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Epidemiology of Barrett's Esophagus and Esophageal Adenocarcinoma - Implications for Screening and Surveillance

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History

Throughout the evolution of the definition of Barrett's esophagus (BE) the one thing that has remained constant is the identification of some form of columnar epithelium upon histological analysis. The first reporting of such a tissue found in the esophagus is attributed to Schmidt in 1805[1]. In the early part of the 20th Century, Stewart and Hartfall[2] and Lyall[3] noted that the presence of columnar epithelium in the esophagus—surrounding "ulcerations"—was an abnormality. Confusion and debate began to center on the origin of columnar epithelium in the esophagus and, in his famous treatise of 1950, Norman Rupert Barrett proposed that a condition existed in which congenitally short esophagus resulted in the stomach being drawn up into the chest cavity—a type of hiatal hernia[4]. However, even though the eponym of Barrett's was to stick, his initial theory of the origin of columnar epithelium was soon to be found incorrect. It was Allison and Johnstone in 1953[5] who initially used the term 'Barrett's ulcer' to refer to what was previously known as 'peptic ulcer of the esophagus', reasoning that this would distinguish it from ulceration of esophageal squamous epithelium, which had been given the name 'reflux esophagitis' by Barrett himself. Allison and Johnstone proposed that Barrett's ulcer was not due to a congenitally short esophagus with herniation of the stomach, but instead to a congenital gastric-lined esophagus. From scrupulous examination of specimens, they noted that there was no peritoneal covering, the musculature was typically esophageal, islands of squamous

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epithelium existed within the columnar lining and that oxyntic (parietal) cells were absent. This led them to propose that:

> "It appears better…to refer to that congenital abnormality which from the outside looks like oesophagus and from the inside looks like stomach as 'oesophagus lined with gastric mucous membrane'."

The association with reflux and hiatal hernia was spoken of, but they still considered BE to be wholly congenital, a view supported by embryological studies of fetal development. Barrett conceded his theory of congenitally short esophagus in 1957[6], now referring to this gastric-like lining as 'lower oesophagus lined by columnar epithelium', a term which in future publications was to be replaced by the eponym 'Barrett's esophagus'. He too still thought the condition to be of congenital origin, yet in 1957 he did acknowledge that an acquired pathogenesis may exist:-

> "If the cardiac valve of a normal person were to become incompetent and if the lower oesophagus were, as a result, to be bathed for a long time by digestive gastric juice, the squamous epithelium could be eaten away and totally replaced by columnar cells."

Thus, perhaps the eponym is merited. Two-years later, in 1959, Moersch, Ellis, and McDonald[7] are credited with the first publication where the changes of the distal esophagus following reflux esophagitis are discussed without inferring a congenital origin, instead referring to 'inflammatory metaplasia'. Their study of 36 esophageal resections was the first convincing evidence that persistent gastroesophageal reflux disease (GERD) was central to the etiology of columnar-lined esophagus. This perspective was strengthened in 1970 in a series of landmark canine experiments by Bremner *et al.*[8] in which they showed normal esophageal squamous repair in the absence of GERD but re-epithelialization with a columnar lining when GERD was induced.

What we now consider the defining feature of BE—goblet cells—were first noted by Bosher and Taylor in 1951[9]. Despite subsequent confirmatory observations[5,10], the histology of BE continued to be debated for the next 20 years. In 1976, some clarity emerged from a study by Paull and colleagues[11] with descriptions of three types of metaplasia, including specialized columnar epithelium—which we now call intestinal metaplasia, synonymous with BE. Paull only hinted at the potential carcinogenic importance of intestinal metaplasia, and it wasn't until early 1990's that intestinal metaplasia was generally accepted to be the most prevalent, distinctive epithelium, and highest in conferring risk of esophageal adenocarcinoma (EA)[12,13].

Epidemiology

POPULATION PREVALENCE OF BARRETT'S ESOPHAGUS

The population prevalence of BE is a crucial statistic upon which all primary and secondary prevention strategies are based, yet it remains largely unknown primarily due to the fact that many individuals with BE are asymptomatic.[14] The BE prevalence in selected populations—such as endoscopic or surgical series—is no substitute, and so there are few studies that provide an accurate estimate. The first reliable study, published in 1990, assessed the

prevalence of long-segment BE in a large series of randomly selected subjects for autopsy and compared this to a prevalence from the endoscopy practice of the Mayo Clinic[15]. The finding of four BE cases was approximately 21 times of that which was expected (0.19), and this equated to an age- and sex-adjusted BE prevalence estimate of 376 per 100,000 population (0.376%). Other estimates of BE population prevalence come from randomly selected populations to undergo endoscopy. A Swedish study[16] of 1,000 randomly selected volunteers detected a total of 16 cases of BE, five of which were classified as long-segment BE (>=2 cm), yielding population prevalences of 1.6% and 0.5%, respectively. An Italian study[17] of 1,033 adults, reported a BE population prevalence of 1.3% (0.2% for long segment and 1.1% for short segment). A computer simulation disease model has also been used to estimate the population prevalence of BE.[18] Aligning simulation models with EA rates from the US Surveillance Epidemiology and End Results (SEER) cancer registry data, the authors estimated a BE population prevalence of 5.6%. Thus, in predominantly European ancestral populations, estimates for BE population prevalence range from 0.4% to 5.6%. Perhaps surprisingly, Asian countries may also have BE population prevalences in this range, despite the lower incidence of EA. A recent meta-analysis of four Asian-based studies indicated a BE population prevalence of 0.7%[19], and a Taiwan-based study of 3,385 subjects undergoing routine esophagogastroduodenoscopy examination as part of a health check-up provided a BE population prevalence of 2.6%.[20] The Taiwan study provided details of segment length, showing that that the vast majority of diagnoses were short-segment BE, a characteristic that has previously been described in other selected endoscopic series from Asian countries, and which is in accordance with the lower incidence of EA in Asian populations.

INCIDENCE TRENDS OF BARRETT'S ESOPHAGUS

Assessing incidence trends of BE is a near impossibility due to the large pool of asymptomatic, undiagnosed subjects that we estimate to exist in most populations. As such, the best estimates are derived from clinical data with the hope that these may mirror relative change of all BE cases, including those never diagnosed. Typically, the denominator in such studies is the number of endoscopies, rather than the total population at risk.

