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Risk of Upper Gastrointestinal Cancers in Patients with Gastroesophageal Reflux Disease Following a Negative Screening Endoscopy

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Abstract

Background & Aims—Practice guidelines recommend a 1-time screening endoscopy for patients with gastroesophageal reflux disease (GERD) who are at high risk for Barrett's esophagus or malignancy. However, little is known about the risk of cancer in patients with negative findings from screening endoscopies.

Methods—We conducted a retrospective cohort study using data from 121 Veterans Health Administration facilities nationwide to determine the incidence rate of esophageal adenocarcinoma (EA) separately, as well as any upper gastrointestinal cancers, in patients with an initial negative screening endoscopy (EGD). We included veteran patients with GERD diagnosed

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between 2004 and 2009 who had a negative screening EGD within 1 year of diagnosis. We estimated the incidence rate of EA, and any upper gastrointestinal cancer, in patients with GERD who had a negative screening EGD. We examined differences in demographic, clinical, and facility factors among patients with and without cancer.

Results—We identified 68,610 patients with GERD and a negative screening EGD (mean age, 55.5 years; 90% men; 67.5% white). During a mean follow up of 3.2 years, 10 patients developed EA and 29 developed any upper gastrointestinal malignancies, including EA. The incidence of subsequent EA in this group was 4.6/100,000 patient-years of follow up, whereas the incidence of any upper gastrointestinal cancers was 13.2/100,000 patient-years of follow up. Patients with a subsequent cancer were significantly older and had higher comorbidity scores than patients without cancer. Other clinical and facility factors did not differ significantly between these 2 groups.

Conclusion—The risk of cancer is low, over a mean 3-year period, for patients with GERD who had a negative screening endoscopy. These findings justify recommendations for a 1-time screening endoscopy for patients with GERD.

Keywords

GERD; Endoscopy; Cancer; Incidence

Background

Gastroesophageal reflux disease (GERD) symptoms, including heartburn and regurgitation, are reported by 14-20% of the general population ¹. GERD is a risk factor for the development of Barrett's esophagus (BE) as well as esophageal adenocarcinoma (EA) ^{2, 3}. Esophagogastroduodenoscopy (EGD) is frequently performed in patients with GERD symptoms to exclude conditions that can have similar manifestations, such as esophageal or gastric cancer, or peptic ulcer disease especially among patients who present with 'red flags' or 'alarm symptoms' such as dysphagia, weight loss or anemia. The overall incidence of upper gastrointestinal cancers in the US in 2008 was estimated to be 11.9 cases per 100,000 ⁴. The American Society for Gastrointestinal Endoscopy recommends EGD for patients who have symptoms suggesting complicated GERD or alarm symptoms ⁵. These guidelines also recommend considering endoscopy for patients at a high risk for Barrett's esophagus (BE) (symptoms for >5 years, white race, male sex, age >50 or family history of BE or esophageal cancer) ⁵.

The yield of EGD in identifying precancerous lesions (BE, gastric dysplasia) is variable (6-12%), and that of cancer is low (0.3%) in this group of patients irrespective of the type of symptoms $^{2, 5-7}$. This group of symptomatic patients is likely to continue with chronic or recurrent symptoms. Therefore, their likelihood of getting considered for repeat EGD for recurring concerns about cancers is also high. In a study of a random sample from Medicare claims, 26.8% of patients who underwent an EGD for reflux disease had repeated exams within 3 years ⁸. A study that followed 515 GERD patients and 169 BE patients for an average of 3.4 years has estimated that up to 6% of GERD and BE patients received more than 1 EGD, and among the GERD patients, they underwent a mean of $3.4 +/- 1.8 \text{ EGDs}^9$.

However, among patients without BE the yield and the determinants of subsequent cancers that are diagnosed after the negative EGD are unknown.

