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Medications (NSAID, Statins, PPI) and the Risk of Esophageal Adenocarcinoma in Patients with Barrett's Esophagus

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Abstract

Background & Aims—Limited evidence suggests that proton pump inhibitors (PPI), non-steroidal anti inflammatory drugs (NSAID)/aspirin and statins may be associated with low risk of esophageal neoplasia. However, the possible effect these medications may have on the risk of esophageal adenocarcinoma (EAC) in patients with existing Barrett's esophagus (BE) is unclear.

Methods—We conducted a nested case-control study in a cohort of patients with BE identified in the national Department of Veterans Affairs (VA) computerized databases. Cases with incident EAC were matched by incidence density sampling to controls with BE who remained without EAC at the date of the EAC diagnosis for the corresponding case. We identified prescriptions for PPI, NSAID/aspirin, and statins that were filled between BE diagnosis and EAC diagnosis. Incidence density ratios were calculated using conditional logistic regression models that adjusted for race, outpatient encounters, a disease comorbidity index, and socio-economic status.

Results—In a cohort of 11,823 patients with first time BE diagnosis, we examined 116 EAC cases and 696 matched controls. Most cases and controls had at least one filled PPI prescription (95% vs. 94%, $p=0.5$). In this setting of almost universal PPI use, filled NSAID/aspirin prescriptions were associated with a reduced risk of EAC (adjusted incidence density ratio: 0.64; 95% CI, 0.42–0.97). Filled statin prescriptions were also associated with a reduction in EAC risk (0.55; 95% CI, 0.36–0.86), with a significant trend toward greater risk reduction with longer duration of statin use. However, the strong inverse associations with even short periods of use raise concerns of uncontrolled confounding.

Conclusion—This observational study indicates that in patients with Barrett's esophagus using PPI, NSAID/aspirin or statin therapy might reduce the risk of developing esophageal adenocarcinoma.

Keywords

epidemiology; chemoprevention; GERD; VA; Medicare

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Background

The incidence of esophageal adenocarcinoma (EAC) in the US has risen by more than 6 folds from 3.8 per 1,000 000 in 1973–1975 to 23.3 per 1,000 000 in 2001.¹ Barrett's esophagus (BE), the precursor lesion for EAC, is a relatively common condition that affects an estimated 1–2% of the general population,² and between 6–10% of patients with gastroesophageal reflux disease (GERD) undergoing endoscopy.^{3, 4} When compared to the general population, patients with BE have a 30–125-fold increased risk of developing EAC.⁵ However, the determinants of progression to neoplasia in patients with BE are largely unknown. In particular, the potential chemopreventive effect of medications such as proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, or statins in patients with BE remains unclear.

Recent observational data have suggested that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) may have protective effects against the development of cancer.^{6, 7} Experimental data suggested that statins may have potential as chemopreventative agents in EAC. Ogunwobi *et al.* showed that statins inhibit proliferation and induce apoptosis in EAC cells via inhibition of Ras farnesylation and inhibition of the ERK and Akt signaling pathways.⁸ However, human studies of statins in BE are lacking.

The association between PPI or NSAID/aspirin and EAC risk was examined in two types of epidemiological studies: case-control studies of esophageal cancer or cohort studies of patients with BE. For PPIs, Garcia Rodriguez *et al.* reported in a case-control study an association between the use of acid suppression medications including PPIs and increased risk of EAC, but this association was no longer significant when adjusted for reflux symptoms.⁹ Corley *et al.* demonstrated in a meta-analysis of 9 observational studies (2 cohort, 7 case control) significantly lower risks of esophageal cancer among those who frequently use NSAIDs or aspirin compared with never users.¹⁰ An important limitation of these case control studies of EAC is the absence of information on BE states in cases or controls. Thus these medications could exert their effect (if any) by either reducing the risk of BE, or by reducing the risk of EAC in BE. Given that BE is the only known preneoplastic condition for EAC, any cancer reducing effect for PPI and NSAID/aspirin is best shown among patients with BE. Four previous retrospective cohort studies indicated an association of PPI use and a reduced risk of dysplasia in patients with BE,^{11–14} and one other cohort study of BE also showed that NSAIDs/aspirin usage was protective against the development of EAC.¹⁵ The main limitation of these cohort studies is the presence of relatively small numbers of patients who developed EAC. There have been limited published studies that adequately examine the possible effect of acid suppressing medication or NSAID/aspirin on the development of EAC as a primary end point in patients with BE.

