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Age- and Gender-Specific Yield of Barrett's Esophagus by Endoscopy Indication

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Abstract

Background—Barrett's esophagus is a precursor of esophageal adenocarcinoma, both of which are associated with gastroesophageal reflux disease (GERD). Screening GERD patients for Barrett's esophagus has been suggested, but it is not known which patients should be screened, and at what age.

Objective—To determine the age-specific yield of endoscopy for Barrett's esophagus stratified by gender and indication for endoscopy.

Design—Retrospective cross-sectional study.

Setting—National Endoscopic Database of the Clinical Outcomes Research Initiative (CORI).

Patients—155,641 patients undergoing their first endoscopy at one of the CORI sites for clinical indication.

Interventions—N/A

Main Outcome Measurements—Age-specific yield of Barrett's esophagus.

Results—Among white men with GERD, the yield for Barrett's esophagus rises steeply from early adulthood (2.1% in 3rd decade of life) to middle adulthood (9.3% in 6th decade), and then plateaus (difference for 8th decade minus 6th decade = -1.1%, 95% confidence interval [CI] = -3.9%, +1.7%). There is no difference in yield of Barrett's esophagus between middle-aged white women with GERD and white men without GERD (difference = -0.46%, 95% CI = -1.23%, +0.31%).

Limitations—Possible bias by selection for endoscopy, and potential for misclassification of GERD status.

Conclusions—The yield of upper endoscopy for diagnosis of Barrett's esophagus increases rapidly among white men with GERD until approximately age 50, then reaches a plateau. White women with GERD are at no increased risk compared to white men without GERD.

Keywords

Barrett's esophagus; Epidemiology

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INTRODUCTION

Barrett's esophagus is an accepted precursor of esophageal adenocarcinoma.(1,2) Both esophageal adenocarcinoma and Barrett's esophagus are associated with long-standing prior symptoms of gastroesophageal reflux disease (GERD).(3,4) There is little consensus among practicing gastroenterologists for who if anyone should be screened with endoscopy for Barrett's esophagus.(5)

Other known *relative* risk factors for Barrett's esophagus include advancing age, male gender, and white race, but the *absolute* age-specific yield of Barrett's esophagus in any particular group is poorly known. (1,2,6–9) In an American multi-center pediatric endoscopic database, Barrett's esophagus was only found in 0.1% of children undergoing upper endoscopy.(10) In prior studies of adults undergoing endoscopy, Barrett's esophagus was diagnosed more commonly among older adults than younger adults,(11–14) but those studies did not provide age-specific yields stratified by GERD symptoms and gender, and likely underestimated the true prevalence of Barrett's esophagus since most patients who have Barrett's esophagus likely never undergo upper endoscopy.(15–17)

We hypothesized that the yield of Barrett's esophagus on upper endoscopy in previously un-investigated patients increases steeply through early and middle adulthood, and then likely plateaus in the 7th decade of life (approximately 15 years before the peak incidence of esophageal adenocarcinoma).(18) We also expected that the yield of Barrett's esophagus is higher among patients with GERD symptoms, and among men.(19,20)

To address these hypotheses, we performed retrospective analyses of the National Endoscopic Database of the Clinical Outcomes Research Initiative (CORI) which is partially linked to pathology records. We also evaluated secular trends in the age-specific yield of Barrett's esophagus on endoscopy and in the length of Barrett's esophagus identified.

METHODS

Clinical Outcomes Research Initiative

The Clinical Outcomes Research Initiative (CORI) was established to study utilization and outcomes of endoscopy in diverse practice settings. 65 adult practice sites, representing 500 physicians, submit more than 250,000 reports annually to the CORI National Endoscopic Database (NED), including 100,000 upper endoscopy reports. Practice sites include private practice (79% of reports), academic sites (10%) and VA sites (11%). All participating sites agree to use a standardized computerized report generator to create all endoscopic reports and to comply with quality-control requirements. The data files from the sites are transmitted electronically to a central data repository. Patient and physician identifiers are removed from the data files before transmission to protect both patient and physician confidentiality. As such, the study was exempt from the requirement for informed consent.

