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Review

Screening for Barrett's Esophagus: Balancing Clinical Value and Cost-effectiveness

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In predisposed individuals with long standing gastroesophageal reflux disease (GERD), esophageal squamous mucosa can transform into columnar mucosa with intestinal metaplasia, commonly called Barrett's esophagus (BE). Barrett's mucosa can develop dysplasia, which can be a precursor for esophageal adenocarcinoma (EAC). However, most EAC cases are identified when esophageal symptoms develop, without prior BE or GERD diagnoses. While several gastrointestinal societies have published BE screening guidelines, these vary, and many recommendations are not based on high quality evidence. These guidelines are concordant in recommending targeted screening of predisposed individuals (eg, long standing GERD symptoms with age > 50 years, male sex, Caucasian race, obesity, and family history of BE or EAC), and against population based screening, or screening of GERD patients without risk factors. Targeted endoscopic screening programs provide earlier diagnosis of high grade dysplasia and EAC, and offer potential for endoscopic therapy, which can improve prognosis and outcome. On the other hand, endoscopic screening of the general population, unselected GERD patients, patients with significant comorbidities or patients with limited life expectancy is not cost-effective. New screening modalities, some of which do not require endoscopy, have the potential to reduce costs and expand access to screening for BE.
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Key Words
Adenocarcinoma of esophagus; Barrett's esophagus; Gastroesophageal reflux

Introduction

Gastroesophageal reflux disease (GERD) typically presents with heartburn and acid regurgitation, afflicting an estimated 18-28% of the North American population.[1] In 5-15% of chronic GERD, esophageal mucosa can transform from normal squamous to columnar mucosa with intestinal characteristics (intestinal metaplasia or Barrett's esophagus [BE]).[2-4] BE confers an estimated 10-fold increase in risk for esophageal adenocarcinoma (EAC) above the general population, prompting screening and surveillance protocols. Time trends demonstrate that the incidence of EAC has continued to escalate in comparison to other cancers (colon, lung, and breast), and that the rising incidence cannot be explained on the basis of increased identification of previously undiagnosed EAC.[5]

Gastroenterology societies across the globe have published BE screening recommendations (Table).[6-12] However, these recommendations are not always based on high-quality evidence.[13] In fact, a systematic analysis and critical appraisal of 8 BE practice guidelines published between 2005 and 2013 found that the majority of guidelines failed to meet the Appraisal of Guidelines for Research and Evaluation II (AGREE II) domains and most recommendations

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Table. Screening Guidelines for Barrett's Esophagus

Society or group	Risk categories for Barrett's esophagus					Recommendations for screening	Recommendations against screening
	Age	Sex	Race	Morphologic features	Clinical history		
American Gastroenterological Association (2011)[6]	≥ 50 years	Male	Caucasian	Elevated BMI; intra-abdominal distribution of body fat	Chronic GERD Hiatus hernia	Patients with multiple risk factors	General population with GERD without risk factors
American College of Physicians (2012)[7]	> 50 years	Male	NA	Elevated BMI Intra-abdominal distribution of fat	Nocturnal reflux symptoms Hiatus hernia Tobacco use	Men > 50 years with > 5 years of GERD symptoms and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated BMI, tobacco use, and intra-abdominal distribution of fat)	Routine screening in women, regardless of GERD symptoms
British Society of Gastroenterology (2014)[8]	≥ 50 years	Male	Caucasian	Obesity	Chronic GERD	Chronic GERD symptoms and at least 3 risk factors Threshold of multiple risk factors should be lowered in the presence of family history (at least one first-degree relative with BE or EAC).	Unselected population with GERD symptoms without risk factors
American College of Gastroenterology (2016)[9]	> 50 years	Male	Caucasian	Central obesity (waist circumference > 88 cm, waist to hip ratio > 0.8)	> 5 years of GERD symptoms and/or frequent (weekly or more) symptoms Current or past smoking history Family history (confirmed family history of BE or EAC in a first-degree relative)	Men with > 5 years of GERD symptoms (heartburn or acid regurgitation) and/or frequent (weekly or more) symptoms, and 2 or more risk factors for BE or EAC	General population screening without risk factors Screening in females
Cancer Council Australia (2015)[10]	Increasing age	Male	NA	Central obesity	Waist-hip ratio Central adiposity Smoking history Family history of EAC and/or BE	Clinical evaluation of future risk of BE should consider age, sex, GERD history, waist-hip ratio, other features of central adiposity, smoking history, and family history of EAC and/or BE.	General population screening, even if conducted coincident with colonoscopy screening, is not cost-effective.

