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Secular Trends in Patients Diagnosed with Barrett's Esophagus

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Abstract

Background—It is not known whether there have been recent changes in demographic or clinical characteristics among patients newly diagnosed with Barrett's esophagus (BE), which could be a result of changes in disease epidemiology or of screening or surveillance effects, and could have clinical implications.

Aims—The aim of this study was to determine whether there has been a shift in age at diagnosis of BE over the past decade. Secondary aims were to determine whether there has been a shift in patient body mass index (BMI) or BE segment length.

Methods—An endoscopic database at a tertiary medical center was used to identify all esophagogastroduodenoscopies (EGDs) performed between 1997 and 2007. The cohort was restricted to patients newly diagnosed with BE. Pathology records were reviewed to confirm biopsy findings of intestinal metaplasia (IM).

Results—BE was diagnosed in 378 subjects between 1997 and 2007. Mean age at diagnosis of BE was 60.7 ± 14.1 years, with mean BMI of 27.4 ± 5.2 kg/m² and mean BE segment length of 4.7 ± 3.7 cm. Between 1997 and 2007 there was no significant change in mean age at diagnosis, BMI, BE segment length or in proportion of men versus women newly diagnosed.

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Disclosures None.

Conclusions—Despite an increase in volume of EGDs performed in an open-access endoscopy unit between 1997 and 2007, there was no appreciable shift in age at diagnosis of BE. BMI and BE segment length among newly diagnosed patients also remained stable over this time period.

Keywords

Barrett's esophagus; Esophageal adenocarcinoma; Upper gastrointestinal endoscopy; EGD

Introduction

Barrett's esophagus (BE) refers to specialized intestinal metaplasia of esophageal mucosa and is a precursor lesion to esophageal adenocarcinoma (EAC) [1]. Increasing incidence of EAC has been reported in the USA and other industrialized Western societies [2, 3]. Although BE typically develops in individuals with long-standing gastroesophageal reflux disease (GERD), there are no telltale signs or symptoms which allow distinction between GERD patients with and without BE. Moreover, BE may develop in the absence of characteristic heartburn or reflux symptoms. Diagnosis of BE therefore requires both endoscopic visualization of salmon-colored mucosa proximal to the anatomic gastroesophageal junction, and histopathologic findings of columnar epithelium with goblet cells.

In an effort to identify individuals with BE and therefore at risk for EAC, targeted endoscopic screening has been proposed. Although somewhat controversial, a rationale for screening and surveillance has been based on cost-effectiveness analyses [4, 5]. Prior American College of Gastroenterology (ACG) practice guidelines, published a decade ago in 1998, advocated screening endoscopy for detection of BE in individuals with long-standing gastroesophageal reflux symptoms, particularly those aged 50 years and older [6]. However, updated ACG guidelines indicate that general population screening cannot be supported and that the decision to screen at-risk individuals must therefore be performed on an individualized basis [7], and an American Gastroenterological Association (AGA) medical position statement cites a lack of sufficient evidence to recommend clearly either for or against screening in individuals with chronic GERD [8].

Nonetheless, the past decade has witnessed the widespread growth of outpatient endoscopy in open-access endoscopy centers. While the practice of open-access endoscopy has been reported to have had a negligible impact on early diagnosis of gastroesophageal cancers [9], the impact of open-access endoscopy on diagnosis of BE is largely unknown.

The primary aim of this study was to identify whether there has been a shift in age at initial diagnosis of BE between 1997 and 2007. We hypothesized that the practice of open-access endoscopy, in the context of screening guidelines, would result in a trend of decreasing age at initial diagnosis of BE during this time period. Such a trend would have potential implications for surveillance strategies and resource utilization, and might also provide insight into the natural history of BE.

In addition to screening strategies and endoscopic practice patterns, certain demographic trends might be expected to impact the diagnosis and natural history of BE. For instance, the past decade has witnessed rising prevalence of obesity and overweight in the USA, and body mass index (BMI) has been associated with both symptomatic GERD [10] and BE [11]. Secondary aims of this study, therefore, were to identify whether there has been a shift in patient body mass index (BMI) or BE segment length at time of initial diagnosis of BE.

