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Characterization of Prevalent, Post-Endoscopy, and Incident Esophageal Cancer in the United States: A Large Retrospective Cohort Study

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Abstract

Background and aims: Efforts to assess and improve the effectiveness of Barrett's esophagus (BE) screening and surveillance are ongoing in the United States. Currently, there are limited population-based data in the United States to guide these efforts.

Methods: We performed a retrospective cohort study using data from large commercial and Medicare Advantage health plans in the United States from 2004 – 2019. We identified individuals with BE and analyzed the proportion who developed EAC. EACs were classified as prevalent EAC (diagnosed within 30 days of index endoscopy), post-endoscopy esophageal adenocarcinoma (PEEC, diagnosed 30 – 365 days after index endoscopy), and incident EAC (diagnosed 365 days or more after index endoscopy). Using this cohort, we performed a nested case-control study to identify factors associated with prevalent EAC at BE diagnosis and study healthcare utilization prior to BE diagnosis.

Results: We identified 50,817 individuals with incident BE. Of the 366 who developed EAC, 67.2%, 13.7%, and 19.1% were diagnosed with prevalent EAC, PEEC, and incident EAC respectively. Factors positively associated with prevalent EAC versus BE without prevalent EAC included male sex, dysphagia, weight loss, and Charlson-Deyo comorbidity score. In those with prevalent EAC, most patients with dysphagia or weight loss had their symptoms first recorded within three months of EAC diagnosis. Healthcare utilization rates were similar between those with and without prevalent EAC.

Conclusions: Two-thirds of EACs among individuals with BE are diagnosed at the time of BE diagnosis. Additionally, PEEC accounts for 14% of these EACs. These results may guide future research studies that investigate novel BE diagnostic strategies that reduce the morbidity and mortality of EAC.

Keywords

Barrett's esophagus; esophageal cancer; screening; surveillance; epidemiology

Introduction

Esophageal adenocarcinoma (EAC) has a sobering five-year survival rate of 16%,[1] and its incidence has been steadily rising in the United States since the 1970s.[2, 3] Because Barrett's esophagus (BE) is the only known premalignant condition for EAC,[4, 5] its identification may attenuate EAC morbidity and mortality. As chronic gastroesophageal reflux disease (GERD) is a risk factor for BE, evaluating individuals with symptomatic GERD is the primary focus of most BE screening programs. Consequently, current guidelines suggest endoscopic evaluation only for individuals with chronic GERD and a combination of secondary risk

factors such as White race, male sex, age over 50, central obesity, tobacco smoking history, and family history of BE or EAC.[5, 6] The effectiveness of such BE screening programs is uncertain as over 90% of individuals with EAC present without a known history of BE.[7-9] Additionally, the cost effectiveness of BE surveillance programs is low because the majority of individuals with BE do not develop EAC.[9-12]

New strategies that could improve the effectiveness and efficiency of BE evaluation are being developed. These include less invasive diagnostic modalities and wide-area transepithelial sampling.[13, 14] Unfortunately in the United States, the only data to guide the deployment of standard and novel screening and surveillance programs are derived from population-based cohort studies from countries in Northern Europe[9-11] and institutional cohort studies from tertiary-care centers.[7, 12] The applicability of the Northern European cohort studies for the development of new BE evaluation programs in the United States is uncertain because the countries where they were performed have substantially different demographic characteristics and health economies from the United States. Additionally, these studies relied on pathology registry data, so they do not include patient-level characteristics that may guide targeted BE screening recommendations. Furthermore, data from the tertiary-care center studies may not reflect care patterns in community practices across the United States.