Table. Continued

Society or group	Risk categories for Barrett's esophagus					Recommendations for screening	Recommendations against screening
	Age	Sex	Race	Morphologic features	Clinical history		
Asia-Pacific Expert Consensus (2016)[11]	Older age	Male	Caucasian	NA	Long duration of reflux symptoms, Abdominal obesity, smoking	NA	94.7% agreement that there is no value for screening for BE in the Asia-Pacific region due to low prevalence and lack of benefit
Asociacion Mexicana de Gastroenterologia (2016)[12]	> 50 years	Male	NA	Obese or overweight	GERD symptoms > 5 years Hiatus hernia Smoking	Intentional search for BE is justified in subjects with various risk factors: men > 50 years, a history of GERD symptoms > 5 years, especially if the patient is obese or overweight.	GERD symptoms alone (not sufficient justification for screening)

BMI, body mass index; GERD, Gastroesophageal reflux disease; NA, not applicable; BE, Barrett's esophagus; EAC, esophageal adenocarcinoma.

were level B (49%) or C (45%) quality evidence.[14] Notably, 40% of EAC cases have no prolonged reflux history,[15] and < 5% carry a prior diagnosis of BE.[16] Within this context, this review addresses the balance between the clinical value and cost-effectiveness of BE screening.[17]

Clinical Value of Screening

In predisposed individuals, BE progresses through low-grade dysplasia (LGD) and high-grade dysplasia (HGD) to EAC. Supporting this concept, the annual risk of progression to EAC is higher in HGD (6.0-7.0%)[18,19] compared to community LGD diagnoses (0.4-0.6%)[20,21] or non-dysplastic BE (0.1-0.3%, which has decreased in recent decades from previous higher estimated ranges).[22-27]

Data suggest superior survival outcomes when EAC is diagnosed in pre-existing BE. In a study based on Surveillance, Epidemiology, and End Results and linked Medicare data, patients diagnosed with EAC in the setting of pre-existing BE had overall lower stage EAC and superior overall survival compared to those diagnosed with EAC without pre-existing BE (hazard ratio, 0.56; 95% CI, 0.50-0.61 that persisted in an adjusted model with hazard ratio, 0.72; 95% CI, 0.65-0.80).[28] Likewise, meta-analysis also demonstrated a survival advantage for EAC detected from screening protocols compared to symptom-based EAC diagnosis (relative risk of mortality, 0.73; 95% CI, 0.57-0.94), associated with earlier-stage EAC diagnosis.[29]

However, adjustment for lead- and length-time biases in these studies substantially attenuated these reported survival benefits. Nonetheless, data from a large Veterans Affairs cohort (> 8500 cases of EAC) suggests that the observed survival benefit in EAC in the setting of pre-existing BE (hazard ratio, 0.69; 95% CI, 0.61-0.80) stems largely from the earlier stage of EAC at diagnosis, finding no evidence for lead-time or length-time biases in their findings.[30] Another report demonstrates that when symptoms prompt advanced EAC diagnosis without prior knowledge of BE, 5-year survival is abysmal (< 3%), while early EAC has a better prognosis (> 20% 5-year survival).[31]

Consequently, screening can identify dysplastic BE or early EAC—when endoscopic ablative therapies could reduce mortality and prolong life while remaining cost-effective.[6,32-36] When applied to dysplastic BE, radiofrequency ablation (RFA), photodynamic therapy, and endoscopic mucosal resection reduce progression to EAC.[36-38] For example, in a multicenter sham-controlled trial of patients with dysplastic BE, progression to EAC was significantly

lower with RFA treatment (1.2% vs 9.3%, $P = 0.045$).[37] Thus, BE screening programs have the potential to impact the natural history of BE in select settings.

