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Prediction of Barrett's Esophagus Among Men

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Abstract

OBJECTIVES—Risk factors for Barrett's esophagus include gastroesophageal reflux disease (GERD) symptoms, age, abdominal obesity, and tobacco use. We aimed to develop a tool using these factors to predict the presence of Barrett's esophagus.

METHODS—Male colorectal cancer (CRC) screenees were recruited to undergo upper endoscopy, identifying newly diagnosed cases of Barrett's esophagus. Logistic regression models predicting Barrett's esophagus using GERD symptoms alone and together with abdominal obesity, tobacco use, and age were compared.

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CONFLICT OF INTEREST

Guarantor of the article: Joel H. Rubenstein, MD, MSc.

Specific author contributions: Conceived and designed the study, acquired data, analyzed and interpreted the data, drafted the manuscript, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis: JHR; designed the study, supervised the statistical analysis, interpreted the data, and critically revised the manuscript: HM; acquired data, interpreted the data, and critically revised the manuscript: HA, JS and PS; interpreted the data, and critically revised the manuscript: LM; acquired data, and critically revised the manuscript: VM, EN, TK and JK; designed the study, interpreted the data, and critically revised the manuscript: JMI.

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Potential competing interest: JHR has received grant support and served as a consultant to Xenoport. JS has served as a consultant to AstraZeneca, Pfizer, Novartis, Pozen, and Stryker. JMI has served as a consultant to Takeda, AstraZeneca, and Roche. These potential conflicts of interest were not disclosed to study participants. HA, HM, VM, EN, TK, JK, and PS have no potential conflicts of interest.

RESULTS—Barrett’s esophagus was found in 70 (8.5%) of 822 CRC screenees. Mutually adjusting for other covariates, Barrett’s esophagus was associated with weekly GERD (odds ratio (OR) = 2.33, 95% confidence interval (CI)=1.34, 4.05), age (OR per 10 years = 1.53, 95% CI = 1.05, 2.25), waist-to-hip ratio (OR per 0.10 = 1.44, 95% CI=0.898, 2.32) and packyears of cigarette use (OR per 10 pack-years = 1.09, 95% CI = 1.04, 1.14). A model including those four factors had a greater area under the receiver operating characteristics curve than did a model based on GERD frequency and duration alone (0.72 vs. 0.61, $P<0.001$), and it had a net reclassification improvement index of 19–25%.

CONCLUSIONS—The prevalence of Barrett’s esophagus was substantial in our population of older overweight men. A model based on GERD, age, abdominal obesity, and cigarette use more accurately classified the presence of Barrett’s esophagus than did a model based on GERD alone. Following validation of the tool in another population, its use in clinical practice might improve the efficiency of screening for Barrett’s esophagus.

INTRODUCTION

Over the last 4 decades, the incidence of esophageal adenocarcinoma has risen sixfold (1). Barrett’s esophagus is a precursor to the cancer. Symptoms of gastroesophageal reflux disease (GERD) are associated with both Barrett’s esophagus and esophageal adenocarcinoma (2,3). Screening efforts have focused on patients with GERD, using frequency and duration of symptoms for selection for endoscopy (4–7). However, in all but one population-based study, the majority of patients with esophageal adenocarcinoma actually did not report significant prior symptoms of GERD (3). If screening and control efforts are to be successful at reducing the full burden of the cancer, they will need to target not only patients with GERD, but also individuals at risk for the cancer who do not experience GERD symptoms. Other factors thought to increase the risk of the cancer include sex, age, obesity, and tobacco use (8–10). The most recent guidelines from the American College of Gastroenterology states that screening the general population cannot be recommended, and that “use of screening in selective populations at higher risk remains to be established and therefore be individualized” (11). The more recent guidelines from the American Gastroenterology Association have recommended that GERD patients with multiple risk factors for esophageal adenocarcinoma should be screened with upper endoscopy for Barrett’s esophagus (5). However, the guidelines do not specify which combination of factors or at what thresholds of these factors should patients be offered screening. We are not aware of any tools utilizing the factors of obesity and tobacco use to predict an individual patient’s probability of having Barrett’s esophagus. We hypothesized that a model including GERD symptoms, age, obesity, and tobacco use would more accurately predict the presence of Barrett’s esophagus than the model based on only GERD symptoms. We also hypothesized that men identified with Barrett’s esophagus through routine clinical care are more likely to have GERD symptoms, are less likely to have other risk factors for Barrett’s esophagus, and have longer segments of Barrett’s esophagus than men with Barrett’s esophagus who had not been referred for clinical evaluation. Therefore, we aimed to create a tool predicting the presence of Barrett’s esophagus among men based on known risk factors for the disease, and compare it to a model using only GERD frequency and duration. The primary outcome was the prevalence of Barrett’s esophagus in previously un-investigated patients.

METHODS

Study design

We conducted a cross-sectional study (“The Newly Diagnosed Barrett’s Esophagus Study”) by enrolling male colorectal cancer (CRC) screenees, aged 50–79, presenting for

colonoscopy and recruited to undergo a research upper endoscopy, thereby identifying newly diagnosed cases of Barrett's esophagus without having preselected patients with a GERD history. Controls were all CRC screenees who were confirmed by the upper endoscopy to not have Barrett's esophagus. In order to compare the cases of Barrett's esophagus identified among the CRC screenees with cases of Barrett's esophagus typically identified in clinical practice, and to enroll sufficient numbers of cases of Barrett's esophagus for future planned analyses of molecular biomarkers, we concurrently recruited consecutive men of the same age range diagnosed with Barrett's esophagus for the first time by endoscopy performed for any clinical indication. The study was terminated after enrollment of the 150th case of Barrett's esophagus based on the *a priori* power calculations for the aims related to the association of Barrett's esophagus with circulating biomarkers (not reported in this paper). The study was approved by the Institutional Review Boards of the University of Michigan (UM) and the Ann Arbor Veterans Affairs Medical Center (AAVA).