For the current study, the cohort was drawn retrospectively from 35 sites that contributed data continuously from 2000 to 2006. Nine of these CORI sites that routinely entered pathology results in at least 75% of all procedure reports during the time period 2000 to 2005 were identified. The analysis of histologically confirmed Barrett's esophagus was restricted to this sub-cohort.

Study Population

The study was limited to adult patients (ages 18 to 79 years) undergoing their first upper endoscopy at a contributing CORI site between 2000 and 2006. Indications for the procedure

were determined by the endoscopist at the time of writing the endoscopy report. The standardized computerized report generator forces endoscopists to choose at least one indication by the use of check boxes (including a choice of “Screening for Barrett’s esophagus”). If more than 1 indication is chosen, the endoscopist is forced to identify a primary indication. Patients undergoing upper endoscopy for “surveillance of Barrett’s” were excluded. Otherwise, patients were classified according to indications of 1) screening for Barrett’s esophagus or evaluation of GERD symptoms (which we have labeled “GERD Screenees”), and 2) all others (“No GERD”). Race (white, black, Asian, Native American, Pacific Islander) and Hispanic ethnicity (yes/no) were entered by the endoscopist at the time of writing the endoscopy report.

Identification of Barrett’s Esophagus

Endoscopically suspected Barrett’s esophagus is a reporting option under Findings in the report software. If the report indicated suspected Barrett’s esophagus, length of Barrett’s was collected when noted directly in the report, or derived from the difference between the distances from the incisors to the gastroesophageal junction and to the squamocolumnar junction. Overall, 12% of Barrett’s esophagus was missing length. Segments were classified as short (< 3 cm) or long ($\geq$ 3 cm). The sites that contributed pathology reports pasted the entire report into the CORI data field electronically, and pathology reports from endoscopies suspicious for Barrett’s esophagus from the years 2000 through 2005 were manually reviewed centrally as previously described for histologic interpretations consistent with Barrett’s esophagus (intestinal metaplasia or goblet cells in tissue obtained from the esophagus).(21) Histologically confirmed Barrett’s esophagus was defined as a patient with both endoscopically suspected Barrett’s esophagus and a pathology report consistent with Barrett’s esophagus.

Statistical Analyses

Patients were categorized into decades of age (18–29, 30–39, 40–49, 50–59, 60–69, and 70–79). The age-, gender-, and indication-specific yields of upper endoscopy for histologically confirmed Barrett’s esophagus were tabulated for patients in the sub-cohort with linked pathology records. The differences in yield of Barrett’s esophagus between two age groups and the 95% CI of each difference were calculated. Multivariate logistic regression was used to estimate the risk of Barrett’s esophagus according to race, after adjusting for known confounders of age, gender and indication. Due to sparse data in many strata among non-white races, and the known association of white race with both Barrett’s esophagus and esophageal adenocarcinoma,(22,23) other analyses were restricted to white non-Hispanics.

The secular trend in yield of endoscopically suspected Barrett’s esophagus in the total cohort was evaluated using the Mantel-Haenszel chi-square test for linear trend, stratifying by age, gender, and indication of endoscopy. Multivariate logistic regression was performed to statistically compare the yield of endoscopically suspected Barrett’s esophagus during late years (2005/2006) versus early (2000/2001), among white male GERD screenees.

The Mantel-Hanszel chi-square test for linear trend was also used to evaluate the change over time in length of suspected Barrett’s esophagus. An a priori determined P-value of 0.05 was considered statistically significant. All analyses were performed using SAS version 9.1 software (SAS Institute, Inc., Cary, NC).

RESULTS

The total study cohort comprised 155,641 unique patients undergoing first documented upper endoscopy at one of 35 sites (Table 1). The majority were performed in the private practice setting on white non-Hispanics, with slightly more men than women. Overall, 48,476 (31.1%) were undergoing upper endoscopy for evaluation of GERD or screening for Barrett’s

esophagus (GERD Screenees). Of the entire study cohort, 7,804 (5.0%) were suspected by the endoscopist of harboring Barrett's esophagus, and among the GERD Screenees, 4,339 (9.0%) were suspected of harboring Barrett's esophagus. Between 2000 and 2006, the annual number of first-time endoscopies performed on GERD Screenees steadily increased from 5,648 to 8,256. However, the total number of first-time endoscopies increased faster such that the proportion of first-time endoscopies performed for GERD or screening for Barrett's esophagus decreased from 32.7% to 30.8%.

