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Comparison of Endoscopic and Clinical Characteristics of Patients with Familial and Sporadic Barrett's Esophagus

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Abstract

Background—A proportion of Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) displays familial aggregation, known as familial Barrett's esophagus (FBE). Pedigrees and characteristics of EAC in these families have been previously described.

Aims—We aimed to evaluate endoscopic and clinical characteristics of Barrett's esophagus in FBE.

Methods—A cohort of 979 BE patients were retrospectively evaluated for FBE, defined as having a first-degree relative with BE or esophageal cancer, confirmed when possible by interview. FBE and sporadic BE were compared regarding demographic, clinical, and endoscopic characteristics. Potential FBE probands were contacted and interviewed to obtain full family pedigrees.

Results—Of 603 BE probands (61.6% of total cohort) with a documented family history, 35 (5.8%) had FBE. There was no difference between FBE and non-FBE probands with regard to BE

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length (median: 3 cm, IQR 2-5 vs. 3 cm, IQR 1-6 cm, respectively; $p = 0.78$) or hiatal hernia size ($p = 0.90$). FBE probands were younger (mean, 58.4 vs. 63.8; $p = 0.02$) and had a significant association with less-advanced neoplasia (adjusted OR 0.41, 95% CI 0.19–0.90). There was no obvious association between FBE and other malignancies.

Conclusions—There were no differences in endoscopic characteristics between FBE and non-FBE probands. While FBE patients were younger and had less-advanced neoplasia, we speculate that these findings may have been the result of more aggressive screening due to the family history. Further studies are warranted to determine whether familial clustering is due to genetic predisposition to development of BE or to risk of neoplastic progression.

Keywords

Barrett's esophagus; Epidemiology; Genetic predisposition to disease

Introduction

Barrett's esophagus (BE) is the primary precursor lesion for the development of esophageal adenocarcinoma (EAC), and BE likely develops in the setting of erosive esophagitis due to gastro-duodenal reflux [1]. As with most malignancies, a combination of genetic and environmental factors is presumably responsible for the development of EAC. Previous reports have shown that a small but distinct proportion of BE and EAC patients demonstrate familial clustering, sometimes termed familial Barrett's esophagus (FBE), and is suggestive of a heritable genetic component to BE and EAC [2–4]. In fact, work by the FBE Consortium, sponsored by the National Institutes of Health, suggests that familial clustering of BE and EAC may be due to multiple inherited rare autosomal dominant alleles [5].

Several malignancies, such as colorectal cancer and breast cancer, have well-defined familial syndromes due to specific gene mutations. For example, patients with Lynch syndrome have germline mismatch repair gene mutations, and develop colorectal cancer at an earlier age than sporadic cases [6]. Hereditary breast cancer can have germline *BRCA1/BRCA2* mutations, and affected individuals develop breast cancer at earlier ages [7].

In familial Barrett's esophagus, affected individuals do not appear to develop EAC at an earlier age or present at different stage of disease as compared to sporadic cases [8]. Little is known with regard to risk of progression from BE to EAC or survival in EAC patients in these families. Certain endoscopic characteristics such as BE length may be associated with risk of neoplastic progression [9]. We therefore aimed to determine the prevalence of FBE in our large BE cohort, to compare endoscopic and clinical characteristics of probands with and without FBE, and to obtain detailed family pedigrees from these FBE probands.

Methods

Our study was performed in two parts. First, a retrospective review was conducted of a cohort of 979 patients with established BE, with or without associated dysplasia or adenocarcinoma. Established BE was defined as endoscopically suspected BE confirmed by the presence of intestinal metaplasia on esophageal biopsies. Charts were reviewed from patients under the care of two of the investigators (CJL and JAA) at Columbia University Medical Center (New York, NY). Data recorded included patient age (at the time of diagnosis of highest degree of neoplasia), sex, race, smoking history (ever, never, unknown), length of Barrett's esophagus (in cm), presence of and size of hiatal hernia (in cm), highest degree of Barrett's-associated neoplasia, and *Helicobacter pylori* status.

Charts were reviewed for notation of whether patients had a fist-degree relative with BE or esophageal cancer (any cell type), categorized as yes, no, or unknown/not specifically noted. Data were recorded on cancers in other first-degree relatives, as well as whether there was a history of other non-esophageal malignancy in the proband. In the current study, familial Barrett's esophagus was defined as the presence of BE or esophageal cancer (EC) in any first-degree relative (based on chart review) and, when possible, confirmed by detailed family history collection.