The availability of administrative health claims data for clinical research provides an opportunity to fill these knowledge gaps by studying risk factors, healthcare utilization, and EAC outcomes using longitudinal data of individuals with BE in the United States. Using these data to understanding the proportion of individuals with BE in the United States who present with EAC at BE diagnosis (prevalent EAC), with EAC soon after BE diagnosis (post-endoscopy esophageal adenocarcinoma, PEEC), and with EAC several years after BE diagnosis (incident EAC) may serve as a guide for resource allocation by determining the relative priority of population-based efforts for BE screening, upper endoscopy quality improvement, or BE surveillance. Additionally, because the majority of individuals with EAC are not known to have BE at the time of diagnosis, identifying novel risk factors for prevalent EAC that supplement guideline-supported BE risk factors may provide high-yield opportunities for improving EAC detection and mortality by targeting new populations for BE screening from the general population.[15]

To accomplish these objectives, we used longitudinal patient-level data from the United States to conduct a retrospective cohort study of individuals diagnosed with BE. First, we describe the development of EAC over time among individuals with newly diagnosed BE. Second, we performed a nested case-control study to determine patient-level factors associated with EAC presenting at the time of BE diagnosis. Finally, we compare patterns of healthcare utilization between individuals who present with EAC at BE versus all others with BE to determine whether there are opportunities to identify EAC at earlier stages.

Methods

Study design and data source

This retrospective cohort study was performed using data from Optum's de-identified Clinformatics® Data Mart Database (Optum). Optum is derived from patient-level administrative health claims for members of large commercial health plans or Medicare Advantage health plans in the United States from April 1, 2000 – June 30, 2019. This study used data from January 1, 2004 – June 30, 2019 to identify EAC among a cohort of individuals with incident BE. We chose 2004 as the study start year because it was the first year Optum contained complete inpatient data. Additionally, data from April 1, 2000 – December 31, 2003 were used to assess exclusion criteria and covariates, but they were not used for BE or EAC assessment. Medical claims were identified by International Classification of Diseases (ICD)-9 codes until they were retired in the United States on October 1, 2015, and ICD-10 codes were used thereafter. Procedures were identified using Current Procedural Terminology-4 (CPT4) codes, and medications were identified using National Drug Codes. Optum has been used to study epidemiology of acute and chronic conditions.[16, 17]

Using these data, we identified a cohort of individuals in the general population who were age 18 or older and had at least 3.5 years of continuous enrollment in the database. For those with gaps in enrollment, only the first enrollment period was considered to avoid misclassification of exposures and outcomes that occurred while the individual was not enrolled. Individuals exited the general population cohort at the earlier of the last day of enrollment, the day of BE diagnosis, or the day of EAC diagnosis (BE and EAC diagnosis criteria described below).

BE cohort

We stipulated strict criteria to identify individuals from the general population cohort who were likely to have incident BE based on ICD codes (codes in Supplemental table 1). These were:

1. Criteria to reduce recording of prevalent BE among those newly enrolled in the database:
    a. At least three years of enrollment in Optum prior to the first recorded BE diagnosis[18]
    b. At least 180 days from the first medical claim in the database prior to the first recorded BE diagnosis
2. Criteria to exclude retroactive recording of prevalent BE:
    a. Claim for an upper endoscopy up to 14 days before the first BE diagnosis (codes in Supplemental table 2)
    b. No claims for esophageal cancer prior to the first BE diagnosis

3. Criterion to confirm tissue-based pathologic diagnosis of BE and to identify underlying BE among individuals with prevalent EAC: A ICD diagnosis code for BE billed by a pathologist within 14 days of the first BE diagnosis

Similar ICD code and endoscopy-based criteria have been demonstrated to have positive predictive value of 93%.[19] The date of the index endoscopy associated with the first BE diagnosis was considered the BE diagnosis date. Individuals with a diagnosis for BE that did not meet all criteria were censored from the general population cohort at the date of the first BE claim. ICD codes in the United States did not specify level of dysplasia until October 1, 2015, and preliminary analyses demonstrated low utilization of these codes. For these reasons, we were not able to stratify results by level of BE dysplasia at index endoscopy.

Identification and classification of EAC

Individuals in the BE cohort were considered to have developed EAC if they met the following criteria on or after entry into the BE cohort:

1. At least one claim with an ICD diagnosis code consistent with esophageal cancer (codes in Supplemental table 3)
2. Claim for an upper endoscopy up to 14 days before the first esophageal cancer diagnosis
3. A ICD diagnosis code for esophageal cancer billed by a pathologist within 14 days of the first esophageal cancer diagnosis

The date of the upper endoscopy associated with the first EAC diagnosis was considered the EAC diagnosis date. Individuals with a diagnosis of EAC that did not meet all three criteria were censored from the BE cohort and the general population cohort at the date of first EAC claim. Because ICD codes do not identify EAC by histology, all diagnoses of EAC in patients with BE were considered to be EAC rather than esophageal squamous cell cancer.[20] Sensitivity analyses were performed to assess the robustness of this assumption.

