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Aspirin Protects Against Barrett's Esophagus in a Multivariate Logistic Regression Analysis

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Abstract

Background & Aims—Better criteria are needed to identify patients that should be screened for Barrett's esophagus (BE), to reduce over-testing and improve the cost effectiveness. There is evidence that chemopreventive agents such as non-steroidal anti-inflammatory drugs—particularly aspirin—reduce the risk of esophageal adenocarcinoma (EAC), but little is known about their effects on BE. We analyzed characteristics of patients with BE for factors that might be used in screening and management.

Methods—In this case-controlled study, we identified 434 patients with BE diagnosed at the first endoscopy (incident cases) at a single institution (1997–2010). BE cases were matched with controls on the basis of indication for endoscopy, year of endoscopy, and endoscopist. Risk factors analyzed included age, gender, BMI, medical and social history, and medications. We performed a multivariate logistic regression analysis to identify clinical risk factors for BE.

Results—In a multivariate regression model, men had a greater risk for developing BE (odds ratio [OR]=3.2; 95% confidence interval [CI], 2.3–4.4), whereas current aspirin users had a lower risk than non-users (OR=0.56; 95% CI, 0.39–0.80). A subset analysis, limited to patients who had endoscopies for symptoms of gastroesophageal reflux disease, yielded similar findings. No interactions were found between aspirin use and smoking, or use of acid suppressive medications.

Conclusions—In a case-controlled study of 434 patients with BE, current aspirin use appeared to reduce the risk of BE; previous studies associated aspirin use with a reduced risk of EAC..

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Author Contribution List:

ZBO: study design, acquisition of data, statistical analysis and interpretation of data, drafting of the manuscript

AA: statistical analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript

KJN: critical revision of the manuscript

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JJL: acquisition of data

CYK: manuscript preparation and review, obtained funding

CH: study conception and design, statistical analysis, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, obtained funding

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Although efforts were made to minimize biases in our analysis, the possibility of residual confounding remains.

Keywords

Esophagus; GERD; cancer risk; NSAID

Introduction

The incidence of esophageal adenocarcinoma (EAC) has been rising at an alarming rate over the past few decades.¹ Current attempts at targeted screening for EAC focus on identifying Barrett's Esophagus (BE), the largest known risk factor for EAC.² However, there is minimal risk stratification in targeting those who undergo endoscopic screening to identify BE, with only age >50 and chronic GERD symptoms used as criteria in previously endorsed guidelines.³ This strategy does not incorporate other possible risk factors for BE and EAC, including gender, race, obesity, tobacco use, and specific medication use. Additionally, based on the lack of convincing trial data demonstrating efficacy, as well as modeling studies suggesting limited effectiveness,⁴⁻⁵ medical societies have voiced concern regarding previously endorsed BE screening and management strategies. An intriguing possibility that has not been sufficiently analyzed is a strategy that incorporates some form of BE prevention in individuals at high risk for both BE and EAC development.

Chemoprevention has been studied primarily as a way to decrease the risk of progression to dysplasia and adenocarcinoma in BE patients. Studies have revealed limited efficacy with proton pump inhibitor (PPI) use in reducing BE progression to cancer.⁶⁻⁸ Additionally, HMG Co-A reductase inhibitors (statins) have some epidemiologic data to suggest activity as a chemoprevention agent.⁹⁻¹⁰ Non-steroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, have been associated with reduced esophageal cancer incidence.¹¹⁻¹² A meta-analysis of nine epidemiologic studies pooling 1813 cancer cases demonstrated a 43% decreased rate of esophageal cancer in patients on NSAIDs, 50% for those on aspirin, and suggested a dose response.¹³ An ongoing study coordinated in the United Kingdom called AspECT (Aspirin Esomeprazole Chemoprevention in Barrett's metaplasia) has enrolled over 2000 patients and plans an eight-year follow-up period to determine whether aspirin and acid suppression affect progression rates to cancer.¹⁴

Increased expression of the enzyme COX-2 has been detected in patients with Barrett's esophagus^{11, 15-17} and esophageal adenocarcinoma,¹⁸⁻¹⁹ and the inhibition of COX-2 by NSAIDs has been postulated as the mechanism for the observed decrease in cancer incidence.²⁰ A growing public awareness about the potential benefits of NSAID therapy has led to a growing trend among both the medical and lay community to consider the prophylactic use of NSAIDs for chemoprevention.

