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Screening for Barrett's Esophagus and Esophageal Adenocarcinoma: Rationale, Recent Progress, Challenges and Future Directions

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Abstract

As the incidence and mortality of esophageal adenocarcinoma continue to increase, strategies to counter this need to be explored. Screening for Barrett's esophagus, which is the known precursor of a large majority of adenocarcinomas, has been debated without a firm consensus. Given evidence for and against perceived benefits of screening, the multitude of challenges in the implementation of such a strategy and in the downstream management of subjects with Barrett's esophagus who could be diagnosed by screening, support for screening has been modest. Recent advances in form of development and initial accuracy of non-invasive tools for screening, risk assessment tools and biomarker panels to risk stratify subjects with BE, have spurred renewed interest in the early detection of Barrett's esophagus and related neoplasia, particularly with the advent of effective endoscopic therapy. In this review, we explore in depth, the potential rationale for screening for Barrett's esophagus, recent advances which have the potential of making screening feasible and also highlight some of the challenges which will have to be overcome to develop an effective approach to improve the outcomes of subjects with esophageal adenocarcinoma.

Keywords

Screening; Barrett's Esophagus; Esophageal adenocarcinoma; screening tools; risk stratification

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Krish Ragunath contributed to the design, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Introduction

Esophageal adenocarcinoma (EAC) is the dominant histological subtype of esophageal cancer in the West. The incidence of EAC has risen by almost 6-fold over the last three and a half decades in Europe and North America¹, along with a dismal 5-year survival rate of less than 20% in cases diagnosed after onset of symptoms². Up to 50% of patients may have incurable disease at symptomatic presentation requiring palliative measures³. On the other hand, 5-year survival rates of subjects diagnosed with early asymptomatic cancers are substantially better than those with symptomatic disease^{4–6}. The high prevalence of Barrett's Esophagus (BE) in subjects with EAC has been reported in several studies and there is consensus that it is the precursor for the majority of EACs^{7–9}. These statistics have provided some impetus to develop strategies for early detection and diagnosis followed by curative therapy as a possible approach to reducing mortality from this lethal cancer.

Recent reports of the feasibility and safety of novel non-endoscopic (sponge based)¹⁰ and additional data on established modified unsedated endoscopic (transnasal endoscopy)^{11–13} techniques have spurred renewed interest in early detection of EAC and its precursors. Recent guidelines from gastroenterology societies from the United States and the United Kingdom have provided more support to screening individuals for BE and EAC, particularly those with “multiple” risk factors, such as chronic reflux symptoms, central obesity and a family history of EAC or BE^{4, 15}, though the number of risk factors which may spur a decision to screen and the tools to screen remain unclear. The aims of this review are to: 1. Provide a summary of the evidence regarding the rationale for and against pursuing select population screening as a possible approach to reduce mortality from EAC. 2. Detail the challenges and recent advances in terms of available tools, identification of a target population and methods for cancer risk stratification, and 3. Identify continuing challenges and areas for future research.

Rationale and Challenges for Screening

It is recognized that there are two main complementary methods to reduce cancer mortality: first, primary prevention (such as smoking cessation) and second, by early detection and treatment¹⁶. There are examples for which screening has already reduced cancer deaths, such as cervical smears to detect cervical intraepithelial neoplasia and more recently, colorectal cancer screening to detect adenomas^{17, 18}. However, the benefits and risks have to be carefully weighed, in particular, the economical and psychological consequences of early detection, as the majority of premalignant lesions in select organs may not progress to cancer even if left untreated¹⁶.

Surveillance for BE is recommended by medical societies and indeed has been practiced for the last two decades even though cancer progression rates in BE without dysplasia are as low as 0.33% per year and only 5%–8% of esophageal adenocarcinomas are diagnosed during surveillance¹⁹. Indeed a recent case control study found no evidence of a survival benefit with surveillance endoscopy in a large population based cohort²⁰. The overall survival of patients with non-dysplastic BE is not different from age and gender matched

individuals²¹. In fact, the majority die from cardiovascular disease and pulmonary disease, while only 7% of BE “surveillance” patients die of EAC in the population²². On the other hand, approximately 66.5% of EACs occur within a year from the initial endoscopic diagnosis of BE⁹, suggesting a high rate of “prevalent” cancers in BE which are excluded from analysis when reporting cancer progression risk in epidemiological studies and may reflect the yield from a screening procedure.