Little is known about the outcomes of patients who undergo a negative screening EGD, including their risk of subsequent cancer. Studies were performed to identify the clinical and demographic factors associated with development of interval colorectal cancer among patients with a prior negative screening colonoscopy. The main reported risk factors were older patient age ^{10, 11}, and quality of the baseline colonoscopy as manifested by the adenoma detection rate of the endoscopist ¹¹. Other patient factors such as gender and family history of colorectal cancer, or endoscopist factors such as cecal intubation rate, age, sex and specialty did not appear to affect the risk of interval neoplasia. Similar to colonoscopy ^{10, 11}, defining the incidence of cancers subsequent to EGD among GERD patients may help with understanding and improving quality of EGD, shed light on disease pathogenesis and risk factors, and inform the need for further endoscopic surveillance after the initial negative EGD.

We therefore conducted a retrospective cohort study of patients with GERD who underwent one negative EGD to evaluate the incidence and risk factors of subsequent EA and any upper gastrointestinal cancers among this population.

Methods

Data Source

The Veterans Health Administration (VHA) maintains Medical SAS® Datasets that contain national administrative data for VHA-provided health care. We used the Outpatient File, which contains up to 10 diagnosis codes for each outpatient visit, according to the 9th revision of the International Classification of Diseases Clinical Modification (ICD-9-CM) and up to 20 Current Procedural Terminology (CPT) codes; and the Inpatient File, which contains ICD-9 diagnoses and procedure codes related to inpatient stays.

Study Cohort

We identified a cohort of patients with a GERD diagnosis between October 1, 2003, and September 30, 2009 (Fiscal Years [FY] 2004 to 2009) with a subsequently negative EGD within one year of GERD diagnosis. GERD was defined by the presence of an ICD-CM-9 code (530.10, 530.11, 530.12, or 530.81; esophagitis, reflux esophagitis, acute esophagitis or esophageal reflux, respectively) in at least 2 outpatient records that were 30 days to 18 months apart. We included GERD patients who were between the ages of 18 and 90 years and who had at least 1 year of follow-up after their GERD index date. We excluded those with existing conditions that would prompt surveillance or diagnostic EGD. These conditions were BE, gastroduodenal or esophageal cancers, abdominal surgery, decompensated liver disease, anemia, GI bleeding, celiac disease, any metastatic cancer, or any chemotherapy, all documented by ICD-9 codes within 5 years preceding the GERD index date. We defined anemia by the presence of ICD-9 codes or hematocrit <33% in women and <39% in men in the year prior to or 6 months after the GERD index date. We restricted our cohort to patients with GERD for two main reasons: 1) GERD is the most

common indication for elective endoscopy; and 2) to minimize the heterogeneity of the study sample, and hence in the applicability of the study findings.

The screening EGD was identified by CPT codes (43200 – 43259, excluding 43246) or ICD-9 procedure codes (422.3, 422.4, 441.3, 441.4, 451.3, 451.4, or 451.6) in the one year after the GERD index date. We subsequently excluded those with screening EGDs and positive findings (using ICD-9 codes), defined as BE, esophageal or gastroduodenal cancer diagnoses recorded within 12 months of the EGD date. The remaining screening endoscopies were considered negative. The duration of follow-up for each patient was calculated from the date of the first negative screening EGD to the date of last VA inpatient or outpatient encounter or the date of upper gastrointestinal cancer before September 30, 2011.

Study Variables

Our outcome of interest was a diagnosis of EA or upper gastrointestinal cancers that we first ascertained by ICD-9 codes, and then we validated based on endoscopic and histological criteria by manually reviewing the electronic medical records. Our main outcome was EA, and our secondary outcome was all upper gastrointestinal cancers (including EA). The two reasons for examining risk of all subsequent cancer not limited to EA for patients with a negative screening EGD were that: 1) GERD patients frequently undergo repeat endoscopy under the auspices of ruling out other non-GERD related diseases; and 2) we wanted to examine the additional benefit to endoscopies done for GERD screening; i.e., the identification of premalignant lesions (i.e., esophageal squamous papilloma, gastric intestinal metaplasia, gastric ulcers, duodenal adenoma), other than Barrett's esophagus.

We assessed several patient-level clinical and risk-factor variables, as well as clinical-care variables. Clinical-care factors included the burden of coexisting conditions using the Deyo comorbidity score within 1 year prior to and after the GERD index date, seeing a GI specialist defined by gastroenterology clinic stop code (307) within 180 days prior to and after the GERD index date, the total number of inpatient and outpatient encounters during the first year of follow-up and home residence located in rural or non-rural areas according to zip codes.

