RISK FACTORS FOR PROGRESSION OF BARRETT'S ESOPHAGUS TO HIGH GRADE DYSPLASIA AND ESOPHAGEAL ADENOCARCINOMA

by

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ABSTRACT

Barrett's esophagus (BE) is the only known precursor to esophageal adenocarcinoma (EAC). Methods of identifying BE patients at high risk for progression to high-grade dysplasia (HGD) or EAC are needed to improve outcomes and identify who will benefit most from intensive surveillance or ablative therapy. Clinical predictors of BE progression to HGD or EAC are poorly understood, with multiple contradictory studies. We performed a retrospective study included 460 patients at Johns Hopkins Hospital who underwent at least 2 upper endoscopies 6 months apart showing biopsy-documented BE between 1992 and 2013. Patients with EAC or HGD at the initial endoscopy were excluded. Demographic, clinicopathological, and endoscopic data were collected. Univariate and multivariate Cox proportional hazards analyses with time to progression to HGD and EAC were performed.

Among 460 patients included in the study, 132 BE patients ultimately progressed to HGD and 62 developed EAC. Two hundreds and seventy two (272) BE patients did not progress to dysplasia or EAC. Significant EAC risk factors included age, abdominal obesity, caffeine intake, and the presence of HGD. Risk factors for HGD or EAC included age, caffeine intake, and low-grade dysplasia while colonic adenomas trended towards significance. Notably, a history of statin or SSRI usage reduced the risk of EAC or HGD by 49% or 61%, respectively. In sum, our study validated several known and identified several novel risk factors, including a history of colonic adenomas or caffeine usage. Low-grade dysplasia (LGD) was a risk factor for progression but various endoscopic characteristics were not, suggesting that screening strategies should focus on histology instead. We identified SSRIs as a new potential chemoprotective medication.

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INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) has increased rapidly in the USA and other nations, but unfortunately, most cases are detected very late, with a fatality rate of 90%.[1] Barrett's esophagus (BE), the only known precursor for EAC, can progress to low-grade dysplasia (LGD), high-grade dysplasia (HGD), or ultimately EAC. BE is defined as salmon-colored mucosa extending ≥1 cm proximal to the gastroesophageal (GE) junction, with biopsy confirmation of replacement of normal squamous epithelium by metaplastic intestinal-type columnar epithelium.[1] Endoscopic surveillance is currently accepted for all patients with BE, as BE surveillance carries an improved prognosis.[2] Although BE patients have an eleven-fold higher risk of EAC than the general population, their annual risk of this malignancy is 0.11%.[3] These observations have generated controversy regarding cancer screening and surveillance practices. Since most BE patients will not develop EAC, and considering the risk and expense of endoscopic surveillance, understanding risk factors for BE progression is important to effectively focus resources on high-risk BE patients, allowing patient stratification and enabling tailored surveillance and therapy.

Predictors of neoplastic progression in BE are incompletely understood. Epidemiologic risk factors considered include male gender, age, white race, obesity (especially central obesity), family history of BE or EAC, BE duration, endoscopic extent of BE, smoking, and GERD history.[4] There is a strong correlation between frequent and prolonged acid exposure and BE development; moreover patients presenting with GERD at younger ages, or with longer GERD symptom duration, are at increased risk.[5] Nevertheless, many EAC and HGD patients do not recall prior reflux symptoms. Proven endoscopic risk factors for BE progression include long BE segment length, hiatal hernia, mucosal abnormalities such as esophagitis, and the presence of BE

in a 12- to 6-o'clock esophageal hemisphere.[1] Histologic factors, including intestinal metaplasia, low-grade dysplasia, and p53 overexpression are also suggested risk factors.[1]

The aims of our study are to comprehensively assess clinical, epidemiological, endoscopic, and histopathologic risk and protective factors for the progression of BE to either HGD or EAC. We reason that a clearer understanding of these factors would help optimize surveillance, since it would enable better resource allocation to surveil patients with positive, high risk factors, promoting more efficient and earlier detection of HGD and EAC.

METHOD AND MATERIALS

This study was approved by the Institutional Review Board (IRB) at the Johns Hopkins University (JHU) School of Medicine. All patients undergoing ≥2 upper endoscopies (EGD) ≥6 months apart, showing histologically confirmed BE from 1992-2013, were included. We excluded patients with <2 EGDs or <6 months between initial and most recent EGDs, or EAC or HGD at initial EGD. Diagnosis was made by expert GI pathologists at JHU. The Center for Clinical Data Analysis (CCDA) at JHU assisted in identifying patients who underwent at least 2 EGDs with 6 months apart. If Barrett's esophagus was noted both endoscopically (at least 1 cm of salmon colored mucosa in the tubular esophagus with intestinal metaplasia on the pathology) the patients were included as potential patients for the study. Those developing HGD or EAC were termed progressors, while those remaining free of dysplasia, developing only LGD, or regressing to normal pathology without intervention were termed non-progressors.

Baseline age, gender, race, and BMI were collected. Age was modeled as a continuous variable. Subjects fell into 3 categories of obesity: overweight (BMI 25-29.9), obese I (BMI 30-34.9), or obese II (BMI > 34.9). Smoking was categorized as never, former, or current, with former subdivided into < 10, 10-30, or >30 pack-years. Alcohol use was categorized as former social, former heavy, current social, or current heavy. Illicit drug use was divided into drug type and categorized as either former or current. Caffeine intake was recorded as rare, weekly to daily, or multiple times daily. Family history of other cancers, BE, esophageal cancer, or GERD/heartburn was recorded. Medications the patient took any time after initial BE diagnosis and before diagnosis of HGD or EAC were recorded. Other epidemiologic risk factors included history of esophagitis, gastric or duodenal ulcer, gastritis, esophageal stricture, esophageal web, and Schatzki's ring. History of GERD, heartburn, dysphagia, regurgitation, and symptom

frequency were recorded, as were history of colonic adenoma, cholecystectomy, anti-reflux surgery, other cancers, hypertension, hyperlipidemia, diabetes, coronary artery disease, stroke, chronic kidney disease, and anemia. Endoscopic risk factors comprised presence and size of hiatal hernia, number and segment length of BE tongues, (long segment BE >3 cm, short segment BE <3 cm), BE circumferentially (>3 cm circumferential extent), presence of esophagitis, and presence of esophageal ulcer. Histopathologic risk factors comprised initial degree of dysplasia (low-grade or non-dysplastic).

Statistical Analyses

Demographic and clinicopathological variables were summarized with means and standard deviations for continuous variables or proportions for categorical variables. We first performed univariate logistic regression analysis with progression to EAC or the composite outcome of progression to EAC or HGD as the dependent variable and epidemiologic and clinical factors, medications and endoscopic features as independent variable. Any variable significantly associated with progression (p-value < 0.05) in the univariate analysis was highlighted as a potential risk or protective factor. Multivariate Cox models used least absolute shrinkage and selection operator (LASSO) penalized regression for model selection, which minimizes the usual sum of squared errors, with a bound on the sum of the absolute values of the coefficients.[6] This method penalizes size of regression coefficients, whereby some predictors have coefficient estimates of exactly zero and can be considered "selected out" of the model. Variables with regression coefficients $\neq 0$ were chosen for the multivariate Cox model. The tests for proportionality of hazards were done using methods as described by P. Grambsch and T.

Therneau where proportional hazards tests and diagnostics were based on weighted residuals.[7] Kaplan-Meier analysis is used for progression to HGD or EAC as outcome.

RESULTS

We identified 460 patients with BE diagnosed during the study period (see Figure 1 for flow chart). Baseline characteristics are in Table 1 for progressors and non-progressors. We identified 272 as non-progressors and 188 as progressors. Among progressors, 19 patients were identified as low-grade dysplasia (LGD) BE and 169 patients were non-dysplastic BE (NDBE) at baseline. Average age for total cohort was 68.51 ± 13.03; 68% were males, 93% were non-Hispanic Caucasians, and 51% had smoked tobacco. Common medications were proton pump inhibitors (94%), statins (37%), aspirin (30%), angiotensin receptor blockers (ARBs, 24%), angiotensin converting enzyme (ACE) inhibitors (18%), beta-blockers (11%) and selective serotonin re-uptake inhibitors (SSRIs, 11%).

Of the 460 BE patients, 62 developed EAC and 132 developed HGD during the study period (Figure 1). The mean (SD) follow-up after BE diagnosis was 7.78 (5.40) years. HGD and EAC incidences were 49.19 and 16.48 per 1,000 person-years of follow-up, respectively; 10-year cumulative HGD and EAC incidences post-BE diagnosis were 0.40 and 0.17, respectively. Cumulative HGD and EAC incidence curves are in Figure 2.