Methods

Institutional review board approval for this study was obtained from the human research committee of the Massachusetts General Hospital (Boston, MA).

This retrospective study was completed at a single tertiary care institution, where both outpatient and inpatient esophagogastroduodenoscopies (EGDs) are performed in a hospital-based endoscopy suite. Referral for outpatient upper gastrointestinal endoscopy is available to referring providers on an open-access basis. Since June 1997, a computer software platform (Provation, Wolters Kluwer Health, Minneapolis, MN) has been used to document all endoscopic procedures. For the purposes of this study, this computer database was initially queried to retrieve all EGDs, both inpatient and outpatient, performed between 1997 and 2007.

The query was further restricted to include only EGDs in which an endoscopic finding consistent with BE had been documented by the endoscopist. For cases in which an individual had undergone multiple EGDs, all but the index EGD were excluded. The database includes information regarding indication(s) for the endoscopic procedure. In an effort to capture only new diagnoses of BE, EGDs for which the indication included follow-up of known BE or esophageal tumor, BE surveillance, therapy of BE or esophageal tumor, or therapy of lesion not otherwise specified (endoscopic mucosal resection, photodynamic therapy, or dysphagia following photodynamic therapy) were all excluded.

Information regarding subject age and gender were retrieved from the database query. Pediatric patients, defined as those of age less than 18 years at time of endoscopy, were excluded. Length of BE was obtained by review of individual endoscopic reports. Subject body mass index (BMI), as well as data pertaining to alcohol and tobacco use, were obtained by medical record review of nursing intake and triage recorded at date of endoscopy. Height and weight were self-reported by the patients. The intake interview process was not standardized.

Once a cohort of subjects with newly diagnosed (by endoscopy) BE had been identified, pathology records were reviewed individually to determine biopsy findings from index endoscopy. In addition to confirming the presence of intestinal metaplasia (IM), rates of prevalent dysplasia and/or esophageal cancer were also documented. If esophageal biopsies had not been obtained, or if biopsies had been obtained but failed to demonstrate IM, the subject was excluded from further analysis. Therefore, the final cohort for analysis consisted only of subjects with both endoscopic and histopathologic confirmation of BE.

Statistical analysis was performed using JMP 7.0 software (SAS Institute, Cary, NC). Univariate testing was performed with either Student's *t*-test or one-way analysis of variance (ANOVA) testing for comparison of continuous variables, and with chi-square testing for comparison of categorical values. All reported *P* values are two-sided, and a value of <0.05 was used as a threshold for statistical significance.

Results

Overall EGD Cohort

Between June 1997 and December 2007, a total of 58,828 EGDs were performed, with a steady annual rise across nearly this entire time period (Fig. 1). The most common reported indication for EGD was overt gastrointestinal bleeding (hematemesis, melena or hematochezia) in 16% of patients, followed by abdominal pain (15%) and dysphagia (10%). GERD/heartburn was reported as the indication for EGD for approximately 8% of subjects.

In addition, dyspepsia was cited as the indication for approximately 5% of subjects, and known or suspected BE in approximately 4% of subjects.

The peak annual volume of EGDs was in 2006, when 8,051 EGDs were performed. Of these 58,828 EGDs, 31,163 represented index EGDs among adult patients. Following a relatively low volume of EGDs in 1997, when the endoscopy database was implemented midway through the calendar year, the mean age of adult patients undergoing EGD decreased significantly ($P < 0.0001$ by ANOVA) between 1998 and 2007, with a peak mean age of 61.1 years in 1998 and a nadir mean age of 55.4 years in 2007 (Fig. 2).