In the US, the first report of BE incidence was from the Mayo Clinic which found a rate of 9.5 per 1,000 endoscopies per annum that was stable over the period 1965 to 1986; the crude rate did dramatically increase but this was wholly accounted for by a similar increase in the number of endoscopies[15]. Two other US studies also presented evidence for no change in BE incidence through the 1990s, once adjusted for number of endoscopies[21,22]. However, a fourth US study did provide evidence for an increase[23]. The authors found that endoscopy suspected BE increased from 32.2 to 82.8 per 1,000 endoscopies and histologically diagnosed BE from 6.7 to 27.6 per 1,000 endoscopies during 1991 to 2000. More recent studies covering the mid-90s through 2010, indicate that BE incidence has been stable and then may have declined[24–26].

In contrast to the US, a majority of European studies have suggested an increase in BE incidence including Scotland[27], UK[28], Switzerland[29], the Netherlands[30], Spain[31], and Northern Ireland[32], as has a study from Australia[33]. The most recent European study from

the UK and the Netherlands provides evidence for a decrease and then stabilization of BE incidence[34].

Statistics of BE incidence need to be interpreted with several caveats in mind: increasing enthusiasm and education about BE, especially short-segment BE, and changes in referral patterns have not been measured and therefore remain unadjusted for. It has been suggested that the increasing epidemiological evidence of the strength of BE as a precursor to EA served to increase the awareness of this lesion[27]. It is unknown what effect this has had referral practices; obviously more patients are being referred for endoscopy but the relative influences of altered incidence of heartburn symptoms and increased awareness of sequelae complications, by both patient and provider, are unknown. Overall, it is likely the evidence supports increased BE incidence in Western Europe and Australia, whilst further evidence is needed to confirm or refute similar trends in the US.

INCIDENCE AND SURVIVAL OF ESOPHAGEAL ADENOCARCINOMA

For the purpose of this review, the most recent data were analyzed from the SEER 9 registries[35] (covering approximately 10% of the United States' population) in which 21,358 cases of invasive EA (defined using International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site codes, C15.0-C15.9; and histologic codes, M8140–8575) were diagnosed between 1975 and 2017. The overall age-adjusted incidence rate for EA during 1975–2017 was 2.0 per 100,000 person-years. EA incidence rates increased from 0.4 per 100,000 person-years in 1975 to 2.8 per 100,000 person-years in 2017 (Figure 1). EA incidence also varies by US state, with NAACCR data[36] showing highest rates predominantly in northern and northeastern states (Figure 2). While EA rates increased dramatically between the mid-1970s through 2000,[37] SEER 18 delay-adjusted data[38] show that the rate of increase has slowed in subsequent years and EA incidence has stabilized in the U.S. through 2017 (Figure 3). Absolute rates of EA remain significantly higher among White males in the U.S. compared with females and non-Whites; however, similar rates of change and secular trends have been observed in all subgroups of the U.S. population. For EA cases in the SEER 18 registries[39], median relative survival has increased from 10.5 months in 2000 to 13.1 months for persons diagnosed in 2016. Overall 5-year observed survival rates increased from 15.4% for patients diagnosed with EA in 2000 to 18.4% for patients diagnosed with EA in 2012. The greatest absolute improvement in survival trends occurred in EA patients diagnosed with localized disease, approximately 32% of patients diagnosed with localized EA in 2000 survived 5 years after their diagnosis, whereas the 5-year observed survival rate for patients diagnosed with localized EA in 2012 was 48% (Figure 4). Less striking improvements in 5-year survival rates were observed among patients diagnosed with regional (19% for patients diagnosed in 2000 vs. 22% for those diagnosed in 2012) or distant (2.5% for patients diagnosed in 2000 vs. 4.1% for those diagnosed in 2012) stage EA.

Nature of the Problem

The central problems in primary prevention (screening) and secondary prevention (surveillance) of EA is the large undiagnosed BE population and the suboptimal ability to

triage risk in the diagnosed BE population, respectively. The large undiagnosed BE population results in a majority of EA cases presenting with late stage disease and a resultant poor prognosis. Below, we review the current epidemiologic evidence of risk factors, biomarkers, and algorithms that may be used to overcome this problem and identify a larger pool of subjects with BE. We then review the current evidence for triaging cancer risk in the diagnosed BE population, a difficulty that will be compounded should the primary prevention hurdle (population screening) be overcome.

Current Evidence

POPULATION SCREENING FOR BARRETT'S ESOPHAGUS

There is a major caveat to this section. A vast majority of the studies that are described have been conducted using selected BE populations; that is, patients who present with symptoms that merit endoscopic and histologic investigation. This should not be glossed over and it is an inherent limitation of studying a rare, largely asymptomatic condition that is expensive and difficult to diagnose.

Risk Factors—While clinical guidelines all recommend screening for BE, the screening population differs[40–43]. All guidelines, except those from the American Gastroenterological Association, condition screening for BE based on the presence of GERD symptoms (Table 1). Risk factors used to define high-risk for purposes of screening generally include age ≥50 years, male sex, Caucasian race, GERD symptoms, smoking, and obesity. Here, we review the literature supporting these high-risk determinants as well as other potential risk factors for BE and EA.

Demographics—EA incidence increases with increasing age and is rare among persons aged <50 years. An intriguing and yet largely unexplained observation in EA is the striking sex disparity; across all countries, EA incidence rates in females remain significantly lower than those of males. The magnitude of the male predominance is greatest in the U.S., where the male:female incidence rate ratio approaches 9:1[44–46]. EA is also more common in non-Hispanic whites than non-whites[47]. Likewise, BE is twice as common in men as in women and more common in non-Hispanic whites than other races/ethnicities[48].

Environmental Risk Factors—Frequent GERD symptoms, cigarette smoking, and obesity are the main risk factors for EA and BE. Together, these three risk factors account for over 70% of all cases of EA in Western populations[49,50], and are observed among the majority of patients with BE.