Although many studies have analyzed NSAID and aspirin chemoprevention for EAC or BE progression to EAC, few have explored NSAIDs for BE prevention. The aim of this case-control study was to explore risk factors and chemoprevention agents, for BE.

Methods

Study Overview

Institutional review board approval was obtained at the Massachusetts General Hospital in Boston, Massachusetts. A retrospective record review was completed on subjects seen at a tertiary referral center that performs inpatient and outpatient esophago-gastro-duodenoscopies (EGDs). Risk factors, including demographic factors, body mass index

(BMI), alcohol use, smoking status and current medications, were extracted from endoscopy nursing intake and electronic medical records, and used to build a multivariate logistic regression model.

A software program (Provation, Wolters Kluwer Health, Minneapolis, MN) that documents all endoscopic procedures at the institution was queried to identify EGDs performed between 1997 and 2010. The queries also retrieved information about the patient and the EGD procedure from the hospital's electronic medical record system including the year when the procedure was performed, the endoscopist who performed the procedure, patient demographic information, indication for the procedure, and findings documented by the endoscopist.

Identification of BE Cases

Endoscopically and histopathologically confirmed BE cases, identified on index EGDs performed between 1997 and 2007 were from a prior analysis that studied possible secular trends in characteristics of BE patients.²¹ Because behavioral modifications due to BE diagnosis could influence the results, we only included index EGDs in order to create a prediction rule that could theoretically be applied to patients prior to endoscopic screening. For the current analysis, we added additional BE cases identified on index EGD between 2008 and June 2010. EGDs in which the indications were follow-up of known BE, BE surveillance, therapy of BE or esophageal tumor were excluded. Pathology reports were individually reviewed to determine biopsy findings from index endoscopy. EGDs in which esophageal biopsies were not obtained or failed to demonstrate the presence of intestinal metaplasia (IM) were excluded from further analysis. Cases were also excluded if the patient had a history of GI cancer, cirrhosis or any surgical procedures that altered the anatomy of the GI tract.

Identification of Controls

The potential control cohort consisted of subjects who had undergone index EGDs between 1997 and 2010 without a finding of BE or EAC on endoscopy or pathologic review. Similar to the cases, exclusion criteria for controls included: history of any malignancy in the GI tract, history of cirrhosis, or end stage liver disease and history of a surgical procedure that altered the anatomy of the upper GI tract.

Once the cohort of potential controls had been identified, each BE case was matched with a control on the basis of three factors: 1) year of EGD; 2) indication for the EGD; and 3) endoscopist who performed the EGD. Due to the large number of different indications for the reviewed EGDs, indications were classified into six categories: 1=Heartburn and GERD symptoms; 2=Dysphagia, odynophagia; 3=Dyspepsia and epigastric pain; 4= Acute GI bleeding; 5= Anemia, guaiac positive stool; 6= Miscellaneous (included nausea, weight loss, and findings suggestive of cancer on prior imaging studies).

