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Medication Usage and the Risk of Neoplasia in Patients with Barrett's Esophagus

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Abstract

Background & Aims—Experimental evidence indicates that proton pump inhibitors (PPI), non-steroidal anti inflammatory drugs (NSAID)/aspirin and statins can protect patients with Barrett's esophagus (BE) from developing neoplasias. However, only limited data are available on chemoprevention in patients with BE.

Methods—A retrospective observational study was performed using data from patients with documented BE. Prescription information was collected from pharmacy records. Cox regression analyses were performed to examine the association between prescriptions for PPI, NSAID/aspirin or statins and the risk of developing esophageal dysplasia or adenocarcinoma during follow-up (from 1982 to 2005).

Results—We examined data from 344 patients diagnosed with BE (mean age 61 years, 90.4% Caucasian, 94.2% male). After BE diagnosis, 67.2% of the patients were prescribed PPI for a mean duration of 5.1 years; 49.1% were prescribed NSAID for a mean duration of 3.6 years and 25.3% were prescribed statins for a mean duration of 2.8 years. During 2,620 patient-years following BE diagnosis, high-grade dysplasia or esophageal adenocarcinoma developed in 33 patients. PPI treatment after BE diagnosis was associated with a reduced risk of high-grade dysplasia or cancer; this association persisted after adjustment for gender, age, and the length of BE at time of the diagnosis. NSAID and/or aspirin therapy were associated with a non-significant trend toward lower incidence of high-grade dysplasia or esophageal cancer.

Conclusions—PPI therapy reduces the risk of neoplasms in patients with BE. NSAID/aspirin appear to reduce cancer risk whereas statin use is not significantly associated with the risk of neoplasia in patients with BE.

Introduction

Barrett's esophagus (BE), defined by the replacement of the normal squamous esophageal epithelium by columnar epithelium with goblet cells, affects between 3% and 13% of people

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with gastroesophageal reflux disease (GERD)¹. In some individuals with BE, metaplasia will progress to dysplasia and in a few of those from dysplasia to adenocarcinoma. Patients with BE have a 30- to 125-fold increased risk of developing esophageal adenocarcinoma when compared to the general population¹. The determinants of progression to neoplasia in patients with BE are generally unknown. In particular, the potential chemopreventive effect of medications such as proton pump inhibitors (PPIs), non steroidal anti inflammatory drugs (NSAIDs), aspirin, or statins remain unclear.

The effect of acid suppressing medications on the risk of esophageal adenocarcinoma (EAC) among patients with BE is controversial. Several population-based case-control studies have demonstrated a strong association between the frequency and severity of GERD symptoms and the increased risk of BE as well as esophageal adenocarcinoma.²⁻⁴ However, evidence regarding the use of acid suppressing medications to reduce the risk of adenocarcinoma from long term randomized controlled trials is lacking. There are limited observational data that demonstrated an association of PPI use and the reduced incidence of dysplasia in BE.⁵⁻⁷ The association of PPI use and the incidence of high grade dysplasia or cancer were not extensively analyzed in these studies due to the small number of patients with high grade dysplasia or cancer.

The effect of NSAIDs/aspirin on the risk of esophageal adenocarcinoma among patients with BE is also unclear. Patients with BE have increased expression of COX-2 with progressive increase along the metaplasia-dysplasia-adenocarcinoma sequence.⁸ Treatment with COX-2 inhibitors in rat model of esophageal adenocarcinoma was associated with reduction of the incidence of esophageal adenocarcinoma.⁹ Observational human studies have reported significantly lower risks of esophageal cancer among those who frequently use NSAIDs or aspirin compared with never users.^{10, 11} However, the effect of NSAID and/or aspirin on the progression of BE to dysplasia or adenocarcinoma have been examined in only a few studies with inconsistent results.¹²⁻¹⁴