Evidence from several retrospective studies has suggested that a previous diagnosis of BE, before the diagnosis of EAC is associated with early stage disease, lower rates of metastatic lymphadenopathy and improved survival²³. A prior diagnosis of gastroesophageal reflux disease (GERD) and prior endoscopy are also associated with early stage EAC and better survival from EAC, respectively²⁴. While the possibility of lead time and length time bias exists, these data suggest that early detection may reduce mortality from EAC, particularly given data from several studies showing substantially improved survival of subjects with early stage (T1a and T1b) EAC compared to those with locally advanced disease^{5, 25}.

Hence, these data present a dilemma: a continuing rise in the incidence of a lethal cancer uncommonly diagnosed at a curable stage, in the face of surveillance programs that target a population of low risk or “benign” BE and appear to have minimal impact on overall survival.

A potential explanation maybe that current strategies are not identifying a majority of subjects with prevalent BE in the community, leading to limiting clinical attention (by surveillance) to the minority of clinically diagnosed BE in the population. This hypothesis is supported, at least in part, by data from autopsy and population based epidemiological studies estimating that only a third of patients with BE in the population are clinically detected, with the remainder remaining undiagnosed, despite the substantial increase in the use of endoscopy²¹. Indeed, more than 90% of patients who present with EAC do not have a previous diagnosis of BE⁷, an indication of the underlying challenge.

Several potential hurdles to the adoption of screening as a widespread strategy exist. These include the lack of an acceptable, accurate and cost effective tool for screening, the lack of a well characterized screening population, absence of real data on the costs of non-invasive screening, the potential downstream costs of performing surveillance as currently recommended (without consideration of an individual’s risk of progression) and lack of prospective evidence that screening will lead to improved outcomes. An additional hurdle to the expansion of screening in BE had been the lack of therapeutic options for subjects diagnosed with high grade dysplasia (HGD) or intramucosal carcinoma, other than esophagectomy which is a morbid procedure with associated mortality and substantial morbidity. With the advent of effective minimally invasive Barrett’s endotherapy techniques, such as endoscopic mucosal resection and ablation, which are cost-effective and safe alternatives to surgery, there is greater impetus to develop and study techniques which can detect precursors to EAC in an acceptable, accurate and cost effective manner^{26, 27}.

In the next few sections, we will review some recent advances, which may partially mitigate and address some of these limitations.

Advances in tools for screening

Standard endoscopy is not ideal for use in large scale screening, given that it has to be performed in an office or hospital based endoscopy suite, with a small but significant risk of morbidity and mortality related to complications from conscious sedation and the procedure itself²⁸. It is also associated with significant direct (sedation, monitoring, staff, recovery) and indirect (time off work and reduced productivity) costs. All these factors have limited the widespread use of standard endoscopy for screening purposes, since screening tests should ideally be simple and safe to perform, acceptable to the population and cost-effective²⁹. As a result, several alternatives to standard endoscopy have been evaluated.

Non-endoscopic techniques

Balloon cytology sampling devices that collect esophageal samples by swallowing and the withdrawing a sizable balloon with a mesh cover have been utilized with limited success. This technique has been compared with standard endoscopy and brush cytology. Adequate samples were obtained in only 83% of patients with balloon cytology compared to 97% with brush cytology. Sensitivity of the former for HGD and EAC was 80% but only 25% for LGD³⁰. A non-endoscopic flexible mesh balloon catheter was also assessed but adequate specimens were obtained in only 73% of patients. The sensitivity of identifying goblet cells in those patients was 87.5%³¹. These techniques were hence limited by the inadequacy of sampling and poor accuracy.

Over the last few years, researchers from Cambridge University have developed the Cytosponge, a novel cell collection device coupled with a biomarker¹⁰. It is a gelatin capsule attached to a string. Once swallowed, the capsule dissolves and releases a mildly abrasive spherical sponge which can be withdrawn orally, with the attached string to collect cytology specimens from the esophagus. The Cytosponge samples are then analyzed for the presence of Trefoil Factor 3 (TFF3), a biomarker of columnar epithelium, using immunohistochemistry. In a large primary care study involving 12 UK general practices, subjects with GERD symptoms were invited to undergo the Cytosponge test followed by standard endoscopy with biopsies at the hospital. 504 patients (18%) agreed to take part. The Cytosponge test was technically feasible in 99% of patients and was well tolerated. The sensitivity and specificity of the test for the detection of Barrett's epithelium was 73.3% and 93.8% (for Barrett's circumferential length ≥ 1 cm). When defining Barrett's as a circumferential length of ≥ 2 cm, the sensitivity increased to 90.0% with a specificity of 93.5%¹⁰. A recent economic modeling study reported that Cytosponge screening in 50 year-old men with GERD symptoms followed by endotherapy in those with dysplasia or intramucosal carcinoma was cost effective compared to no screening and could reduce the number of cases of incident symptomatic EAC by 19%, compared with 17% for screening by standard endoscopy³².