Data Collection

The subjects' nursing intake charts at the time of endoscopy were reviewed to extract the following information: current height and weight (to calculate body mass index), current medications, history of cancers, surgical procedures and other medical conditions related to the GI tract. This information was obtained and documented by the GI intake nurse directly from the patient in a pre-endoscopy interview. Whenever possible (>80% of the time), medications and medical conditions documented on the nursing intake sheet were confirmed by cross-checking it with the annual physical note closest to the time of endoscopy within the patient's medical record; if and when a conflict existed, the physician's note took precedence. Additionally, each subject's full electronic medical record was searched to

estimate current and history of tobacco smoking (cigarette, cigars and pipe use) and alcohol use. Alcohol use was classified based on previous studies as follows: Low: < 2 glasses of wine or beer per week; Moderate: 2 glasses of wine or beer per week to 2 glasses per day (males) or 1 glass per day (females); High: > 2 glasses of wine or beer per day (males) or > 1 glass per day (females).^{22–23}

Statistical Analysis

Statistical analysis was performed using Stata Intercooled 11.0 software (StataCorp, College Station, TX USA). Univariate testing was performed with Student's t-test or Wilcoxon rank-sum test for comparison of continuous variables, and with Chi-square testing (with Fischer's correction where necessary) for comparison of categorical variables. Variables that met statistical significance on univariate analysis at $p < 0.05$ were included in the multivariate model, in addition to variables decided a priori based on risk factors that were previously shown to have an effect on Barrett's esophagus development, progression to cancer, or biologic plausibility. The multivariate model was constructed by performing backward stepwise regression, eliminating non-significant variables. All reported values are two-sided, and a value of $p < 0.05$ was used as a threshold for statistical significance in the multivariate model. We also performed a planned subgroup analysis stratifying by PPI use, and among those cases/controls whose index procedure was performed for the acid reflux related symptoms.

Results

Querying the database for EGDs with a finding of Barrett's esophagus resulted in 6,274 cases between 1997 and June, 2010. For patients who underwent multiple EGDs with a finding of BE, only the first EGD was included. In order to identify only the first endoscopy where BE was diagnosed, we excluded patients who were previously diagnosed with BE outside of our institution. Pathologic observation confirmed intestinal metaplasia in 535 index cases with endoscopic findings of BE. We also excluded cases with a history of GI cancer, cirrhosis or any surgical procedures that altered the anatomy of the GI tract. 434 cases found to have endoscopically and histopathologically confirmed BE at index endoscopy performed at a tertiary care referral center between 1997 and 2007 were included in this analysis. Figure 1 outlines the number of excluded patients and the process we followed to create the final group of BE cases used for our analysis. Controls were identified in the same manner, but starting with exclusion of EGDs with endoscopic findings of BE. They were matched with cases on three factors: EGD year, indication, and endoscopist.

The majority of the subjects in both groups were white. Male-to-female ratio was higher among the cases than the controls. Light to moderate alcohol use and rate of current and past smoking were similar between the two groups. As shown in Table 1, the majority of subjects with BE had a segment that was 3 cm or longer (56%) and did not have dysplasia (94%). Of note, the number of cases and controls in the smoking and alcohol count do not always add up to 434 because of missing data.

Table 2 shows the distribution of indications for endoscopy and the years of BE diagnoses. Almost half (44%) of endoscopies were for the indication of GERD (heartburn, acid reflux). No significant differences were observed in the number of BE diagnoses by calendar year (1997–2010) included in our analysis.

Univariate Analysis

On univariate analysis, more cases than controls were found to be below 60 years of age. There were no differences in race, light to moderate alcohol use, current or history of

smoking habits, and current NSAID use between the two groups. Statistically significant predictors for a diagnosis of BE were male gender ($p < 0.001$), obesity ($p = 0.04$), and current or history of heavy alcohol use ($p = 0.007$). On the other hand, age of over 60 years at endoscopy ($p = 0.04$), current use of H2 blockers ($p = 0.004$), aspirin use ($p = 0.002$) and statin use ($p = 0.04$) were associated with a decreased risk of BE. Table 3 shows odds ratios for the analyzed variables.

Regression Model

In our multivariate regression model, we included covariates that were significant in the univariate analysis, as well as others that we had determined should be included a priori. These included age, gender, race, BMI, history of smoking and alcohol, use of acid-suppressive medications, aspirin, NSAIDs, and statins.