CRC screenees

Men were recruited upon presentation for colonoscopy for CRC screening to either the UM's East Ann Arbor Medical Procedures Center (UM-MPC) or the AAVA Endoscopy Suite from February 2008 through December 2011. UM-MPC is an ambulatory endoscopy center and the AAVA Endoscopy Suite is a hospital-based endoscopy unit. Patients were screened for eligibility using electronic schedules and medical records, and confirmed by patient interview. Exclusion criteria were female sex; age < 50 or ≥ 80; prior history of an upper endoscopy, Barrett's esophagus, or esophagectomy; diagnostic indication for the colonoscopy (e.g., bleeding, occult fecal blood, diarrhea); inflammatory bowel disease; known ascites or esophageal varices; cancer within the prior 5 years with the exception of non-melanoma skin cancer; significant coagulopathy; inpatient status; or inability to comprehend or cooperate with the study.

Patients had their weight, height, waist circumference, and hip circumference each measured in duplicate while wearing hospital gowns or pajamas (12–14). Before the endoscopy, patients answered questions regarding GERD symptoms and medication use. During the endoscopy, the distal esophagus and gastroesophageal junction were inspected using narrow band imaging. If Barrett's esophagus was suspected, the length of circumferential columnar mucosa (C) and the maximal tongue (M) were obtained in centimeters (15). Biopsies were obtained from any suspected Barrett's esophagus in four quadrants every 2 cm in addition to biopsies of any visible irregularities for review by an expert pathologist (HA). All endoscopies were either performed by the principal investigator (PI) (JHR, 27%) or photographs were reviewed by him (73%). Barrett's esophagus was confirmed if the PI suspected columnar mucosa proximal to the gastroesophageal junction, and the pathologist reported the presence of specialized intestinal metaplasia. If Los Angeles Class C or D esophagitis was found (16), patients were instructed to repeat the endoscopy after a healing course of a proton pump inhibitor, and disease status was determined from the repeat endoscopy.

Barrett's esophagus diagnosed by clinically indicated endoscopies

In order to assess whether the cases of Barrett's esophagus identified among the CRC screenees were typical for the sort of cases diagnosed in routine clinical practice, we also enrolled patients with Barrett's esophagus diagnosed by clinically indicated upper endoscopies. During the same period, male patients aged 50–79 with a first diagnosis of Barrett's esophagus were identified from the endoscopy schedules at the UM or AAVA, and recruited by mail followed by phone within 1 month of their initial diagnosis. Exclusion criteria were the same as for the CRC screenees (therefore cases of esophageal

adenocarcinoma were excluded) with the exception that prior upper endoscopies were allowed if the patient was not previously diagnosed with Barrett's esophagus. Endoscopic photographs and pathology slides were reviewed to confirm case status. Patients then reported while fasting to undergo body measurements and complete the questionnaires. These subjects were compared with the cases of Barrett's esophagus identified among the CRC screenees, but they were not utilized in the development of the predictive model.

Questionnaires

At the time of planning the study, the available validated instruments assessing GERD symptoms assessed only recent symptoms and made no distinction with regards to whether the subject was using potent acid reducing medications (proton pump inhibitors and histamine receptor type-2 antagonists). As patients with GERD symptoms in the past, including those that had been successfully treated with medication would likely still be at risk for Barrett's esophagus, we used a novel instrument to obtain a more complete history of GERD symptoms. Heartburn was defined as "a burning sensation in the chest, behind the breastbone, that rises up toward the neck or mouth," and regurgitation as "the effort-less movement of stomach contents up into the chest, throat, or mouth." Patients were queried regarding the first onset of each symptom and past and current acid-reducing medication use. The frequencies of heartburn or regurgitation, and of nocturnal symptoms were queried. If the subject reported taking acid-reducing medications, the frequencies of symptoms both while taking such medications were queried, as well as recalled symptom frequency while not taking such medications. The portion of the questionnaire regarding GERD symptoms can be found in the Supplementary Material. For approximately the last one quarter of the study, the Mayo Clinic Gastroesophageal Reflux Questionnaire (GERQ) was also administered in order to assess concordance with our GERD instrument (17,18). The GERQ has been previously validated, but does not query symptoms both while on and off acid reducing medications, and instead queries symptoms over the preceding year. Tobacco use was characterized by age at onset, age at cessation or continued use, and maximal use for each of cigarettes, cigars, and pipes. The study personnel administered the questions on GERD, and for CRC screenees these were completed before the endoscopies. The tobacco questions and the GERQ were typically self-administered, completed after the procedures at home, and returned by postal mail.