Thirty-seven patients were identified as potential FBE probands based on chart review. These patients were then mailed an invitation to participate in a phone interview to obtain a detailed family pedigree. Those who returned a signed informed consent and agreed to participate in the study were contacted by telephone. A three-generation family history was ascertained including the age, vital status, cause of death, and major medical problems in each of the patient's first, second, and third-degree relatives. In addition, the participants were queried about any history of consanguinity as well as ethnicity. If anyone in the family had esophageal cancer, attempts were made to determine likelihood of a particular cell type by asking if the patient knew the cell type; if the family member in question smoked cigarettes, drank a significant amount of alcohol, or had cancer of the mouth, tongue, or throat (more likely squamous cell); or had frequent acid reflux or a hiatal hernia (more likely adenocarcinoma). All interviews were conducted by a single trained genetic counselor (MKD).

Categorical variables were analyzed using Fisher's exact tests. Continuous variables were analyzed using Student's *t* tests for normally distributed data and Wilcoxon rank-sum tests for non-normally distributed data. All tests were two-sided. Multivariable logistic regression was performed to assess for an association between family history of BE or esophageal cancer and personal history of advanced neoplasia (high-grade dysplasia or adenocarcinoma), adjusted for age, sex, BE length (per cm), and smoking history. Statistical significance was defined as $p < 0.05$. All analyses were performed using Stata 11.0 (College Station, TX).

This study was approved by the Columbia University Institutional Review Board.

Results

A total of 979 BE patients had records available for review and 603 (61.6%) had documentation of family history of BE or esophageal cancer. Of these, 37 (6.1%) had a first-degree family member with BE or EC. After detailed family history interview, two subjects were found not to have a first-degree family member with BE or EC. Thirty-five (5.8%) patients were classified as FBE. The demographic characteristics of the patients are shown in Table 1. Patients with FBE were younger than those with sporadic BE (58.4 years vs. 63.8 years, respectively; $p = 0.02$). No statistically significant difference was found between those with and without a FBE with regard to sex, race, smoking history, or personal history of other cancers.

Endoscopic and pathologic characteristics of BE probands are shown in Table 2. There was no difference in BE length between the FBE and non-FBE groups (median: 3 cm (IQR 2-5) vs. 3 cm (IQR 1-6), respectively; $p = 0.78$). Similar proportions with hiatal hernia were observed in the two groups (FBE, 97.1%; non-FBE, 93.3%; $p = 0.72$), with no significant difference in the size ($p = 0.90$).

A smaller proportion of FBE probands as compared to non-FBE probands had a history of high-grade dysplasia (HGD) or EAC, either at diagnosis or developed during follow-up (34.3 vs. 60.7%, $p = 0.002$). Adjusted for age, sex, smoking history, and BE length, a

positive family history of BE or esophageal cancer was associated with a significant decreased odds of HGD or EAC (OR 0.41, 95% CI 0.19–0.90) (Table 3). Adjusted for history of advanced neoplasia, there was no significant association between FBE and age ($p = 0.15$).

Of the 37 probands with a positive family history, 17 (46%) were successfully contacted and interviewed to obtain a detailed three-generation pedigree. Of those who were successfully contacted, two (12%) did not have a first-degree relative with BE or esophageal cancer (false-positives). In the 15 FBE families, there was a total of 111 first-degree relatives over the age of 18, 21 (19%) of whom had BE or esophageal cancer. Out of 262 second-degree relatives, one had BE and none had esophageal cancer. The mean age of esophageal cancer in these families was 65.5 (SD 13.7). The male-to-female ratio among the 36 affected individuals (15 probands plus 21 first-degree relatives) was 3.5:1.

Ten families had two first-degree relatives with BE or esophageal cancer, and five families had three or more. In six families, the only affected relative had esophageal cancer of unknown cell type. Forty first- and second-degree relatives had 42 non-esophageal malignancies, as listed in Table 4.