Barrett's Esophagus Cohort

BE was reported as an endoscopic finding in 4,595 EGDs performed during this time period. Following exclusion of EGDs performed in patients with known prior BE, this number was reduced to 2,080 EGDs. Following exclusion of all but the index EGD for patients with multiple EGDs, the number was reduced to 1,349 new endoscopic diagnoses of BE between 1997 and 2007.

Histopathologic confirmation of BE was available for 378 of these 1,349 patients. Among the excluded patients, 588 were excluded because biopsies failed to demonstrate intestinal metaplasia, and the remainder were excluded because biopsies had not been obtained. The 378 patients with both endoscopic and histopathologic documentation of BE constituted the final cohort for analysis.

The mean age at new diagnosis of BE was 60.7 ± 14.1 years. BE segment length had been documented in 311 of 378 cases (82%), and among these the mean BE segment length at diagnosis was 4.7 ± 3.7 cm. Prevalent dysplasia or cancer was documented in 7% (26/378) of subjects. Of subjects, 50% (190/378) reported regular outpatient use of proton pump inhibitors (PPI) at time of index EGD. Overall demographic data are summarized in Table 1.

The majority of patients diagnosed with BE were male (71%) and of Caucasian ethnicity (92%). In comparing men with women newly diagnosed with BE, there were no significant differences with respect to age or BMI at diagnosis, prevalence of reported alcohol or tobacco use, or BE segment length (Table 2). Rates of prevalent dysplasia/cancer were higher in men than in women (9% versus 3%, $P = 0.03$). Among nine cases of prevalent invasive EAC, eight occurred in men.

There was not a discernible increase in diagnosed cases of BE per year during this time period, either in absolute numbers (mean 34.2 cases/year, with a minimum of 16 cases in 1997 and a maximum of 57 cases in 1999) or as a percentage of all EGDs performed (mean 0.7% of EGDs/year, range 0.4–1.4%).

Secular Trends

During the time period 1997–2007 there was no significant change in the mean age of patients newly diagnosed with BE ($P = 0.88$ by ANOVA) (Fig. 3a). Similarly, between 1997 and 2007 there was no significant change in the mean BMI among patients newly diagnosed with BE ($P = 0.24$ by ANOVA) (Fig. 3b), and no significant change in BE segment length at diagnosis ($P = 0.57$ by ANOVA) (Fig. 3c).

In gender-specific analysis, there was no significant change in age, BMI or BE segment length in either men alone or women alone newly diagnosed with BE during this time period (data not shown). Among annual new diagnoses of BE during this time period, the proportion of men compared with women did not change ($P = 0.42$).

Discussion

The increasing utilization of EGD as a screening tool has the potential to impact the diagnosis and influence the natural history of several upper gastrointestinal disease states. BE and early-stage EAC often exist without specific symptoms, and it is therefore tempting to hope that EGD might lead to early and timely diagnosis of these conditions. However, data from Scotland indicate that, despite a rapid growth in the volume of EGDs performed between 1994 and 2003, there was no perceived benefit with respect to earlier diagnosis of EAC [9]. On the other hand, there was evidence of an increased prevalence of BE in a Kaiser Permanente cohort between 1994 and 2006 [12]. What is largely unknown, however, is whether the growing volume of outpatient EGD has resulted in a demographic shift in the diagnosis of BE.

We hypothesized that the growth of open-access endoscopy and evolving endoscopy referral patterns would have resulted in a trend over time of a younger age at initial diagnosis of BE. Such a shift in demographics might have considerable implications from a health-care systems perspective. Strict adherence to a BE surveillance strategy ostensibly requires a lifelong commitment to endoscopic follow-up. A younger age at diagnosis of BE, in the context of serial EGD surveillance, would on average result in a greater number of EGDs over the life expectancy of the typical patient. While such an effect might not be notable for the individual patient or endoscopist, the requisite investment in time and resources necessary to perform an increased volume of EGDs would have tangible effects on a system-wide scale and third-party payers.