Recent observational data suggest that statins may have protective effects against the development of cancers.^{15, 16} Ogunwobi *et al.* showed that statins inhibit proliferation and induce apoptosis in esophageal adenocarcinoma cells via inhibition of Ras farnesylation and inhibition of the ERK and Akt signaling pathways; therefore, they may have some potential as chemopreventative agents in esophageal adenocarcinoma, however human studies are lacking.¹⁷

We therefore conducted this observational cohort study with the aim of evaluating the association between the use of PPIs, NSAIDs/aspirin, and statins and the future development of dysplasia or adenocarcinoma in a large well-characterized cohort of patients with BE. This study expands on the original study that our group⁵ had previously published by evaluating new study hypothesis on a larger cohort with longer follow-up and adds pharmacy data on NSAID/aspirin and statin prescriptions.

Methods

This study is a retrospective cohort study of patients with documented BE diagnosed between 1982 and 2004 at the Southern Arizona VA Healthcare System-Tucson. The patients included in this study are made up of the patients in the BE cohort previously described by El-Serag *et al.* (236 patients with BE diagnosis from 1982-2000)⁵ and those patients with newly documented BE diagnosis from 2000 to 2004. A single experienced endoscopist (RES) was responsible for performing endoscopy and collecting information on therapy of newly referred patients with diagnosed or suspected BE over the study period. Medical information was obtained through scheduled patient interviews and scheduled endoscopy with systematic

biopsies. The demographic, clinical, therapeutic, endoscopic, and histological information were obtained from BE study research files. For this study, manual review and abstraction of all research files was performed for the following information on all patients included in this analysis: date of birth, date of first BE diagnosis, gender, race/ethnicity (Caucasian, African-American, Hispanic, other), vital status, presence of dysplasia or cancer.

Endoscopy data

Criteria for BE diagnosis were endoscopic identification of the squamocolumnar junction proximal to the gastroesophageal junction and targeted biopsies with histology revealing columnar epithelium with goblet cells. These findings had to be present on two consecutive endoscopies at least six months apart. The length of BE was defined as the difference between the lengths of the gastroesophageal junction and squamocolumnar junction from the incisor teeth. BE of all lengths were included in the current analysis. Patients with no recorded second endoscopy following the initial BE diagnosis were excluded.

Histopathology data

Given the variability of histologic definition of BE and dysplasia over the past 20 years, a single gastrointestinal pathologist (AB) using standard definitions reviewed all histologic specimens for diagnosis of BE and dysplasia. Indeterminate cases of dysplasia were not considered in this analysis. In 1990, the study pathologist began reviewing all BE histologic slides prospectively at regular sessions. Specimens acquired prior to 1990 were reviewed and investigated using the same standard criteria for dysplasia. The pathologist was blinded to previous interpretation and the use of PPIs, NSAIDs/aspirin, or statins.

Pharmacy data

In 1994, the pharmacy at the Southern Arizona VA Healthcare System-Tucson started a computerized database in which information of prescription and dispensation of medications has been maintained. Using the VA pharmacy database, we collected information on dispensed/filled prescriptions for PPIs (omeprazole, lansoprazole, rabeprazole), NSAIDs including COXIBs (celecoxib, rofecoxib, indomethacin, meloxicam, piroxicam, etodolac, naproxen, ibuprofen, diclofenac, sulindac, nabumetone, salsalate, diflunisal), aspirin, and statins (atorvastatin, fluvastatin, lovastatin, simvastatin) among veterans with newly diagnosed BE. Prior to 1994 the information on the medications was abstracted from the research files while after 1994 both research files and electronic records were used. The duration (days) of nonoverlapping dispensing episodes of use for each category of medication was calculated. For any given patient, the total duration of filled prescriptions was calculated by adding the duration of the individual prescriptions and subtracting overlap in dates (if any) among the prescriptions. An “ever” and an “after BE diagnosis” variables were created for each category of medication. The “ever” variable is defined as having received a dispensed prescription for the medication of interest either before or after index BE diagnosis. The “after BE diagnosis” variable is defined as having received a dispensed prescription for a medication after index BE diagnosis.