Discussion

The results of our study suggest that BE patients with a positive family history of BE or esophageal cancer are similar in clinical presentation to those without a positive family history. Notably, there was no difference between the two groups with regard to length of Barrett's esophagus. This finding suggests that BE length may be determined less by heritable factors and more directly by factors related to damage from gastro-duodenal reflux. We also found no difference in hiatal hernia size between patients with and without FBE. Prior twin studies have shown that there is a distinct genetic component to GERD symptoms [10–12]. While presence of a hiatal hernia predisposes to GERD, our data suggest that this heritable component is not mediated by larger size of hiatal hernia.

Based on our retrospective chart review, we found that 6% of BE patients had a positive family history of BE or esophageal cancer. This estimate is consistent with the 7.3% prevalence reported by Chak et al. and the FBE Consortium [4]. There were differences between the definitions of a positive family history between the two studies. The probands from the current study had histologically confirmed BE of any length, and a positive family history was defined as having an affected first-degree relative with either BE or esophageal cancer. In a retrospective chart review, it was not possible to reliably assess for affected second degree relatives. The above-referenced study by Chak et al. restricted probands to those with long-segment BE, and a positive family history—defined as having an affected first- or second-degree relative. It is unclear to what degree the different definitions of a positive family history limit the applicability of the results of the present study.

There was an inverse association between FBE and a history of advanced neoplasia. While plausible, we feel that it is unlikely that any genetic alterations associated with FBE result in a decreased risk of progression from BE to EAC. We speculate that this finding was an artifact of more aggressive screening. Patients with a known family history of BE or esophageal cancer may be more likely to undergo screening endoscopy and subsequently be diagnosed with non-dysplastic BE, which is statistically more likely than an initial diagnosis of dysplasia or cancer at screening endoscopy. Additionally, BE probands with FBE may be more likely to self-refer to a tertiary center for endoscopic therapy of BE without dysplasia, potentially reducing the likelihood that these individuals would ever develop high-grade dysplasia or adenocarcinoma. Unfortunately, indication for the original endoscopy (usually

performed by the referring gastroenterologist) or reason for initial referral was not available on chart review for a significant proportion of the patients.

In our cohort, FBE probands were younger in age at presentation, possibly due in part to screening starting at an earlier age. This finding was also partially due to a higher proportion of non-FBE patients with a history of advanced neoplasia, and one would expect such patients to present at an older age. In fact, there was no association between FBE status and age after adjustment for history of advanced neoplasia. Also, the mean age of esophageal cancer in FBE families was similar to that previously reported in sporadic cases [8]. The FBE Consortium previously demonstrated no difference in age of EAC diagnosis between patients with and without a family history of BE or EAC [8].

The male-to-female ratio in affected members of FBE families was not significantly different as compared to non-FBE probands. Again, this is consistent with prior published data of familial clustering of BE as well as with the general epidemiology of BE and EAC [3, 13]. While the number of patients was relatively small, we found no obvious association between FBE and other primary malignancies.

Prior studies indicate that BE and EAC in families with clustering have similar clinical behavior compared to sporadic cases. In affected members of FBE families, BE length, age of EAC diagnosis, and stage of EAC presentation are all similar to sporadic cases, suggesting that there is no increased risk of progression from BE to EAC. There appears to be familial clustering with regard to gastro-duodenal reflux (as measured by GERD symptoms) [10–12]. Therefore, one could hypothesize that the observed familial clustering of BE and EAC is due to any combination of the following factors: genetic predisposition to gastro-duodenal reflux, increased likelihood of development of BE in the setting of reflux, and shared environmental exposures.

Our study has several strengths. We were able to analyze data from a large cohort of BE patients, and a high proportion of these had family history of BE or esophageal cancer documented in the medical chart. Quantitative measurements of both BE length and hiatal hernia size allowed for accurate comparisons between FBE and non-FBE probands. Additionally, approximately half of the FBE probands were successfully contacted and interviewed to collect family history.