Results of univariate and multivariate analyses with progression to EAC as outcome are in Figure 3. In univariate analysis, age, Hispanic race, abdominal obesity, history of diabetes mellitus, and oral non-metformin anti-diabetic medications were significant risk factors for progression, while SSRI usage trended strongly toward significance as protective (p=0.08). Metformin did not significantly increase or decrease progression risk. Weekly/daily caffeine (p=0.07), heavy smoking (p=0.07), family history of BE (p=0.09), and dysphagia (p=0.09) trended positively as risk factors. Significant endoscopic risk factors were long-segment BE, presence of LGD, and development of HGD on subsequent endoscopies (patients with initial

HGD were excluded). As in univariate analysis, age, abdominal obesity, weekly caffeine intake, and oral anti-diabetic medications conferred significant risk, while family history of BE trended toward significance (p=0.10) in multivariate analysis. SSRIs were significantly protective in multivariate analysis (Figure 4). Endoscopic risk factors in multivariate analysis included only LGD and development of HGD on subsequent endoscopies. Notably, long-segment and circumferential BE were not risk factors in multivariable analysis after adjustment for confounding factors.

A multivariate model was also performed with composite outcome of progression to either HGD or EAC (Figure 5). Significant risk factors in this model included age, weekly/daily and multiple daily caffeine usage; heavy smoking (>30 pack-years; p=0.09), colonic adenomas (p=0.08), and calcium channel blockers (p=0.06) trended positively as risk factors. Anemia, statins, and SSRIs (Figure 4c) were statistically significantly protective, while supplemental calcium/vitamin D trended towards significance as protective (p=0.08). Significant histologic risk factors for progression included low-grade dysplasia (LGD).

DISCUSSION

In this retrospective study of 460 patients with histologic BE, we applied multivariate regression model to identify clinical, epidemiologic, endoscopic, and histologic risk factors for progression BE to HGD or EAC. Our results validated known risk factors for progression, including age, abdominal obesity, and smoking, but also demonstrated, to our knowledge for the first time, that caffeine intake and colonic adenomas increase progression risk. While dysplasia increased progression risk, previously reported endoscopic factors - circumferential BE, long-segment BE, and hiatal hernia - were not significant after multivariate adjustment for potential confounders. We also demonstrated protective effects for known chemoprotective medications, particularly statins, as well as several novel medications, notably SSRIs and supplemental calcium and vitamin D.

Age constituted a strong risk factor for progression to either HGD or EAC in our study, consistent with prior studies and the increased incidence of EAC reported in the Surveillance, Epidemiology, and End Results (SEER) registry.[8] Male gender is also a known risk factor for BE progression to EAC but was not significant in our study. However, SEER indicates that the largest gender difference occurs in patients younger than 65.[8] Since our average age was 68, this may explain why our gender difference was not as large. Additionally regarding obesity, we found that central abdominal obesity was a significant risk factor for both HGD and EAC, but not increased BMI, suggesting that fat distribution primarily contributed to this risk. Tobacco usage is an established risk factor for BE progression, with conflicting data on caffeine usage. We found that heavy smoking (>30 pack-years) increased the composite risk of HGD or EAC by 111%. Our study also found that caffeine was a significant risk factor for the composite outcome of HGD or EAC. This is consistent with the finding that caffeine induces gastric acid secretion,

relaxes the LES, and worsens GERD.[9] However, multiple studies on caffeine have yielded mixed results, with one study finding an inverse association with coffee consumption and EAC rates, while another involving 400,000 participants did not.[10, 11] Only 1 study addressed BE progression risk *vs.* coffee/tea consumption: it did not find any association.[12] Our data showed that coffee and tea or caffeinated soft drink consumption, which had not been studied significantly, increased progression risk.

Colonic adenomas trended toward significance for progression to either HGD or EAC in our study. Previous studies have shown that patients with colonic adenomas have a higher risk of BE, and patients with BE have a higher risk of colonic adenomas.[13] However, to our knowledge, no studies looked at the relationship between colonic adenomas and BE progression risk. Several potential reasons may explain why colonic adenomas increase BE progression risk. First, they constitute a pre-malignant lesion with low-grade dysplasia and may represent a field defect evincing a genetic predisposition to the development of dysplasia. Indeed, inducible nitric oxide synthase and cyclooxygenase-2 are mediators of inflammation, regulators of cell growth, and elevated in colonic adenomas, colonic adenocarcinomas, BE, and EAC.[14] Additionally, 17p and 5q allelic losses are associated with progression of both colonic adenomas and BE.[15] These common genetic alterations may explain why patients with colonic adenomas have a higher risk of BE progression.

We found anemia to be potentially protective against progression to either HGD or EAC. One explanation is that anemic patients (who often undergo EGD for evaluation of anemia) represent a distinct population with a lower risk of BE progression *vs.* other BE patients, many of whom have longstanding GERD and additional risk factors and thus are screened for BE. Indeed, 2 studies in patients undergoing colonoscopy for colon cancer screening showed high rates (11%

and 6.8%) of BE in asymptomatic patients.[16] These studies also demonstrated that asymptomatic patients had a lower risk of long-segment BE, previously associated with progression. Thus, anemia *per se* may not protective, but patients found to have BE without GERD or other risk factors may not be at the same risk of progression to HGD/EAC.

Previously identified endoscopic factors for BE progression include circumferential or long-segment BE[17] and LGD[3] or HGD[18]. In our study, long-segment BE and circumferential BE were significant only in univariate analysis but not after adjustment for other factors, divergent from prior studies. [17] Indeed, 69 different demographic, clinical, medication-related and endoscopic risk factors were measured in our multivariate analysis. Patients with long-segment BE or circumferential BE may also have concomitant risk factors increasing their progression risk. LGD was a significant risk factor to the composite outcome of HGD or EAC, and development of HGD during the study period was also a significant risk factor for progression to EAC, consistent with previous findings.[19] These findings may also explain why current endoscopic surveillance has not reduced the incidence of EAC.[20] Indeed, a recent meta-analysis demonstrated that 25% of patients with BE or BE with LGD developed an incident cancer within 1 year of endoscopic screening, questioning the ability of endoscopy to appropriately risk-stratify patients.[21] Another meta-analysis demonstrated that only 20% of EACs in BE patients were diagnosed via surveillance, whereas most EACs were prevalent, detected shortly after BE diagnosis and before potential intervention.[22] This finding, combined with our study, suggests that the priority for screening is early dysplasia detection, rather than other endoscopic findings such as length or circumferential extent, since dysplasia confers the greatest progression risk. This argues that better methods/technologies facilitating early dysplasia detection are needed to improve detection of HGD early and intervention before EAC development.

Chemoprevention of cancer is a worthy goal, particularly in BE, given the increasing incidence of EAC and the widespread prevalence of GERD and BE. Multiple studies have shown that statins reduce neoplastic progression in BE, with proposed mechanisms including anti-proliferative, anti-angiogenic, and pro-apoptotic effects.[1] In our study, statins reduced the risk of progression to the composite outcome of HGD or EAC by 48% (OR = 0.52, 95% CI = 0.34 – 0.79, p=0.002). NSAIDs and aspirin have also been shown in multiple studies to be protective, but were not in our study.[23]

Two protective medications discovered by us were SSRIs and supplemental calcium or vitamin D. SSRIs have not been previously associated with a reduction in BE progression or EAC incidence. However, they exert anti-tumor effects relevant to colonic neoplasia. Specifically, SSRIs decrease cultured human colon cancer cell viability; suppress cell division in rat colonic tumors, and slow human colorectal tumor xenograft growth.[24] Additionally, SSRIs reduce growth hormone and insulin-like growth factor (IGF) levels, and IGF participates in progression of BE to EAC, based on immunohistochemical analysis of human BE, LGD, HGD and EAC.[25] Either of these mechanisms could potentially account for the protective effect of SSRIs. Vitamin D receptor expression is upregulated in BE, indicating a potential mechanism for the protective effect of vitamin D.[26]

Our study possesses several strengths. We investigated a large cohort of patients previously diagnosed with BE over a 21-year period, some of whom developed EAC or HGD during follow-up. This study comprehensively examined clinical, epidemiological, endoscopic, and histopathological risk factors. We documented not only basic clinical information, but also all medications taken, prior medical history, family history, endoscopy reports, and pathology findings. Many prior studies assessing risk factors were not so comprehensive. We also used

multivariate regression modeling to limit confounding factors, unlike most published studies. Additionally, we included large sub-cohorts of patients with HGD (132 patients) or EAC (62 patients), allowing us to explore differences between progressors and non-progressors.