Relationship of Age with Yield of Barrett's Esophagus

In order to determine the age-, gender-, race-, and indication-specific yield of histologically confirmed Barrett's esophagus, analysis was performed on the sub-cohort of 25,337 patients undergoing first documented upper endoscopy at one of 9 sites from which pathology reports were available from the years 2000 to 2005 ("histologic sub-cohort"). Academic and Veterans Affairs sites were over-represented in this histologic sub-cohort, and private practices under-represented (Table 1). The histologic sub-cohort included a relatively larger proportion of men, and slightly fewer non-Hispanic blacks than the total cohort. But there was a similar proportion of screening endoscopies in the histologic sub-cohort and total cohort. Overall of the histologic sub-cohort, 704 patients (2.8%) were confirmed histologically to have Barrett's esophagus.

Among white non-Hispanic male GERD Screenees, the yield of histologically confirmed Barrett's esophagus increased sharply from 3.3% in the 4th decade of life to 6.3% in the 5th decade, and 9.3% in the 6th decade of life, and then reached a plateau (difference in yield for 5th decade minus 4th decade = 3.0%, 95% confidence interval [CI] = 0.4%, 5.5%; 6th minus 5th decades = 3.0%, 95% CI = 0.7%, 5.4%; 8th minus 6th decades = -1.1%, 95% CI = -3.9%, +1.7%) (Figure 1). Among white female GERD Screenees younger than the age of 30, zero patients were found to have histologically confirmed Barrett's esophagus. 2.4% of white female GERD Screenees between the ages of 40 and 79 were found to have Barrett's esophagus. Remarkably, white female GERD Screenees were found to be no more likely to have Barrett's esophagus than white men *without* GERD (for 40–79 years of age, difference for female GERD Screenees minus males without GERD = -0.46%, 95% CI = -1.23%, +0.31%) (Figure 1). Less than 1% of white women without GERD were found to have Barrett's esophagus, regardless of age. Blacks had four-fold lower odds of histologically confirmed Barrett's esophagus than whites (odds ratio, OR = 0.26, 95% CI = 0.13 – 0.53, adjusting for age, gender, and indication), and given the small sample size within strata, the estimates of age-, gender-, and indication-specific yields among Blacks would therefore likely be unreliable estimates.

Secular Trend in Yield of Barrett's Esophagus

A concern influencing a provider's decision whether to offer endoscopy in younger patients might be that Barrett's esophagus may be becoming more common at younger ages. Due to sparse data in the strata of years, we could not analyze the secular trends in histologically confirmed Barrett's esophagus for each group of patients. Instead, we analyzed the trends in endoscopically suspected Barrett's esophagus across the years 2000 through 2006 in the total cohort (n = 168,866). No time-trend in age-specific yield of Barrett's esophagus was identified among white women with or without GERD during this time frame, or among white men without GERD. However, among white male GERD Screenees, the age-specific yield of Barrett's esophagus decreased over this time frame (Figure 2). In 2005 and 2006, a white male GERD Screenee was less likely to be suspected endoscopically of harboring Barrett's esophagus than in 2000 and 2001 (OR = 0.78, 95% CI 0.70 – 0.87, adjusting for age).

Over this same time frame, the proportion of suspected Barrett's esophagus that was classified as long-segment decreased from 36% to 24% ($p < 0.0001$ for trend), while the proportion classified as short-segment increased from 57% to 60% (Figure 3). Although the proportion

with missing data for length of Barrett's esophagus also increased during this time period, the decrease in the proportion of long-segment Barrett's esophagus was greater than the increase in the missing proportion in 2006 compared to 2000.

DISCUSSION

From these retrospective analyses of a large, national endoscopic database, we found a substantial increased yield for Barrett's esophagus in middle adulthood compared to early adulthood among white men with GERD, with a plateau in yield after approximately age 50. It is therefore likely that the metaplastic event occurs at some point between the ages of 20 and 50 in most patients. Another important finding is the yield of endoscopy in women with GERD. In women younger than the age of 30, zero patients were found that have Barrett's esophagus in this large study. Remarkably, we found that older white women with GERD were no more likely to have Barrett's esophagus than white men without GERD. This result might have been biased by differential reporting of GERD symptoms in the indication for the endoscopies, or differential selection for endoscopy between men and women.