As shown in Table 4, out of these factors, male gender was identified as a significant independent predictor of BE in the stepwise multivariate regression model (OR = 3.2; 95% CI 2.3–4.4; $p < 0.001$). In addition, the analysis revealed aspirin use to be a protective factor for BE (OR = 0.56; 95% CI 0.93–0.80; $p = 0.001$).

To explore possible confounding of the effect of aspirin by acid suppression, i.e. more patients using aspirin may also have been on concomitant acid suppressive therapy, we repeated our multivariate analysis stratifying by acid suppression. In this analysis, aspirin use was associated with a significantly lower likelihood of Barrett's esophagus among those using acid suppressing medications (OR = 0.59, 95% CI 0.36–0.99, $p = 0.045$) and showed a non-significant trend among those not on acid suppression (OR = 0.58, 95% CI 0.30–1.1, $p = 0.11$). However, this finding could be due to the smaller size of the cohort not on acid suppression and does not strongly favor confounding by acid suppression. Similarly, since more people on aspirin (for cardiovascular reasons) may also have been on a statin, and because statins had a protective effect against BE on univariate analysis, we stratified the original cohort by statin use. In this analysis, aspirin use showed a trend towards protecting against BE among both the subgroup of statin users and non-statin users; however, this effect did not reach statistical significance (Statin users: OR = 0.59, 95% CI 0.32–1.1, $p = 0.082$; Non-statin users: OR = 0.63, 95% CI 0.36–1.1, $p = 0.10$). Aspirin use was inversely associated with BE in both subgroups of smokers; however, this association reached significance only in the subgroup of smoking subjects that pooled both current smokers and those with a history of smoking, likely due to larger numbers and improved power (Current and Past Smokers OR = 0.54, 95% CI 0.32–0.90, $p = 0.018$; Non-smokers OR = 0.61, 95% CI 0.31–1.2, $p = 0.15$).

In order to examine whether there was a dose-response relationship, we further stratified current aspirin use by dosage, into categories of low (< 325 mg/day) and high dose (> 325 mg/day). Information on dose was available in 224 / 240 aspirin users (93%) of whom 129 were on low dose (58%) and 95 were on high-dose aspirin (42%). On univariate analysis, only the high dose (> 325 mg/day) was significantly associated with decreased BE risk (OR = 0.53; 95% CI 0.33–0.85; $p = 0.009$). In our multivariate regression model, using 325 mg daily or higher aspirin was significantly associated with a decreased risk of BE (OR = 0.36; 95% CI 0.20–0.64; $p = 0.001$) while the lower dose was not (OR = 0.92; 95% CI 0.57–1.4; $p = 0.74$).

Subgroup Analysis

In a subgroup analysis, we limited the subjects to those who had symptoms of GERD ($n=388$: 189 cases and 189 controls). In this GERD cohort, there were no differences between the cases and controls in terms of age at index endoscopy, race, use of PPIs, H2-

blockers, statins or NSAIDs, alcohol use or smoking history. As shown in Table 5, significant predictors for Barrett's esophagus remained unchanged from those in the original cohort and included male gender and aspirin. The dose-response relationship we found in the regression analysis with the entire cohort remained strong in the GERD cohort, in which aspirin use at only 325 mg or higher was significantly associated with decreased BE risk (OR = 0.30; 95% CI 0.12–0.72; $p = 0.007$)

Discussion

The aim of our study was to identify clinical predictors of BE. We analyzed BE cases identified at index EGDs at a single institution over more than thirteen years. The cohort included 434 patients with endoscopically and histologically confirmed BE on index EGD.