Analysis

Data were manually entered into Microsoft Access (Microsoft, Bellevue, WA, USA), then imported into SAS 9.1. (SAS Institute, Cary, NC, USA). Waist-to-hip ratios (WHR) were calculated and patients assigned within tertiles based on the distribution found among all CRC screenees. The cases of Barrett's esophagus identified by clinically indicated upper endoscopies were compared in crude (unadjusted) analyses to the cases of Barrett's esophagus identified among CRC screenees, using *t*-tests for continuous variables and χ^2 for categorical variables. Cases of Barrett's esophagus among CRC screenees were compared across sites of enrollment using similar statistical tests. Likewise, CRC screenees without Barrett's esophagus were compared across sites.

To avoid possible selection bias, the logistic regression analyses were restricted to CRC screenees to estimate the effects of GERD symptoms, age, tobacco use, and obesity on the presence of Barrett's esophagus. The most parsimonious use of the data regarding GERD symptoms was found to be dichotomizing patients as (1) those with either heartburn or regurgitation at least weekly while not taking acid-reducing medications, or (2) those without either symptom or symptoms less frequently than weekly. Among those who had completed the GERQ, those results were used to classify subjects in terms of the Montreal definition of GERD (mild heartburn or regurgitation at least several days a week or at least

moderate symptoms occurring at least once a week) (19). Concordance between weekly GERD using our questionnaire and Montreal defined GERD by the GERQ was found in 82% of the 204 subjects completing both. Among subjects not taking acid-reducing medications, there was 88% concordance.

Tests for trends among CRC screenees were conducted by analyses treating variables as continuous. Measures of four probable risk factors for Barrett's esophagus were included in a multiple (adjusted) logistic model: age, GERD, obesity, and tobacco use. The specific measures and coding of these factors were selected to make the model both predictive of Barrett's esophagus and parsimonious. A variable whose effect was substantially attenuated by another measure of the same factor (e.g., WHR and body mass index (BMI) or waist circumference, or pack-years of cigarette smoking and current/former/never smoking status) was not included in the multivariable model. Interactions (departures from homogeneity of the estimated odds ratios (ORs)) between GERD and age, obesity, or tobacco use, and between each predictor and the site of enrollment were examined by comparing fully adjusted models among the CRC screenees with and without selected product terms using likelihood ratio tests. Interactions were considered for inclusion in the final model if the pattern of results was judged to be biologically plausible with $P < 0.15$. The final multivariable logistic regression model is called the Michigan Barrett's Esophagus pREdiction Tool (M-BERET). As Barrett's esophagus status was not known at the time of enrollment of the CRC screenees, the estimated logistic coefficients from the fitted model can be used to algebraically estimate the probability of Barrett's esophagus for individual patients with any combination of predictor values, i.e.,

$$\text{Probability} = \frac{1}{1 + \exp[-(b_0 + \sum b_i X_i)]}$$

where X_i = i -th predictor in the final model, b_0 = estimated intercept, b_i = estimated logistic coefficient for i -th predictor, and $\exp$ = natural antilog of the quantity in brackets ($e^{[\]}$).

The estimated probabilities of Barrett's esophagus were analyzed in two ways. One objective was to compare the area under the receiver operating characteristic curves between the M-BERET model and a conventional model using only GERD frequency and duration, which are the typical factors utilized for selecting patients for endoscopic screening (4–7). The conventional model based on GERD symptoms utilized frequency of symptoms categorized as at least weekly vs. less frequent or no symptoms, and duration of symptoms parameterized as a continuous variable. The effects of these parameters were estimated from the cohort of CRC screenees. The other objective was to estimate the net reclassification improvement (NRI), which reflects the sum of proportions of cases and controls more accurately classified for probability of Barrett's esophagus by M-BERET than by GERD symptoms alone (20–22). Ideally, the thresholds used in calculating the NRI should be based on clinically relevant cut-points that reflect different diagnostic or treatment decisions, but we are not aware of data that could guide the choice of thresholds. Instead, *ad hoc* thresholds used for defining low (< 7%), intermediate (7–15%), and elevated prevalence (> 15%) of Barrett's esophagus were used based on the prevalence of Barrett's esophagus identified among the CRC screenees in this study with weekly GERD symptoms for 5 years (15%) and among those with GERD symptoms of any duration and frequency (7%). The thresholds used were varied in sensitivity analyses. Calibration of each prediction model was also assessed using the Hosmer-Lemeshow statistic for model fit.

RESULTS

Patient enrollment

Eight hundred and twenty-two CRC screenees completed the upper endoscopy (consent rate = 71%) (Figure 1), including 463 at UM-MPC and 359 at AAVA. According to the medical records, CRC screenees who enrolled had slightly greater mean BMI than those who declined (30.7 vs. 29.4kg/m², $P = 0.0004$), but no substantial difference in age (58.7 vs. 58.3 years, $P = 0.30$). In addition, 176 cases of Barrett's esophagus were recruited within 1 month of their initial diagnosis from a clinically indicated endoscopy, and 80 completed the study (45% of eligible), including 36 from UM and 44 from AAVA. According to the medical records, clinical cases of Barrett's esophagus who consented had a slightly greater BMI than those who declined (30.7 vs. 29.5kg/m², $P = 0.25$), and no substantial difference in age (61.4 vs. 61.1 years, $P = 0.78$), or median length of Barrett's esophagus (C0M2 for both).