We also assessed several facility-level variables including total hospital operating beds and academic affiliation, as indicated by the number of resident slots per 10,000 patients in 2003. We classified VA facilities into 5 regions in the United States according to where each facility is located (Midwest, Northeast, South, West, and Puerto Rico/Virgin Islands). Finally, the cumulative number of EGDs performed at each facility during 2004-2010 was examined.

Statistical Analysis

Subsequent EA was defined as EA that was diagnosed after a negative screening EGD up until September 30, 2011. Subsequent upper gastrointestinal cancers were defined as esophageal, gastric or duodenal cancers diagnosed after a negative screening EGD up until the same date. We calculated the incidence rates of EA separately, as well asupper gastrointestinal cancers per patient year of follow up subsequent to negative endoscopy. We

examined the differences between the upper gastrointestinal cancer group and the group of patients with no subsequent cancer development with respect to patient, clinical care and facility factors. Chi-square or Fisher's exact tests identified significant differences between two groups.

We conducted all analyses using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina).

Results

We identified 76,737 patients with GERD who received an EGD within a year after their index diagnosis date, and fulfilled the study inclusion and exclusion criteria. From this group, we excluded 423 (0.6%) patients who had an ICD-9 code for esophageal or gastroduodenal cancer, 7,630 (9.9%) who had an ICD-9 code for BE and 74 (0.1%) who had ICD-9 codes for both BE and esophageal or gastroduodenal cancer, within 1 year of the EGD date (Figure 1).

Among the remaining 68,610 patients, the mean available follow up was 3.2 years (standard deviation (SD) 2.0). In this group, 29 patients had an ICD-9 code for upper gastrointestinal cancers during 219,178 patient-years follow up in the VA health system, all of whom had the diagnosis confirmed by systematic chart reviews. Of these 29 patients with cancer, 10 developed EA and 19 developed other upper gastrointestinal cancers. Therefore, the incidence rate of subsequent EA among patients with GERD and a negative screening EGD was 4.6 (95%CI 2.2-8.3) per 100,000 person-years of follow up, and the incidence of all upper gastrointestinal cancers was 13.2 (95%CI 8.9-19) per 100,000 person-years of follow up

Table 1 provides a comparison of patient, clinical, clinical-care and facility variables between GERD patients who developed cancers subsequent to a negative endoscopy to those who did not. Most of the demographic and clinical characteristics were not significantly different between the two groups. Most patients in both groups were men (89.6%, and 93.1%, respectively) and of white race (67.4% and 79.3%, respectively). Patients who developed subsequent cancer were significantly older than patients without cancer; 34.5% were older than 65 compared with 18.4% in the non-cancer group. Approximately 62% of the cancer patients were in the highest quartile of total number of clinic visits in 1 year compared with 44.2% in the group without cancer, however this difference was not statistically significant. Most patients with cancers subsequent to a negative endoscopy lived in urban settings, while most non-cancer patients lived in a rural setting. There were no significant differences related to hospital size or number of EGDs performed per facility. Patients who developed subsequent cancers had statistically significant higher modified Deyo scores (p<0.0001).

In Table 2, we provide more details on the 29 patients who developed subsequent cancers, using information contained in the electronic medical records. These cancers were equally distributed between the esophagus (n=14) and the stomach (n=13) with only 1 cancer identified in the duodenum. Most esophageal cancers were of the adenocarcinoma subtype