Our logistic regression model found that male gender confers a threefold increased risk (adjusted OR = 3.2) for the development of Barrett's esophagus. Both the direction and size of the effect is in line with previously published data. Male gender has been reported as a significant risk factor for BE in several multicenter studies conducted in the US and Europe.^{24–25} Similarly, in a meta-analysis conducted by Cook et al., over 75% of the studies indicate a male to female ratio of at least 1.5:1.²⁶ A possible explanation for this association may be that women experience less severe and less frequent reflux, and studies have suggested esophageal injury to be more prominent in males than in females among individuals with reflux.^{27–28} Others have suggested that female sex hormones may play a protective role in the development of BE.²⁹

The more notable finding of our analysis was the correlation between aspirin use and decreased risk of BE. The adjusted OR of 0.56 from the logistic regression model was statistically significant. The protective effect of aspirin use appears robust as our analysis suggests a dose response relationship in which the high-dose aspirin (> 325 mg/day) is significantly associated with decreased BE risk. Furthermore, our findings persisted in the subset analysis limited to patients with GERD symptoms as the indication for endoscopy. Additionally, as further detailed in the ensuing paragraphs, prior clinical studies have suggested such an association with aspirin and/or NSAIDs and plausible mechanisms of action have been postulated and supported.

Mechanism of Action

Numerous analyses have studied and documented the chemopreventive effects of NSAIDs, particularly aspirin, on the EAC incidence^{11–13} with an ongoing randomized trial that could confirm the benefit of aspirin in patients with BE.¹⁴ The proposed mechanism of action for this effect is through COX-2 inhibition²⁰ as increased expression of the enzyme COX-2 has been detected in patients with Barrett's esophagus^{11, 15–17} and esophageal adenocarcinoma.^{18–19}

Previous Studies

Relatively few studies have specifically addressed the effect of aspirin and NSAIDs on BE. A case-control study (224 cases and 260 controls) performed in Ireland (FINBAR) reported that both aspirin and NSAIDs were significantly associated with a reduced risk of BE, OR=0.53 and 0.40 respectively.³⁰ The analysis found a protective effect of NSAIDs for both patients with BE or EAC when compared to controls, leading the authors to conclude that the protective effects of NSAIDs could occur early in the metaplasia-dysplasia-carcinoma sequence. The analysis was limited to long-segment BE patients and included both incident and prevalence cases of BE; dysplastic cases were excluded.

A more recently published Australian population-based case control study did not find aspirin use associated with BE; however, an association was found with non-aspirin NSAIDs (OR = 0.69, 95% CI 0.49–0.97).³¹ The effect was weaker and not significant when compared with controls who had esophagitis (OR = 0.82, 95% CI 0.57–1.18) and no dose-response effect was present, leading the investigators to be wary about drawing any conclusions regarding the effect of NSAID or aspirin use on BE.

Our study found that aspirin use is protective against BE, but that non-aspirin NSAID use was not. Stratifying aspirin use by dosage revealed that only the high-dose aspirin (> 325 mg/day) is significantly associated with a decreased risk of BE. This finding indicates a dose-response relationship, strengthening the possibility of aspirin being protective against the development of BE. Strengths of our study include the size, as our study is the largest study to date that addresses aspirin/NSAID effect on BE. Additionally, we chose to limit cases to BE diagnosed on index endoscopy and required histopathologic confirmation of intestinal metaplasia, creating a higher bar for phenotypic consistency in disease definition. It is also the first such analysis performed using US patients.

Our study has limitations. Our analysis is subject to biases inherent in a case-control study. Although we attempted, as much as possible, to adjust for many of these biases using multivariate regression modeling, some biases cannot be fully accounted for. Additionally many of the risk factors (including NSAID use) were patient-reported and retrieved retrospectively by chart review, introducing possibilities for data inaccuracies.

Instead of using population controls as is typically done in case-controlled studies, we matched our BE cases with hospital controls, which could be a limitation. However, matching on indication for endoscopy, year, and endoscopist allowed us to account for temporal variations in endoscopy practices as well as variation between different providers (both for indication of procedure as well as endoscopic method). Our strategy also allowed us to maximize the possibility that the controls are selected from an identical population (with comparable healthcare access reducing ascertainment bias), thus minimizing any biases that may arise from selecting hospital-based cases compared to population-based controls. This point is particularly important as BE may be asymptomatic, and thus population-based controls who may not have had an upper endoscopy could potentially be misclassified as controls when they may harbor BE.