EAC classification.—EACs diagnosed in the interval from the day of BE diagnosis to day 29 after BE diagnosis were considered prevalent EAC. The 30-day interval after BE diagnosis was incorporated into the definition to allow for additional procedures required to appropriately stage neoplasia identified at the time of BE diagnosis. EACs diagnosed from 30 – 365 days from the index endoscopy that diagnosed BE were considered PEEC (i.e. EACs that may have been prevalent and missed at the time of BE diagnosis).[21] EACs diagnosed more than 365 days after BE diagnosis were considered incident (i.e. EACs that were likely not present at the time of BE diagnosis). Figure 1 illustrates the EAC classification scheme and study design. Sensitivity analyses were performed to assess the impact of changes to the EAC classification scheme.

Statistical analysis: Retrospective cohort study of EAC after BE diagnosis

The development of EAC among individuals with BE was analyzed using Kaplan-Meier survival analysis. The proportions of patients diagnosed with prevalent EAC, PEEC, and incident EAC were determined from the total group of patients who were diagnosed with EAC on or after the day of BE diagnosis. Incidence rates (IR) were calculated by dividing

the number of individuals who developed an EAC outcome by the total number of person-years of individuals in the cohort who could have experienced the EAC outcome (detailed definitions in Supplemental methods). The 95% confidence intervals (CI) of the IRs were calculated assuming that EAC counts were Poisson-distributed.

Statistical analysis: Nested case-control study of patient factors associated with prevalent EAC among individuals with BE

All individuals diagnosed with BE from the retrospective cohort study were included in the nested case-control study. Cases were individuals who were diagnosed with prevalent EAC at BE diagnosis. Because the goal of this analysis was to identify risk factors associated with simultaneous diagnosis of BE and EAC, controls were all other individuals without prevalent EAC (i.e. individuals with PEEC, incident EAC, and no EAC). The impact of reclassifying PEEC as prevalent EAC was assessed in a sensitivity analysis. Covariates considered for adjustment are described in Supplemental methods. Covariates were initially assessed for association with prevalent EAC by univariable logistic regression. Covariates with $p < 0.15$ by Wald test were iteratively added to a multivariable logistic regression model using forward selection. Only covariates with $p < 0.05$ by Wald test were retained in the multivariable model.

Utilization trends among individuals with BE.—Because the majority of EACs are diagnosed at the time of BE diagnosis, we compared patterns of healthcare utilization between individuals who present with prevalent EAC versus all others with BE to determine whether there are opportunities to identify EAC at earlier stages (Supplemental methods).

Sensitivity analyses

We performed several sensitivity analyses to assess the robustness of the study assumptions related to BE definition, EAC definition, and EAC classification (Supplemental methods).

Results

Cohort description

From 2004 – 2019, 19,713,635 individuals older than age 18 met inclusion criteria for the general population cohort by having at least 3.5 years of continuous follow-up. The median follow-up was 6.2 years (IQR 4.5 – 9.6 years). Of these, 50,817 ultimately met inclusion criteria for the incident BE cohort (Supplemental figure 1). The IR of BE among the general population was 33.7 per 100,000 person-years (95% CI 33.4 – 34.0 per 100,000 person-years). The median follow-up of patients in the BE cohort was 2.3 years (IQR 1.0 – 4.6 years) after BE diagnosis.