In a pooled analysis of individual-level data from 5 case-control studies participating in the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON; https://esocan.org/beacon/), there was a strong, dose-dependent relationship between frequency of GERD symptoms and EA risk. Compared to individuals with infrequent or no GERD symptoms, those with at least weekly and daily symptoms had five-fold (odds ratio [OR]=4.81, 95% confidence interval [CI], 3.39–6.82) and eight-fold (OR=7.96, 95%CI:4.51–14.04) higher risk of EA, respectively[51]. For BE, individuals with frequent GERD symptoms occurring in

early adulthood have especially high-risk (first reported symptoms at age <30 years, OR=15.1, 95%CI:7.91–28.8)[52].

Cook et al.[53], using pooled individual-level data from 10 case-control and 2 cohort studies in BEACON, found that ever smoking was associated two-fold increased risk of EA (vs. never smoking; OR=1.96, 95%CI:1.64–2.34) and showed that EA risk increased with increasing pack-years smoking history. While EA risk among ever smokers appears to decline with increased years of smoking cessation, risk in formers smokers does not return to the level observed for never smokers[53,54]. The evidence is less clear for BE. In the largest study to date, risk of BE was 1.7-fold as high among ever smokers as it was among never smokers (OR=1.67, 95%CI:1.04–2.67)[55]. However, unlike for EA, BE risk does not increase with increasing cumulative exposure.

Compared to individuals with a normal body mass index (BMI <25.0 kg/m^2), individuals with BMI of 30.0–34.9 kg/m^2 and ≥40.0 kg/m^2 have two-fold (OR=2.39, 95%CI:1.86–3.06) and five-fold (OR=4.76, 95%CI:2.96–7.66) higher risk of EA, respectively[56]. Obesity in childhood and adolescence may also confer increased risk of EA independent of adult BMI[57,58]. Increasing evidence suggests that abdominal obesity confers greater risk for EA and BE than overall obesity[59,60]. A meta-analysis found over two-fold increased risk of EA associated with abdominal obesity (OR=2.51, 95%CI:1.54–4.06)[61]. Likewise, abdominal obesity was associated with two-fold higher risk of BE (OR=1.98, 95%CI:1.52–2.57)[61]. These associations remained after controlling for BMI, while there were weak or no associations with BMI after controlling for abdominal obesity.

Alcohol consumption is not associated with increased risks of EA or BE[62,63]. The Continuous Update Project Report on diet, nutrition and physical activity by the World Cancer Research Fund/American Institute for Cancer Research, which considers results from only cohort studies, reported that no dietary factors were judged to have strong evidence of an association with risk of EA and that there were limited suggestive evidence for an inverse relationship between physical activity and risk of EA[64].

Helicobacter pylori is a gram-negative bacterium that infects half the world's human population and causes gastric cancer[65]. Conversely, *H. pylori* infection is associated with lower risks of EA and BE. Two meta-analyses both reported over 40% lower risk of EA for individuals infected with *H. pylori* (in particular, those with the CagA-positive *H. pylori* strain) compared with individuals uninfected with *H. pylori*[66,67]. There is also strong evidence that *H. pylori* infection is associated with lower risk of BE[68,69].

Frequent users of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have lower risk of EA. A pooled analysis of individual-level participant data in BEACON found that any use of aspirin or NSAIDs was associated with 30% lower risk of EA (OR=0.68, 95%CI:0.56–0.83)[70]. Current users had especially lower risk for EA (OR=0.40, 95%CI:0.24–0.97), and risk was shown to decrease linearly with both increased frequency and duration of use[70]. In contrast, a pooled analysis among BE studies in BEACON found no association between any NSAIDs and BE (OR=1.00, 95%CI:0.76–1.32)[71]. Statins have also been shown to be associated with lower risks of EA and BE[72,73].

Given the male predominance in BE and EA risk, studies have considered whether or not sex hormones might be involved. Case-control studies have found increased risk of EA associated with increased androgen:estrogen[74], and increased risk of BE associated with higher levels of free testosterone and free dihydrotestosterone[75,76]. In a prospective study, pre-diagnostic concentrations of circulating dehydroepiandrosterone (highest quartile vs. lowest quartile: OR=0.28, 95%CI:0.13–0.64), estradiol (highest quartile vs. lowest quartile: OR=0.55, 95%CI:0.31–0.99), and free estradiol (highest quartile vs. lowest quartile: OR=0.56, 95%CI:0.30–1.03) were associated with lower risk of a combined outcome of EA and gastric cardia adenocarcinoma[77]. In a second prospective study of EA, contrary to long-standing hypotheses,[78] higher circulating levels of testosterone were associated with lower risk for EA in males.[79] A recently published Mendelian randomization study found an association between genetically predicted levels of follicle-stimulating and luteinizing hormones and risk of BE and EA but no associations with other sex hormones, including dehydroepiandrosterone sulfate, testosterone, and estradiol.[80]

Genetic Factors—Genome-wide association studies have identified and validated germline (inherited) loci associated with risk of EA and BE, including CRTC1, a transcription coactivator associated with increased cancerous activity, BARX1, a transcription factor that promotes esophageal differentiation, FOXF1, FOXP1, and TBX5, which encode transcription factors involved in esophageal development, and GDF7, which encodes a protein in the bone morphogenetic pathway which has been associated with BE.[81–84]

Algorithms—Early strategies to select patients for BE screening were based on only frequency and severity of GERD symptoms. However, as only around half of BE patients report symptoms of GERD[16,17], symptoms alone discriminate poorly between persons with and without BE[85–88]. A number of risk stratification tools have since been developed that use demographic, lifestyle and clinical information to discriminate between individuals at high- and low-risk for BE, with varying degrees of success with respect to discriminatory accuracy[85,89,90]. They also require further examination in external populations and prospectively before clinical implementation can be recommended[91,92]. Three recent validation efforts have shown that the Michigan Barrett's Esophagus pREdiction Tool (M-BERET) which incorporates GERD symptoms, age, waist-to-hip ratio, and pack-years of cigarette use to predict BE risk is robust and transportable to other populations[88,93,94]. However, the discriminatory ability of this tool (area under the receiver operating characteristic curve [AUC], ~0.70) is not at the level required for clinical application. To address this shortcoming, other factors including blood-based biomarkers[86] and genetic information[95,96] have been added to baseline models using demographic, lifestyle and clinical factors, with modest success.