On meta-analysis, long-standing GERD symptoms increase the risk of long-segment BE 5-fold,[39] yet BE is associated with esophageal hyposensitivity despite high reflux burden.[40,41] Thus, heartburn symptoms diminish as BE develops, and focusing solely on heartburn may miss these hyposensitive patients. Supporting this concept, BE is reported in asymptomatic individuals, with a prevalence of 1.3-1.6% in European population studies,[42,43] and 5.6-6.8% in United States populations.[2,44] The frequency of identification of BE was similar between patients with heartburn (8.3%) and without heartburn (5.6%, $P = 0.1$) among 1000 patients enrolled from a screening colonoscopy cohort, although the likelihood of long-segment BE was higher when heartburn was present (2.6% vs 0.36%, $P = 0.01$).[2] Further, GERD can present with atypical symptoms (chest pain, cough, sore throat, and laryngitis) or regurgitation without heartburn, and acid suppressive therapy can modify or resolve symptoms; BE and EAC are identified in these patients as well.[45,46] Consequently, if heartburn were the sole symptom prompting screening, BE in atypical GERD, hyposensitive, or asymptomatic populations would likely be missed. For a BE screening program to be successful, all individuals with risk factors in the setting of documented evidence of GERD ("proven GERD," includes erosive esophagitis, biopsy-proven intestinal metaplasia, abnormal pH study, and peptic strictures)[47] may need to be targeted, regardless of presenting symptoms. However, screening of the general population and of low-risk groups is clearly not cost-effective and not recommended (Table).

Costs of Screening

Beyond the relatively rare but real medical risks associated with endoscopy and endoscopic therapies, the resources utilized for BE screening and therapy are tremendous. In a study conducted among the West Virginia Medicaid population in the late 1990s, limited by its prevalence-based approach prior to the widespread use of endoscopic ablative therapies, and exclusion of Medicare-eligible recipients, BE patients incurred 21.2% higher costs than GERD patients and 62.4% higher costs than the general Medicaid population.[48] In this study, the authors estimated that about two-thirds of the total medical costs in this population stemmed from pharmacy costs. Another cost analysis performed at the Durham Veterans Affairs Medical Center in North Carolina prior to the widespread use of ablative approaches suggested that the annual cost of outpatient care for BE approximated United States dollar ($) 1241, with medications accounting for over half of total costs.[49] The authors found that these monthly medication costs among patients with BE approximated those for patients with insulin-requiring diabetes mellitus in patients at this medical center. However, endoscopic ablative BE therapies carry risks as well as the need for more frequent endoscopies, incurring higher resource utilization compared to GERD without BE.[48,49] A European study, which included 6000 GERD patients from Germany, Austria, and Switzerland, found that a diagnosis of BE resulted in more than double the yearly direct medical costs compared to those with non-erosive reflux disease (Euros 631 vs 270), again driven primarily by increased medication costs.[50]

The highest-quality cost estimates of BE screening for GERD patients fall within a range of $10K-$25K per life-year saved, comparing favorably in cost-effectiveness with other accepted cancer screening strategies.[51-55] These estimates are limited in methodology, as there is a paucity of randomized trial evidence to accurately develop cost estimates, and most available studies are limited by lack of consideration of newer endoscopic ablative techniques, such as RFA.[56] Incorporating endoscopic therapy for dysplasia and intramucosal EAC, this estimate shifts to around $22K,[55] demonstrating how dysplasia found on BE screening can prompt endoscopic ablative therapies, further improving cost-effectiveness over continued surveillance or esophagectomy.[36,57-59] In contrast, performing upper endoscopy for upper gastrointestinal cancer screening in the general population at the time of screening colonoscopy costs $116K per quality-adjusted life-year when compared with no screening—significantly higher than targeted screening, despite the reduced costs of performance at the time of colonoscopy.[60]