We therefore conducted a study within a large cohort of patients with BE identified in the national VA databases to evaluate the association of PPIs, NSAIDs/aspirin, and statins use and the risk of EAC in patients with BE.

Methods

Study Design

This is a nested case-control study, conducted in a cohort study of patients with BE identified in the VA healthcare system. The study was conducted using VA administrative records. The VA Patient Treatment File (PTF) contains inpatient records, including demographic data, dates of admission and discharge, endoscopic procedures, vital status at discharge, and up to 10 discharge diagnoses (by International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9] codes) for all hospitalizations at any of the over 150 VA hospitals. The VA Outpatient Clinic (OPC) file contains similar data for all outpatient encounters at all VA

facilities. We obtained prescription data from the Pharmacy Benefit Management (PBM), which contains prescription dispensing elements, including dates of fill and refill, prescription identifiers, dosing instructions, days supply, and total quantity of the drug dispensed. Finally, we used the Beneficiary Identification Records Locator System (BIRLS) Death File, which records date of death.

This study was approved by the Institutional Review Board for Human Subject Research for Baylor College of Medicine, and the VA Research and Development Committee of the Michael E. DeBakey VA Medical Center.

Study Population

The sampling frame was a convenience sample comprised of patients aged 18–90 years with diagnostic code for BE (ICD-9 code 530.2) in outpatient or inpatient VA files between January 2000 and December 2002. The first appearance in the records of BE diagnosis served as the BE index date in the study. Patients with BE recorded before this frame as far back as October 1996 were excluded. We also required that a procedure code for upper endoscopy (CPT code 43200 to 43259, excluding 43246 “PEG placement”) was recorded within 1 year before BE index to 9 months after BE index. To avoid prevalent or existing cases of cancer, patients with esophageal or stomach cancer (ICD-9 150.xx and 151.xx) recorded between October 1996 and 6 months following BE index were excluded from the analysis.

Case subjects were patients with incident EAC defined by ICD-9 code 151.0 recorded in PTF or OPC at least 6 months following BE index date through December 2004. Cases were matched by incidence density sampling to control subjects with BE who remained without EAC up to 30 days after the date of EAC diagnosis for the corresponding case.¹⁶ This entailed matching on age (± 5 years) and the BE index date (± 14 days). Controls were selected randomly with replacement such as one subject could be a control for more than one case. For cases and controls, we excluded patients without any VA pharmacy use, which was defined by the presence of at least one filled prescription.

Pharmacy Data

The exposures of interest were the presence of filled or dispensed outpatient prescriptions for PPI, NSAID/aspirin, or statin following BE diagnosis and ending 3 months before EAC diagnosis (or corresponding dates in controls). We collected information for medication groups of interest available in the VA by formulary or non-formulary request in any VA pharmacy. We collected information on filled prescriptions for PPI (omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole), oral histamine H₂-receptor antagonist (H₂RA) (cimetidine, ranitidine, nizatidine, famotidine), NSAID/aspirin (celecoxib, rofecoxib, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclfenamate, meloxicam, nabumetone, naproxen, oxaprozin, sulindac, tolmetin, salsalate, choline magnesium trisalicylate, aspirin), and statin (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and cerivastatin). We collected the dates of filled prescriptions, daily dose, days supply and the number of pills per prescription. For any given patient, the total duration of filled prescriptions was calculated by adding the duration of these individual prescriptions and subtracting overlap in dates (if any) among the prescriptions. Partial fills, which represent medication fills accounting for a lost or spoiled medication but not detracting from total refills, were not counted towards total prescription days.