PRECISION SURVEILLANCE OF BARRETT'S ESOPHAGUS

A similar caveat to that mentioned under population screening also applies to this section: all studies to have assessed preneoplastic (BE) tissues of EA cases have, by definition, been restricted to the BE subpopulation that is currently identified (symptomatology justifies endoscopic investigation). Rapid progressors, less symptomatic, and asymptomatic BE case

populations—which comprise the majority as well as important, high-risk subsets of BE—are typically not identified and thus not studied. As such, evidence from studies of pre-neoplastic BE tissues may not be generalizable to the wider BE population, from which a majority of EA cases derive. It is here that case-control (cross-sectional) studies of EA compared with BE controls may offer additional insights for putative risk prediction markers by studying unselected and complete EA populations[97].

Risk Factors—Risk factors for neoplastic progression in BE include age, sex, and cigarette smoking. Increasing age as a risk factor for neoplastic progression is inferred from cancer registry data which shows EA incidence of 1.0 per 100,000 person years aged 40–49 years, 3.9 for ages 50–59, 9.3 for ages 60–69, 13.7 for ages 70–79, and 13.6 for 80+ years[38] and has empirical support as an independent predictor.[98–103] Male BE subjects have been shown to have 2–3 times higher risk of developing EA compared with female BE subjects[104] which is not attenuated in multivariable models.[98–101,103,105] Cigarette smoking and pack-years have shown fairly consistent moderate associations with EA when compared with BE[100,102,105–107], with a recent meta-analysis finding a 30–50% increased risk of ever-smoking compared with never-smoking [98]. Other lifestyle factors and demographics, such as GERD, excess adiposity, alcohol consumption, and race do not have good evidence for being risk factors for neoplastic progression in BE. GERD has consistently been inversely associated with EA when compared with BE[97,107,108]. In a study that conducted separate analyses of EA by prior diagnosis of BE, GERD was positively associated with the 13% of EA cases that had a prior diagnosis of BE[97], yet inversely associated with the remaining 87% of EA cases that did not have a prior diagnosis of BE, when each were compared with a BE control group. A plausible interpretation is that a majority of individuals diagnosed with EA do not have a recent history of severe GERD exposure[109]. With regards to excess adiposity, overweight at age 20 years (OR=2.6, 95%CI:1.2–5.5) and 10 years prior to questionnaire (OR=1.8, 95%CI:1.1–3.3) were associated with EA compared with BE controls in a hospital-based case-control study from The Netherlands[107]; however, this observation does not have support from a majority of other studies that have compared EA with BE[98,100,102,106]. In addition, abdominal obesity has been similarly null in relation to neoplastic progression in BE populations[102,106]. Studies of alcohol and neoplastic progression in BE have been null[105,106,110] while race has been difficult to study due to the fact that most BE patients are of European ancestry.

Biomarkers

Endoscopic and Histologic Features—Various endoscopic features have been associated with neoplastic progression in BE, including metaplastic segment length with studies showing a 17–19% increased risk per cm after multivariable adjustment[98,111,112]. Moreover, a recent pooled analysis of 10 studies showing annual rates of progression from non-dysplastic BE to high-grade dysplasia or EA of 0.24% for short segment BE (<3 cm) compared with 0.76% for long-segment BE (≥3 cm)[113]. Other endoscopic features associated neoplastic progression in BE include esophageal contractility[114], esophageal ulcer[108,115], and nodularity [115,116]. The evidence for whether hiatal hernia is associated with neoplastic progression in BE is mixed with many studies finding no association [99,108,111,117], although one of the largest case-control studies did report an OR of 1.2 per cm

(95%CI:1.0–1.4)[112]. Esophageal stricture[108] and esophagitis[99,108] do not appear to be risk factors for neoplastic progression in BE.

The primary histologic feature associated with EA risk in BE is dysplasia. Diagnosis of high-grade dysplasia is often clinically treated as EA[43] due to the high-risk of prevalent malignancy or subsequent progression. Low-grade dysplasia has a more contentious history as a marker of neoplastic risk due to low interobserver agreement and the possibility of true regression back to a non-dysplastic state[118]. Larger specimen size[119] and simplified descriptive histologic criteria[120] appear to improve interobserver agreement, while expert confirmation[118] and persistence of low-grade dysplasia[121–123] are associated with higher risks of neoplastic progression. However, cancer risk still varies markedly between studies of low-grade dysplasia populations[98,113,118,124]. In the US, this has resulted in low-grade dysplasia being used as a marker for either clinical intervention or increased surveillance, depending on patient-provider discussions[118].

Molecular Biomarkers—Initial molecular biomarkers to stratify neoplastic risk in BE focused on using histochemistry to distinguish three subtypes of intestinal metaplasia[125–127]. Although subtype III was hypothesized to be a marker of disease progression[128], further studies cast doubt upon the specificity[129,130] and accuracy[131] of this biomarker. Despite this initial disappointment, further histochemical studies have provided more promising results. For example, in a nested case-control study of 29 cancer cases and up to 5 matched controls per case, diffuse/intense *TP53* staining in baseline BE biopsy was associated with an 11-fold increased risk of EA[132]. Prior smaller IHC studies of low-grade dysplastic BE cases had suggested this association[133–135], and subsequent studies and meta-analyses offered corroborating evidence[136,137]. This body of evidence led the British Society of Gastroenterology to recommend considering *TP53* immunohistochemistry as an adjunct diagnostic[41,138].

A recent multiplexed immunofluorescence discovery and validation study of 14 markers implicated in BE progression or carcinogenesis more generally were tested in a multi-institutional case-control study comprised of 79 progressors matched with 287 nonprogressors[139]. A 3-tier (low-, intermediate-, and high-risk), 15-feature classifier based on ten biomarkers (TP53, HER2, K20, COX2, CD68, HIF1a, p16INK4A, AMACR, CD45RO, and nuclear morphology) estimated a hazard ratio of 9.4 (95%CI:4.6–19.2) when comparing high- with low-risk in the validation sample set, providing independent prognostic information. A subsequent external validation study estimated an OR of 4.7 (95%CI:2.5–8.8) when comparing high- and low-risk groups within 58 progressors and 210 matched nonprogressors[140]. A prevalence-adjusted positive predictive value of 23% at 5 years[140] and evidence of costeffectiveness[141] further emphasize the potential clinical value of this test. In a separate study, the authors also found that this risk classifier could detect prevalent high-grade dysplasia/EA as a field effect in BE biopsies without dysplasia, indefinite for dysplasia or low-grade dysplasia[142], with an OR of 46 (95%CI:15–169) when comparing high- and low-risk groups. Therefore, this test may offer diagnostic as well as prognostic information which may be of particular value for BE patients in which intervention is not clearly indicated or desired.