Statistical Analysis

The cumulative incidence of dysplasia or cancer was calculated by dividing the number of patients with these conditions by the available person-year follow-up in the BE cohort. Patients with dysplasia or esophageal adenocarcinoma diagnosed at or before the time of BE diagnosis were excluded. The incidence rates for dysplasia and cancer were calculated for the entire group and for subgroups of patients defined by the filled prescriptions for PPIs, NSAIDs/

aspirin, or statins. The potential effect of medications on the risk of dysplasia or cancer was also estimated in Cox proportional hazards (PH) models. The exposure of interest was dispensed prescriptions for PPIs, NSAIDs/aspirin, or statins defined by at least one dispensed prescription following the BE diagnosis date. We also examined several categories representing different cumulative durations of prescribed medications. We also examined for the effect of PPI, NSAID/aspirin, or statin prescriptions on risk of developing dysplasia or esophageal adenocarcinoma by using Cox PH models that adjusted for the length of BE at the time of diagnosis, ethnicity, and age at BE diagnosis. Parameter estimates and standard errors obtained from these models were used to calculate hazard ratios (HR) and their accompanying 95% confidence intervals. The HR assumptions were met in all models.

Results

A total of 408 patients were identified, 64 patients were excluded because they presented with BE and either dysplasia or adenocarcinoma at the initial endoscopy, leaving 344 patients with documented non-dysplastic BE diagnosed between 1982 and 2004 to be included in this analysis. The mean age at the time of BE diagnosis was 60.7 years (SD 11.8). There were significant differences in age distribution among the groups. Patients in the high grade dysplasia or esophageal adenocarcinoma group were older (62.2 years, SD 11.7) than patients without dysplasia (60.4 years, SD 12.0). The majority were Caucasian (311, 90.4%). Most patients were men (324, 94.2%). The mean duration of follow-up between BE diagnosis and development of dysplasia/cancer, death, or end of study was 7.6 years (SD 4.7) with a total follow-up of 2,620 patient-years (PY). Patients without any dysplasia had a longer mean follow-up time (8.1 years) than patients with high grade or cancer (6.5 years). The baseline characteristics and follow up durations of the subgroups of patients in the study BE cohort are listed in table 1.

After BE diagnosis, 231 patients (67.2%) were prescribed a PPI, 169 patients (51.0%) an NSAID/aspirin, and 87 patients (25.3%) a statin. There was a high correlation among the groups with prescriptions for PPI, NSAID/aspirin, or statin before BE diagnosis and the groups with prescriptions for PPI, NSAID/aspirin, or statin after BE diagnosis. Among the 344 patients in this analysis, 80 patients developed dysplasia (20 were high grade) and 13 patients developed esophageal cancer (10 of the 13 patients were diagnosed with both high grade dysplasia and esophageal adenocarcinoma) during the 2,620 patient-years follow up. The incidence rate of any grade dysplasia was 3.1 per 100 PY and the incidence rate of esophageal cancer was 0.5 per 100 PY.

Twenty seven out of 80 patients with BE diagnosis who developed dysplasia did not have a dispensed PPIs prescription after BE diagnosis, 42 patients did not have a dispensed prescription for NSAIDs/aspirin, and 57 patients did not have a dispensed prescription for statins (Table 2). Among the patients with dysplasia, the incidence rate for patients with dispensed PPI prescriptions after BE diagnosis was 3.3 per 100 PY compared to incidence rate for patients without PPI prescription of 4.5 per 100 PY with an incidence rate ratio of 0.74 (95% CI: 0.46-1.17). Among the patients with high grade dysplasia or esophageal adenocarcinoma, the incidence rate for patients with PPI prescriptions after BE diagnosis was 1.2 per 100 PY compared to incidence rate for patients without PPI prescription of 2.9 per 100 PY with an incidence rate ratio of 0.42 (95% CI: 0.21-0.82). For the 13 patients with esophageal adenocarcinoma, the incidence rate for those with PPI prescriptions after BE diagnosis was 0.45 per 100 PY compared to incidence rate for patients without PPI prescription of 1.36 per 100 PY with an incidence rate ratio of 0.33 (95% CI: 0.11-0.98).