This device is promising in terms of cost-effectiveness, applicability for community use, and acceptability to patients. Nonetheless, it is a non-endoscopic technique; therefore mucosal visualization is not possible and will still need a confirmatory endoscopy. An important aim of a BE screening program is to identify patients with dysplasia and early EAC, thus further evaluation of the Cytosponge ability to detect these two conditions is needed. Multicenter

studies are currently underway to validate these results in other UK and international centers.

Imaging-based techniques

Wireless Capsule Endoscopy (WCE) is a technology which can visualize the esophagus, small bowel and colon. While initial studies were promising with respect to accuracy in detecting BE³³, later studies revealed somewhat disappointing results³⁴. Bhardwaj et al³⁵ performed a meta-analysis of 9 studies comprising a total of 618 patients. The pooled sensitivity and specificity of WCE for the diagnosis of BE was 77% and 86%, respectively. While WCE is an attractive tool for screening because it is safe, non-invasive, acceptable, does not require sedation, and can be carried out by a single trained technician¹³, it is remains limited by its low sensitivity, inability to take biopsies, need for confirmatory endoscopy, and lack of cost-effectiveness compared to standard endoscopy³⁶. It is therefore not a suitable tool for BE screening at the present time.

String capsule endoscopy is a modified technique with a string attached to the capsule device allowing for controlled movement up and down the esophagus. The device is also re-usable which reduces the cost. The sensitivity and specificity is 78.3% and 82.8%, respectively, when compared with standard endoscopy³⁷. While this technology is less costly, its accuracy remains suboptimal for use in screening.

Unsedated ultrathin transnasal endoscopy (TNE) has been evaluated for the diagnosis of BE. A meta-analysis of five studies (439 patients) was presented recently³⁸. All patients underwent both TNE (diameter 4–6 mm) and standard endoscopy (gold standard). The pooled sensitivity and specificity of TNE in detecting BE was 91% and 96%, respectively. The procedure was successful (95% to 100) and well tolerated in the majority of patients. The current available TNE devices on the market unfortunately require dedicated endoscopy suites with specialized equipment and decontamination facilities. This could hamper their use for widespread screening. More recently, The EndoSheath[®] transnasal esophagoscopy (Vision-Sciences Inc., Orangeburg, New York) has been developed. It utilizes a disposable rubber sheath technology that covers the scope obviating the need for sterilization and utilizes a more compact processing system allowing for easy portability. Initial reports on the acceptability and feasibility of using this device in a clinic based setting have been encouraging¹¹. This device is also currently being evaluated for BE screening in the community ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01288612) NCT01288612). Another promising device is the EG Scan[®] (Intromedic Ltd., Seoul, South Korea), which incorporates a disposable probe omitting the need for decontamination equipment. It is highly compact and portable therefore can be used in the community. TNE can also be performed successfully by physician extenders reducing operator costs³⁹. These technologies require comprehensive evaluation in the setting of screening for BE and EAC.

Over the last few years, advances in “endomicroscopic” imaging technologies have emerged. Researchers have recently developed a tethered capsule endomicroscopy device which has the opportunity to open up new possibilities for screening and diagnosis in the GI tract. It employs optical frequency domain imaging technology to provide cross-sectional and three-dimensional architectural microscopic images of the esophagus. Image

information is spatially correlated with histopathology from corresponding areas enabling the comprehensive assessment of subsurface microstructures that cannot be visualized by endoscopy. The training required to conduct the procedure is minimal. It can be performed in a primary care physician's office. It can be retrieved and disinfected, therefore reducing the cost, making it feasible for large population screening. Data on its accuracy are awaited⁴⁰.

Hence in the last few years, several new and promising techniques for BE screening which are potentially acceptable, reasonably accurate, widely applicable and potentially cost effective, have emerged (figure 1), providing a possible solution to the issue of the lack of availability of a screening tool.