Limitations of Screening

Endoscopic screening for BE has shortcomings. Adherence to screening recommendations is suboptimal; only 35% of practitioners reported screening all chronic GERD patients with endoscopy in one survey.[61,62] EAC is predominantly diagnosed without prior GERD or BE,[16] and the majority with BE derive limited benefit from surveillance directed by findings on screening.[63,64] Nationwide population-based work from Denmark suggests that the absolute annual risk of EAC among BE is 0.12%, lower than previously suspected.[23] Moreover, work from the UK indicates that among BE, only 1.9% will die of esophageal cancer within 10 years; the remainder succumb more frequently to other diseases, such as ischemic coronary disease.[63]

The yield of endoscopic screening improves when adequate time is spent inspecting the esophagus and the identified BE segments, which increases detection of HGD and EAC.[65] There is inter-observer variation in the histopathologic diagnosis of dysplasia in BE, particularly LGD, necessitating further biopsy review by expert pathologists before confirmation of dysplasia.[66] Going forward, alternative or adjunctive screening tools under development (such as transnasal endoscopy, sponge devices,[67] biomarkers,[68] breath testing, and genetic testing[69]) have the potential to improve cost-effectiveness and potentially expand screening to populations that may not have easy access to endoscopy and sedation. Specifically, transnasal endoscopy (as compared to traditional sedated transoral endoscopy) may be performed in the outpatient clinic setting without sedation, leading to superior patient acceptability, safety, and cost-effectiveness.[70] The cytosponge device consists of a spherical mesh compressed within a gelatinous capsule, that dissolves in the stomach upon being swallowed. This mesh then samples the esophagus as it is withdrawn orally via string, with immunohistochemical staining for the Trefoil Factor 3 biomarker performed on the obtained specimen. Multicenter data suggest sensitivity of 80% (higher for long-segment BE) and specificity of > 90% for a diagnosis of BE with the cytosponge device.[71]

Targeted Screening for Barrett's Esophagus

Given these benefits, limitations, and costs, screening programs for BE among selected populations has value—the cardinal question becomes "who" to screen and "how" to screen.

Guidelines are concordant in recommending targeted screening when risk factors are identified (age > 50 years, male sex, Caucasian race, long-standing GERD, hiatal hernia, elevated body mass index, central obesity, smoking history, family history of BE or EAC)[6,9] but "not" in the general asymptomatic or GERD populations (Table).[72] In the absence of other risk factors, females are generally not targeted for screening for BE, since the risk of EAC in females approximates the risk of breast cancer in males.[7] Since chronic heartburn predicts long-segment BE,[2,39,73] heartburn in the presence of other risk factors should trigger BE screening. In this context, expanding screening to proven GERD with any presenting symptom (past evidence of erosive esophagitis, peptic stricture, or abnormal esophageal reflux burden)[47] in patients fulfilling other risk categories has potential to increase the diagnostic yield of screening.

Conclusions

Education of clinicians—gastroenterologists as well as primary care providers—in recognizing GERD symptoms and risk factors for BE/EAC can improve screening of susceptible populations.[74] Screening should target high-risk individuals with GERD symptoms, but not with limited life expectancy (proposed as < 5 years)[72] or profound comorbidities. While the focus remains on typical reflux symptoms, clinicians should consider screening patients with proven GERD with risk factors for BE/EAC. New modalities under investigation may decrease the costs associated with BE screening and expand access to screening. The selective use of endoscopic screening when risk factors for BE/EAC are identified (with adequate time spent inspecting the esophagus), the use of endoscopic ablative therapies in dysplastic BE, and prospective outcome analysis can maximize cost-effective clinical outcomes.

Take-Home Points

- BE represents a complication of GERD that confers an increased risk for EAC.
- Because endoscopic ablative therapies can reduce the progression of dysplastic BE to EAC, screening programs can impact the natural history of BE.
- BE screening in selected at-risk populations compares favorably in cost-effectiveness with other accepted cancer screening programs.
- However, screening of the general population for BE or unselected patients with GERD is neither cost-effective nor recommended by consensus guidelines.
- Instead, guidelines recommend targeted screening for BE in the presence of risk factors—including age > 50 years, male sex, Caucasian race, long-standing GERD, hiatal hernia, elevated body mass index, central obesity, smoking, and family history.
- Looking forward, alternative screening tools may improve the cost-effectiveness of and enhance access to screening for BE.

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