Unadjusted Cox PH models showed that having a dispensed PPI prescription after BE diagnosis was associated with a significant reduction in the risk of developing high grade dysplasia or

esophageal adenocarcinoma (HR: 0.43; 0.21-0.83). Adjusted Cox PH models were used to examine the association between developing dysplasia or cancer and having a dispensed PPI prescription. Having a dispensed PPI prescription after BE diagnosis was a significant predictor of reduced risk of high grade dysplasia or esophageal adenocarcinoma development during follow-up (HR: 0.39; 0.19-0.80) when adjusted for gender, age at BE diagnosis, BE length. The results of several adjusted Cox PH models evaluating the risk of high grade dysplasia or esophageal adenocarcinoma with regard to dispensed PPI prescription are shown in Table 3. There is a trend toward a duration response relationship between PPI prescriptions and the development of high grade dysplasia or esophageal adenocarcinoma as shown in Table 4. Having filled PPI prescriptions for at least 36 months was associated with greater reduction in the risk of high grade dysplasia or esophageal adenocarcinoma than that with PPI use for less than 36 months or with no PPI use. As a sensitivity analysis, we also examined the association between PPI prescription dispensed before or after BE diagnosis, and found no differences in the magnitude or direction of associations between PPI and high grade dysplasia or cancer to those seen in the primary analysis (Table 3).

Having at least one dispensed NSAID/aspirin prescription after BE diagnosis was associated with a non-significant trend toward lower incidence of high grade dysplasia or esophageal adenocarcinoma with HR of 0.51 (95% CI: 0.25-1.04) in unadjusted Cox PH models. The association persisted when we excluded aspirin from the analysis by examining NSAID/COX prescriptions with unadjusted HR of 0.46 (95% CI: 0.20-1.07). The magnitude and direction of the association between dispensed NSAID/aspirin prescriptions and the development of high grade dysplasia or esophageal adenocarcinoma persisted in adjusted Cox PH model corrected for gender, age at BE diagnosis, BE length (HR: 0.56; 0.27-1.18). The result for the duration response relationship analyses for dispensed NSAID/aspirin prescriptions are shown in Table 4.

Having dispensed statin prescriptions was not associated with the development of dysplasia or cancer with unadjusted HR of 0.73 (95% CI: 0.30-1.78). A total of (n=87, 25%) patients had at least one filled statin prescription after BE diagnosis with a mean duration of 2.8 years. Sixty-three (25.1%) patients who did not develop dysplasia during follow-up had at least one filled statin prescription as compared to only (n=6, 18.2%) patients who developed high grade dysplasia or esophageal adenocarcinoma had at least one filled statin prescription after BE diagnosis.

Discussion

Our result indicated that patients with BE who developed high grade dysplasia or esophageal adenocarcinoma were less likely to have been dispensed PPI prescriptions. Multivariable analysis adjusting for gender, age at BE diagnosis, and BE length showed that PPI prescription independently associated with approximately 61% lower risk of developing high grade dysplasia or esophageal adenocarcinoma compared to those with no PPI therapy. On the other hand, NSAID and/or aspirin prescriptions were associated with non-significant trend toward lower incidence, and statin prescriptions were not associated with high grade dysplasia or esophageal adenocarcinoma.

The current results are consistent with our previous study⁵ which analyzed data from 236 patients with follow-up of 1,170 PY from 1981-2000, and found that the use of PPI after the diagnosis of BE was associated with 75% reduction in the risk of any grade dysplasia. The current study extended findings from the previous study by evaluating a larger cohort of 344 patients (236 patients were included in the previous study) with longer follow-up of 2,620 PY (through 2005), and adds pharmacy data on NSAID/aspirin and statin prescriptions.