EAC diagnoses

Of the 50,817 individuals with BE, 366 were diagnosed with EAC. Of these individuals with EAC, 246 (67.2%) were diagnosed with prevalent EAC at BE diagnosis. Among the general population, the IR of a diagnosis of EAC at the time of BE was 0.2 per 100,000 person-years (95% CI 0.1 – 0.2). PEEC was diagnosed in 50 of the 366 individuals diagnosed with EAC (13.7%). Among individuals with BE, the IR of PEEC was 31.5 per

100,000 person-years (95% CI 23.4 – 41.6). The median number of days from BE diagnosis to PEEC was 99 (IQR 56 – 186). Incident EAC was diagnosed in 70 of the individuals diagnosed with EAC (19.1%). Among individuals with BE, the IR of incident EAC was 44.1 per 100,000 person-years (95% CI 34.4 – 55.8). The median number of days from BE diagnosis to incident EAC was 1164.5 (IQR 734 – 1905). A Kaplan-Meier curve illustrating the development of EAC over time among individuals with BE is presented in Figure 2. Demographic, comorbidity, symptom, and utilization characteristics of individuals in the BE cohort and the EAC categories are presented in Table 1. In general, individuals with EAC were older than those without EAC and had higher Charlson-Deyo comorbidity scores.

Factors associated with prevalent EAC at diagnosis among individuals with BE

Results of the univariable logistic regression models are presented in Supplemental table 6. In the final multivariable logistic regression model, dysphagia, weight loss, and Charlson-Deyo score were positively associated with prevalent EAC versus BE without prevalent EAC. Female sex, GERD, and number of upper endoscopies before BE diagnosis were negatively associated with prevalent EAC versus BE without prevalent EAC (Table 2).

Utilization trends among individuals with BE

To determine whether there are opportunities to identify EAC at earlier stages, we assessed the duration of symptoms of GERD, dysphagia, and weight loss prior to BE diagnosis in those who were eventually diagnosed with prevalent EAC versus all others with BE (Figure 3). The prevalence of diagnosed GERD was initially similar between those with prevalent EAC and all others at approximately 15%. By 3 months before BE diagnosis, the prevalence increased to 35% in those with prevalent EAC compared to 47% in all others. The prevalence of dysphagia was similar between those with prevalent EAC and all others until three months prior to BE diagnosis. After this time, the prevalence increased from 10 to 47% in those with prevalent EAC compared to 10 to 19% in all others. Similarly, the prevalence of weight loss was similar until three months prior to BE diagnosis, after which the prevalence increased from 11 to 22% in those with prevalent EAC compared to 7 to 10% in all others.

To assess whether the late recording of dysphagia and weight loss among individuals with prevalent EAC was due to low utilization of healthcare services, we then compared patterns of health care utilization between those with prevalent EAC and all others (Figure 4). The level of utilization was similar between individuals with prevalent EAC and all others for any type of office visit, primary care office visits, and gastroenterology office visits. Individuals with prevalent EAC had slightly lower emergency room utilization (−0.8%, 95% CI −1.5 – −0.2%) and slightly slower uptake of any office visit utilization (−0.2% per month, 95% CI −0.4 – −0.01%, Supplemental table 7). While these were statistically significant results, the clinical difference in utilization was less than 1%.

Sensitivity analyses

Overall, the sensitivity analyses were consistent with the main analysis (details in Supplemental results).

Discussion

In this cohort study of individuals in the United States, we identified over 50,000 individuals with newly diagnosed BE and determined that 366 developed EAC. Among individuals with BE who were subsequently diagnosed with EAC, 67.2% were diagnosed with prevalent EAC at the time of BE diagnosis, 13.7% were diagnosed with PEEC within one year of BE diagnosis, and 19.1% were diagnosed with incident EAC at least one year after BE diagnosis. These proportions are consistent with prior population-based cohort and meta-analytic studies.[7, 9, 22]

