affairs hospitals, but again, because the diseases under consideration are predominantly seen in male populations, the bias associated with studying a predominantly male veteran population may also be somewhat attenuated.

Because the putative susceptibility gene(s) for familial Barrett's esophagus has not been identified, it is difficult to determine the exact proportion of these cases that are truly genetic. As with susceptibility genes in other complex diseases, once the susceptibility gene(s) is identified, that gene might also play a role in sporadic Barrett's esophagus. The results of this study show that familial Barrett's esophagus can be determined in ~7% of patients seen with Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction. The high rate of reportedly false positive family histories highlights the importance of determining the diagnosis of Barrett's esophagus or esophageal cancer in affected relatives using strict criteria. Given that these diseases are not very common, larger multi-center studies are required to recruit and ascertain enough families for the linkage analyses necessary to identify the gene(s) that confers an inherited susceptibility to the development of Barrett's esophagus and Barrett's-related adenocarcinomas.

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