This study has several strengths including its large sample size of patients with BE, long follow-up time (average of 7.6 years), and the consistent use of strict criteria of BE diagnosis based on positive endoscopic and histologic criteria on 2 consecutive examinations. A single investigator (RES) was responsible for performing the endoscopy and ensuring that all patients met strict and standardized criteria for the diagnosis of BE.

A single pathologist (AB) with extensive experience in evaluating BE biopsy was responsible for interpreting all histopathology slides throughout the study which ensured consistency and reduced interobserver variability in the diagnosis of dysplasia. While some patients may have developed dysplasia or cancer outside the VA, we limited the analyzable follow up to patients with known findings; we made the study end points: cancer, death, or a negative endoscopy. In addition, the internal validity of our findings was strengthened since the association persisted in direction and magnitude after multivariable analysis adjusted for confounding factors such as gender, the length of BE at time of the diagnosis, age, and NSAID/aspirin prescriptions.

The inverse association between PPI use and the risk of high grade dysplasia or esophageal adenocarcinoma in patients with BE diagnosis is consistent with findings from other observational studies.⁵⁻⁷ While one explanation is that PPI reduce the risk of neoplasia by reducing acid reflux, alternate explanations are also possible.¹⁸ The presence of a demonstrable duration response relationship strengthened the causal association argument. Ascertainment bias in which patients not on PPI (hence more symptomatic) may undergo more frequent or more extensive endoscopy. However, the average number of EGD was not different between the two groups. Patients with existing (prevalent) neoplasm may be less likely to have used PPI in the past. We excluded all patients in whom neoplasia was detected on the second EGD required for BE diagnosis. However, indolent neoplasia may have been missed especially given the possibility of sampling error.

This study also has several limitations. First, the study only included veterans who received care at the Southern Arizona VA Healthcare System-Tucson. This may have resulted in a selection bias because the patients included were likely to be male, older age, and were healthy enough to receive outpatient endoscopy. This selection bias may affect the generalizability nature of the study but it should not affect the internal validity of our result. Second, since the information on PPI, NSAID/aspirin, and statin prescriptions were abstracted from research files and VA pharmacy electronic records, we were unable to obtain prescription data for those who used non-VA pharmacies for their medicines. Since PPI, statins, and certain NSAIDs are considerably less expensive in the VA pharmacy compared to non-VA pharmacies, patients were more likely to obtain their medication through the VA pharmacy. Data on intermittent or continuous use of medication were not available, therefore the degree of acid suppression was not known. The total duration of filled prescriptions was calculated by adding the duration of the individual prescriptions and subtracting overlap in dates (if any) among the prescriptions. However, the total duration calculation did not account for the differences between intermittent or continuous use. This may be important since achieving adequate reduction of esophageal acid exposure may require continuous PPI use, but these limitations should not affect one treatment group more than the others. Lastly, since this is an observational study, which was unblinded and nonrandomized, we were unable to account for all confounding factors that determine the use of PPI, NSAID/aspirin, or statin prescriptions and that chance may influence the findings. We did not have information on body mass index or waist measurements to adjust for obesity. We did not have information regarding socioeconomic status, tobacco smoking, alcohol use, H. pylori status, or information on hiatal hernia, which may be important factors in the development of dysplasia.