(n=10), while 4 esophageal cancers were squamous cell cancers. Only 6 out of the 29 patients (21%) had an early stage cancer (i.e. stages 0 and 1) and 7 (24%) were already metastatic by the time they were diagnosed. All gastric cancers were of the intestinal histological subtype. The mean duration of time between the negative screening EGD and the cancer diagnosis date was 43.3 (SD 38.7) months with a median of 29 months (range 9-183 months). There were 7 patients who had dysphagia in addition to GERD at the time of screening EGD. These 7 patients (patients #3, 16, 20, 22, 23, 25 and 29 in Table 2) developed cancer many months after the initial negative EGD. There was only 1 patient who had early satiety (patient #9) who subsequently developed esophageal squamous cell carcinoma 129 months later. All the other patients had the screening EGD because of GERD symptoms only. All screening EGDs were complete and none were aborted prematurely according to the procedure notes reviewed. Two of the 10 patients with subsequent EA had suspected BE on screening endoscopy; one (patient #6) had esophageal biopsies obtained at the time of screening EGD that did not confirm BE but an EGD at a later date did confirm BE, and the other patient (patient #4) had no esophageal biopsies. Two other patients with EA (patients #5 and #8) had one or more interval EGD(s) that diagnosed BE. In the 12 patients with gastric cancer, 4 had intestinal metaplasia in the stomach or chronic gastritis identified at time of screening EGD, but most (n=8) did not have gastric biopsies obtained.

Discussion

We identified a large retrospective cohort of GERD patients without alarm symptoms who underwent a screening endoscopy that was negative for BE or GI cancers. By combining administrative data and electronic medical chart reviews, we identified 10 patients in this cohort who subsequently developed EA among 29 overall who developed an upper gastrointestinal cancer despite the initial 'negative' endoscopy. The incidence rates of subsequent EA specifically, and upper gastrointestinal cancers overall were 4.6 and 13.2 per 100,000 person-years of follow up, respectively. Most cancers in the upper gastrointestinal cancer group were esophageal or gastric carcinoma.

The very low incidence of subsequent cancers in this cohort supports clinical practice guidelines recommending against repeating endoscopy for patients with GERD unless new symptoms arise ¹². Advanced age and high disease comorbidity were the only significant demographic or clinical predictors of subsequent cancers among those who had a negative screening EGD.

There were some possible missed opportunities identified from the chart review of patients who were diagnosed with an upper gastrointestinal cancer following a negative endoscopy. These included obtaining biopsies from 'suspected BE' among those who developed EA, and obtaining gastric biopsies to evaluate for atrophic gastritis or intestinal metaplasia in those who developed gastric cancer. If these precursor lesions had been properly diagnosed, they may have received potentially curative treatment (i.e. ablation) which would have prevented the development of cancer. To date, there have been no recommendations in the US to perform surveillance endoscopy in patients with gastric intestinal metaplasia, mostly due to lack of evidence ^{13, 14}.

Guidelines recommending screening endoscopy in patients with long-standing reflux have largely based these recommendations on indirect, weak evidence of improved prognosis of patients with EA, with a high potential for lead-time and length bias ¹⁵. We did not evaluate survival in our study, but 2 studies that have compared survival in patients with GERD reported conflicting results. One found that in patients who had an EGD 1-8 years prior to index date had an adjusted odds ratio of 0.66 (95%CI 0.45-0.96) for dying from EA compared to GERD controls ¹⁶. In the other study ¹, those with an EGD 1-5 years prior to EA diagnosis were diagnosed at an earlier stage (p=0.02) but did not have improved survival with an adjusted hazard ratio of 0.93 (95%CI 0.58-1.50) compared to those with no prior EGD.

Our study is the only large US cohort study to examine the risk of upper GI cancers subsequent to a negative endoscopy in GERD patients. Most studies examining the risk of interval upper GI cancers come from East Asia and are specific to gastric cancers. A study examining the risk of gastric cancer among 3,672 patients who underwent prior endoscopic examination, found 32 (0.9%) new cases of gastric cancer, with an increased risk in the 60-69 age group and in those with marked gastric atrophy on the initial exam ¹⁷. Another study evaluating the effect of prior endoscopies on the stage and survival of Korean patients with gastric cancer found a significant association between the length of time between the last EGD before cancer diagnosis with a higher stage at time of diagnosis (p<0.001)¹⁸. They also found that patients who have had an EGD prior to cancer diagnosis had decreased odds of developing an advanced stage cancer compared to those who have never had an EGD (adjusted odds ratios ranged from 0.31 to 0.53). In a study of 305 patients with esophageal and gastric cancers in the UK, 30 (9.8%) had at least 1 endoscopy exam within the previous 3 years, and 20 (67%) within the previous year ¹⁹. Most of these patients had detected abnormalities on initial examination such as esophagitis, stricture, gastritis, ulcers or a "suspicious lesion". The authors determined that the endoscopists accounted for the majority of missed lesions.