One limitation of our study was its retrospective nature and its restriction to one academic center. Also, some bias may have occurred due to the tertiary nature of our center and the fact that many higher-risk patients were referred from other centers because of advanced endoscopic therapies available at our hospital. Thus, 29.4% of patients with BE in our study progressed to develop HGD or EAC, a rate higher than the general BE population. Therefore, one could argue this poses a threat to external validity. However, we should be aware that our study period includes the period of 1990's where low-resolution endoscopes were used; thus, subtle abnormalities or early neoplastic lesions in the BE segment could have easily been missed. This could lead to inclusion of patients with prevalent advanced neoplasia at baseline that was missed on the initial endoscopy, explaining for the high progression rate among patients with NDBE.

In conclusion, this retrospective study validates several previously identified risk factors for BE progression, including age, heavy smoking, abdominal obesity, long-segment BE, and dysplasia, but it also identifies novel risk factors, including colonic adenomas and caffeine intake. We also identified statins, SSRIs, and supplemental calcium and vitamin D as potential protective agents, each with its own biologically plausible mechanisms. These medications merit further exploration in prospective studies, along with risk factors we identified, to improve identifying patients at greatest progression risk and thus likely to benefit from more frequent endoscopic surveillance and/or earlier endoscopic therapy.

Table 1. Baseline characteristics of BE patients identified as progressors vs non-progressors

	Non-Progressors (272)	**Progressors** (188)
Demographics		
Age	67.01 +/- 12.99	74.34 +/- 11.73
Gender (% Male)	174(64%)	146 (78%)
Race		
Non-Hispanic Caucasian	247 (91%)	184 (98%)
African American	16 (6%)	0 (0%)
Hispanic	3 (1%)	4 (2%)
Asian	6 (2%)	0 (0%)
BMI		
< 25	62 (23%)	30 (16%)
25-30	100 (37%)	67 (36%)
> 30	110 (41%)	91 (49%)
Alive	263 (97%)	178 (95%)
Smoking History		
Never	138 (51%)	84 (45%)
Former Smoker	100 (37%)	84 (45%)
Current Smoker	34 (12%)	20 (10%)
Alcohol Use		
Never	133 (49%)	72 (38%)
Former Social Drinker	11 (4%)	9 (5%)
Former Heavy Drinker	15 (5%)	12 (6%)
Current Social Drinker	108 (40%)	93 (49%)
Current Heavy Drinker	5 (2%)	2 (1%)
Illicit Drug use		
Never	253 (93%)	180 (96%)
Former User	8 (3%)	2 (1%)
Current User	11 (4%)	6 (3%)
Family History of Cancer	98 (36%)	96 (51%)
Family History of BE	5 (2%)	5 (3%)
Family History of Esophageal Cancer	8 (3%)	8 (4%)
Family History of GERD	5 (2%)	11 (6%)

Medications		
NSAIDs	35 (13%)	28 (15%)
PPIs	253 (93%)	184 (98%)
H2 Blockers	27 (10%)	7 (4%)
Statins	103 (38%)	66 (35%)
Aspirin	82 (30%)	54 (29%)
Metformin	22 (8%)	7 (4%)
Oral Diabetic Medications	8 (3%)	2 (1%)
Insulin	11 (4%)	13 (7%)
ACEI	46 (17%)	38 (20%)
ARB	68 (25%)	45 (24%)
B-Blocker	27 (10%)	23 (12%)
CCB	38 (14%)	34 (17%)
Benzos	19 (7%)	9 (5%)
SSRI	35 (13%)	9 (5%)
ACEI/ARB	73 (27%)	58 (31%)
Calcium/Vitamin D	56 (19%)	17 (9%)
Diuretics	54 (20%)	36 (19%)
Medical History		
Esophagitis	90 (33%)	60 (32%)
Gastric Ulcer	5 (2%)	4 (2%)
Duodenal Ulcer	5 (2%)	7 (4%)
H. pylori	8 (3%)	2 (1%)
Gastritis	40 (15%)	23 (12%)
Esophageal stricture	11 (4%)	15 (8%)
Esophageal Web	2 (1%)	0 (0%)
Schatzki Ring	16 (6%)	4 (2%)
GERD	266 (98%)	186 (99%)
Colonic Adenomas	65 (24%)	70 (37%)
Prior Cholecystectomy	33 (12%)	34 (18%)
Prior Anti-Reflux Surgery	16 (6%)	7 (4%)
Personal History of Cancer	35 (13%)	19 (15%)
Hypertension	141 (52%)	113 (60%)
Diabetes Mellitus	32 (12%)	24 (13%)
Hyperlipidemia	87 (32%)	46 (34%)
Coronary Artery Disease	35 (13%)	38 (20%)
Prior stroke	5 (2%)	5 (3%)
Chronic Kidney Disease	8 (3%)	5 (3%)

Anemia	29 (11%)	7 (4%)
Solid Organ Transplant	3(1%)	2 (1%)
Caffeine Use	112 (41%)	105 (56%)
Heartburn	264 (97%)	180 (96%)
Dysphagia	27 (10%)	38 (20%)
Regurgitation	33 (12%)	36 (19%)
Endoscopic Characteristics		
Hiatal Hernia	133 (49%)	100 (53%)
Size of Hiatal Hernia		
Small	76 (28%)	43 (23%)
Medium	22 (8%)	19 (10%)
Large	35 (13%)	36 (19%)
Circumferential BE	35 (13%)	107 (57%)
Single BE Tongue	256 (94%)	173 (92%)
Multiple BE Tongues	16 (6%)	15 (8%)
Short Segment BE	215 (79%)	71 (38%)
Long Segment BE	52 (19%)	116 (62%)
Esophageal Ulcer Presence	5 (2%)	4 (2%)

Figure 1. Flow-chart of patients enrolled in the study and their outcomes in regard to progression.

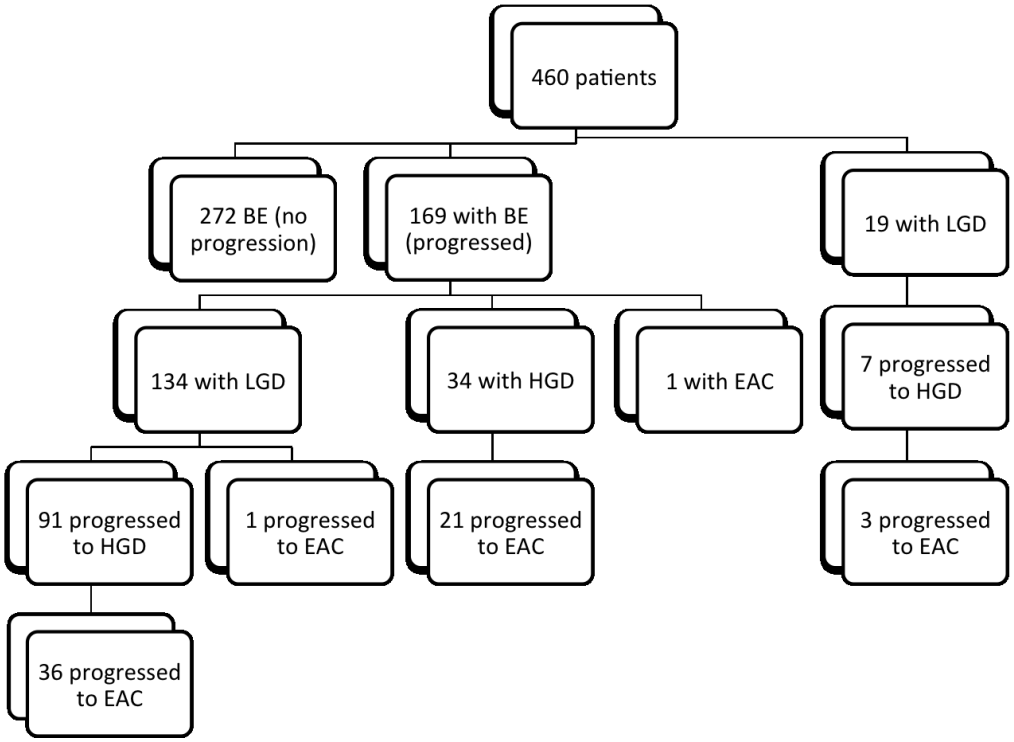


Figure 2. Cumulative Incidence Curves for progression to HGD and EAC for BE patients.