Despite the greater risk of Barrett's esophagus in older patients, and in males, a survey of gastroenterologists found that 73% would screen a 35 year-old man with long-duration GERD, and 42% would screen a 55 year-old woman with chronic GERD.(5) The efficacy of screening has only been explored in observational studies with inherent limitations,(15–17) and the cost-effectiveness of screening patients younger than age 50 or of screening female patients has not been explored extensively.(24–29)

Since screening has not been examined in high quality prospective controlled studies, an argument could be made for not screening patients for esophageal adenocarcinoma at all. However, given the recent improvements in endoscopic treatments of dysplasia, and the burgeoning development of endoscopic and biologic markers of risk of progression of Barrett's esophagus, we believe screening may be warranted, but that it should be limited to men over the age of 50 who have GERD symptoms. Our findings suggest that screening should not be performed in younger men due to the still increasing yield at those ages, and the potential for falsely stratifying patients as low risk who may yet develop Barrett's esophagus at an older age. While esophageal adenocarcinoma may present at ages younger than 50 years, it is an exceedingly rare phenomenon, and unlikely to warrant the inefficient use of resources to screen those patients. Furthermore, given the apparent equivalent yield of Barrett's esophagus among women with GERD and men without GERD, we believe that screening should not be performed in women. Otherwise, we should consider also screening men without GERD. Cost-effectiveness analyses are needed to evaluate screening in particular populations.

The yield for Barrett's esophagus among white men without GERD in this study was lower than the yield found among asymptomatic men undergoing screening colonoscopy who were recruited to undergo a research upper endoscopy in 3 studies.(23,30,31) The lower yield in our retrospective study may have been due to inattention by the endoscopists and therefore under-diagnosis of short-segment Barrett's esophagus in a group of patients undergoing upper endoscopy for other clinical indications. This may be a particular issue in patients not fitting the pre-conceived notions of who is most likely to harbor Barrett's esophagus. Another possible explanation may be factors protective from Barrett's esophagus (i.e., *Helicobacter pylori*) that led to these patients without GERD being referred for upper endoscopy. But the yield of Barrett's esophagus in white men without GERD older than 39 years of age in our study was higher than the yield found in a random sample of 2 Swedish communities.(32) The different finding is likely in part due to lack of stratification by age in the Swedish study, and may have been due to differences with the Americans in factors such as obesity or dietary habits.

A few prior studies have suggested that the incidence of Barrett's esophagus is increasing. (11,14) Since Barrett's esophagus is asymptomatic beyond any associated symptoms of GERD, and is only diagnosed incidentally or as the result of screening, those results are unlikely to reflect true incidence, and may reflect changes in selection of patients for endoscopy or changes in practice of endoscopic diagnosis. In our study, we did not find any evidence of an increasing yield of Barrett's esophagus; in fact, we found that the yield for endoscopically suspected Barrett's esophagus actually decreased among white men with GERD in recent years. This may have been due to changes in practice of selecting patients for endoscopy. It could also be due to a decrease in the practice of diagnosing short-segment Barrett's esophagus, but we found evidence for the opposite – that diagnosing short-segment Barrett's esophagus is becoming relatively more common.