Can the subsequent cancers examined in this study be considered 'interval' cancers? An interval cancer is typically defined as a cancer that is diagnosed between screening and postscreening surveillance examinations ¹¹. Given the recommended surveillance recommendations in patients with Barrett's esophagus, subsequent cancer development in such patients could be considered 'interval' cancers. For patients without BE who developed subsequent cancer (27 patients in our study population), there are no known criteria or guidelines for surveillance endoscopy, and hence we avoided using the term interval cancer throughout the study.

There are some limitations to our study. Not all veterans received their care solely at the Veterans Health Administration. This can lead to an underestimate of the true incidence of subsequent cancers (if the cancers were diagnosed elsewhere and not identified in the VA system) or an overestimate of the incidence (if the negative screening EGDs were done elsewhere, so that they would not be included in the study cohort).Our ability to systematically examine other risk factors such as smoking, baseline gastric ulcers, diet or *Helicobacter pylori* was limited. Due to the male veteran composition of the study population, the findings might not be generalizable to non-veterans or women. We detected

a small number of subsequent cancers, limiting the statistical power necessary to detect differences in some of the variables we examined.

These weaknesses are outweighed by several strengths including the supplemental use of electronic medical chart reviews to confirm each cancer diagnosis and obtain more details on pre-cancer care. We also used a large nationwide cohort with relatively long follow up time, increasing our ability to detect these rare cancers and to examine different clinical, facility and patient-related factors. Most of the patients in our study were White men and older than 50; part of the high-risk profile presented in major guidelines.

This study is a step towards evaluating characteristics of GERD patients who might be at high risk of developing EA, and warrant surveillance endoscopy, even without identifying BE. Preferably, a large, national or international dataset should be used to develop a statistical model that would provide us with a multivariable predictive score for the development of EA for patients with GERD and a negative screening EGD.

In summary, the incidence of subsequent cancers during a mean follow-up of 3.2 years among patients with GERD and a negative screening EGD is low enough to justify not recommending repeating an EGD in these patients. This is in agreement to the guidelines published by major gastrointestinal societies 5 .

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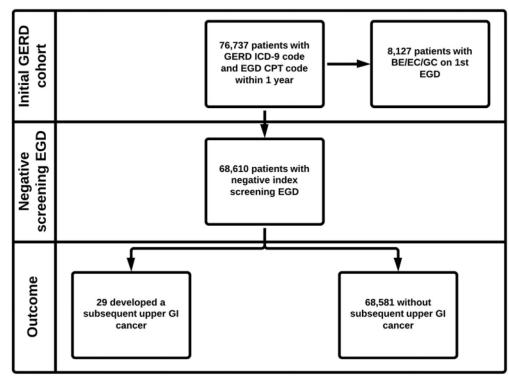
Abbreviations

| BE | Barrett's Esophagus |
|----------|-----------------------------------------------------------------------------|
| СРТ | Current Procedural Terminology |
| EGD | Esophagogastroduodenoscopy |
| FY | Fiscal Years |
| GERD | Gastroesophageal Reflux Disease |
| ICD-9-CM | International Classification of Diseases 9th edition, Clinical Modification |
| VHA | Veterans Health Administration |
| EA | Esophageal Adenocarcinoma |
| CI | Confidence Interval |
| SD | Standard Deviation |

References

 Rubenstein JH, Sonnenberg A, Davis J, et al. Effect of a prior endoscopy on outcomes of esophageal adenocarcinoma among United States veterans. Gastrointestinal endoscopy. 2008; 68:849–855. [PubMed: 18547567]