Because prevalent EAC accounts for two-thirds of EAC among individuals with BE, identifying at-risk individuals for screening is paramount for reducing EAC morbidity and mortality. To study this, we performed a nested case-control study to identify patient factors associated with prevalent EAC at BE diagnosis versus BE without prevalent EAC. Unfortunately, the only patient symptoms associated with prevalent EAC were dysphagia and weight loss, which are late indicators of EAC.[23, 24] While we cannot determine when these symptoms were first noticed by the patient, this study indicates that the majority of these symptoms did not come to the attention of medical providers until the three months prior to prevalent EAC diagnosis. However, this study also demonstrates that individuals with prevalent EAC have similar levels of healthcare utilization in the three years prior to diagnosis compared to individuals with BE without prevalent EAC. This provides hope that BE prediction tools could be effective in identifying individuals at risk for prevalent EAC before the development of advanced stage cancer. A recent study that examined several BE prediction tools that incorporate GERD history, symptom questionnaires, and anthropometrics demonstrated that these tools have good discrimination for BE and BE-related neoplasia among patients referred for outpatient upper endoscopy.[25] Application of these tools to the general population may help identify individuals at risk for prevalent EAC, but they will need external validation among populations with low GERD symptom prevalence to assess their discrimination, calibration, and thresholds that trigger screening. Additionally, these tools may help advance the implementation of less invasive and inexpensive screening tools.

Additionally, this study adds to the growing body of literature on the estimates of PEEC (EAC diagnosed within one year of BE diagnosis). We demonstrated that 13.7% of EACs among individuals with BE were PEEC. As these likely represent EACs that were missed at index endoscopy,[21] the delay in EAC diagnosis may lead to progression of EAC to advanced stages, thereby worsening morbidity and mortality. Efforts to improve endoscopic identification of BE, dysplasia, and EAC through advanced optical modalities, longer inspection times, adherence to the Seattle biopsy protocol, and utilization of standard classification systems could appreciably improve population-based EAC outcomes.

This study has several strengths. First, it uses longitudinal, patient-level administrative health data to estimate the development of EAC among individuals with BE in the United States. Second, it measures EAC diagnoses and patient factors for prevalent EAC in a cohort of over 50,000 individuals with newly diagnosed BE. This large sample size, allowed us to assess the association of several patient factors that could be potentially associated with

prevalent EAC with adequate power and with low risk of overfitting. Third, the main study results were upheld in several sensitivity analyses, demonstrating that the main conclusions are robust to variations in the study assumptions.

Like all observational studies, there are potential limitations to consider when interpreting these results. First, because ICD codes do not distinguish EAC from esophageal squamous cell cancer, we used codes for esophageal cancer in general as the main study outcome. While it is possible that some of the estimates in this study are biased by misclassification of the outcome, a sensitivity analysis including only esophageal cancers in the lower third of the esophagus, which are more likely to be EAC than esophageal squamous cell carcinoma, was consistent with the main study conclusions. Second, because ICD codes did not account for level of BE dysplasia until October 1, 2015, we were unable to incorporate high-grade dysplasia in our EAC definitions or stratify EAC outcomes by level of dysplasia at index endoscopy. While better information on BE dysplasia at the time of BE diagnosis may help inform risk factors for the development of PEEC and incident EAC, it would not alter conclusions regarding patient factors for prevalent EAC as BE dysplasia level is unknown prior to index upper endoscopy. Improved recording of level of dysplasia will also allow for future studies that assess progression of non-dysplastic BE and low-grade dysplasia. Third, we were not able to assess stage of EAC at diagnosis, which could provide important insights about the effectiveness of BE screening and surveillance. Fourth, we were not able to assess physician-level or endoscopic factors associated with PEEC. Future studies of these factors are paramount for improved understanding of the natural history of PEEC and for the development of endoscopic quality standards to reduce the rate of missed EAC. Fifth, due to relatively short follow-up after BE diagnosis, we could not adequately study risk factors for incident EAC; this should be the subject of future studies.

In conclusion, this large, retrospective cohort study from the United States demonstrates that among individuals with BE who are diagnosed with EAC, 67.2% are diagnosed with prevalent EAC, 13.7% are diagnosed with PEEC, and 19.1% are diagnosed with incident EAC. Furthermore, it identifies that alarm symptoms of dysphagia and weight loss among individuals with prevalent EAC do not come to medical attention until just prior to diagnosis. These results may help guide future efforts to develop innovative BE screening and surveillance programs that reduce the morbidity and mortality of EAC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BE	Barrett's esophagus
CI	Confidence interval
CPT4	Current Procedural Terminology-4
GERD	Gastroesophageal reflux disease
H2RA	Histamine$_2$ receptor antagonist
ICD	International Classification of Diseases
IR	Incidence rate
IQR	Interquartile range
EAC	Esophageal adenocarcinoma
PPI	Proton pump inhibitor
PEEC	Post-endoscopy esophageal adenocarcinoma