Our study describes the experience in a single tertiary care center during the decade 1997–2007. Our cohort of over 58,000 outpatient and inpatient EGDs included 378 patients with newly diagnosed BE. Despite a decrease in the mean age of patients undergoing EGD, and contrary to our hypothesis, the mean age at diagnosis of BE was remarkably stable during this time period. This finding is consistent with data reported from an earlier 20-year cohort in the UK, which reported a constant mean age at diagnosis of BE between 1977 and 1996 [13]. Our study analyzed a US cohort in a later time period when the increase in endoscopic utilization was more pronounced.

With respect to secular trends, several additional findings from our study bear emphasis. Epidemiologic data have suggested an association between BMI and both symptomatic GERD [10] and BE [11], and an increasing burden of overweight and obesity in the USA over the past decade might ultimately be expected to translate into an increasing burden of symptomatic GERD and diagnosed BE. However, BMI at diagnosis of BE was unchanged over the study time period in our cohort. BMI data for the overall EGD cohort were not available, and we therefore cannot assess whether any BMI trend was evident in the EGD cohort as a whole. Abdominal obesity and waist-to-hip ratio may be more robust factors than BMI in predicting risk of BE [14, 15], and these data were not available for analysis in our retrospective database.

Our study also detected no significant change or trend in mean BE segment length at diagnosis. This is in contrast to a prior study in a Veterans Affairs population which reported a progressive decline in the length of newly diagnosed BE, albeit over a longer time span (1981–2000) [16]. Factors influencing BE segment length at diagnosis may include proton pump inhibitor (PPI) use [17]. Of BE patients in our cohort, 50% reported regular PPI use at the time of EGD; however, our study was not designed to assess and cannot determine the impact of PPI use on BE length. Data from several prior studies suggest an association between BE segment length and both prevalent and incident dysplasia/cancer [18–21]. BE segment length may predict response to ablation therapy among patients with dysplastic BE

who undergo endoscopic ablation therapy [22, 23]. For each of these reasons, changing patterns in BE segment length would have implications for BE disease burden and management.

Mean BE segment length was longer (4.7 cm) in our cohort than in other previously reported referral center cohorts [24, 25], and this may reflect dissimilar demographic profiles among the cohorts, or a failure to biopsy or failure to detect IM by biopsy in patients with short-segment BE—although this bias should theoretically be constant over time, and would therefore not alter the finding of a lack of change in newly diagnosed BE segment length over time.

Finally, in our cohort, there was no difference between men and women with respect to clinical characteristics at diagnosis. Mean age at diagnosis was similar in men and women. This contrasts with other retrospective cohorts, which have reported a younger mean age at diagnosis in men as compared with women [11, 26]. A cohort from the Cleveland Clinic reported a longer mean BE segment length in men as compared with women [26], although our study detected no gender-specific difference in mean BE segment length at diagnosis. The finding of higher prevalence rates of dysplasia in men as compared with women is consistent with previously published data [26]. There was no change in the proportion of men versus women newly diagnosed with BE during the study time period.

A strength of our study includes the strict definition used to define a case of BE, requiring both endoscopic and histologic criteria, thus minimizing the likelihood of including false-positive diagnoses. And, although the study cohort was derived from a tertiary referral center with subspecialty expertise in endoscopic therapy of BE, we excluded patients with a known diagnosis of BE or patients referred for therapy of BE, in an effort to capture only new diagnoses of BE. A sizable number of patients with endoscopically suspected BE had not undergone biopsy to confirm the presence of IM. The endoscopists' decision-making process on a case-by-case basis cannot be evaluated in this retrospective study, therefore it is uncertain whether this reflects systematic practice variability in a large endoscopic practice, or a deliberate decision to forego biopsy in patients undergoing EGD for specific indications. It is the authors' practice to biopsy visible esophageal mucosa consistent in appearance with BE, in order to both confirm the presence of IM and exclude the presence of dysplasia.

We felt it important to include both outpatients and inpatients in the study. Inpatients might represent a fundamentally different population than outpatients, with potentially different indications for undergoing EGD. Nonetheless, the endoscopic finding of BE has the same potential implications for future endoscopic surveillance and management, regardless of the initial procedural indication.