- Farrow DC, Vaughan TL, Sweeney C, et al. Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. Cancer causes & control: CCC. 2000; 11:231–238. [PubMed: 10782657]
- Rubenstein JH, Scheiman JM, Sadeghi S, et al. Esophageal adenocarcinoma incidence in individuals with gastroesophageal reflux: synthesis and estimates from population studies. The American Journal of Gastroenterology. 2011; 106:254–260. [PubMed: 21139576]
- 4. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology. 2012; 143:1179–87. [PubMed: 22885331]
- 5. Standards of Practice Committee. Lichtenstein DR, Cash BD, et al. Role of endoscopy in the management of GERD. Gastrointestinal endoscopy. 2007; 66:219–224. [PubMed: 17643692]
- Vakil N, Moayyedi P, Fennerty MB, et al. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology. 2006; 131:390–401. quiz 659-60. [PubMed: 16890592]
- Nason KS, Wichienkuer PP, Awais O, et al. Gastroesophageal reflux disease symptom severity, proton pump inhibitor use, and esophageal carcinogenesis. Archives of surgery (Chicago, Ill.: 1960). 2011; 146:851–858.
- Pohl H, Robertson D, Welch HG. Repeated Upper Endoscopy in the Medicare PopulationA Retrospective Analysis. Annals of Internal Medicine. 2014; 160:154–160. [PubMed: 24658692]
- Stoltey J, Reeba H, Ullah N, et al. Does Barrett's oesophagus develop over time in patients with chronic gastro-oesophageal reflux disease? Alimentary Pharmacology & Therapeutics. 2007; 25:83–91. [PubMed: 17229223]
- Rex DK, Cummings OW, Helper DJ, et al. 5-Year Incidence of Adenomas After Negative Colonoscopy in Asymptomatic Average-Risk Persons. See Comment. Gastroenterology. 1996; 111:1178–1181.
- Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. The New England journal of medicine. 2010; 362:1795–1803. [PubMed: 20463339]
- Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. The American Journal of Gastroenterology. 2013; 108:308–28. quiz 329. [PubMed: 23419381]
- Fennerty MB. Gastric intestinal metaplasia on routine endoscopic biopsy. Gastroenterology. 2003; 125:586–590. [PubMed: 12891560]
- Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointestinal endoscopy. 2006; 63:570–580. [PubMed: 16564854]
- Shaheen NJ, Provenzale D, Sandler RS. Upper endoscopy as a screening and surveillance tool in esophageal adenocarcinoma: a review of the evidence. The American Journal of Gastroenterology. 2002; 97:1319–1327. [PubMed: 12094844]
- Kearney DJ, Crump C, Maynard C, et al. A case-control study of endoscopy and mortality from adenocarcinoma of the esophagus or gastric cardia in persons with GERD. Gastrointestinal endoscopy. 2003; 57:823–829. [PubMed: 12776027]
- Hosokawa O, Watanabe K, Hatorri M, et al. Detection of gastric cancer by repeat endoscopy within a short time after negative examination. Endoscopy. 2001; 33:301–305. [PubMed: 11315889]
- Nam JH, Choi IJ, Cho SJ, et al. Association of the interval between endoscopies with gastric cancer stage at diagnosis in a region of high prevalence. Cancer. 2012; 118:4953–4960. [PubMed: 22806878]
- 19. Yalamarthi S, Witherspoon P, McCole D, et al. Missed diagnoses in patients with upper gastrointestinal cancers. Endoscopy. 2004; 36:874–879. [PubMed: 15452783]



GERD: Gastroesophageal reflux disease. EGD: Esophagogastroduodenoscopy. ICD-9: International Classification of Diseases, 9th edition. CPT: Current Procedural Terminology. BE: Barrett's Esophagus. EC: Esophageal Cancer. GC: Gastric Cancer. GI: Gastrointestinal.

Figure 1.

Flow diagram of study population.