Initial nucleic acid studies used flow cytometry to find that increased aneuploid and tetraploid cell fractions correlated with disease stage[143,144]. A cohort study[12] showed that 13 of 62 patients had increased G2/tetraploid cell fractions in baseline BE biopsies, nine of which subsequently progressed to high-grade dysplasia/EA. A later study of the Seattle Barrett's Esophagus Study cohort[145] reported increased baseline tetraploidy and aneuploidy had five-year EA incidences of 56% and 43%, respectively, although a majority of progressors had high-grade dysplasia at baseline. Many additional studies have been conducted in support of aneuploidy and tetraploidy as biomarkers of neoplastic progression[146], albeit with evidence of publication bias and significant heterogeneity, the latter of which likely stems from variable BE study populations, technologies and assays, and thresholds of exposure.

A recent retrospective case-control study has shown that *TP53* mutations were more common (OR=13.8, 95%CI:3.2–61.0) in baseline BE biopsies of progressors (46%, 11/24) than nonprogressors (5%, 4/73) with significant associations also observed for *ARID1B*, *APC*, and *ERBB2*[147]. Importantly, Stachler and colleagues noted that these mutations are early biomarkers that appear to precede aneuploidy in esophageal adenocarcinogenesis, which is in agreement with their prior cross-sectional study[148] and forms the backbone of the current molecular model. Building on this model, a study using a high-resolution SNP array has provided evidence that somatic copy number alterations of *CDKN2A/B* and *FHIT* were also predictive of neoplastic progression in nondysplastic baseline BE biopsy samples from 16 progressors and 42 nonprogressors[149].

Other prospective studies have assessed multiple nucleic acid biomarkers in relation to neoplastic progression. One study based in the Seattle Barrett's Esophagus Study cohort found that 17p loss of heterozygosity (LOH), tetraploidy, aneuploidy, and 9p LOH estimated a relative risk of 38.7 (95%CI:10.8–138.5) for EA diagnosis at 10-years of follow-up[150], while another derived a 29 chromosomal feature model which was reported to have an AUC of 0.94 for predicting EA risk[151]. Timmer et al[152] conducted a similar nucleic acid analysis study, but restricted to a BE population without dysplasia, finding that *p16* loss, *MYC* gain, and aneusomy—when combined with age and BE circumferential segment length—identified a high-risk group with a hazard ratio of 8.7 (95%CI:2.6–29.8) for neoplastic progression when compared with the low-risk group.

Other biomarkers of neoplastic progression in BE to have recently been assessed include methylation[153,154], mutational load[155,156], and cellular apoptosis susceptibility gene (CAS/CSE1L)[157]. An in-depth discussion of these putative biomarkers is beyond the scope of this article but highlights the expansion of biomarkers being assessed in this field.

Finally, in addition to the prospective and retrospective studies described to have assessed preneoplastic (BE) tissues of EA cases, case-control (cross-sectional) studies comparing EA with BE are also of interest, as described at the outset of this section. Many of these discriminative markers are also in their infancy but include gene expression[158], microRNA expression[159–161], stromal lymphocytic phenotype[162], neutrophil-lymphocyte ratio[163], T-cell phenotype[164,165], microbiome diversity[166,167], and serum glycoproteins[168], amongst others.

Algorithms

There are a limited number of algorithms for estimating risk of neoplastic progression in BE. One of the first was the Barrett's Esophagus Assessment of Risk (BEAR) score by Brown et al in 2018[169]. This model estimated the risk of progressing from nondysplastic BE (N=2,591) to dysplasia (low-/high-grade) or EA (n=133). Using 10-fold cross validation, the model of age, sex, proton-pump inhibitor use, segment length, and history of esophageal candidiasis estimated an AUC of 0.76. Shortly thereafter, Parasa et al[170] published their model—Progression in Barrett's Esophagus (PIB) score using a BE cohort of 2,697 with 133 outcomes. This algorithm estimated risk of progressing from BE without dysplasia, indefinite for dysplasia, or with low-grade dysplasia to high-grade dysplasia or EA using 70% of the study population and included sex, smoking, segment length, and baseline-confirmed low-grade dysplasia resulting in an AUC of 0.76; the remaining 30% of the population demonstrated high model calibration. An external validation study, based in Northern Ireland and comprising 1,198 BE patients with 54 progressors, estimated the AUC of this model as 0.70[171]. This is the only external validation study to-date of any BE neoplastic progression model. A final model to be based on demographic/lifestyle/clinical factors was published by Holmberg et al[99]. This nested case-control study based in the Swedish National Patient Registry compared BE without dysplasia, indefinite for dysplasia, or with low-grade dysplasia (n=1,089) with high-grade dysplasia or EA previously diagnosed with BE (n=279). A final model of age, sex and maximal segment length estimated an AUC of 0.71.

Recently, Hoefnagel et al developed a prediction model that combined molecular markers with demographic and clinical variables[172]. This Dutch multicenter study included 334 nondysplastic BE patients, 32 of which progressed to high-grade dysplasia or EA. A model including age, BE circumferential length, and a clonicity score (based on fluorescence in-situ hybridization probes for 20q13.2, c-MYC [8q24.12], and centromeres of chromosomes 7 and 17) estimated an AUC of 0.88.

Finally, Vaughan et al[109] brought together an array of demographic, lifestyle, clinical and molecular evidence to build an online risk calculator named IC-RISC (https://ic-risc.fredhutch.org). This calculator emphasizes the importance of simplicity of use and communication of risk. The latter is especially important for providers and patients if professional guidelines are to advocate for personalized decisions in individuals with low-grade dysplasia.