Our study was limited by the number of endoscopy reports with linked pathology records. Instead, we examined trends using patients with endoscopically suspected Barrett's esophagus, which may not reflect trends in histologically confirmed cases. Although there was no trend detected in other groups, the decrease in yield among white men with GERD over time may have been due to alterations in practice or observer bias. Such an effect might also explain the trend in increased proportions of SSBE versus LSBE over time. A smaller proportion of endoscopically suspected SSBE may actually be confirmed by histology than LSBE; the secular increase in proportion of endoscopically suspected BE that is short-segment should be interpreted cautiously. Furthermore, bias may have been introduced by selection of patients for endoscopy, or misclassification of indication for endoscopy. For example, if GERD is more strongly associated with LSBE than SSBE, and endoscopies were used more exclusively for patients with severe GERD during the earlier years of the study, and less exclusively as time went on, this change in practice could explain the observed change in proportion of SSBE. Similarly, since intestinal metaplasia may be patchy within the columnar segment, and if that sampling error is a particular issue for SSBE, then a change in practice of the number of biopsies obtained could also explain the observed change in proportion of SSBE. Barrett's esophagus may be misclassified by endoscopists as a hiatal hernia, and vice versa, and such misclassification could have biased the observed yields in an unpredictable direction. A secular improvement in the classification of Barrett's esophagus vs. hiatal hernia might explain the secular increase in yield of SSBE, but if so, we would have expected the overall yield of Barrett's esophagus to also have increased, which we did not observe. While we required strict criteria for classification of Barrett's esophagus, we relied on the local pathology reports and local endoscopic interpretation. Finally, some unknown number of our subjects may have in fact had prior upper endoscopies at another site or at the CORI site before 2000; since we excluded patients with an indication of surveillance of known Barrett's esophagus, most of these previously investigated patients likely did not have Barrett's esophagus, thereby biasing our results toward a lower yield, but with an unpredictable magnitude. The major strength of our design is the large number of endoscopies performed at multiple sites across the United States, representing the variety of practice settings in the country. Since CORI is used as the electronic medical record for these procedures, complete capture of data is likely.

In conclusion, the yield for Barrett's esophagus among white men with GERD increases steeply from young adulthood until the 6th decade of life, and then plateaus. Women with GERD symptoms are at no more risk for Barrett's esophagus than white men without GERD. If screening for Barrett's esophagus is efficacious for reducing mortality from esophageal adenocarcinoma, then screening efforts should likely focus on white men with GERD older than the age of 50.

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Abbreviations

CI	confidence interval
CORI	Clinical Outcomes Research Initiative
GERD	gastroesophageal reflux disease
OR	odds ratio

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Figure 1. Yield of Upper Endoscopy for Histologically Confirmed Barrett's Esophagus

The x-axis represents age at time of endoscopy. Patients were categorized by decade of age, and the proportion of endoscopies with histologically confirmed Barrett's esophagus for each decade is shown at the midpoint of that age category. Each line represents the yield for each gender with and without an indication of evaluation of GERD or screening for Barrett's esophagus ("GERD Screenees" or "without GERD"). Data were obtained from sub-cohort with pathology reports available.

Figure 2. Age-Specific Trend in Yield of Endoscopically Suspected Barrett's Esophagus Among White Male GERD Screeners

The x-axis represents the year of the endoscopy, and each line represents the time trend in the proportion of endoscopies with findings consistent with Barrett's esophagus for each age group. This figure only shows results for white men with an indication of evaluation of GERD or screening for Barrett's esophagus. No trend was detected in other groups. Data were obtained from the total cohort.

Figure 3. Trend in Length of Suspected Barrett's Esophagus

Each stacked column represents the sum of endoscopies with suspected Barrett's esophagus for each year. The proportion of suspected Barrett's esophagus that was at least 3 cm in length (long segment) decreased during the time frame, while the proportion of short segment (< 3 cm) increased. Data were obtained from the total cohort.

Table 1

Baseline Features of the Total Cohort, and of the Sub-Cohort from Sites with Linked Pathology Reports

	Total Cohort (n = 155,641)	Histologic Sub-Cohort (n = 25,337)
Number of Sites	35	9
Practice Setting		
Private	103,312 (66%)	9,943 (39%)
Veterans Affairs	33,301 (21%)	9,442 (37%)
Academic	19,028 (12%)	5,952 (24%)
Gender		
Male	81,865 (53%)	15,680 (62%)
Female	73,776 (47%)	9,657 (38%)
Race & Ethnicity		
White non-Hispanic	123,014 (79%)	20,453 (81%)
Black non-Hispanic	9,130 (6%)	888 (4%)
Other or unknown	23,497 (15%)	3,996 (16%)
Indication: GERD or BE Screening	48,476 (31%)	7,741 (31%)

BE: Barrett's esophagus

GERD: Gastroesophageal reflux disease