Advances in identification of target population for screening

One of the major challenges to screening for BE remains the absence of a well-defined high risk population. While GERD symptoms remain the strongest risk factor for BE and EAC, raising the risk of BE and EAC by 5 and 8 fold, respectively^{41, 42}, it should also be noted that prevalence rates of 14.9%, 25% and 45% for BE have been reported in patients who were asymptomatic for GERD^{43–45}. Indeed a recent meta-analysis demonstrated the lack of association of symptomatic GERD with short segment BE⁴¹. Therefore a screening program that only relies on the presence of GERD as a selection criterion will likely miss a significant proportion of patients with BE. Conversely, the target population will be very large because of the high prevalence of GERD in Western populations (15–20%)⁴⁶.

Numerous studies have reported additional risk factors for developing BE (table 1) namely: male gender; Caucasian race; age; central obesity, smoking and family history⁴⁷. The typical median age of diagnosis is 60 years and prevalence increases with age⁴⁸. Central adiposity (visceral adipose tissue area, increased waist-hip ratio, or waist/abdominal circumference) rather than BMI has also been implicated in the pathogenesis of BE⁴⁹. Several studies have demonstrated a consistent association between central obesity and risk of BE (OR, 1.98; 95% CI, 1.52–2.57) independent of BMI and symptomatic GERD⁵⁰. Central obesity is also strongly associated with EAC and the effects may be mediated by reflux-dependent and independent mechanisms⁵⁰.

Family history of BE or EAC is also associated with an increased risk of BE and as many as 28% of first degree relatives of patients with EAC or Barrett's HGD have BE in some reports⁵¹. A recent large genome-wide association study (GWAS) study identified genetic variants associated with BE risk at two loci; one at chromosome 6p21 (OR 1.21, 95% CI 1.13–1.28), and another on chromosome 16q24 (OR 1.14, 95% CI 1.10–1.19). The closest protein-coding gene to this chromosome was FOXF1, which is a transcription factor involved in esophageal development and structure⁵². ASCC1, MSR1, and CTHRC1 genes germline mutations have also been associated with BE and EAC⁵³. Patients with BE are significantly more likely to have ever smoked compared to population-based controls (OR: 1.67; 95% CI: 1.04–2.67) or GERD controls (OR: 1.61; 95% CI: 1.33–1.96). This association was strengthened with increased exposure to smoking until approximately 20 pack-years, when it began to plateau. Smoking also had synergistic effects with heartburn or regurgitation⁵⁴.

Rubenstein et al⁵⁵ performed the largest study so far by extracting data from a USA national standardized endoscopic database established by the Clinical Outcomes Research Initiative (CORI). 9% (4,339 out of 48,476) of GERD patients had suspected BE on endoscopy and this was confirmed histologically in 2.8% of patients who had both endoscopy and histology reports available (histological sub-cohort n=25,337). Prevalence of BE in white non-Hispanic male GERD subjects increased sharply from 3.3% in the 4th decade, to 6.3% in the 5th decade, to 9.3% in the 6th decade of life, and then reached a plateau afterwards. Remarkably, white women with GERD symptoms were no more likely to have BE than white men without GERD. However, this may have been biased by the differential reporting of GERD symptoms in the indication for the endoscopies, or differential selection for endoscopy between men and women. Results from a recent modeling study suggest that screening for EAC should be considered in white men age ≥60 with weekly GERD and those aged ≥55 who have daily GERD. Authors estimated the symptom-, age-, and sex-specific incidences of EAC, and compared these figures to other cancers for which screening is endorsed, namely, colorectal and breast cancer (figure 2a and 2b)⁵⁶. The projected incidence of EAC in women with GERD was estimated to be comparable to that of breast cancer in men. Incidence in women with GERD remained lower than a threshold at which screening for colon cancer in women is endorsed and the utility of screening for BE in women was questioned.

Most recently, BE risk prediction models have been developed. They incorporate multiple established risk factors and have the potential for use as an inexpensive preselection tool for screening. So far, three models with different sets of predictors have been published^{57–59}. Thrift et al⁵⁷, initially evaluated a large number of putative risk factors in a case-control study with external validation. The final risk model included age, sex, smoking status, BMI, highest level of education and frequency of use of acid suppressant medications. The area under the receiver operating characteristic curve (AUROC) was 0.70 and 0.61 in the derivation and validation groups, respectively. Another modestly accurate model is the online Michigan Barrett's Esophagus pRediction Tool (M-BERET) (<http://mberet.umms.med.umich.edu/>). This model is based on a population of colonoscopy screenees who consented to a study endoscopy and included four variables (weekly GERD, age, waist-to-hip ratio and pack-years of cigarette smoking). It performed better (AUROC = 0.72) than a model with reflux parameters alone (AUROC = 0.61, $p < 0.001$)⁵⁸.