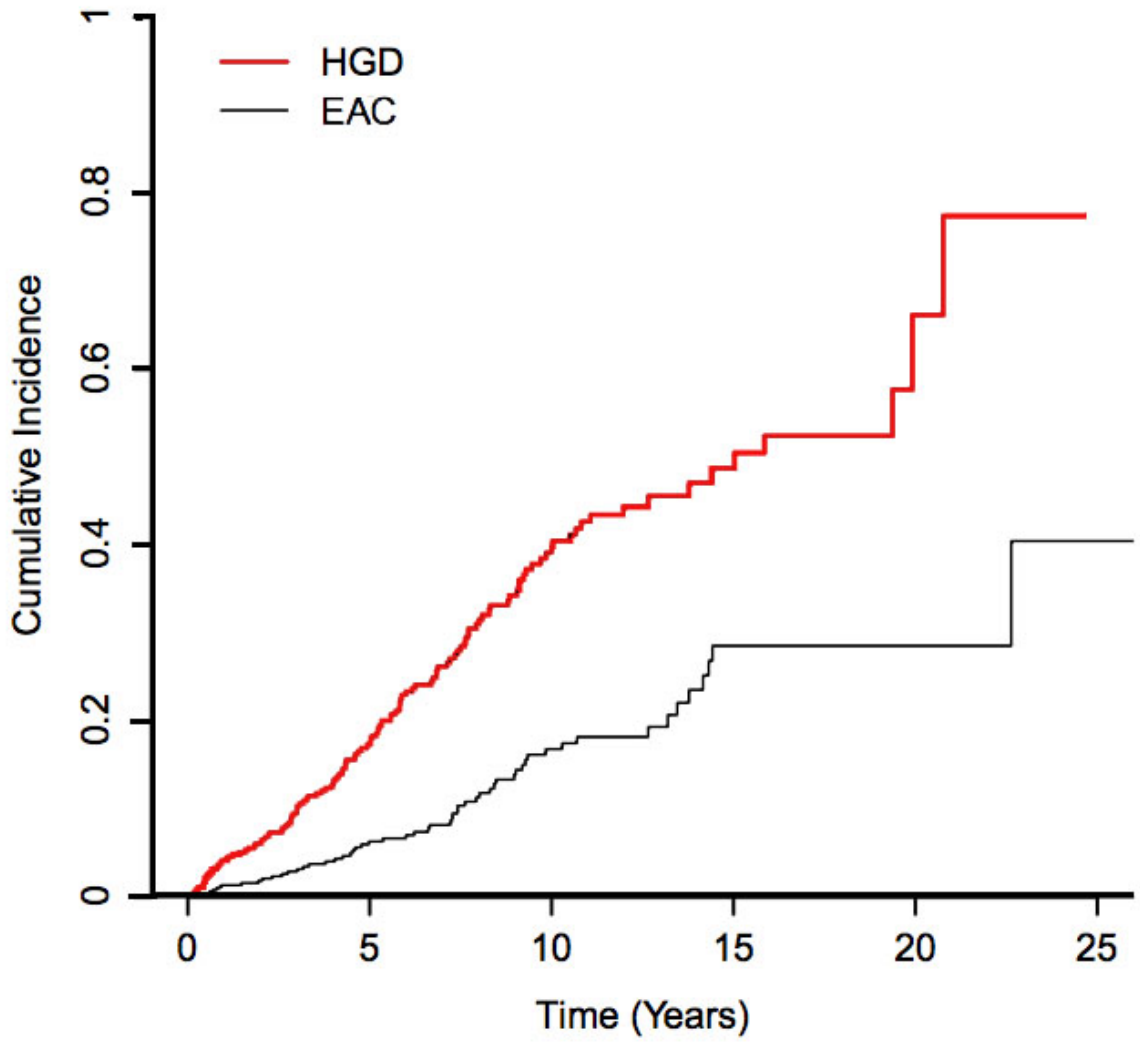
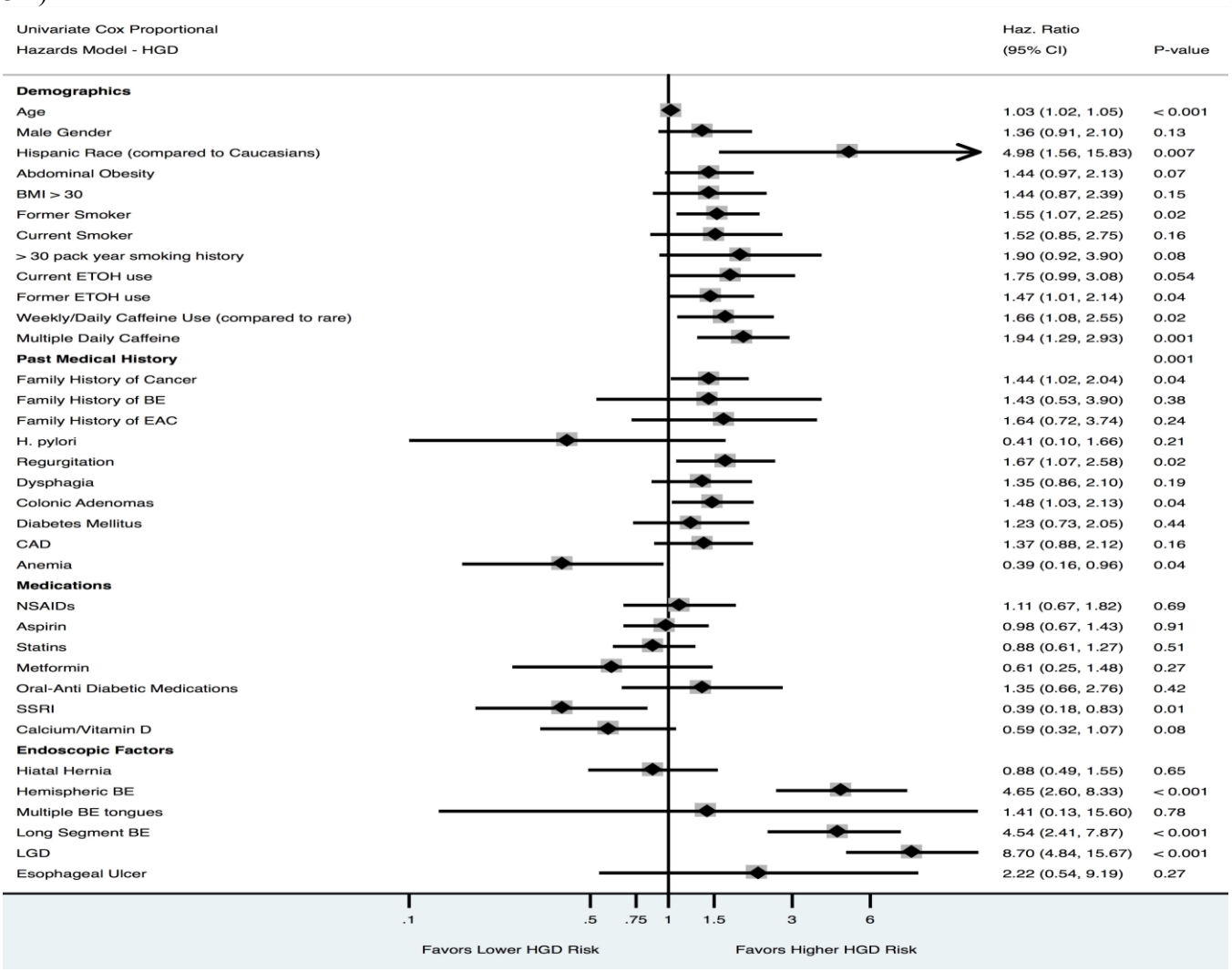


Figure 3. Univariate (3A) and Multivariate (3B) Cox Proportional Hazards Ratios for EAC.

3A)



3B)