CRC screenees

Means and proportions for age, BMI, WHR, GERD symptoms, and tobacco use of CRC screenees completing the upper endoscopy, by Barrett's esophagus status, are shown in Table 1. Barrett's esophagus was found in 70 patients (8.5%), including 15.5% of patients with GERD symptoms at least weekly and 7.1 % of patients without weekly GERD (Figure 1). The median length of Barrett's esophagus was C0M2 (interquartile range = C0M1, C1M3), and 11 (15.7%) were longer than 3 cm. Adenocarcinoma was initially found in 2 of the 70 patients with Barrett's esophagus (2.9%), both staged IIIa. No cases of Barrett's esophagus with high-grade dysplasia were identified at the initial endoscopy. Three CRC screenees were found to have Barrett's esophagus with low-grade dysplasia (4.3%), one of whom was found to have high-grade dysplasia on surveillance endoscopy 3 months after enrollment and underwent endoscopic resection. Biopsies from two CRC screenees with Barrett's esophagus were interpreted as indefinite for dysplasia (2.9%), one of whom was found to have high-grade dysplasia suspicious for invasive adenocarcinoma on endoscopic resection 31 months following enrollment. Of these four men found to have invasive cancer or eventually to have high-grade dysplasia, all denied dysphagia, one reported daily GERD symptoms for 20 years, one denied any GERD symptoms, and two reported GERD symptoms occurring once monthly for < 1 year. CRC screenees at the AAVA had a slightly higher prevalence of Barrett's esophagus than those at UM-MPC (34/359 (9.5%) vs. 36/462 (7.8%), $P = 0.45$). Those with Barrett's esophagus identified at the AAVA may have been more likely than those identified at the UM-MPC to have smoked greater than 35 pack-years (69% vs. 46%, $P = 0.06$). Otherwise, there were no differences between the AAVA and UM-MPC patients with Barrett's esophagus in terms of age, race, BMI, waist circumference, WHR, GERD frequency, duration of GERD symptoms, or use of acid reducing medications. Compared with the CRC screenees without Barrett's esophagus from the UM-MPC, those from the AAVA were older (61 vs. 57 years, $P < 0.001$), had a greater mean BMI (30.6 vs. 29.4kg/m², $P = 0.001$), had a greater mean waist circumference (109 vs. 106 cm, $P = 0.002$), had a greater mean WHR (1.01 vs. 0.99, $P < 0.001$), were more likely to have weekly GERD symptoms (24% vs. 13%, $P < 0.001$), and more likely to have greater than 35 pack-years of cigarette smoking (45% vs. 17%, $P < 0.001$).

Comparison to cases of Barrett's esophagus diagnosed by clinically indicated endoscopies

Cases of Barrett's esophagus who had been recruited after initial diagnosis by a clinically indicated upper endoscopy were similar to the cases diagnosed among CRC screenees with regards to age, BMI, and WHR, but were less likely to be heavy smokers, and much more likely to report GERD symptoms and to be using acid reducing medications (Table 1). These cases of Barrett's esophagus had similar length (median = C0M2; interquartile range =

COM1, COM3) as cases diagnosed among CRC screenees. Of the clinically diagnosed cases, 16 (20%) were longer than 3 cm ($P = 0.52$ vs. CRC screenee cases). None of these patients had invasive adenocarcinoma as it was an exclusion criterion for the clinically diagnosed cases. None had high-grade dysplasia, two had low-grade dysplasia (2.5%), and one was interpreted as being indefinite for dysplasia (1.3%). By the completion of the study, none of the cases of Barrett's esophagus diagnosed by clinically indicated upper endoscopy had progressed to invasive adenocarcinoma or high-grade dysplasia.

Risk factors for Barrett's esophagus among CRC screenees

The estimated crude and adjusted effects of all predictors (treated as both categorical and continuous variables) on Barrett's esophagus using logistic regression among the CRC screenees from both sites combined are shown in Table 2. Both GERD frequency and duration were associated with Barrett's esophagus (Table 2), but their associations were somewhat attenuated by adjusting for each other (≥ weekly vs. < weekly or no GERD: adjusted OR = 2.18; 95% confidence interval (CI) = 1.25, 3.81; per increments of 10 years: adjusted OR = 1.31; 95% CI = 0.904, 1.86). Weekly GERD symptoms were more strongly associated with longer segments of Barrett's esophagus than shorter segments (≥ 2 cm: OR = 3.35, 95% CI = 1.71, 6.56; < 2 cm: OR = 1.54, 95% CI = 0.675, 3.50).

Barrett's esophagus was positively associated with age (Table 2). Total body obesity measured by BMI and abdominal obesity measured by WHR were both strongly associated with Barrett's esophagus in unadjusted analyses (Table 2). Adjusting for BMI, WHR remained strongly associated with Barrett's esophagus (OR for 3rd vs. 1st tertile WHR = 2.56; 95% CI = 1.22, 5.37; P for trend = 0.003), but the association with BMI was substantially attenuated after adjustment for WHR (OR for obese vs. normal BMI = 1.81; 95% CI = 0.692, 4.72; P for trend = 0.31). Adjusting for GERD frequency, age, and tobacco use, the estimated effects of WHR were attenuated (e.g., OR for 3rd vs. 1st tertile WHR = 1.65; 95% CI = 0.816, 3.33) (Table 2).