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WHAT YOU NEED TO KNOW

Background:

Ninety percent of individuals diagnosed with esophageal adenocarcinoma (EAC) do not have known Barrett's esophagus (BE) at the time of diagnosis. Additionally, characteristics of individuals who are diagnosed with EAC at the time of BE diagnosis (prevalent EAC) are poorly understood.

Findings:

In this study, 67.2% of EACs were prevalent EAC, 13.7% were diagnosed with within one year of BE diagnosis, and 19.1% were diagnosed more than one year after BE diagnosis. Late EAC symptoms of dysphagia and weight loss were associated with prevalent EAC versus BE without prevalent EAC, but most of these were not identified until 0 – 3 months prior to EAC diagnosis.

Implications for patient care:

These results may guide the implementation of new BE screening strategies and the development of interventions to reduce rates of PEEC through improved detection of BE-related neoplasia.

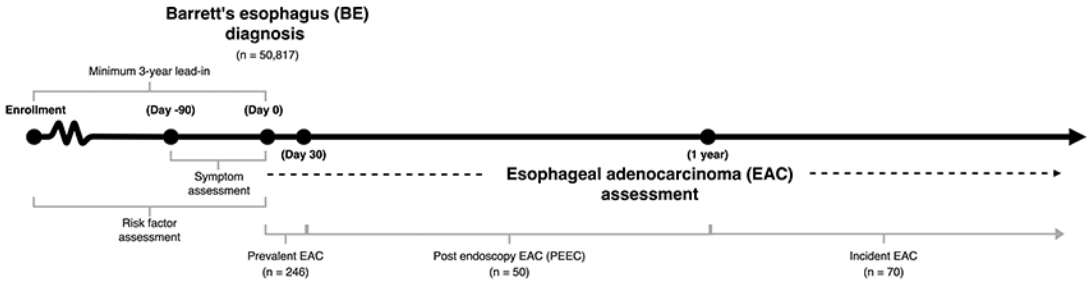

Figure 1. Study design and EAC classification

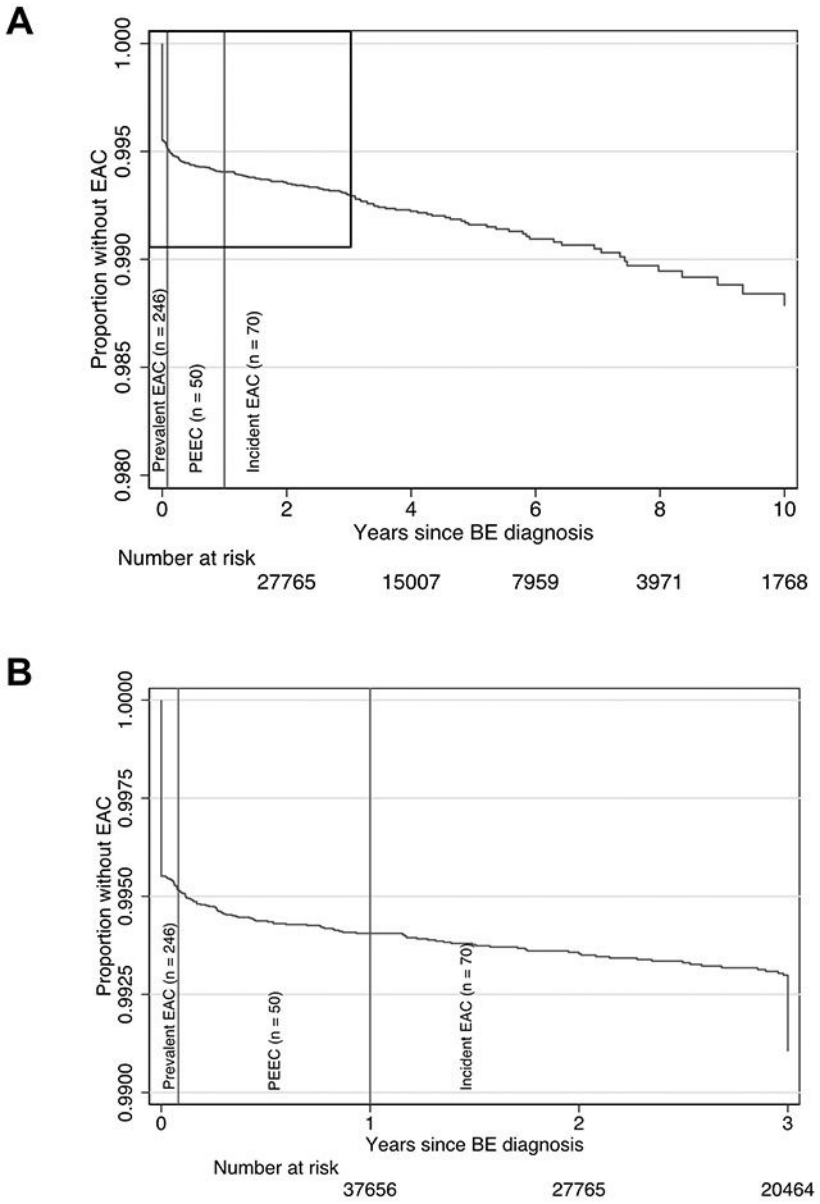

Figure 2. Kaplan-Meier survival curve of EAC among 50,817 individuals with BE

Panel A: 10 years of follow-up

Panel B: 3 years of follow-up (zoomed graph illustrating box in panel A)

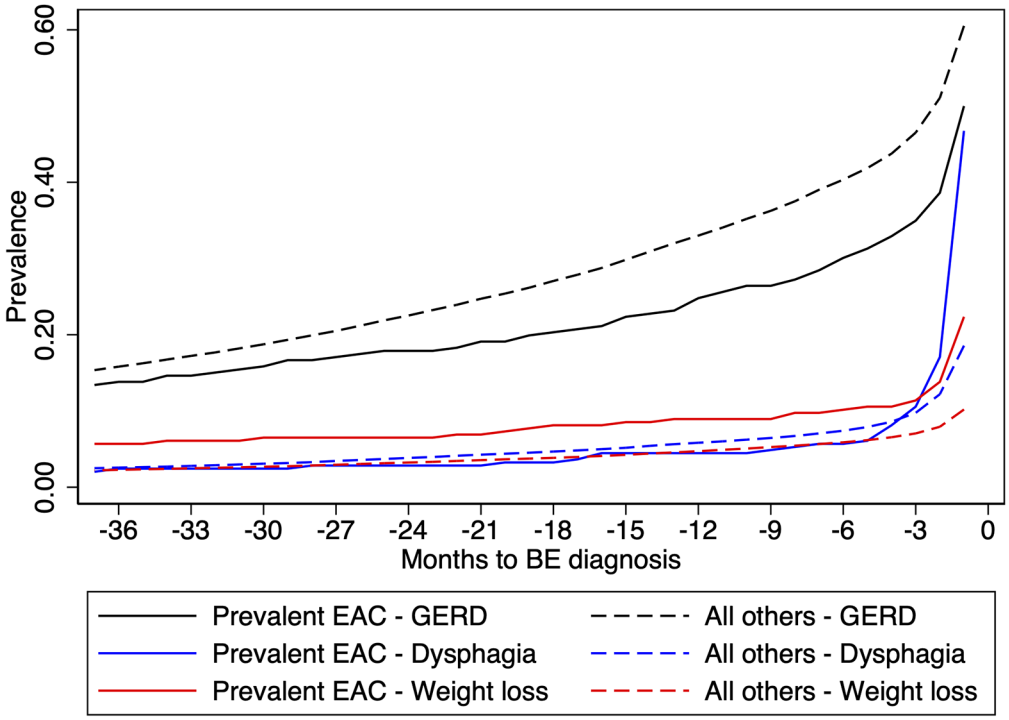

Figure 3. Prevalence of symptoms associated with prevalent EAC prior to BE diagnosis

Prevalence of at least one ICD claim for GERD (black), dysphagia (blue), or weight loss (red) by month prior to BE diagnosis. Trends stratified by prevalent EAC (n = 246, solid lines) versus all other individuals with BE (n = 50,571, dashed lines).