Table I

Characteristics of veteran patients with GERD who underwent one EGD negative for BE and gastroesophageal cancer; 29 were diagnosed with interval upper GI cancers during 219,178 patient-years of follow up and the rest (68,581) were not

| Variable | Upper GI cancer n=29 n (%) | No cancer n=68,581 n (%) | p-value |
|--------------------------------------------|-------------------------------------|--------------------------------|---------|
| Male | 27 (93.1) | 61,452 (89.6) | 0.76 |
| Age at first EGD | | | |
| <50 | 1 (3.5) | 19,712 (28.7) | < 0.005 |
| 50-64 | 18 (66.0) | 36,247 (52.9) | |
| 65+ | 10 (34.5) | 12,622 (18.4) | |
| Race | | | 0.33 |
| White | 23 (79.3) | 46,234 (67.4) | |
| Black | 4 (13.8) | 8,283 (12.1) | |
| Other | 0 (0) | 2,606 (3.8) | |
| Missing | 2 (6.9) | 11,458 (16.7) | |
| Total visits in 1 year (quartiles) | | | 0.26 |
| 1 (1-5) | 2 (6.9) | 6,296 (9.2) | |
| 2 (6-9) | 4 (13.8) | 11,300 (16.5) | |
| 3 (10-17) | 5 (17.2) | 20,691 (30.1) | |
| 4 (18-391) | 18 (62.1) | 30,294 (44.2) | |
| Setting | | | 0.42 |
| Rural | 11 (37.9) | 47,275 (68.9) | |
| Urban | 18 (62.1) | 21,306 (31.1) | |
| GI Visit | | | 0.67 |
| Yes | 9 (31.0) | 18,851 (27.5) | |
| No | 20 (69.0) | 49,730 (72.5) | |
| Number of EGDs per facility (Quartiles) | | | 0.09 |
| 1 (0-3616) | 11 (37.9) | 16,908 (24.7) | |
| 2 (3617-5872) | 5 (17.2) | 17,309 (25.2) | |
| 3 (5873-8655) | 10 (34.5) | 16,829 (24.5) | |
| 4 (8656-21843) | 3 (10.3) | 17,535 (25.6) | |
| Region | | | 0.83 |
| Midwest | 8 (27.6) | 15,054 (22.0) | |
| Northeast | 2 (6.9) | 8,193 (12.0) | |
| South | 12 (41.4) | 30,218 (44.1) | |
| West | 7 (24.1) | 14,449 (21.1) | |

| Variable | Upper GI cancer n=29 n (%) | No cancer n=68,581 n (%) | p-value |
|---------------------------------------|-------------------------------------|--------------------------------|----------|
| PR,VI | 0 (0.0) | 667 (1.0) | |
| Academic Affiliation * (quartiles) | | | 0.60 |
| 1 (0-3.7) | 5 (17.2) | 16,845 (24.6) | |
| 2 (3.8-12.6) | 8 (27.6) | 17,502 (25.5) | |
| 3 (12.7-19.2) | 6 (20.7) | 16,985 (24.8) | |
| 4 (19.3-47.3) | 10 (34.5) | 17,249 (25.2) | |
| Hospital size (quartiles) | | | 0.14 |
| 1 (<99) | 8 (27.6) | 16,526 (24.1) | |
| 2 (99-158) | 9 (31.0) | 17,930 (26.1) | |
| 3 (159-290) | 10 (34.5) | 16,871 (24.6) | |
| 4 (291-450) | 2 (6.9) | 17,254 (25.2) | |
| Modified Deyo score | | | < 0.0001 |
| 0 | 13 (44.8) | 43,787 (63.9) | |
| 1 | 5 (17.2) | 16,677 (24.3) | |
| 2+ | 11 (37.9) | 8,117 (11.8) | |

EGD: Esophagogastroduodenoscopy VA: Veteran Affairs PR: Puerto Rico VI: Virgin Islands