Tobacco use, particularly current use and cumulative cigarette use, was also positively associated with Barrett's esophagus (Table 2). Adjusting for any type of tobacco use (current or former), cumulative cigarette use remained strongly positively associated with Barrett's esophagus (OR for ≥ 35 vs. 0 pack-years = 4.43; 95% CI = 1.32, 14.9; P for trend < 0.001), but the association with any tobacco use was attenuated by adjustment for cumulative cigarette use (OR for current vs. never tobacco use = 0.725; 95% CI = 0.185, 2.85). Inclusion of maximal use and duration of use in addition to cumulative cigarette use did not improve the fit of the model ($P > 0.10$). We did not find evidence for modification of the OR by GERD for the effects of age, BMI, WHR, tobacco use, or cumulative cigarette use. The effect of WHR on the frequency of Barrett's esophagus was greater among patients from the UM-MPC than among those at the AAVA (OR for each increment of 0.10 adjusted for GERD, age, and cumulative cigarette use: at UM-MPC = 2.76, 95% CI = 1.28, 5.96; at AAVA = 0.883, 95% CI = 0.459, 1.70; P -value for interaction = 0.03). The effect of cigarette use was also greater among UM-MPC patients than AAVA patients (OR for each increment of 10 pack-years adjusted for GERD, age, and WHR: at UM-MPC = 1.18, 95% CI = 1.07, 1.30; at AAVA = 1.07, 95% CI = 0.999, 1.14; P -value for interaction = 0.10).

Final model and estimated probability of Barrett's esophagus among CRC screenees

Based on the results presented above, we created a final logistic model for predicting Barrett's esophagus as a function of four variables: age (continuous), WHR (continuous), pack-years of cumulative cigarette use (continuous), and GERD frequency (at least weekly symptoms vs. less frequent or no symptoms) (Table 3). This fitted model, referred to as the "Michigan Barrett's Esophagus pREdiction Tool" or "M-BERET", is used to predict the

probability of a man, aged 50–79, having Barrett’s esophagus, according to the following expression:

$$\text{Probability(Barrett's esophagus)} = \frac{e^x}{1+e^x}, \text{ where } e \text{ is the exponential function and}$$

$$x = -9.1422 + (0.04278 \times \text{age}) + (0.8453 \text{ if weekly GERD}) + (3.6682 \times \text{WHR}) + (0.00835 \times \text{packyears})$$

We compared the M-BERET to a conventional model utilizing only GERD symptoms (“GERD model”) also fitted among the CRC screenees. The GERD model included both the frequency and duration of symptoms. The patient-specific probabilities of Barrett’s esophagus estimated from the M-BERET model were moderately correlated with those estimated by the GERD model (Pearson correlation coefficient=0.53), but the M-BERET had a greater range of estimated probabilities (2.0 to 58.0%) than the GERD model (6.7 to 25.7%). The M-BERET also had a greater area under the receiver operating characteristic curve (AUC) for Barrett’s esophagus (0.72; 95% CI = 0.66, 0.79) compared with the GERD model (AUC = 0.61; 95% CI = 0.54, 0.67; $P < 0.001$ for M-BERET vs. GERD) (Figure 2). The M-BERET was similarly accurate for discriminating segments of Barrett’s esophagus greater than 2 cm from those without Barrett’s esophagus (AUC = 0.74) as it was for discriminating short segments from those without Barrett’s esophagus (AUC = 0.72). Among CRC screenees at the UM-MPC, the AUC of the M-BERET was 0.78 vs. 0.60 for the GERD model ($P < 0.001$). Among those at the AAVA, the AUC of the M-BERET was 0.66 vs. 0.60 for the GERD model ($P = 0.20$).

Examples comparing the sensitivity, specificity, and prevalence of Barrett’s esophagus are shown in Table 4. At a specificity of 80%, the M-BERET has a sensitivity of 52%, and the GERD model has a sensitivity of 39%. At a sensitivity of 81%, the M-BERET has a specificity of 56%. In order for the GERD model to have a sensitivity greater than 46% (corresponding to a threshold of any frequency of GERD for any duration), would require selecting 100% of patients with a specificity of 0%. If the threshold for selecting men for screening based on the GERD model were set at the probability corresponding to 5 years of weekly symptoms (prevalence of Barrett’s esophagus = 15%), the sensitivity of the GERD model for Barrett’s esophagus would be 15% and specificity would be 93%. Using the M-BERET and setting the specificity to the same value, the sensitivity would increase to 25% (prevalence 17%). If the threshold used for selecting men for screening based on the GERD model were any frequency of GERD for any duration (prevalence of Barrett’s esophagus = 7%), the sensitivity would be 46% and the specificity 73%. Using the M-BERET and setting the sensitivity to the same value, the specificity would be 82% (prevalence to 11%).

The NRI index is a measure for comparing two models, reflecting differences in triggering management decisions at clinically relevant thresholds of prevalence of Barrett’s esophagus. We used 3 *ad hoc* thresholds of the prevalence of Barrett’s esophagus (low (<7%), intermediate (7–15%), and elevated (> 15%)), based on the prevalence of Barrett’s esophagus in men with weekly GERD symptoms for 5 years (15%) and prevalence in men with any frequency of GERD for any duration (7%). Using those thresholds, the GERD model was poorly calibrated ($P < 0.001$), but the M-BERET was not ($P = 0.39$). Among men found to have Barrett’s esophagus, the M-BERET classified 45% more accurately than the GERD model. Among those without Barrett’s esophagus, the M-BERET classified 20% less accurately than the GERD model. The NRI index was therefore 25% ($P = 0.007$). In sensitivity analyses, we varied the *ad hoc* thresholds used for classifying low, intermediate, and elevated prevalence. Using thresholds of 10 and 20% prevalence resulted in 27% of Barrett’s esophagus patients more accurately classified and 8% of patients without Barrett’s esophagus less accurately classified (NRI = 19%, $P < 0.01$). Thresholds of 5 and 20%

resulted in 1% of Barrett's esophagus patients less accurately classified and 30% of patients without Barrett's esophagus more accurately classified (NRI = 29%, $P < 0.001$).