Controversies

A central controversy to the primary (screening) and secondary (surveillance) prevention strategies that underlie this review is whether BE is a necessary precursor of EA. Previous studies have reported that not all EA cases have concomitant BE.[173] A study using a rigorous biopsy protocol found that only 62% of EA patients had detectable BE[174], whilst previous EA series have detected a BE prevalence range of 23–100% [175–185]. Sampling error as well as overgrowth and elimination by the expanding tumor are possible reasons for the variation of these estimates and the failure to observe BE in all EA subjects. The study of Chandrasoma and colleagues[183] found the prevalence of intestinal metaplasia decreased with

increasing tumor size and stage, supporting the overgrowth/elimination theory. Meanwhile, Smith et al[186] conducted a comprehensive retrospective and prospective review of clinical records and pathology specimens of 21 EA patients who underwent esophageal mucosal resection, finding evidence for intestinal metaplasia in all cases. Despite this, the controversy continues with a recent study going so far as to suggest that presence/absence of adjacent BE defines two distinct EA phenotypes[187]; a concept previously contemplated[182,188] but, overall, considered unlikely from the limited biological evidence that exists[189–191].

Future Directions

Biomarkers for BE screening and risk triaging that have been discovered using biopsies will need to be validated in whole esophageal sampling specimens as well as total, unselected BE populations. A low-cost, single-timepoint specimen collection that can be used for sequential assessment of BE presence and neoplastic risk would be optimal. Algorithms that combine biomarkers and clinical parameters will need to be optimized and validated in external populations, and risk communication should be a central feature. If BE is determined to be an unnecessary pre-requisite for EA, then population BE screening programs should collect information on other putative biomarkers of neoplastic progression gleaned from prospective and case-control studies.

Future BE biomarker studies could be strengthened in the following ways: state the *a priori* plan for building statistical models; consider interactions, transformations, and splines; refrain from categorizing predictors; use and report betas for risk models; use cross-validation and aim for external validation; use informed and *a priori* stated criteria for desired sensitivity and specificity; and assess model performance by incorporating population disease risk.

Conclusions

Epidemiological studies of demographic, clinical, and molecular biomarkers for BE screening and surveillance provide optimism for accurate risk prediction and precision surveillance. Movement towards larger scale, collaborative studies—particularly focused on unselected BE populations without dysplasia, indefinite for dysplasia, or with low-grade dysplasia—is needed, as is further discovery and validation studies of biomarkers and algorithms. Cost-effective approaches for primary and secondary prevention of EA are within our grasp but it is imperative that we conduct larger studies with a stronger and more clinically-focused statistical framework.

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KEY POINTS

- In the United States, the incidence of esophageal adenocarcinoma increased markedly during recent decades and has now stabilized.
- The causes of the striking male predominance and racial difference in the incidence of esophageal adenocarcinoma remain unknown.
- The main risk factors for esophageal adenocarcinoma and its precursor, Barrett's esophagus, are gastroesophageal reflux disease, abdominal obesity, and cigarette smoking, yet these features occur in only a subset of cases and are largely prevalent in the general population, which weakens their discriminatory ability for screening and surveillance.
- Esophageal adenocarcinoma patients that have a prior diagnosis of Barrett's esophagus (less than 10% of all esophageal adenocarcinoma patients) have better outcomes compared with patients without a prior diagnosis of Barrett's esophagus.
- Biomarker discovery and validation studies in unselected Barrett's esophagus populations using whole esophageal sampling are warranted, and all biomarker studies should strive to be larger and have a strengthened statistical framework.
- Multiple prediction models have been derived for use in selecting high-risk patients for screening and surveillance; however, these models need further validation (temporal and geographic) and optimization before their clinical application can be recommended.

SYNOPSIS

In the United States, the incidence of esophageal adenocarcinoma increased markedly since the 1970s with a recent stabilization. Despite evolving screening and surveillance strategies to diagnose, risk triage, and intervene in Barrett's esophagus patients to prevent esophageal adenocarcinoma, most cases present with advanced disease and poor resultant survival. Epidemiological studies have identified the main risk factors for these conditions, including increasing age, male sex, white race, gastroesophageal reflux disease, abdominal obesity, cigarette smoking, and lack of infection with *Helicobacter pylori*. This review summarizes the current epidemiologic evidence with implications for screening and surveillance in Barrett's esophagus and esophageal adenocarcinoma.

Clinics Care Points

- Screening for Barrett's esophagus needs to go beyond patients reporting current symptoms of gastroesophageal reflux disease to include other established risk factors, such as smoking history and obesity.
- To date, no screening or surveillance algorithm has sufficient discriminatory accuracy or external validation to support clinical use.
- It is important to note that the vast majority of evidence for etiology and neoplastic progression is derived from selected Barrett's esophagus populations.
- Despite potential reverse-causation, case-control studies comparing esophageal adenocarcinoma with Barrett's esophagus may derive additional neoplastic predictors given the ability to characterize all cancer patients with greater statistical power, as opposed to assessing a small subset of esophageal adenocarcinoma cases previously diagnosed with Barrett's esophagus.
- Biomarker studies must strive to use stronger statistical frameworks.
- Larger, collaborative studies—particularly those focused on Barrett's esophagus populations without dysplasia, indefinite for dysplasia, or with low-grade dysplasia—are needed to enhance biomarker discovery and validation efforts to increase the accuracy of predictive algorithms.