Our patients were limited to those in a single large urban hospital, raising concerns about the external generalizability of our results. The majority of BE cases had a segment 3cm or greater (long-segment), which could be more plausible in BE cases from the 1990's, when short-segment BE was less likely to be biopsied. When we examined the proportion of long to short BE in more modern data (2008–2010), the majority of BE cases were short-segment in support of our hypothesis. Another concern is regarding the generalizability of our results to centers outside of the U.S., per our requirement for BE cases to have histologically confirmed IM. While we recognize in some countries outside of the US, the definition of BE does not require the presence of IM, we believe that our stringent inclusion criteria for BE cases improves the specificity for our study, and is consistent with practice within the US.

Future studies that prospectively assess the potential protective effects of aspirin in patients at high risk of developing both BE and EAC in a multi-center context would be ideal. However, a study with the sufficient size and necessary follow-up may not be feasible so alternative study designs could involve surrogate endpoints in the proposed mechanistic pathways such as COX expression.

The association between aspirin and a diminished BE risk was with current aspirin use. Although we found a dose-response relationship in the current use of aspirin, the protective

effect of aspirin in BE prevention could take years. Without a history of aspirin use it was not possible to test a dose-duration relationship. Future studies could be directed towards examining such a relationship in aspirin use in greater depth to build a stronger case for causation.

If additional studies confirm the benefit of aspirin, its use could be incorporated into a management strategy for individuals at high risk for developing BE and EAC (e.g. obese males with reflux esophagitis), although recommending aspirin in an indiscriminant manner would not be advisable.

Conclusions

Our multivariate regression model finds that aspirin use is inversely correlated with being diagnosed with BE on first endoscopy. The possibility of this association is supported by the following observations. First, the protective effect of aspirin persisted in the subset analysis of patients who underwent an endoscopy for indications of GERD symptoms. Second, our logistic regression model's finding that male gender is predictive of BE is consistent with numerous prior analyses. And third, a plausible, studied and supported mechanism of action has been proposed. Although numerous studies have demonstrated an association between aspirin use and decreased risk of EAC, our study is the largest and first US study to find a diminished risk of BE in aspirin users. As with most case-controlled studies, our analysis is subject to inherent biases and certain limitations. We used a stringent definition of BE and matched our BE cases with hospital controls to maximize the similarities between the cases and controls. Further studies should be directed towards examining the dose-duration relationship between ASA use and risk of BE and compare the robustness of our findings using population controls.

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Abbreviations

BE	Barrett's esophagus
EAC	Esophageal AdenoCarcinoma
GERD	gastroesophageal reflux disease
IM	intestinal metaplasia
NSAID	non-steroidal anti-inflammatory drug

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Figure 1.

(Case Identification Schema): The process of identifying patients with Barrett's esophagus that met criteria for inclusion in our analysis as a case is presented. Reasons for exclusion and the number of subjects within that category are shown in rectangular boxes.

Abbreviations: *BE*=Barrett's esophagus; *IM*=intestinal metaplasia

Table 1

Clinical Characteristics

Variable	BE Cases (n=434)		Controls (n=434)	
	n	%	n	%
Mean Age $\pm$ SEM	60.8 $\pm$ 0.6		62.5 $\pm$ 0.7	
> 60 years of age	231	53	261	60
Gender				
Male	311	72	202	47
Race				
White	400	92	389	90
Non-white	26	6	36	8
Not reported	8	2	9	2
Mean BMI $\pm$ SEM	27.2 $\pm$ 0.3		27.1 $\pm$ 0.3	
BMI > 30	162	37	133	31
Alcohol Use *				
None	143	41	199	48
Light (<2 drinks/wk)	73	21	88	21
Moderate (2–14 drinks/wk)	82	24	98	23
Heavy (>14 drinks/wk)	47	14	33	8
Smoking History *				
Never a smoker	162	38	177	42
Current smoker	53	12	50	12
Current or past smoker	268	62	253	59
Acid Suppression				
Current PPI use	218	52	237	55
Current H2RA use	43	11	76	18
Other Medications				
Current aspirin use	100	23	140	32
Current NSAID use	50	15	50	12
Current Statin use	87	29	154	36
BE length				
Short segment (< 3 cm)	181	42	-	-
Long segment (≥ 3 cm)	245	56	-	-
Length Unclear	8	2	-	-
Dysplasia				
None (IM only)	407	94	-	-
Low-Grade	10	2	-	-