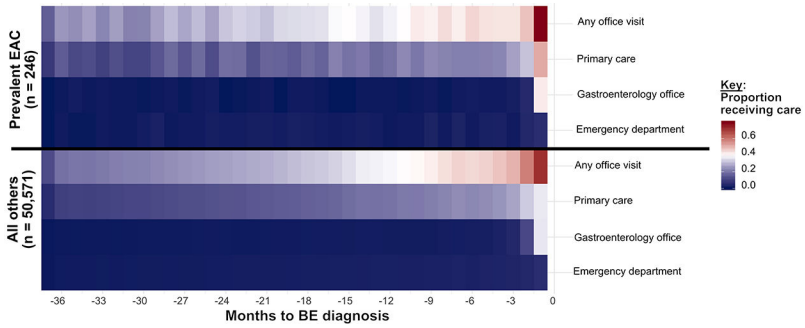

Figure 4. Healthcare utilization over time prior to BE diagnosis

Proportion of individuals with at least one healthcare visit in four categories, stratified by prevalent EAC versus all others with BE. Overall, utilization patterns were similar between groups (see Supplemental table 7 for quantification).

Table 1.

Demographic, comorbidity, symptom, and utilization characteristics

	BE cohort (n = 50,817)	Prevalent EAC (n = 246)	PEEC (n = 50)	Incident EAC (n = 70)	No EAC (n = 50,451)
Female (%)	42.3	11.4	26.0	18.6	42.5
Age at BE diagnosis (years)	62.9	70.2	70.0	69.2	62.8
Race/ethnicity (%)					
Asian	2.6	0.4	2.0	0.0	2.6
Black	5.5	4.9	4.0	8.6	5.5
Hispanic	7.7	6.1	2.0	5.7	7.7
Unknown	8.2	5.7	10.0	4.3	8.2
White	76.1	82.9	82.0	81.4	76.0
Risk factors (%)					
GERD	72.7	59.3	74.0	70.0	72.8
Helicobacter pylori	5.6	4.1	0.0	0.0	5.6
Obesity	16.3	16.7	14.0	12.9	16.3
Alcohol abuse	4.4	8.1	8.0	5.7	4.3
Tobacco use	26.3	39.4	34.0	32.9	26.3
Symptoms (%)					
Abdominal pain	33.1	24.4	32.0	27.1	33.1
Dysphagia	18.5	52.8	28.0	8.6	18.3
Iron deficiency anemia	16.0	23.6	26.0	22.9	16.0
Nausea/vomiting	12.4	8.9	14.0	8.6	12.4
Rectal bleeding	13.6	13.8	26.0	24.3	13.6
Weight loss	6.3	17.9	16.0	2.9	6.2
Utilization					
Charlson-Deyo score	3.9	6.9	5.1	4.8	3.9
Months of H2RA use	0.7	1.5	1.1	1.2	0.7
Months of PPI use	8.4	7.5	7.3	7.4	8.4
Months of statin use	11.4	18.1	13.8	10.6	11.4
Mean gastroenterology office visits before BE diagnosis	1.5	1.2	1.1	0.7	1.5
Mean upper endoscopies before BE diagnosis	0.3	0.2	0.2	0.1	0.3

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Table 2.

Patient factors associated with prevalent EAC (n = 246) versus no prevalent EAC (n = 50,571) at BE diagnosis by multivariable logistic regression

	OR	95% CI
Dysphagia	4.99	(3.86 - 6.45)
Weight loss	1.84	(1.31 - 2.60)
Charlson-Deyo score	1.19	(1.16 - 1.23)
GERD	0.60	(0.46 - 0.78)
Number of upper endoscopies before BE diagnosis	0.50	(0.38 - 0.67)
Female	0.18	(0.12 - 0.27)