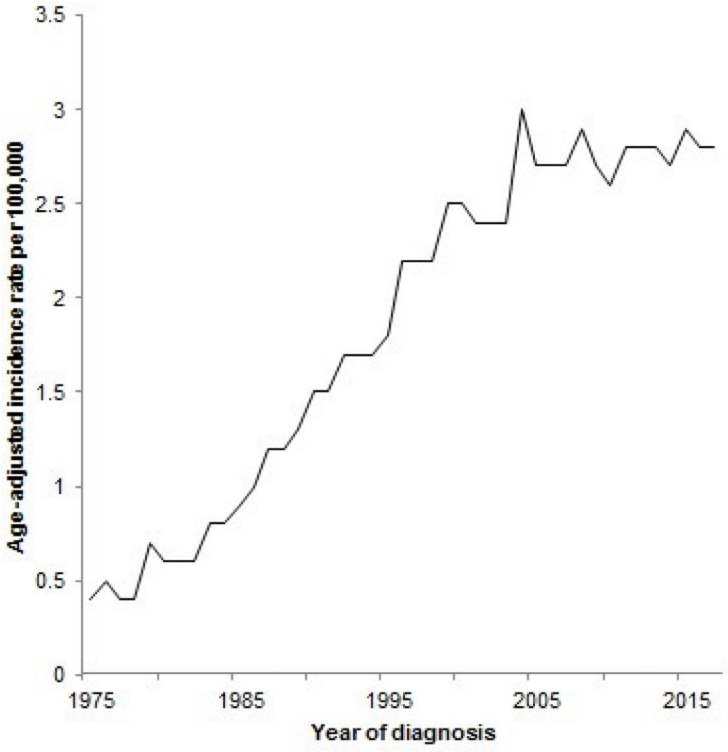

Figure 1.

Age-adjusted incidence rates of esophageal adenocarcinoma in the United States, 1975–2017. Rates are per 100,000 person-years. Data source: Surveillance, Epidemiology, and End Results (SEER) 9 Registries.

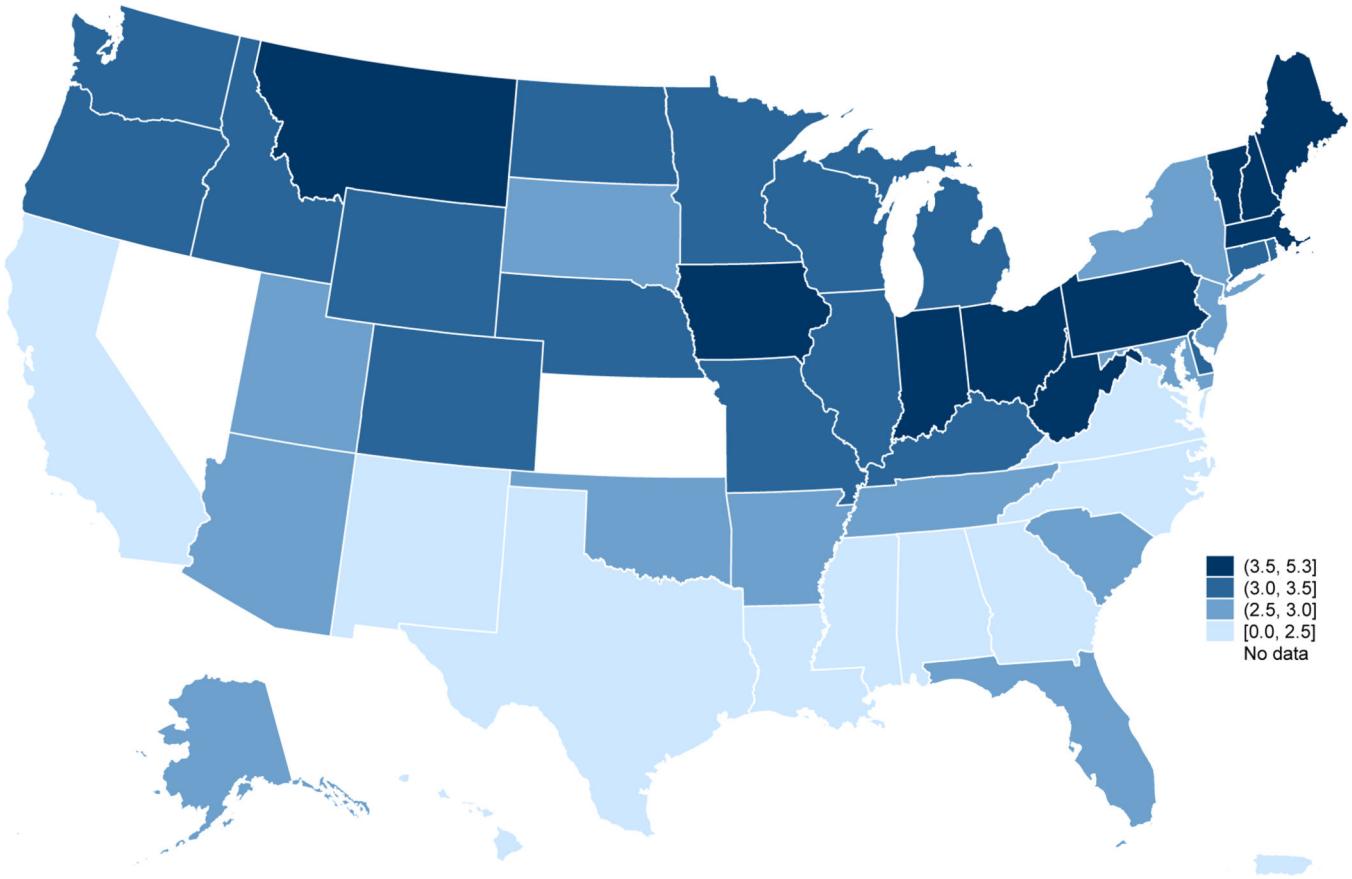

Figure 2 .

Age-adjusted incidence rates of esophageal adenocarcinoma in the United States by state, 2012–2016. Rates are per 100,000 person-years. Darker blue hues denote higher incidence rate categories of esophageal adenocarcinoma. There were no data for the time period assessed for the states filled white. Alaska, Hawaii, and Puerto Rico have been repositioned for maximal resolution. (Data from North American Association of Central Cancer Registries (NAACCR) Incidence Data - CiNA Analytic File, 1995–2016.