Variable	BE Cases (n=434)		Controls (n=434)	
	n	%	n	%
High-Grade	11	3	-	-
Indefinite	4	1	-	-

* Numbers of subjects do not always add up to 434 because of missing data; see Results section for details

Table 2

Endoscopy Variables Matched

	Cases (n=434) n (%)
Indication for EGD	
GERD (Heartburn, acid reflux)	189 (44)
Dysphagia, odynophagia	82 (19)
Dyspepsia, epigastric pain	63 (14)
Acute GI bleeding	43 (10)
Guaiac positive stool, anemia	44 (10)
Other	13 (3)
Year of EGD	
1997	18 (4)
1998	36 (8)
1999	53 (12)
2000	35 (8)
2001	19 (4)
2002	29 (7)
2003	19 (4)
2004	26 (6)
2005	28 (7)
2006	19 (4)
2007	30 (7)
2008	55 (13)
2009	40 (9)
2010 (until July)	27 (6)

Table 3

Univariate Analysis Results

Variable	Unadjusted OR	95% CI	P-value
Age > 60 years of age	0.75	0.58–0.99	0.04 [*]
Male gender	2.9	2.2–3.8	<0.001 [*]
White Race	1.4	0.84–2.4	0.19
BMI > 30	1.4	1.0–1.8	0.04 [*]
Alcohol Use			
Light (<2 drinks/wk)	1.2	0.79–1.7	0.46
Moderate (2–14 drinks/wk)	1.2	0.81–1.7	0.41
Heavy (>14 drinks/wk)	2.0	1.2–3.2	0.007 [*]
Smoking History			
Current or past smoker	1.2	0.88–1.5	0.30
Acid Suppression			
Current PPI use	0.87	0.66–1.1	0.30
Current H2RA use	0.55	0.37–0.82	0.004 [*]
Other Medications			
Current Aspirin use	0.63	0.47–0.85	0.002 [*]
Current NSAID use	1.4	0.91–2.1	0.14
Current Statin use	0.72	0.52–0.98	0.04 [*]

^{*} Statistically significant

Table 4

Predictors of BE (Multivariate Analysis Results)

Variable	Adjusted OR	95% CI	P-value
Age > 60 years	0.97	0.68–1.4	-
Male gender	3.2	2.3–4.4	<0.001 *
White Race	1.0	0.56–1.9	-
BMI > 30	1.2	0.84–1.7	-
Alcohol Use			
Light (<2 drinks/wk)	1.0	0.65–1.5	-
Moderate (2–14 drinks/wk)	0.83	0.55–1.3	-
Heavy (>14 drinks/wk)	1.1	0.59–1.9	-
Smoking History			
Current or past smoker	1.2	0.84–1.6	-
Acid Suppression			
Current PPI use	0.91	0.64–1.3	-
Current H ₂ RA use	0.71	0.39–1.3	-
Other Medications			
Current Aspirin use	0.56	0.39–0.80	0.001 *
Current NSAID use	0.92	0.53–1.6	-
Current Statin use	0.79	0.54–1.2	-

* Statistically significant

Table 5

Predictors of BE among Patients with Gastroesophageal Reflux (Subgroup)

<i>(n=388; 189 Cases, 189 Controls)</i>	Adjusted OR	95% CI	P-value
Male gender	3.0	1.9–4.7	<0.001*
Current aspirin use	0.49	0.33–1	0.005*