DISCUSSION

We found that the prevalence of Barrett's esophagus among a group of mostly overweight older men is considerable, even among those without GERD symptoms. Using age, abdominal obesity, cigarette use, and GERD symptoms, we created a prediction tool, which had a NRI index of ~20% for classifying the probability of Barrett's esophagus compared with a model based on GERD frequency and duration alone. The tool may have been more useful among patients enrolled at the university satellite endoscopy center than at the Veterans Affairs medical center, a finding that may have been driven by the higher prevalence of risk factors for Barrett's esophagus among the veteran population than among the university population. The prediction tool needs to be validated before clinical use.

A few studies have demonstrated a substantial prevalence of Barrett's esophagus in American, largely asymptomatic populations (23–25). However, European studies have suggested much lower prevalences (26,27). Our study found a prevalence similar to those reported in previous American studies. Our high estimate relative to the European studies may have been due to the high-risk population in which it was conducted—older, mostly white overweight men.

Prior studies have demonstrated the associations of age, obesity, and tobacco use with esophageal adenocarcinoma, even in populations without GERD symptoms (9,10). There have also been studies demonstrating these associations with Barrett's esophagus, but those studies included only cases of Barrett's esophagus identified by clinical referral for endoscopy, typically for GERD symptoms (28,29). Our study minimized the possibility for referral bias by identifying cases and controls from a single population, namely CRC screenees undergoing upper endoscopy without a referral for a clinical indication. We found that GERD symptoms had a much weaker association with Barrett's esophagus than earlier studies utilizing only clinically referred patients would suggest, some with ORs greater than 10 (2,29,30). Compared with cases of Barrett's esophagus identified by clinically indicated endoscopies, those identified among the CRC screenees had less GERD symptoms and more heavily used tobacco, but were similar in terms of obesity and length of Barrett's esophagus.

Using the data from CRC screenees, we created a model estimating an individual's probability of Barrett's esophagus (M-BERET), which is available for use on the internet (<http://mberet.umms.med.umich.edu/>). Prior tools developed among patients referred for upper endoscopy estimated the effects of age, sex, and duration or severity of GERD symptoms on Barrett's esophagus, but they did not include the effects of obesity or tobacco use (18,31). We found that the M-BERET more accurately classified the presence of Barrett's esophagus than GERD symptoms alone. Synthesizing prior reports, we estimate that ~2 million upper endoscopies are performed annually in the United States in patients with GERD at a cost of over \$1 billion (32–34). Nonetheless, fewer than 15% of patients with esophageal adenocarcinoma undergo upper endoscopy before presenting with cancer (35). This may be in part due to the rather low sensitivity of frequent, long-duration GERD symptoms for Barrett's esophagus among older men, the demographic group most at risk for the cancer. If validated, the use of the M-BERET to select high-risk patients for endoscopic screening would be a step toward more efficient utilization of endoscopic resources. Patients with intermediate probabilities of Barrett's esophagus could be counseled to modify their behaviors, which would likely have a greater benefit for their overall health than focusing on the risk of esophageal cancer alone. Further studies are required to determine if inclusion of

additional factors can improve the accuracy of the tool and to define the ideal threshold of the estimated probability of Barrett's esophagus that should trigger endoscopic screening.

The findings from our study are limited to the population studied—older white men. We excluded men younger than age 50 and women due to the expectation that their prevalence of Barrett's esophagus would be much lower (36), thereby limiting the statistical power of the study or greatly increasing the number of subjects needed to be enrolled. We did not include race in the predictive model due to the imprecise estimates of its effects related to the small proportions of men from non-White races enrolled. The study is also limited by the rare events of neoplasia included. There may have been self-selection of CRC screenees with esophageal symptoms such as GERD or dysphagia for enrollment in the study. We did not assess symptoms in those who declined enrollment, but those who enrolled had slightly higher BMIs than those who did not enroll, which might be explained by such self-selection. Self-selection may account for the somewhat high proportion of CRC screenees found to have esophageal adenocarcinoma (0.24%), but both of those subjects denied dysphagia, and the proportion of new cases of Barrett's esophagus with the cancer (2.9%) is similar to that found in previous reports, suggesting that the cancer may have a long preclinical phase in at least some patients (37–42). Our primary questionnaire for assessing GERD has not been previously validated which might diminish the accuracy of the prediction tool. This questionnaire was used because of the lack of available validated questionnaires for assessing symptoms both while taking and not taking acid-reducing medications. However, the questions meet face validity and had good concordance with a previously validated questionnaire overall, and high concordance with that questionnaire when limited to subjects not taking acid-reducing medications. Finally, the M-BERET was fitted and tested in the same cohort that likely led to overestimating its accuracy, but the factors assessed are all well-established as associated with Barrett's esophagus, so the magnitude of that overestimation may be small. We did not divide the CRC screenees into development and validation cohorts due to the small numbers of cases which would have been in each group. Thus, the model needs to be replicated in other clinical populations before clinical use.