NSAIDs taken with PPIs may reduces cyclooxygenase-2 level, which is believed to play an important roles in cell proliferation and inhibition of apoptosis,⁸ While NSAID intake has been

associated with significant reduction in the risk of esophageal adenocarcinoma, it is not clear whether this possible benefit is a results from reduce risk of BE, reduced risk of cancer in BE, or both. Our study only showed a non-statistically significant trend toward lower incidence of high grade dysplasia or cancer associated with NSAID/aspirin prescriptions. The three published studies that have examined risk of dysplasia or cancer in relation to NSAID use in patients with BE arrived at inconsistent findings. Vaughan *et al.* demonstrated in a prospective cohort of 350 people with BE followed for 20,770 person-months that the hazard ratios (HR) for esophageal adenocarcinoma for current NSAID users was 0.20 (95% CI 0.1-0.41) compared with never user of NSAID.¹² Tsibouris *et al.* also showed that used of NSAIDs of any type and at any frequency was more prevalent in BE patients (38%) as compared to patients with esophageal adenocarcinoma (26%).¹⁴ In contrast, Heath *et al.* demonstrated that 200 mg of celecoxib twice daily for 48 weeks does not prevent progression of Barrett's dysplasia in a multicenter randomized placebo controlled trial of 100 BE patients with low- or high-grade dysplasia.¹³ The possible beneficial role of NSAID needs to be further examined with special attention to the progression from BE to cancer.

Our study is the only study that examined statin use and the risk of dysplasia or esophageal adenocarcinoma in patient with BE. Ogunwobi *et al.* have shown that statins inhibit proliferation and induce apoptosis in esophageal adenocarcinoma cells,¹⁹ but no study examined the affect of statins in patients with BE. Our study indicated that there was no association between statin use and the progression of BE to dysplasia or cancer. One explanation could be that BE cells are different than esophageal cancer cells; therefore, the affect of statins on esophageal cancer cells cannot be translate to BE cells. Another explanation is that *in vitro* findings sometime do not correspond to findings seen *in vivo*. An alternative explanation may be that this study is under powered (due to low number of events) to detect a significant association between filled statin prescriptions and the risk of neoplasia in patients with BE.

In conclusion, this cohort study suggests that PPI therapy may reduce the incidence of high grade dysplasia or esophageal adenocarcinoma in patients with BE. NSAIDs/aspirin may also have a role as chemopreventive agents in BE. Ongoing randomized controlled trials such as the Aspirin Esomeprazole Chemoprevention Trial (AsPECT)²⁰ may provide more insight into the role of PPI and NSAID as chemoprevention agents in BE.

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Table 1

Characteristics of the cohort of patients with BE and comparison of baseline features among subgroups with or without dysplasia or esophageal adenocarcinoma that developed during follow up.

	Total Cohort n=344 # (%)	No dysplasia or cancer n=251 # (%)	Any dysplasia (no EAC) n=80 # (%)	EAC or high grade dysplasia n=33 # (%)	p-value no vs. any dysplasia (no EAC)	p-value no dysplasia vs. EAC or HGD
Gender:						
Male	324 (94.2)	238 (94.8)	74 (92.5)	29 (87.9)	0.42	0.12
Female	20 (5.8)	13 (5.2)	6 (7.5)	4 (12.1)		
Race:						
Caucasian	311 (90.4)	222 (88.5)	77 (96.3)	32 (97.0)	0.04	0.22
Non-Caucasian	33 (9.6)	29 (11.6)	3 (3.8)	1 (3.0)		
Age at BE dx						
Mean (sd)	60.7 (11.8)	60.4 (12.0)	60.9 (11.7)	62.2 (11.7)	0.78	0.41
Follow-up (yrs)						
Total	2620	2051	497	214		
Mean (sd)	7.6 (4.7)	8.1 (4.6)	6.2 (4.6)	6.5 (4.9)	<0.01	0.05
BE length						
Mean (SD)	3.6 (3.1)	3.3 (3.0)	4.2 (3.3)	4.3 (2.9)	0.04	0.10
<=3 cm	153 (44.5)	119 (47.4)	32 (40.0)	11 (33.3)		
>3 cm	100 (29.1)	60 (23.9)	33 (41.3)	16 (48.5)		
Missing	91 (26.5)	72 (28.7)	15 (18.8)	6 (18.2)	<0.01	0.01
Year of BE diagnosis						
1982-1986	60 (17.4)	37 (14.7)	21 (26.3)	5 (15.2)	0.07	0.73
1987-1992	79 (23.0)	58 (23.1)	20 (25.0)	7 (21.2)		
1993-1998	156 (45.4)	121 (48.2)	28 (35.0)	14 (42.4)		
1999-2004	49 (14.2)	35 (13.9)	11 (13.8)	7 (21.2)		

EAC: esophageal adenocarcinoma

HGD: high grade dysplasia

Table 2

Medication usage after BE diagnosis among subgroups with or without dysplasia or esophageal adenocarcinoma that developed during follow up.