Additional limitations of the study include the retrospective study design, with incomplete availability of covariate patient data beyond that included in the endoscopic database, including presence of comorbid illness, and presence/severity of symptomatic GERD. Moreover, these data were abstracted from the medical record retrospectively, and had not been obtained in a standardized or validated fashion at the time of initial clinical care. And, despite a large database of EGDs, the relatively modest number of BE cases allows for type II error. The study was not designed to assess incident dysplasia/cancer rates, which happened to be significantly different between men and women in subset analysis, or provide any long-term follow-up beyond initial diagnosis of BE.

Assuming the internal and external validity of our study results, the absence of any notable trends in patient age, BMI, or BE segment length at diagnosis of BE may be interpreted in one of two ways. Either the clinical presentation and initial diagnosis of BE remains a stable

target, despite a changing population of patients undergoing index EGD; or, alternatively, any pending demographic trends among patients diagnosed with BE will lag behind changing demographic and practice patterns, and are yet to be observed.

In summary, in a tertiary referral cohort of patients diagnosed with BE between 1997 and 2007, there were no detected secular trends in age at diagnosis, BMI at diagnosis, or BE segment length at diagnosis. The proportion of men versus women newly diagnosed with BE remained stable over time, with no gender-specific difference or trends in age, BMI, or BE segment length at diagnosis. Rates of dysplasia/cancer prevalence were higher in men than in women. Further attention to patient characteristics at diagnosis, and emergence of any evident secular trends, may be used to optimize and target BE screening, surveillance, and management strategies.

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Fig. 1.
Annual volume of EGDs at study hospital, 1997–2007

Fig. 2.
Mean age among adult patients undergoing first EGD, 1997–2007

Fig. 3.

a Mean age among patients newly diagnosed with Barrett's esophagus, by year, 1997–2007
b Mean BMI among patients newly diagnosed with Barrett's esophagus, by year, 1997–2007
c Mean Barrett's segment length among patients newly diagnosed with Barrett's esophagus, by year, 1997–2007

Table 1

Cohort demographics: new diagnoses of Barrett's esophagus, 1997–2007

N	378
Gender	
Male	268 (71%)
Female	110 (29%)
Age	60.7 ± 14.1 years
Caucasian ethnicity	341 (92%)
BMI	27.4 ± 5.2 kg/m ²
Alcohol use	
Yes	157 (42%)
No	161 (43%)
Unknown	60 (16%)
Tobacco use	
Yes	48 (13%)
No	272 (72%)
Unknown	58 (15%)
Barrett's segment length	4.7 ± 3.7 cm
Prevalent pathology at index EGD	
Intestinal metaplasia alone	326 (86%)
Indefinite for dysplasia	26 (7%)
LGD	9 (2%)
HGD	4 (1%)
IMC	4 (1%)
Invasive adenocarcinoma	9 (2%)

LGD low-grade dysplasia, *HGD* high-grade dysplasia, *IMC* intra-mucosal carcinoma

Mean values are represented as mean ± standard deviation (SD)

Table 2

Cohort demographics by gender: new diagnoses of Barrett's esophagus, 1997–2007

	Male	Female	<i>P</i> value
<i>N</i>	268	110	
Age	60.0 ± 14.0 years	62.3 ± 14.1 years	0.14
BMI	27.4 ± 5.0 kg/m ²	27.5 ± 5.9 kg/m ²	0.88
Alcohol use			
Yes	116 (47%)	41 (41%)	0.51
No	110 (44%)	51 (51%)	
Unknown	23 (9%)	8 (8%)	
Tobacco use			
Yes	35 (14%)	13 (13%)	0.88
No	192 (77%)	80 (79%)	
Unknown	23 (9%)	3 (8%)	
Barrett's segment length	4.8 ± 3.6 cm	4.4 ± 3.9 cm	0.39

Mean values are represented as mean ± SD