The current study also has limitations. The initial screen to identify patients with a positive family history was based on retrospective chart review. Such an approach could lead to misclassification of study subjects. However, among the patients identified in this manner and subsequently interviewed, the false-positive rate for a positive family history was only 12%, not dissimilar to other studies with more rigorous assessment of familiality [4]. It is difficult to estimate the false-negative rate, although data from colon cancer suggest that probands frequently underreport cancers in both first- and second-degree relatives [14]. False-negative rates are especially difficult to determine in FBE, as patients with Barrett's esophagus are frequently asymptomatic and never diagnosed. An additional limitation to the current study was the lack of pedigree data on sporadic BE cases. As such, analyses including family size and age of relatives could not be performed comparing the sporadic and familial BE groups. The initial definition of FBE included any esophageal cancer, as cell type of the affected relative was rarely recorded in the medical charts. Additionally, esophageal cancer cell type was often not ascertainable in the pedigrees. The Barrett's patients were part of a large cohort from a single referral center, although it is unclear how this bias would have impacted the findings. We were also unable to capture body mass index in our analyses, an additional risk factor for BE and EAC.

In summary, patients with FBE do not differ from sporadic BE patients with regard to length of BE and size of hiatal hernia. These data, combined with that from prior studies, raise the possibility that familial clustering of BE and EAC may be due to increased likelihood of gastro-duodenal reflux and development of BE and possibly less related to an increased risk of progression from BE to EAC. Ongoing work by the FBE Consortium will hopefully result in the identification of specific genes responsible for familial clustering of BE and EAC, and may also provide insights into genetic factors that influence the development of BE.

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Table 1

Demographic and clinical characteristics of Barrett's esophagus probands with and without FBE

	FBE		Non-FBE		*p* value
	n	**%**	***n***	**%**	
Total number	35	5.8	568	94.2	
Male sex	25	71.4	429	75.5	0.55
Mean age, years	58.4	±13.1	63.8	±12.9	0.02
Race					0.40*
White	20	57.1	365	64.3	
Black	0	0.0	9	1.6	
Hispanic	1	2.9	7	1.2	
Asian	0	0.0	5	0.9	
Other/unknown	14	40.0	182	32.0	
Smoking history					0.29[a]
Ever	7	20.0	183	32.9	
Unknown	11	31.4	140	24.7	
Personal history of other cancers	5	14.3	96	16.9	0.37

FBE Familial Barrett's esophagus

*For comparison of White vs. non-White (or other/unknown)

[a]Overall *p* value

Table 2

Comparison of endoscopic and histological characteristics of FBE and non-FBE probands

	FBE		Non-FBE		*p* value
BE length, median (cm)	3	IQR 2-5	3	IQR 1-6	0.78
Hiatal hernia size, median (cm)	2	IQR 2-4	3	IQR 2-4	0.90
H. pylori-positive	1	2.9%	15	2.7%	0.89
Barrett's-associated pathology					0.03*
No dysplasia	10	28.6%	91	16.0%	
Indefinite for dysplasia	6	17.1%	38	6.7%	
Low-grade dysplasia	7	20.0%	91	16.0%	
High-grade dysplasia	6	17.1%	164	28.9%	
Adenocarcinoma	6	17.1%	176	31.0%	
Unknown[a]	0	0.0%	8	1.4%	

FBE Familial Barrett's Esophagus, *BE* Barrett's esophagus

*Overall *p* value

[a]Original pathology reports unavailable

Table 3

Multivariable logistic regression analysis of factors associated with a history of advanced neoplasia (high-grade dysplasia or adenocarcinoma) in a cohort of patients with Barrett's esophagus

	Odds ratio	95% CI
FBE	0.41	0.19–0.90
Age*		
60–70 years	2.55	1.62–4.02
> 70 years	4.13	2.55–6.67
Male sex	2.04	1.31–3.19
BE length, per cm	1.01	0.96–1.07
Smoking history, ever	2.30	1.42–3.69

CI Confidence interval, *FBE* Familial Barrett's esophagus, *BE* Barrett's esophagus

* Reference group age <60

Table 4

Non-esophageal malignancies in first- and second-degree relatives of 15 patients with FBE

Primary site	First-degree (*n*)	Second-degree (*n*)
Colon	4	3
Lung	1	3
Brain	1	3
Uterus/ovary	0	3
Breast	1	1
Leukemia	1	1
Prostate	0	2
Stomach	1	0
Testicular	1	0
Bladder	1	0
Melanoma	1	0
Basal cell	1	0
Bone	0	1
Thyroid	0	1
Pancreas	0	1
GI, not further specified	0	7
Unknown	0	3
Total	13	29

FBE Familial Barrett's esophagus, *GI* gastrointestinal