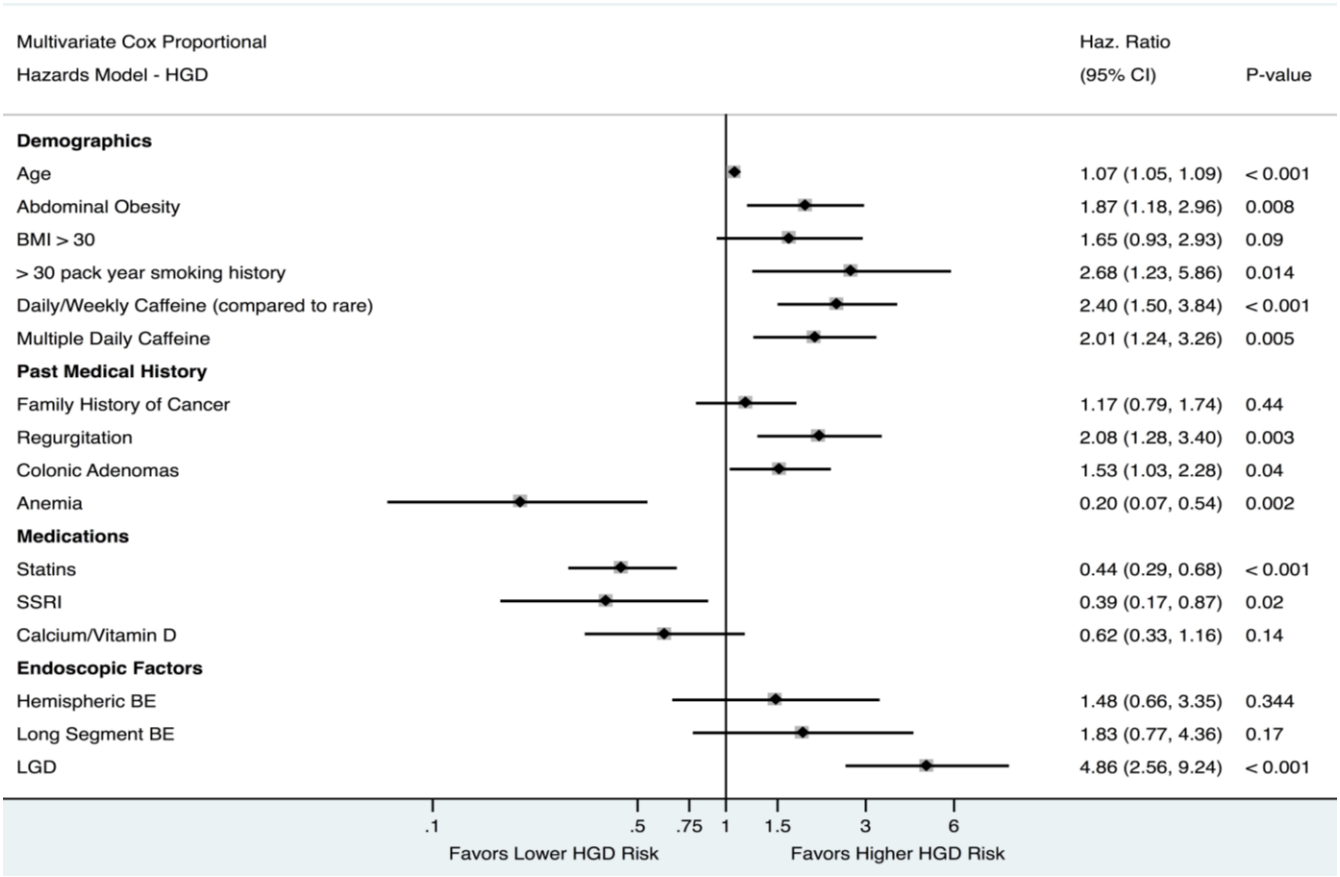
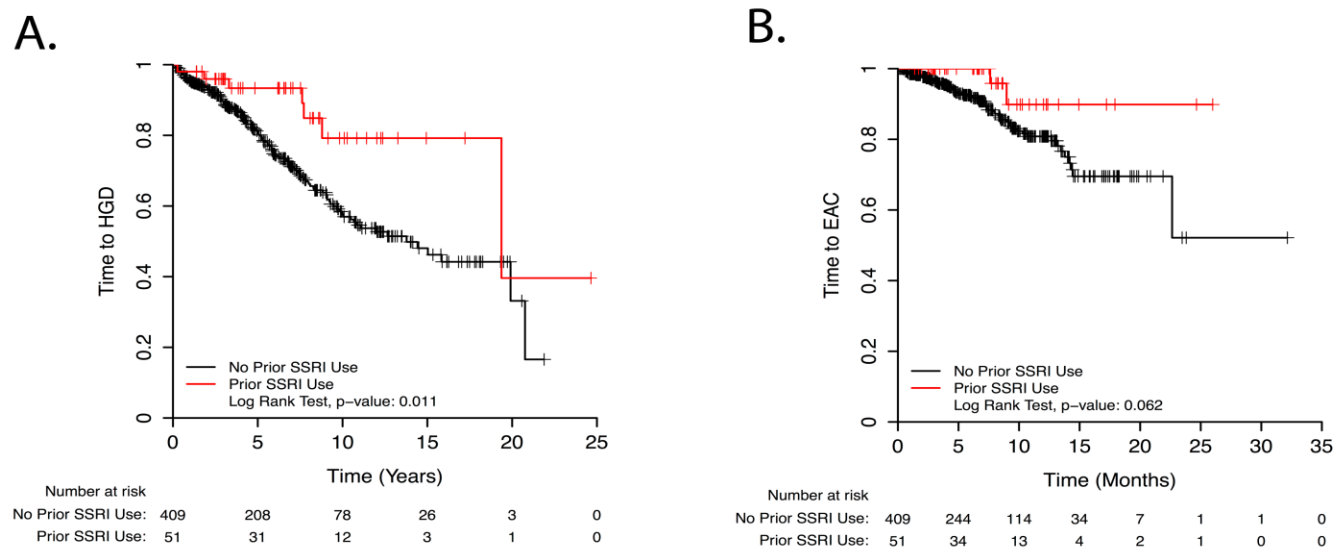

Multivariate Cox Proportional Hazards Model - HGD
Haz. Ratio (95% CI)
P-value
Demographics
Age 1.07 (1.05, 1.09) < 0.001
Abdominal Obesity 1.87 (1.18, 2.96) 0.008
BMI > 30 1.65 (0.93, 2.93) 0.09
> 30 pack year smoking history 2.68 (1.23, 5.86) 0.014
Daily/Weekly Caffeine (compared to rare) 2.40 (1.50, 3.84) < 0.001
Multiple Daily Caffeine 2.01 (1.24, 3.26) 0.005
Past Medical History
Family History of Cancer 1.17 (0.79, 1.74) 0.44
Regurgitation 2.08 (1.28, 3.40) 0.003
Colonic Adenomas 1.53 (1.03, 2.28) 0.04
Anemia 0.20 (0.07, 0.54) 0.002
Medications
Statins 0.44 (0.29, 0.68) < 0.001
SSRI 0.39 (0.17, 0.87) 0.02
Calcium/Vitamin D 0.62 (0.33, 1.16) 0.14
Endoscopic Factors
Hemispheric BE 1.48 (0.66, 3.35) 0.344
Long Segment BE 1.83 (0.77, 4.36) 0.17
LGD 4.86 (2.56, 9.24) < 0.001
.1
.5
.75
1
1.5
3
6
Favors Lower HGD Risk
Favors Higher HGD Risk

Figure 4. Kaplan–Meier Survival Curves for progression to HGD (4A), EAC (4B), and HGD/EAC (4C) comparing SSRI users and non-SSRI users.