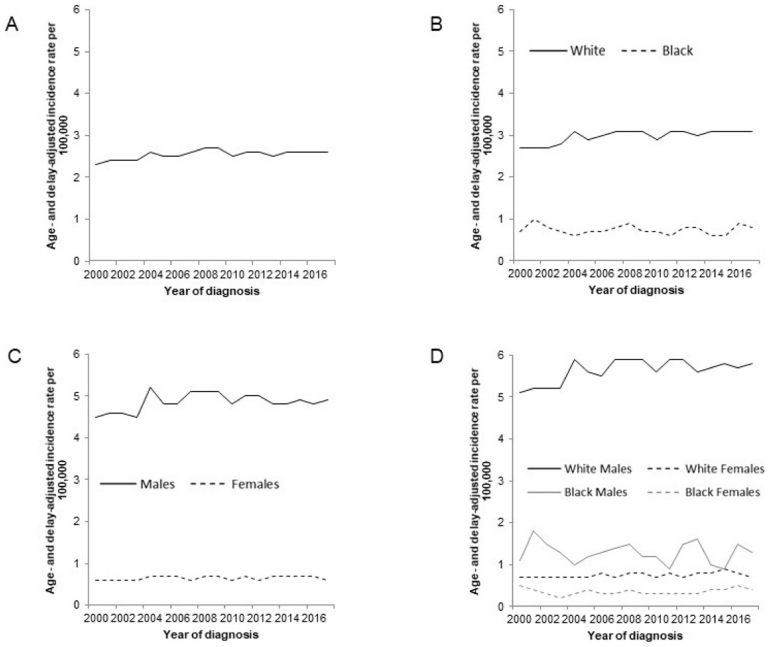

Figure 3.

Age- and delay-adjusted incidence rates of esophageal adenocarcinoma in the United States, 2000–2017. Rates are per 100,000 person-years. Age- and delay-adjusted incidence rates of esophageal adenocarcinoma are shown for: (A) All; (B) by race (White and Black); (C) by sex (Males and Females); and (D) by sex and race (White Males, Black Males, White Females and Black Females). (Data from Surveillance, Epidemiology, and End Results (SEER) 18 Registries.)

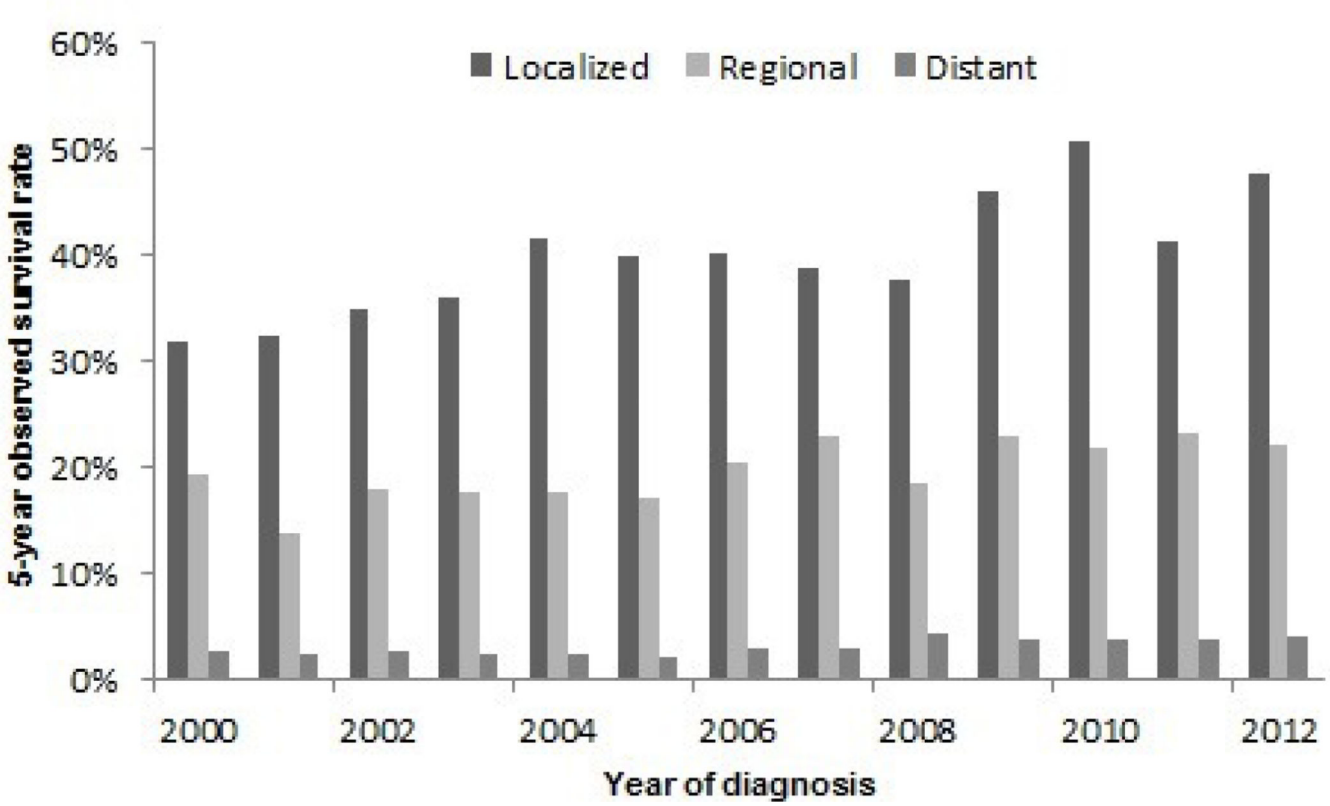

Figure 4.

Five-year survival rates for esophageal adenocarcinoma in the United States, 2000–2012, by stage at diagnosis (localized, regional and distant stage). (Data from Surveillance, Epidemiology, and End Results (SEER) 18 Registries.)

Table 1.

Barrett's esophagus screening guidelines for select gastroenterological societies

Society	Year	Screening Population
American College of Gastroenterology	2016	Men >5 years GERD, or with >weekly symptoms + ≥2 risk factors: >50 years, central obesity (waist circumference >102cm or WR >0.9), Caucasian, smoking, first-degree relative w/ BE or EA
British Society of Gastroenterology	2014	GERD with ≥3 risk factors: >50 years, Caucasian, male, obesity +/− (+) family history
American Society for Gastrointestinal Endoscopy	2019	Individuals with a family history of EA or BE (high risk) OR GERD with ≥ 1 risk factors (moderate risk): >50 years, male gender, Caucasian, smoking, obesity
American Gastroenterological Association	2011	Multiple risk factors: >50 years, Caucasian, male, chronic GERD, hiatal hernia, obesity