The major strengths of the study include the enrollment of patients regardless of underlying GERD, thereby identifying cases cross-sectionally within the same population as the controls, which minimizes the opportunity for selection bias and allows estimation of the probability of Barrett's esophagus. We also assessed for differences in these cases of Barrett's esophagus from those that are routinely diagnosed by clinically indicated endoscopies.

In summary, in a population of older, mostly white overweight men, Barrett's esophagus was found in 8.5%, including 7.1% of those who deny having substantial GERD symptoms. Risk factors for Barrett's esophagus in this population include older age, tobacco use, and abdominal obesity. Our novel prediction tool more accurately classifies the presence of Barrett's esophagus than does a model based on GERD symptom frequency and duration alone. Further studies validating this tool, and evaluating its use to better target efforts aimed at reducing the burden of esophageal adenocarcinoma are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Most individuals with GERD do not have Barrett's esophagus, and the vast majority will not develop esophageal cancer.
- ✓ Many individuals with esophageal adenocarcinoma deny prior GERD symptoms.
- ✓ Other risk factors for Barrett's esophagus and esophageal adenocarcinoma include male sex, age, abdominal obesity, and tobacco use.

WHAT IS NEW HERE

- ✓ The prevalence of Barrett's esophagus among older, mostly overweight white men is substantial, even among those without GERD symptoms.
- ✓ A prediction tool incorporating GERD frequency, age, waist-to-hip ratio, and pack-years of cigarette use more accurately classifies the probability of Barrett's esophagus than a model based only on GERD frequency and duration.
- ✓ The tool is quick to use and freely available on the internet (<http://mberet.umms.med.umich.edu/>), but needs to be further validated.

Figure 1.

Flow diagram of recruitment and classification of subjects. Gastroesophageal reflux disease (GERD) is defined as symptoms of heartburn or regurgitation at least once a week while not taking acid-reducing medications. Sixteen colorectal cancer (CRC) screenees had missing GERD status, none of whom had Barrett's esophagus. There was also 1 CRC screenee without GERD and with suspected Barrett's esophagus, but biopsies were not obtained due to coexisting esophageal varices. That subject was unclassified regarding Barrett's esophagus status, and not included in further analyses.

BE, Barrett's esophagus; EGD, esophagogastroduodenoscopy.

Figure 2.

Receiver operating characteristic (ROC) curves for Michigan Barrett's Esophagus pREdiction Tool (M-BERET) and gastroesophageal reflux disease (GERD) Models of Barrett's esophagus risk among colorectal cancer screenees. The GERD model includes frequency and duration of symptoms. The M-BERET model includes GERD frequency, age, waist-to-hip ratio, and pack-years of cigarette use.

Table 1

Descriptive characteristics of subjects

	Colorectal cancer screeners			Barrett's esophagus diagnosed by clinically indicated endoscopy (n=80)	P value for BE from CRC screeners vs. clinically indicated endoscopy
	All screeners (n=822)	No Barrett's esophagus (n=751)	Barrett's esophagus (n=70)		
Age (years) ^a	58.7 (6.7)	58.5 (6.7)	61.0 (6.5)	61.4 (7.1)	0.76
BMI (kg/m ²) ^a	30.0 (5.5)	29.9 (5.6)	30.3 (4.2)	31.0 (5.6)	0.35
Waist circumference (cm) ^a	107.7 (13.6)	107.5 (13.8)	109.7 (11.8)	110.4 (13.8)	0.77
WHR ^a	1.002 (0.056)	1.001 (0.056)	1.020 (0.053)	1.021 (0.054)	0.93
GERD Weekly (%) ^b	155 (19%)	131 (18%)	24 (34%)	65 (81%)	< 0.001
Nocturnal GERD Weekly (%) ^b	73 (9%)	59 (8%)	14 (20%)	50 (63%)	< 0.001
GERD 5 years (%) ^b	108 (13%)	92 (12%)	16 (23%)	37 (46%)	< 0.001
PPI use (%) ^b	96 (12%)	52 (7%)	18 (26%)	74 (93%)	< 0.001
H2RA use (%) ^b	28 (3%)	67 (8%)	3 (4%)	14 (18%)	0.01
PPI or H2RA use (%) ^b	123 (15%)	102 (14%)	21 (30%)	76 (95%)	< 0.001
Never smoker (%) ^b	236 (39%)	224 (40%)	12 (25%)	15 (26%)	0.86
35 pack-years (%) ^b	243 (31%)	205 (29%)	38 (57%)	32 (41%)	0.05
White race (%) ^b	697 (89%)	640 (90%)	57 (88%)	76 (95%)	0.11

Abbreviations: BE, Barrett's esophagus; BMI, body mass index; CRC, colorectal cancer; GERD, gastroesophageal reflux disease; H2RA, histamine receptor type-2 antagonist; PPI, proton pump inhibitor; WHR, waist-to-hip ratio.

^aData expressed as mean (s.d.)

^bor number (proportion)

Proportions are among subjects with available data.

Never smoker refers to cigarette, pipe, and cigar. Pack-years refer to cigarette only.