Thrift et al⁵⁹, reported a significant association between a multi-biomarker risk score model (based on serum levels of interleukin (IL) 12p70, IL6, IL8, IL10 and leptin) and risk of BE. Subjects with a score of 3 or more had a greater than 10-fold increase risk of BE compared to those with a score of 0 (OR 11.9; 95%CI 4.06, 34.9). The combination of the multi-biomarker risk score model with a demographic and clinical features model (based on GERD frequency and duration, age, sex, race, waist-to-hip ratio, and H. Pylori status) was significantly more accurate at predicting the presence of BE compared to a combination of the risk score with a model based on GERD frequency and duration alone (AUROC 0.85 vs. 0.74; $p = 0.01$). Data from this case-control study was based on a predominantly white male Veterans population. This prediction model represents a significant improvement in accuracy compared to previous methods. Despite the progress made in attempting to define the target population for screening, several challenges to screening remain.

Methods and recent developments in BE cancer risk stratification

In order to render any future population screening and surveillance program feasible and cost effective, a cancer risk prediction algorithm that incorporates demographic, clinical, histological and molecular biomarkers would be vital. This will help to riskstratify patients with BE and focus surveillance and therapy on the high risk group. Several independent risk factors for increased risk of EAC in BE subjects have been identified.

Demographic and clinical risk factors

Men with BE are at increased risk for development of EAC compared to women. The overall risk is around 0.28% per year in men and 0.13% per year in women⁶⁰. Data on the association of male gender and risk of progression are somewhat scarce and inconsistent; therefore recommendations for surveillance in both men and women are currently the same. Increasing age is another risk factor reported in some studies, but these findings were not replicated in larger cohort studies⁶¹. Active tobacco smoking has been associated with an increased risk of progression (hazard ratio = 2.03; 95% confidence interval, 1.29–3.17) across all classes of smoking intensity in some, but not all studies⁶², while no link has been found with alcohol consumption. Increased waist to hip ratio, but not BMI, was associated with risk of aneuploidy, 9p loss of heterozygosity (LOH) and 17p LOH, suggesting that visceral adipose tissue may be a risk factor for malignant progression⁶¹.

There is substantial evidence that the length of BE segment is a significant risk factor although in few studies the association was not statistically significant¹⁴. Besides segment length, the presence of mucosal nodularity, ulceration and strictures have been associated with risk of EAC; however, this may indicate prevalent neoplasia rather than risk of future cancer⁶³. Risk of progression to HGD and cancer are higher in the presence of hiatus hernia and esophagitis, likely as a result of esophageal inflammation driving this process through increased risk of mutations⁶⁴. Ideally, a future risk prediction model should take into account all these factors; however as of yet, a definitive model has not been developed and validated, hence at present time, segment length appears to be the only factor which can be used to suggest surveillance intervals in patients with NDBE¹⁴.

Histological and molecular risk factors

While the grade of dysplasia remains the most widely used risk assessment tool¹⁴, poor interobserver agreement among pathologists and sampling error remain major limitations in the use of dysplasia as a risk stratification tool⁶⁵. Hence attempts have been made to develop biomarkers as complementary methods to predict risk of EAC in BE.

The use of biomarkers in combination with clinical markers is appealing. This was evaluated in one study by analyzing data from an age-, sex-, and year of BE diagnosis-matched case-control cohort. A panel of established (abnormal DNA content, p53 and cyclin A expression) and new biomarkers (levels of sialyl Lewis^a, Lewis^x, and *Aspergillus oryzae* lectin and binding of wheat germ agglutinin) was assessed. A combination of low grade dysplasia, abnormal DNA ploidy, and *Aspergillus oryzae* lectin was most accurate at predicting histologic progression. For each additional factor of these three, BE patients with

LGD had an approximately 4-fold increased odds of progressing to develop EAC or HGD (OR, 3.74; 95% CI, 2.43 – 5.79), whereas the risk increased by a 3-fold (OR, 3.31; 95% CI, 1.81– 6.05) for each additional factor in patients with no dysplasia⁶⁶. Prospective randomized controlled trial evidence needs to be available before these markers can be recommended for use in clinical practice.