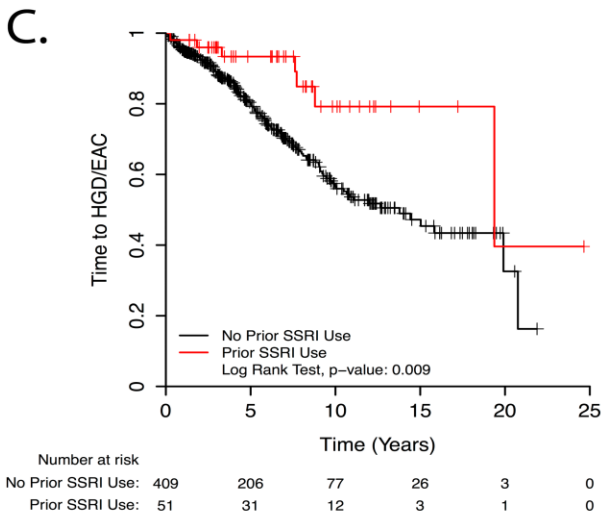
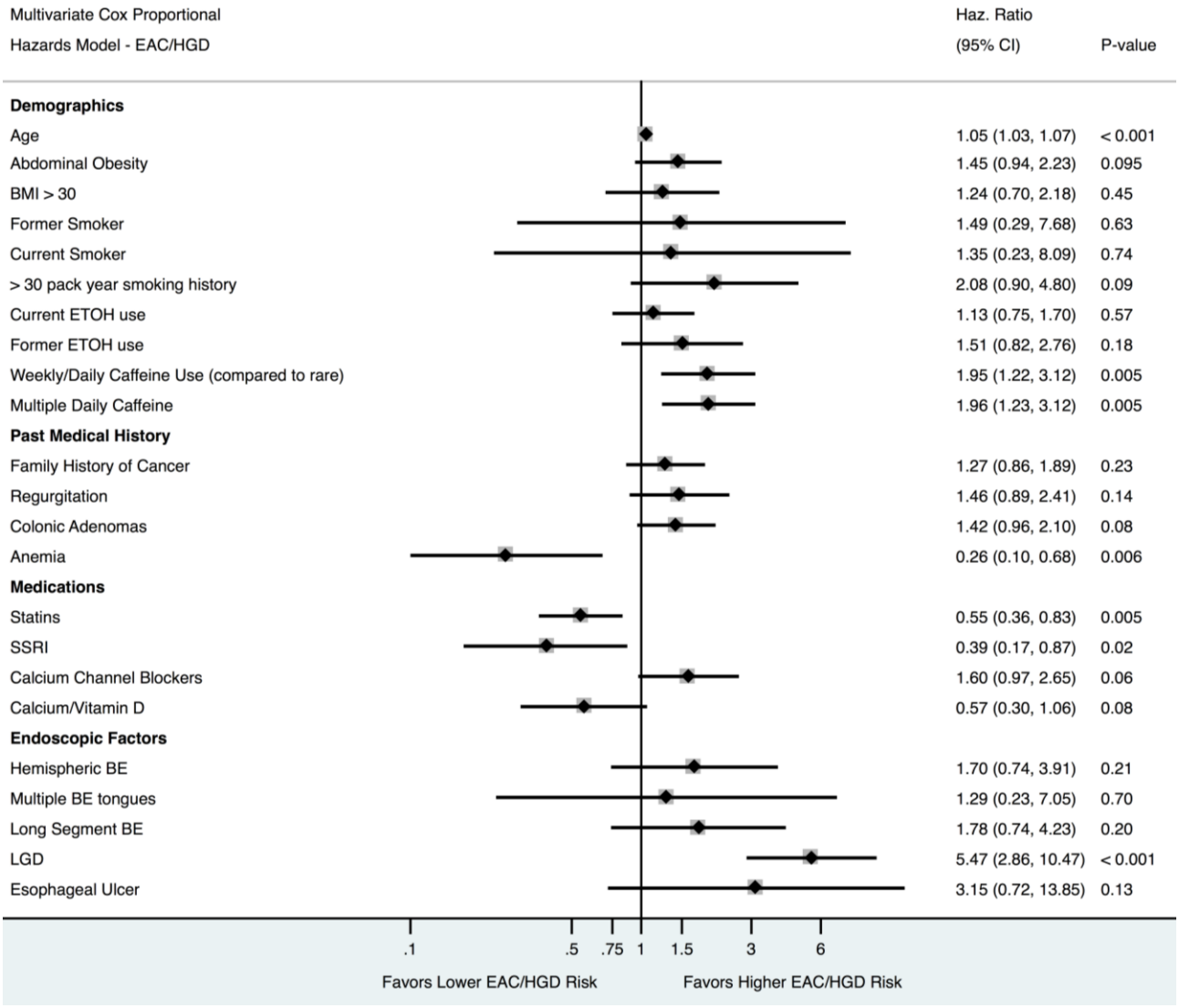


Figure 5. Multivariate Cox Proportional Hazards Ratio for EAC/HGD.



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12. Sajja KC, El-Serag HB, Thrift AP. Coffee or Tea, Hot or Cold, Are Not Associated With Risk of Barrett's Esophagus. Clin Gastroenterol Hepatol 2016;14:769-72.
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20. Corley DA, Mehtani K, Quesenberry C, et al. Impact of endoscopic surveillance on mortality from Barrett's esophagus-associated esophageal adenocarcinomas. Gastroenterology 2013;145:312-9 e1.
21. Visrodia K, Singh S, Krishnamoorthi R, et al. Magnitude of Missed Esophageal Adenocarcinoma After Barrett's Esophagus Diagnosis: A Systematic Review and Meta-analysis. Gastroenterology 2016;150:599-607 e7; quiz e14-5.
22. Visrodia K, Singh S, Krishnamoorthi R, et al. Systematic review with meta-analysis: prevalent vs. incident oesophageal adenocarcinoma and high-grade dysplasia in Barrett's oesophagus. Aliment Pharmacol Ther 2016;44:775-84.
23. Kastelein F, Spaander MC, Biermann K, et al. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett's esophagus. Gastroenterology 2011;141:2000-8; quiz e13-4.
24. Yue CT, Liu YL. Fluoxetine increases extracellular levels of 3-methoxy-4-hydroxyphenylglycol in cultured COLO320 DM cells. Cell Biochem Funct 2005;23:109-14.
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26. Trowbridge R, Mittal SK, Sharma P, et al. Vitamin D receptor expression in the mucosal tissue at the gastroesophageal junction. Exp Mol Pathol 2012;93:246-9.
27. Sangle NA, Taylor SL, Emond MJ, et al. Overdiagnosis of high-grade dysplasia in Barrett's esophagus: a multicenter, international study. Mod Pathol 2015;28:758-65.

CURRICULUM VITAE

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Citizenship Status: USA

Education & Academic Training

9/2002-6/2006	University of California, San Diego (UCSD), La Jolla, CA Bachelor of Science (BS) in Biochemistry and Cell Biology; Minor in Chinese Studies, *Magna Cum Laude, Phi Beta Kappa (PBK)*
7/2008-5/2012	Howard University College of Medicine, Washington, DC Doctor of Medicine (M.D), *Top Honors*, *Alpha Omega Alpha (AOA)*
7/2012-6/2013	The Johns Hopkins Hospital, Department of Medicine, Baltimore, MD Internship, Osler Internal Medicine Residency Program
7/2013-6/2015	The Johns Hopkins Hospital, Department of Medicine, Baltimore, MD Residency, Osler Internal Medicine Residency Program
7/2015-present	The Johns Hopkins Hospital, Division of Gastroenterology and Hepatology, Department of Medicine, Baltimore, MD Clinical and Research Fellowship, Gastroenterology and Hepatology, Clinical Investigator Track (NIH-T32 Track)
7/2016-present	The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD Master of Science (ScM) in Clinical Investigation, Graduate Training Program in Clinical Investigation (GTPCI)

Current Position

7/2018-6/2019	The Johns Hopkins Hospital, Division of Gastroenterology and Hepatology, Department of Medicine, Baltimore, MD Chief Fellow of Gastroenterology and Hepatology

Licensures

10/2015-present	Marlyland License D81226; Maryland CDS #M86740; DEA #FT5904518 Certified in American Board of Internal Medicine (ABIM) #374182

Peer-Review Journal Publications

1. El Zein M, Kumbbari V, **Tieu A**, Saxena P, Messallam A, Azola A, Li Z, Weiss M, Khashab M. Duodenal perforation as a consequence of biliary stent migration can occur regardless of stent type or duration. Endoscopy 2014; 46:E281-E282. PMID: 24906101

2. **Tieu AH**, Saxena A, Singh V, Lennon A, Kumbhari V, Messallam A, El Zein M, Kalloo A, Khashab M. Fenestrations of a covered metallic stent during cystoduodenostomy by using argon plasma coagulation (with Video). Endoscopy. 2014; 46(S 01):E512-E513. PMID: 25409043

3. Kumbhari V, Storm A, **Tieu AH**, Saxena P, Messallam A, El Zein M, Azola A, Khashab M, Okolo P. Percutaneous flexible endoscopic necrosectomy for a retroperitoneal abscess (with Video). Endoscopy 2014; 46:E340-1. PMID: 25090470

4. Kumbhari V, Saxena P , Messallam A, Aguila G, **Tieu AH** , El-Zein M, Kalloo A, Khashab M. Fluoroscopy to Document the Extent of Cardiomyotomy During POEM. Endoscopy 2014 0;46(S 01):E369-E370. PMID: 25254580

5. Kumbhari V, Azola A, **Tieu AH**, Sachdeva R, Saxena P, Messallam A, El Zein M, Okolo P, Khashab M. Iatrogenic Pharyngoesophageal Perforations Treated with Fully Covered Self-Expandable Metallic Stents (with Video). Surg Endosc. 2014 Aug 23. PMID: 25149633

6. Kumbhari V, **Tieu AH**, Saxena P, Khashab M, Okolo P. Closure of a Large, Persistent Enterocutaneous Fistula Using a Ventricular Septal Occluder. Gastrointestinal Endoscopy 2014; Aug 15. pii: S0016-5107(14)01952-X. PMID: 25135689

7. **Tieu AH**, Edelstein D, Axilbund J, Romans K, Brosens L, Wiley E, Hylind L, Giardiello FM. Clinical Characteristics and Natural History of Multiple Colorecta Adenoma Patients Without Germline APC or MYH/MUTYH Mutations. J Clin Gastroenterol. 2015 Oct 17. PMID: 26485104

8. **Tieu AH**, Kumbhari V, Jakhete N, Onyimba F, Patel Y, Shin EJ, Li Z. Diagnostic and therapeutic utility of Spyglass peroral cholangioscopy in intraductal pancreaticobiliary disease: a single-center, retrospective, cohort study. Digestive Endoscopy 2014 Nov 13 doi: 10.1111/den.12405. PMID 25394296