*Academic Affiliation: Resident slots per 10,000 patients

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| | Age at initial EGD | Sex | Race | Cancer type | Interval time (months) after negative EGD | Cancer Stage | BE on screening | Gastric IM on screening | Indication of cancer diagnostic EGD |
|----|--------------------------|--------|-------|----------------|-------------------------------------------------|-----------------------------|---------------------------------|-------------------------------|----------------------------------------|
| 1 | 60 | Male | AA | EA | 59 | T3N1M0 (3A) | No | No | Food impaction |
| 17 | 56 | Male | White | ESCC | 22 | T2N0M0 (2) | No | No | GI bleed |
| 3 | 60 | Male | White | ESCC | 24 | TxN0M1 (4) | No | No | Dysphagia, weight loss |
| 4 | 86 | Female | White | EA | 22 | T _X N0M0 (UK) | Possible BE, not biopsied | No | Weight loss, early satiety |
| Ś | 66 | Male | White | EA | 60 | T3N1M0 (3A) | No | UK | Dysphagia |
| 9 | 75 | Male | White | EA | 60 | T3N1M0 (3A) | Yes- endoscopic only | No | Dysphagia, weight loss |
| ٢ | 58 | Male | White | ESCC | 29 | T3N0M0 (2A) | No | Yes | Epigastric pain |
| × | 56 | Male | White | EA | 78 | T3N1M0 (3A) | No | No | Dysphagia, weight loss |
| 6 | 65 | Male | White | ESCC | 129 | T4N1M0 (3) | No | No | Dysphagia |
| 10 | 58 | Female | AA | GC (cardia) | 22 | T4N1M0 (4a) | No | UK | Belching/ Worsening GERD |
| 11 | 59 | Male | White | GC | 22 | T4NxMx (3a) | No | UK | Abdominal pain, weight loss |
| 12 | 64 | Male | White | GC | 26 | TxNxM1 (4) | No | Chronic gastritis | Abdominal pain, vomiting |
| 13 | 61 | Male | White | GC | 16 | T3N0M0 (2) | No | UK | GOO |
| 14 | 71 | Male | AA | GC | 22 | T1N0M0 (1A) | No | Chronic gastritis | Abdominal pain |
| 15 | 53 | Male | White | GC | 54 | T2N0M0 (1B) | No | Yes | Nausea and vomiting |
| 16 | 81 | Male | White | GC | 30 | T2bN0M0 (1B) | No | UK | Worsening GERD |
| 17 | 58 | Male | White | GC | 71 | T2bN2M0 (3A) | No | UK | Persistent GERD, anemia |

| | Age at initial EGD | Sex | Race | Cancer type | Interval time (months) after negative EGD | Cancer Stage | BE on screening | Gastric IM on screening | Indication of cancer diagnostic EGD |
|----|--------------------------|------|-------|----------------|-------------------------------------------------|-----------------|--------------------|-------------------------------|----------------------------------------|
| 18 | 72 | Male | White | GC | 29 | TINIM0 (1B) | No | Chronic gastritis | Anemia |
| 19 | 62 | Male | White | GC | 183 | T1N0M0 (1A) | No | UK | Abdominal pain |
| 20 | 58 | Male | White | EA | 34 | TxNxM1 (4) | No | UK | UGI bleed |
| 21 | 69 | Male | White | Duodenal | 25 | T3N0M0 (2A) | No | UK | UGI Bleed |
| 22 | 58 | Male | White | EA | 30 | TxN1M0 (3) | No | UK | Dysphagia |
| 23 | 64 | Male | White | EA | 18 | TisN0M0 (0) | No | UK | UK |
| 24 | 58 | Male | White | EA | 23 | TxNxM1 (4) | UK | UK | Workup of metastatic carcinoma |
| 25 | 84 | Male | White | GC | 18 | T1N0M1 (4) | No | UK | Anemia |
| 26 | 49 | Male | AA | GC | 11 | T3N1M0 (3A) | No | No | Anemia |
| 27 | 62 | Male | White | EA | 29 | TxNxM1 (4) | No | UK | UK |
| 28 | 54 | Male | AA | GC | 6 | UK | No | No | UK |
| 29 | 76 | Male | AA | GC | 100 | T4N0M1 (4) | No | UK | Dysphagia anemia |

Abbreviations: EGD: Esophagogastroduodenoscopy. BE: Barrett's Esophagus. IM: Intestinal Metaplasia. AA: African American. EA: Esophageal Adenocarcinoma. ESCC: Esophageal Squamous Cell Carcinoma. GC: Gastric carcinoma. GERD: Gastroesophageal reflux disease. GI: Gastrointestinal. UK: Unknown. GOO: Gastric Outlet Obstruction.