Immunohistochemistry for nuclear p53, a tumor suppressor gene, is perhaps currently the most promising potential biomarkers for risk stratification in clinical practice. It is easily applicable; reproducible; and serves as a good predictor of malignant progression⁶⁵. In a prospective cohort study of 720 patients with BE, p53 overexpression was associated with an increased risk of neoplastic progression (HGD or EAC) independent of age, gender, BE segment length and esophagitis (adjusted relative risk 5.6; 95%CI 3.1, 10.3), and the risk was even higher with loss of p53 expression (adjusted relative risk 14.0; 95%CI 5.3, 37.2). Moreover, the positive predictive value for neoplastic progression increased from 15% with LGD to 33% with LGD and aberrant p53 expression⁶⁷. While the presence of dysplasia confirmed by two expert histopathologists remains the best tissue biomarker available for assessment of cancer risk in patients with BE currently¹⁴, the addition of biomarkers such as p53 to enhance the prediction of progression appears to be on the horizon. This has been recently endorsed by some gastroenterology guidelines, as a complement to histology¹⁴.

Thrift et al⁶⁸ recently developed a logistic regression model using epidemiological data from 364 patients with incident EAC and 1580 population controls. The final risk model included highest level of education, BMI, smoking status, frequency of GERD and/or use of acid-suppressant medications, and frequency of non-steroidal anti-inflammatory drugs use. The absolute risk of developing EAC was estimated with an AUROC of 0.75 indicating good discrimination. External validation of this model and other biomarker panels may allow more targeted surveillance and therapy in the future.

Continuing challenges to screening and future directions

Despite these advances, several challenges to widespread BE screening remain. Non-endoscopic methods for BE remain to be validated in large populations in terms of acceptability, accuracy, safety and cost effectiveness. Despite encouraging data on the accuracy and acceptability of TNE^{11, 13}, acceptance by physicians remains low⁶⁹. Novel non-invasive markers identifiable in blood or stool would be ideal for widespread application, but are currently not available.

BE risk prediction models with adequate sensitivity can significantly reduce the number of “missed” patients in a screening program and be used as an inexpensive pre-selection tool for screening. While encouraging, the current accuracy of BE prediction models likely is insufficient for widespread clinical use (AUROC 0.6–0.85). The MBERET and other scores require external validation in unselected populations, testing in females, and likely addition of other circulating biomarkers. Iterative refinements of such models combined with a simple diagnostic test may potentially make screening for BE more cost-effective. As a result, it is likely that the use of prediction models based on multiple risk factors, will emerge as the means of identifying at risk populations for EAC. Limiting screening to

higher risk subgroups (table 2) such as men with chronic reflux (daily or weekly) reflux symptoms as advocated by some studies may have to be considered.

Any screening program is likely to result in an increased workload and costs to the healthcare system which are challenging to justify. Management of screening-diagnosed patients with NDBE remains unclear, particularly with the majority not likely to progress to cancer. In these subjects performing routine endoscopic surveillance may potentially expose patients to unnecessary harm and lead to escalating costs without substantial benefit. Therefore, methods to predict individuals at increased risk of EAC merit serious and careful consideration. Further validation, refinement and cost effectiveness of models of predictors of progression, likely combining clinical and biomarker variables, will be crucial in allowing the identification of low and high risk subsets. Subjects with a low risk of progression could likely be discharged from surveillance while those at a higher risk could be placed in intensive surveillance with advanced imaging or offered ablation to decrease the risk of developing EAC. A conceptual flow diagram outlining an approach to decrease the incidence of and mortality from EAC is presented in Figure 3. This represents a future vision of how this process could potentially be effective in reducing EAC incidence and mortality..

In summary, while significant progress had been made in the early detection and treatment of esophageal Neoplasia, several challenges to the widespread application to screening remain. Nevertheless, this area is ripe for research, particularly focusing on the comprehensive evaluation of emerging minimally-invasive and novel screening tools as well as deriving and validating BE and EAC risk prediction models.

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Abbreviations

AUROC	receiver operating characteristic curve
BE	Barrett's Esophagus
BMI	body mass index
Bra	breast cancer
CI	confidence interval
CRC	colorectal cancer
EAC	esophageal adenocarcinoma
GERD	gastroesophageal reflux disease
GWAS	genome-wide association study

HGD	high grade dysplasia
LGD	low grade dysplasia
LOH	loss of heterozygosity
LSBE	long segment Barrett's Esophagus
M-BERET	Michigan Barrett's Esophagus pREdiction Tool
NDBE	nondysplastic Barrett's Esophagus
OSA	obstructive sleep apnea
OR	odds ratio
SIM	small intestinal metaplasia
TFF3	Trefoil Factor 3
TNE	transnasal endoscopy
WCE	wireless capsule endoscopy

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Figure 1. Tools currently undergoing evaluation for use in BE screening. A, Cytosponge; B, EG scan system (disconnected); C, EG Scan system (connected); D, EndoSheath system.