	Total Cohort n=344 # (%)	No dysplasia or cancer n=251 # (%)	Any dysplasia (no EAC) n=80 # (%)	EAC or high grade dysplasia n=33 # (%)	p-value no dysplasia (no EAC)	p-value no dysplasia vs. EAC or HGD	HR (95% CI) no dysplasia vs. EAC or HGD
PPI							0.43 (0.21-0.83)
Yes	231 (67.2)	172 (68.5)	53 (66.3)	17 (51.5)	0.70	0.05	
No	113 (32.9)	79 (31.5)	27 (33.8)	16 (48.5)			
Duration, mean in years (sd)	5.1 (3.1)	4.8 (3.1)	5.8 (3.1)	6.3 (3.9)	0.05	0.07	
NSAID/cox2/aspirin							0.51 (0.25-1.04)
Yes	169 (49.1)	127 (50.6)	38 (47.5)	12 (36.4)	0.63	0.12	
No	175 (50.9)	124 (49.4)	42 (52.5)	21 (63.6)			
Duration, mean in years (sd)	3.6 (3.3)	3.5 (3.1)	4.3 (3.6)	5.1 (4.3)	0.18	0.11	
Stain							0.73 (0.30-1.78)
Yes	87 (25.3)	63 (25.1)	23 (28.8)	6 (18.2)	0.52	0.38	
No	257 (74.7)	188 (74.9)	57 (71.3)	27 (81.8)			
Duration, mean in years (sd)	2.8 (2.4)	2.7 (2.4)	3.1 (2.4)	1.9 (2.1)	0.48	0.47	

HR: Hazard ratio

EAC: esophageal adenocarcinoma

HGD: high grade dysplasia

PPI: proton pump inhibitors

Table 3

Results of Cox PH models for patients with high grade dysplasia or esophageal adenocarcinoma compared to patients without dysplasia with regard to dispensed PPI prescriptions.

	PPI after BE diagnosis HR (95%CI)	PPI before or after BE diagnosis HR (95%CI)
Unadjusted	0.43 (0.21-0.83)	0.44 (0.20-0.80)
Adjusted		
sex, age, BE length	0.39 (0.19-0.80)	0.38 (0.18-0.77)
sex, age, BE length, NSAID/COX2 after BE diagnosis	0.42 (0.19-0.92)	0.41 (0.19-0.89)
sex, age, BE length, NSAID/COX2 ever	0.45 (0.21-0.99)	0.44 (0.20-0.96)
sex, age, BE length, NSAID/COX2/Aspirin after BE diagnosis	0.42 (0.18-0.99)	0.40 (0.17-0.95)
sex, age, BE length, NSAID/COX2/aspirin ever	0.42 (0.17-1.00)	0.40 (0.16-0.97)

HR: Hazard ratio

PPI: proton pump inhibitors

Table 4

Duration response relationship between filled prescriptions and the development of high grade dysplasia or esophageal adenocarcinoma.

Filled prescriptions duration	Number of patients with BE	Number of events (high grade dysplasia or cancer)	Hazard ratio (95% CI)
PPI			
0 months	95	16	Reference
>0 to 36 months	62	5	0.57 (0.21-1.57)
>36 months	127	12	0.38 (0.18-0.80)
NSAIDS/aspirin			
0 months	145	21	Reference
>0 to 36 months	80	6	0.49 (0.20-1.22)
>36 months	59	6	0.53 (0.21-1.32)