9. Abdelgelil A, Kumbhari V**, Tieu AH**, Beshrati S, Ngamruengphong S, El-Zein M, Aguila G, Khashab MA. Snare-Over-Scope Technique for Retrieval of a Proximally Migrated Biliary Stent. Endoscopy. 2014 0;46 (S 01):E650-E651. PMID: 25526408

10. Kumbhari V, **Tieu AH**, Onimaru M, El Zein M, Modayil R, Teitelbaum E, Azola A, Hungness E, Gitelis M, Messallam A, Stavropoulos S, Ujiki M, Shiwaku H, Chiu P, Saxena P, Inoue H, Khashab M. Peroral Endoscopic Myotomy (POEM) versus Laparoscopic Heller Myotomy (LHM) for the Treatment of Type III Achalasia in 75 Patients: An International Multicenter Experience. Endosc Int Open. 2015 Jun;3(3):E195-201. doi: 10.1055/s-0034-1391668. PMID: 26171430

11. Kumbhari V, Besharati S, Abdelgelil A, **Tieu AH**, Saxena P, El-Zein M, Ngamruengphong S, Aguila G , Kalloo A, Khashab MA. Intraprocedural Fluoroscopy to Determine the Extent of

the Cardiomyotomy During POEM (with Video). Gastrointestinal Endoscopy 2015 Apr 14. pii: S0016-5107(15)00103-0. doi: 10.1016/j.gie.2015.01.052. PMID: 25887723

12. Kumbhari V, **Tieu AH**, Khashab MA. Common Indications for Transoral Flexible Endoscopic Suturing. Gastrointestinal Endoscopy 2015 Feb 5. pii: S0016-5107(14)02394-3. doi: 10.1016/j.gie.2014.10.038. PMID: 25660976

13. Kumbhari V, **Tieu AH**, Khashab MA. EUS-guided Biliary Drainage Made Safer Using The Combination of Hepaticogastrostomy and Antegrade Transpapillary Stenting. Gastrointestinal Endoscopy 2014 Dec 5. pii: S0016-5107(14)02375-X. PMID 25484328

14. **Tieu AH,** Kumbhari V, Saxena P, Khashab MA. Flexible Endoscopic Zenker's Diverticulotomy. Gastrointestinal Endoscopy 2015 Apr 9. pii: S0016-5107(15)00006-1. doi: 10.1016/j.gie.2015.01.004. PMID 25865389

15. Sachdeva R, Tsai SD, El-Zein M, **Tieu AH**, Abdelgilil A, Besharati S, Khashab MA, Kalloo A, Kumbhari V. Predictors of Incomplete Optical Colonoscopy using Computed Tomographic Colonography. Saudi J Gastroenterol. 2016 Jan-Feb;22(1):43-9. doi: 10.4103/1319-3767.173758. PMID 26831606

16. Onyimba F, Kumbhari V, **Tieu AH**, Cai JX, Abdelgelil A, Reddy A, Khashab MA, Okolo P. Benign Distal Juojenal Stricture Treated by Partially Covered Esophageal Stent with the Use of Spiral Enteroscopy. Endoscopy 2015 0;47(S 01):E117-E118. PMID 25857468.

17. Kumbhari V, Cai JX, **Tieu AH**, Kalloo A, Khashab MA. Over-the-scope clips for Transoral Gastric Outlet Reduction as Salvage Therapy for Weight Regain post RYGB. Endoscopy. 2015;47 Suppl 1:E253-4. doi: 10.1055/s-0034-139195. PMID: 26099077

18. Kumbhari V, **Tieu AH**, Ngamreungphong S, Aguila G, Schweitzer MA, Khashab MA, Singh VK. Endoscopic Management of Stomal Stenosis After Roux-en-Y Gastric Bypass. Gastrointest Endosc. 2015 Jun 25. pii: S0016-5107(15)02486-4. doi: 10.1016/j.gie.2015.05.032. PMID: 26119649

19. Kumbhari V, **Tieu AH**, Cai JX, Okolo P III, Schweitzer MA, Khashab MA. Novel Technique for the Management of Staple Line Leaks Following Sleeve Gastrectomy. Gastrointest Endosc. 2015 Jun 25. pii: S0016-5107(15)02487-6. doi: 10.1016/j.gie.2015.05.033

20. Khashab MA, Besharati S, Ngamreungphong S, Kumbhari V, El Zein M, Stein E, **Tieu AH**, Mullin G, Dhalla S, Nandwani M, Singh V, Canto M, Kallo A, Clarke JO. Refractory Gastroparesis Can Be Successfully Managed with Endoscopic Transpylori Stent Placement and Fixation. Gastrointest Endosc. 2015 Aug 5. pii: S0016-5107(15)02623-1. doi: 10.1016/j.gie.2015.06.051. PMID: 26253017

21. Ngamneungphong S, Kumbhari V, **Tieu AH**, Okolo P III. Endoscopic Reversal of Gastric Bypass for Severe Malnutrition following Roux-en-Y Gastric Bypass Surgery. Gastrointest Endosc. 2015 Jun 9. pii: S0016-5107(15)02408-6. doi: 10.1016/j.gie.2015.05.004. PMID: 26071065

22. Kumbhari V, Peñas I, **Tieu AH,** De la Serna C, Juneje M, Maufa F, Ngamreungphong S, El-Zein M, Haddad N, Krishnan S, Gonzalez S, Renny P, Saxena P, DiMaio C, Buscaglia J, Perez-Miranda M, Khashab M. Interventional EUS using the flexible 19-gauge EUS-FNA needle: An International Multicenter Experience in 162 patients. Dig Dis Sci. 2016 Oct 6. PMID: 27714511

23. Kumbhari V, **Tieu AH**, Azola A, Saxena P, Ngamreungphong S, El Zein M, Khashab MA. Double POEM for Achalasia. Gastrointest Endosc. 2015 Jun 25. pii: S0016-5107(15)02490-6. doi: 10.1016/j.gie.2015.05.036. PMID: 26119650

24. Khashab MA, **Tieu AH**, Azola A, Ngamreungphong S, El Zein M, Kumbhari V. EUS-guided Gastrojejunostomy for Management of Complete Gastric Outlet Obstruction. Gastrointest Endosc. 2015 Jun 16. pii: S0016-5107(15)02436-0. doi: 10.1016/j.gie.2015.05.017. PMID: 26092615

25. Kumbhari V, **Tieu AH**, Azola A, Ngamreungphong S, El Zein M, Khashab MA. Novel Endoscopic Approach for a Large Intraluminal Duodenal ("Windsock") Diverticulum. Gastrointest Endosc. 2015 Jun 25. pii: S0016-5107(15)02513-4. doi: 10.1016/j.gie.2015.05.055. PMID: 26119648

26. Ngamneungphong S, Kumbhari V, **Tieu AH**, Haito-Chavez Y, El-Zein M, Aguila G, Khashab MA. EUS-Guided Rescue of Early Dislodgement of a Lumen-Apposing Stent. Gastrointest Endosc. 2015 Jul 11. pii: S0016-5107(15)02533-X. doi: 10.1016/j.gie.2015.06.009. PMID: 26175334

27. Khashab MA, El Zein M, Kumbhari V, Besharati S, Ngamreungphong S, Messallam A, Abdelgalil A, Saxena P, **Tieu AH**, Raja S, Stein E, Dhalla S, Garcia P, Singh VK, Pasricha PJ, Kallo A, Clarke JO. Comprehensive analysis of efficacy and safety of peroral endoscopic myotomy performed by a gastroenterologist in the endoscopy unit: a single-center experience. Gastrointest Endosc. 2015 Jul 24. pii: S0016-5107(15)02540-7. doi: 10.1016/j.gie.2015.06.013. PMID: 26212369

28. Khashab MA, El Zein M, Ngamreungphong S, Chavez YH, Kumbhari V, Ismail A, **Tieu AH**, Aguila G, Singh VK, Lennon AM, Canto MI, Kallo AN. Double endoscopic bypass by using lumen-apposing stents (with videos). Gastrointest Endosc. 2016 Feb;83(2):435-9. doi: 10.1016/j.gie.2015.09.041. PMID: 26773639

29. Sharaiha RZ, Tyberg A, Khashab MA, Kumta NA, Karia K, Nieto J, Siddiqui UD, Waxman I, Joshi V, Benias PC, Darwin P, DiMaio CJ, Mulder CJ, Friedland S, Forcione DG, Sejpal DV, Gonda TA, Gress FG, Gaidhane M, Koons A, DeFilippis EM, Salgado S, Weaver KR, Poneros JM, Sethi A, Ho S, Kumbhari V, Singh VK, **Tieu AH**, Para V, Likhitsup A, Womeldorph C, Casey B, Jonnalagadda SS, Desai AP, Carr-Locke DL, Kahaleh M, Siddiqui AA, Endoscopic Therapy With Lumen-apposing Metal Stents is Safe and Effective for Patients With Pancreatic Walled-off Necrosis, Clinical Gastroenterology and Hepatology (2016), doi: 10.1016/j.cgh.2016.05.011. PMID: 27189914