Figure 2.

a: Estimated incidence of EAC in populations with weekly GERD symptoms.

Incidences of colorectal cancer (CRC) and breast cancer (Bra) are displayed for context. The benchmark incidence of cancer for endorsed screening is demonstrated by the green horizontal line. Thick lines represent EAC, thin lines represent CRC, and dotted lines represent Bra. Thin dashed lines represent the upper and lower confidence limits of the incidence of EAC in men with weekly GERD, and the upper confidence limit of EAC in women with weekly GERD. The lower confidence limit for women with GERD overlap the point estimate incidence of EAC in women and are not visible on the figure. (*Reproduced with permission from Rubenstein JH, et al⁵⁶. Copyright Nature Publishing Group*).

b: Estimated incidence of EAC in populations with daily GERD symptoms.

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Figure 3. Proposed future approach to reducing mortality from EAC by utilizing screening and targeted surveillance coupled with endotherapy

BE, Barrett's Esophagus; EAC, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; HGD, high grade dysplasia; LGD, low grade dysplasia; LSBE, long segment Barrett's Esophagus; TNE, transnasal endoscopy

Table 1

Studies reporting risk factors for BE

Study author	Year & country	Sample size	Study design	Risk factors for BE**
		BE		
Eloubeidi MA, et al⁴⁸	2001, USA	107 BE 104 GERD	Prospective case-control study Questionnaire based	Age>40 (p=0.008) Heartburn or acid regurgitation (p=0.03) Heartburn > once per week (p=0.007)
Gerson LB, et al⁷⁰	2001, USA	517 GERD (99 known)	Prospective cohort 7-symptom questionnaire	Male gender Heartburn Nocturnal pain Odynophagia.
Avidan B, et al⁷¹	2002, USA	256 BE 229 GERD	Prospective case-control study	Number reflux episodes Hiatus hernia Excess alcohol and smoking
Chak A, et al⁷²	2002, USA	58 BE 106 controls	Case control study	family history (OR 12.2; 95%CI 3.3, 44.8)
Smith KJ, et al⁷³	2005, Australia	167 BE 261 controls	Population based case-control study, self-completed questionnaires	Weekly GERD (OR 29.7; 95%CI 12.2, 72.6) Smoking (OR 3.1) BMI not associated
Cook MB, et al^{74*}	2005, UK	32 studies	Meta-analysis	Pooled Male: female ratio of 1.96:1 (95%CI 1.77, 2.17/1)
Corley DA, et al⁷⁵	2007, USA	320 BE 316 GERD 317 controls	Case-control study	Larger waist circumference (OR 2.24; 95%CI 1.21, 4.15); circumference >80 cm vs. <80 cm. No association with BMI
Johansson J, et al⁷⁶	2007, Sweden	604 undergoing endoscopy 160 controls	Prospective case-control study self-administered questionnaire	GERD and smoking indicated a 10.7- and 3.3-fold risk, respectively, for BE (95%CI 3.5, 33.4 and 1.1, 9.9, respectively). BMI was unrelated to risk.
Edelstein ZR, et al⁷⁷	2007, USA	193 BE 211 controls	Prospective Case-control study	Waist-to-hip ratio (OR 2.4; 95%CI 1.4, 3.9 all cases and 4.3; 95%CI 1.9, 9.9 for LSBE) independent of BMI. Association with BMI and smoking weaker
Anderson LA, et al⁷⁸	2007, Northern Ireland	224 BE 227 EAC 260 controls	Population based case-control study	GERD (OR 12.0; 95%CI 7.64, 18.7). BMI and smoking not associated with BE
Cook MB, et al^{79*}	2008, UK	9 studies (BE/GERD controls). 3 studies (BE/population controls)	Meta-analysis	BMI 9 studies pooled OR 0.99 per kg/m ² (95%CI 0.97, 1.01 and 3 studies OR 1.02 per kg/m ² (95%CI 1.01, 1.04