Table 2

Associations with Barrett's esophagus among CRC screenees

	# BE/# No BE	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
<i>GERD frequency</i>			
Less than weekly or none	46/604	1 (Reference)	1 (Reference)
At least weekly	24/131	2.41 (1.42,4.08)	2.33 (1.34,4.05)
Per 1 day increments	70/735	1.18 (1.05, 1.32)	1.17 (1.04, 1.31)
<i>P</i> -value for trend		0.006	0.01
<i>GERD duration</i>			
None	42/568	1 (Reference)	1 (Reference)
<5 years	11/73	2.04 (1.01,4.13)	2.02 (0.980,4.17)
5 years	16/92	2.35 (1.27,4.36)	2.02 (1.05, 3.86)
Per 10 year increments	69/733	1.49 (1.08, 2.06)	1.33 (0.942, 1.86)
<i>P</i> -value for trend		0.02	0.10
<i>Age</i>			
50–59 years	26/410	1 (Reference)	1 (Reference)
60–69 years	35/291	1.90 (1.12,3.22)	1.53 (0.871, 2.69)
70–79 years	9/50	2.84 (1.26, 6.40)	2.93 (1.27,6.79)
Per 10 year increments of age	70/751	1.69 (1.89, 2.40)	1.53 (1.05, 2.25)
<i>P</i> -value for trend		0.004	0.03
<i>Body mass index (BMI)</i>			
Underweight (BMI < 20kg/m ²)	0/8	Not estimable	Not estimable
Normal weight (20 kg/m ² BMI < 25kg/m ²)	6/130	1 (Reference)	1 (Reference)
Overweight (25 kg/m ² BMI < 30kg/m ²)	25/278	1.95 (0.780, 4.87)	1.88 (0.738, 4.77)
Obese (BMI ≥ 30 kg/m ²)	39/326	2.59 (1.07,6.27)	2.03 (0.819, 5.04)
Per 5 kg/m ² increments of BMI	70/742	1.06 (0.850, 1.32)	0.980 (0.774, 1.23)
<i>P</i> -value for trend		0.60	0.86
<i>Waist-to-hip ratio (WHR)</i>			
1st tertile (< 0.979)	13/258	1 (Reference)	1 (Reference)
2nd tertile (0.980–1.024)	28/246	2.26 (1.14,4.46)	1.53 (0.749,3.12)

	# BE/ No BE	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
3rd tertile (> 1.024)	29/246	2.34 (1.19,4.61)	1.65 (0.816, 3.33)
Per 0.10 increments of WHR	70/750	1.86 (1.20, 2.88)	1.44 (0.898, 2.32)
<i>P</i> -value for trend		0.006	0.13
<i>Tobacco use^b</i>			
Never tobacco user	12/224	1 (Reference)	1 (Reference)
Ever tobacco user	56/496	2.11 (1.11,4.01)	1.75 (0.908, 3.37)
Former tobacco user	36/338	1.99 (1.01,3.90)	1.56 (0.782,3.12)
Current tobacco user	20/158	2.36 (1.12,4.97)	2.17 (1.02,4.62)
<i>Cumulative cigarette use</i>			
0 Pack-years	15/295	1 (Reference)	(Reference)
>0, < 35 pack-years	14/208	1.32 (0.625, 2.80)	1.21 (0.569, 2.59)
35 pack-years	38/205	3.65 (1.95, 6.80)	2.90 (1.53, 5.49)
Per increments of 10 pack-years	67/708	1.11 (1.06, 1.16)	1.09 (1.04, 1.14)
<i>P</i> -value for trend		< 0.001	< 0.001

Abbreviations: BE, Barrett's esophagus; BMI, body mass index; CI, confidence interval; OR, odds ratio; WHR, waist-to-hip ratio.

^a Adjustments are made for GERD frequency (dichotomous), age (continuous), WHR (continuous), and pack-years of cigarette use (continuous), except that GERD duration is not adjusted for frequency, BMI is not adjusted for WHR, and tobacco use is not adjusted for pack-years of cigarette use.

^b Tobacco use includes cigarette, cigar, and pipe.

Table 3

Final model for the Michigan Barrett's Esophagus pREdiction Tool (M-BERET)

	OR (95% CI) mutually adjusted for each variable
<i>Intercept</i>	
GERD (weekly vs. not weekly)	2.33 (1.34, 4.05)
Age (per 10 year increments)	1.53 (1.05, 2.25)
Waist-to-hip ratio (WHR) (per 0.10 increments)	1.44 (0.898, 2.32)
Pack-years cigarette use (per increments of 10 pack-years)	1.09(1.04, 1.14)

Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio; WHR, waist-to-hip ratio.

Table 4
Examples of performance characteristics comparing M-BERET and GERD models for Barrett's esophagus

Threshold setting	M-BERET			GERD model		
	Sensitivity	Specificity	Prevalence	Sensitivity	Specificity	Prevalence
Sensitivity ~80%	81%	56%	7%	<i>a</i>	<i>a</i>	<i>a</i>
Specificity ~80%	52%	80%	11%	39%	80%	9%
Specificity of GERD model using 5 years of weekly GERD (93%)	25%	93%	17%	16%	93%	15%
Sensitivity of GERD model using any frequency of GERD for any duration (46%)	46%	82%	11%	46%	73%	7%

Abbreviations: GERD, gastroesophageal reflux disease; M-BERET, Michigan Barrett's Esophagus pREdiction Tool.

^aThe GERD model does not have a true point on the ROC curve representing sensitivity of 80%. The sensitivity is 46% using a threshold of any frequency of GERD for any duration. To increase the sensitivity further would require including all individuals without GERD symptoms, and the sensitivity immediately jumps to 100% (with specificity of 0%).