30. El Zein M, Kumbhari V, Ngamruengphong S, Carson KA, Stein E, **Tieu AH**, Chaveze Y, Ismail A, Dhalla S, Clarke J, Kalloo A, Canto MI, Khashab MA. Learning curve for peroral endoscopic

myotomy. Endosc Int Open. 2016 May;4(5):E577-82. doi: 10.1055/s-0042-104113. PMID:27227118

31. Ngamruengphong S, Kumbhari V, **Tieu AH**, Haito-Chavez Y, Bukhari M, Hajiyeva G, Ismail A, Aguila G, Chen YI, Khashab MA. A novel "balloon/snare apparatus" technique to facilitate easy creation of fistula tract during EUS-guided gastroenterostomy. Gastrointest Endosc. 2016 Apr 2. pii: S0016-5107(16)30009-8. doi: 10.1016/j.gie.2016.03.1493. PMID 27048972

32. **Tieu AH**, Kumbhari V, Ngamruengphong S, Haito-Chavez Y, Chen Y-I, Bukhari M, Khashab MA, Two-staged endoscopic approach for the management of a large symptomatic epiphrenic diverticulum in the setting of achalasia, *Gastrointestinal Endoscopy* (2016), doi: 10.1016/ j.gie.2016.06.005.

33. Cai JX, Diehl DL, Kiesslich R, Storm AC, El Zein MH, **Tieu AH**, Hoffman A et al. A multicenter experience of through-the-scope balloon-assisted enteroscopy in surgically altered gastrointestinal anatomy. *Surg Endosc.* 2017 Jul;31(7):2753-2762. doi: 10.1007/s00464-016-5282-2. Epub 2016 Dec 30. PMID 28039647

34. Khashab MA, Kumbhari V, **Tieu AH**, El Zein MH, Ismail A et al. Peroral endoscopic myotomy achieves similar clinical response but incurs lesser charges compared to robotic heller myotomy. *Saudi J Gastroenterol.* 2017 Mar-Apr;23(2):91-96. doi: 10.4103/1319-3767.203360. PMID 28361839

35. Kumbhari V, Familiari P, Bjerregaard NC, Pioche M, Jones E, Ko WJ, Hayee B, Cali A, Ngamruengphong S, Mion F, Hernaez R, Roman S, **Tieu AH**, El Zein M et al. Gastroesophageal reflux after peroral endoscopic myotomy: a multicenter case-control study. *Endoscopy.* 2017 Jul;49(7):634-642. doi: 10.1055/s-0043-105485. Epub 2017 May 4. PMID 28472834

36. Brotman DJ, Shihab H, Bertram A, **Tieu AH**, Cheng H, Hoyer E, Durkin N et al. Patient Perceptions of readmission risk: an exploratory survey. *J Hosp Med. 2018* Mar 26. doi: 10.12788/jhm.2958. PMID 29578549

37. Wang Z, Kambhampati S, Cheng Y, Ma K, Simsek C, **Tieu AH**, Abraham J et al. Methylation Biomarker Panel Performance in EsophaCap Cytology Samples for Diagnosing Barrett's Esophagus: A Prospective Validation Study**.** *Clin Cancer Res*. 2019 Jan 22. pii: clincanres.3696.2018. doi: 10.1158/1078-0432.CCR-18-3696. PMID 30670490

38. **Tieu AH**, Song JH, Cheng Y, Ma K, Prasath V, Abraham JM et al. Novel Long Non-Coding RNA *MIR205HG*: an Esophageal Tumor-Suppressive Hedgehog Inhibitor. (Submitted to Gastroenterology)

Book Chapters

1. **Tieu AH**, Kumbhari V, Khashab MA (2016). The Management of Mallory-Weiss Syndrome. Current Surgical Therapy 12th edition. Philadelphia: Elsevier; 2016. **ISBN-10:** 0323376916

In Press

1. Test for esophageal cancer could save millions of lives.
   https://www.sciencedaily.com/releases/2019/01/190122114915.htm
2. Flexible endoscopic Zenker's diverticulotomy
   https://endoscopedia.com/2015/06/13/flexible-endoscopic-zenkers-diverticulotomy/

Teaching Experiences

07/2017-present — Medical Students Small Group Leader, The Johns Hopkins School of Medicine
- Lead and teach 2nd and 3rd year medical students in gastroenterology physiology and pathology topics

5/2009-7/2009 — MedSTARS Teaching Instructor, Howard University College of Medicine, Washington, D.C.
- One of 3 students selected by faculty to instruct first year medical students in disciplines of anatomy, histology, embryology, cardiovascular, respiratory, and reproductive physiology**.**
- Prepared 10 oral presentations, provided structured review and developed examination questions.

3/2010-2012 — YMCA Tutor, Washington, D.C.
- Served as mentor and role model for elementary, middle, and high school students.
- Assisted with homework and advises students on study habits.

9/2008-2012 — Assistant Coach, Evergreen Badminton Club, Alexandria, Virginia
- Served as teacher and coach for badminton to youth.

2005 — Teaching Assistant, UC San Diego, Department of Biology, La Jolla, CA
- Taught and supervised introductory biology labs and organized review sessions before exams.

Honors and Awards

2016 — Teaching Fellow Award of the Year, Department of Medicine, Johns Hopkins Hospital, Baltimore, MD
- Awarded as only one fellow in the entire department of medicine by the Osler medicine housestaff and faculty

2012 The Lee B. Ashe Memorial Student Research Award, Howard University College of Medicine, Washington, D.C.
- Awarded to the graduating senior who have demonstrated excellence in research and scholarship

2011 *Alpha Omega Alpha (AOA)* Honor Medical Society Inductee, Gamma Chapter , Howard University College of Medicine, Washington, D.C.

2008- 2012 Class rank: #5
- Ranking out of a class of 120 matriculants at Howard University College of Medicine, Washington, D.C.

2011 Pfizer Minority Medical Student Scholarship and Award, Washington, D.C.
- Awarded per Dean's nomination based on academic performance, excellence in biomedical research, leadership and service.

2011 Dr. JC Carr Foundation Merit Achievement Award and Scholarship
- Awarded to the student top 25% of the respective class at Howard University College of Medicine, Washington, D.C.

2010-2012 Howard University Board of Trustees Academic Scholarship
- One half tuition offer after demonstrating academic excellence during the second and third year medical school.

2010 Dr. Linda Fardan Scholarship, Howard University College of Medicine
- Awarded to student based on personal needs and academic performance.

2009 Outstanding MedStars Teaching Award, Howard University College of Medicine, Washington, D.C.
- Awarded for teaching first year medical students in disciplines of anatomy, embryology, physiology, and histology.

2009 Howard University Robert Lee Academic Scholarship, Washington, D.C.
- One half tuition offer after demonstrating academic excellence during the first year medical school.

2008 Howard University College of Medicine, Endowed Scholarship Fund
- One third tuition offer upon acceptance to medical school for high academic achievement.

2008-2012 HRSA Scholarships for Disadvantaged Students (SDS), Washington, D.C.
- US Department of Health and Human Services Federal Scholarships for underserved health professional students based on academic performance and personal needs.

2006 Phi Beta Kappa, Sigma Chapter, UC San Diego, La Jolla, CA

- Elected in senior year at UC San Diego on basis of high scholastic achievement and the breadth of academic background.

2002-2006 Provost's Honors, UC San Diego, La Jolla, CA
- Awarded quarterly based upon the completion of twelve graded units or greater, with a GPA of 3.5 or higher.

2002-2006 UCSD Millenium Scholar, UC San Diego, La Jolla, CA
- Merit scholarship offered upon acceptance.

2002 UC San Diego Community Service Award
- Awarded for excellence in volunteer work within the greater area of San Diego, CA.

Professional Memberships and Affiliations

- American College of Physicians (ACP)
- *Phi Beta Kappa* Honors Society, life member
- *Alpha Omega Alpha (AOA)* Medical Honors Society, life member
- American Gastroenterological Association (AGA), member
- American College of Gastroenterology (ACG), member
- American Society of Gastrointestinal Endoscopy (ASGE), member

Personal Hobbies & Interests

Traveling, cooking, competitive badminton player, having won multiple local tourmanents, and coach badminton.

Languages

Intermediate reading, writing, and conversational skills in Vietnamese.