Study author	Year & country	Sample size	Study design	Risk factors for BE**
Edelstein ZR, et al ⁸⁰	2009, USA	197 BE 418 controls	Case control study	Older age (OR per decade for SIM=1.3; 95%CI 1.1, 1.5; LSBE =1.5; 95%CI 1.2, 1.9) Male gender (OR SIM=1.5; 95%CI 1.1, 2.2; LSBE= 3.9; 95%CI=1.9, 8.1) waist-to-hip ratio (male high= 0.9, female high= 0.8) SIM (OR 1.3; 95%CI 0.9, 2.1), LSBE (OR 4.1; 95%CI 1.5, 11.4) Smoking (ever) SIM (OR 1.8; 95%CI 1.2–2.6), LSBE (OR 2.6; 95%CI 1.3, 4.9)
Kubo A, et al ⁸¹	2009, USA	320 BE 316 GERD 317 controls	Case-control study using interview questionnaires	Alcohol not associated. Wine consumption & education status inversely associated
Anderson LA, et al ⁸²	2009, Northern Ireland	230 GERD 224 BE 227 EAC 260 controls	Case-control study using structured Interview	No association between total alcohol consumption and BE. Wine consumption may reduce risk of BE
Taylor JB, et al ^{41*}	2010, USA	26 studies	Meta-analysis	GERD (OR in all studies 2.90; 95% CI 1.86, 4.54) Strong association with LSBE (OR 4.92; 95%CI 2.01, 12.0), no association with SSBE
Orloff M, et al ⁵³	2011, USA	Validation cohort 176 BE/EAC 200 controls	Model-free linkage analyses	MSR1, ASCC1, and CTHRC1 genes associated with BE/EAC (P< .001)
Su Z, et al ⁵²	2012, UK	Discovery cohort 1,852 BE 5,172 controls replication cohort 5,986 cases 12,825 controls	genome-wide association study (GWAS)	Chromosome 6p21 locus (OR 1.21; 95%CI 1.13, 1.28) Chromosome 16q24 (OR 1.14; 95% CI 1.10, 1.19)
Cook MB, et al ⁵⁴	2012, USA	1059 BE 1332 GERD 1143 controls	Analyzed data from 5 case-control studies ^{81–84}	Ever smoked (OR 1.67 and 1.61 compared to controls and GERD controls respectively. Association strengthened with increased exposure until 20 pack-years)
Balasubramanian G, et al ⁴⁷	2012, USA	1058 patients with GERD	Prospective cohort using validated GERD questionnaire	Heartburn >5 years (OR 1.50; 95% CI 1.07, 2.09), Caucasian race (OR 2.40; 95% CI 1.42, 4.03), hiatus hernia (OR: 2.07; 95% CI 1.50, 2.87)
Leggett CL, et al ⁸⁵	2013, USA	36 BE 78 OSA 74 BE+OSA 74 no BE or OSA	Case-control study	OSA (OR 1.8; 95%CI 1.1, 3.2). Independent of age, sex, BMI, GERD, and smoking history. Risk higher with more severe OSA
Thrift AP, et al ⁸⁶	2013, Australia	258 BE 453 primary care controls 1145 endoscopy controls	Case-control study	Smoking : no association (status, intensity, age at initiation, duration, pack-years and cessation). Alcohol : not associated, moderate intake inversely associated.
Garcia JM, et al ⁸⁷	2013, USA	141 BE 139 controls	Prospective case-control	OR 2.62 (95%CI 1.0, 6.8), 5.18 (95%CI 1.7, 15.7), and 8.02 (95% CI 2.79, 23.07) for highest vs. lowest quintile of levels of IL-12p70 , IL-8 , and leptin , respectively,

Study author	Year & country	Sample size	Study design	Risk factors for BE**
Singh S, et al ⁵⁰	2013, USA	40 studies	Meta-analysis	central adiposity had a higher risk of BE (17 studies; OR 1.98; 95% CI 1.52, 2.57)

* where available, meta-analysis of established risk factors (GERD, male gender, obesity) presented instead of individual studies. OR, odds ratio; CI, confidence interval; BMI, body mass index; LSBE, long segment Barrett's esophagus; SIM, small intestinal metaplasia; OSA, obstructive sleep apnea.

Table 2

Currently accepted demographic risk factors to be considered for BE screening^{14, 15, 88, 89}

Demographic profile to be considered for screening:	
1	- White male.
2	- Age 50 years.
3	- Chronic GERD symptoms.
4	- Centrally obese : Waist circumference $\geq$ 102 cm in men
5	- Family history of at least one first degree relative with BE or EAC.
6	- Current or ex-smokers.