Statistical Analysis

We compared the proportions of patients who had at least one week filled prescription of antisecretory medications (PPI or H₂RA), NSAID/aspirin, and statin. To examine possible duration-response relationship, we evaluated the following categories of cumulative duration

of filled prescriptions: 0, (>0 to 12), and (>12) months. The Cochran-Armitage trend test was used to assess the statistical significance for linear relationship between duration of filled prescriptions and EAC risk.

Incidence density ratio, as estimates of the relative risk for EAC associated with filled prescription for PPI, H2RA, NSAID/aspirin, and statin, and 95% confidence intervals (CIs) were calculated in a conditional logistic regression model. In multivariable models, adjustments were carried out for possible confounders including race, the number of outpatient encounters, a modified non cancer disease comorbidity index, and socioeconomic status. A disease comorbidity index derived from the Deyo comorbidity score with the malignancy and metastasis components of the score excluded from the calculation. VA priority levels were used a surrogate for socioeconomic status. There are 8 VA priority levels based on degree of service-related disability and income level. We classified the two lowest ranked priority levels, 7 and 8, as low priority; veterans in this group have no service-connected disability and have incomes or net worth exceeding the VA Income Threshold and are hence not exempt from co-pays. In addition to matching variables (age and date of BE diagnosis), statistical significance in the regression models was assessed by Wald chi-square tests of the parameter estimates.

Results

We identified 11,823 patients with first time BE diagnosis in the VA healthcare system between 1/2000 and 12/2002, who fulfilled the inclusion and exclusion criteria. In this cohort, we identified 116 cases with incident EAC and 696 controls without EAC that were matched in 1:6 ratio on age and date of BE diagnosis as described in the Methods section. Demographic characteristics and information regarding filled prescription for cases and controls are shown in Table 1. As expected from incidence density matching, there were no significant differences between cases and controls with regard to age and exposure duration between index BE date and date of matching. The majority of cases and controls were Caucasians (78% vs. 73%) and most were men (97%) and there were no significant difference in race or gender distribution between cases and controls.

Most cases (n =110, 95%) had at least one filled PPI prescription between the date of BE diagnosis and 3 months before EAC diagnosis, of whom approximately half had filled PPI prescriptions for 63.9% of their total follow-up duration (time between BE index date and date of EAC diagnosis or corresponding date in control). During the same time most controls (n=653, 94%) also had at least one filled PPI prescription, of whom half had filled PPI prescriptions for 75.7% of their total exposure duration. A smaller proportion of cases and controls filled at least one H2RA prescription (34.5% vs. 33.8%, p=0.5). In unadjusted conditional logistic regression analyses, there were no significant differences between cases and controls in the proportions of patients with filled PPI prescriptions (incidence density ratio, 1.21; 95% CI, 0.50–2.9) or filled H2RA prescriptions (incidence density ratio, 1.17; 95% CI, 0.78–1.76). The associations between filled PPI prescriptions and EAC diagnosis remained non-significant in multivariable analyses that adjusted for race, number of outpatient encounters, non cancer disease comorbidity index, VA priority level, and filled prescriptions for NSAID/aspirin and statin (Table 2). Similarly there was no significant difference for filled PPI prescriptions >24 months and the development of EAC (Table 3).

A smaller proportion of cases were prescribed at least one NSAID/aspirin prescription compared to controls (49.1% vs. 59.1%, p=0.04) between the time of BE diagnosis and 3 month prior to EAC diagnosis (or corresponding date in controls). There was a significant inverse association between filled NSAID/aspirin prescriptions and the diagnosis of EAC. In unadjusted analyses, filled prescription for NSAID/aspirin was associated with a significant reduction in EAC risk (incidence density ratio, 0.66; 95% CI: 0.44–0.99). In multivariable

regression analyses that adjusted for race, number of outpatient encounters, non cancer disease comorbidity index, VA priority level and filled prescriptions for PPI and statin, the inverse association between filled NSAID/aspirin prescription and EAC remained significant (incidence density ratio, 0.64; 95% CI: 0.42–0.97). Having filled NSAID/aspirin prescriptions for at least 12 months was associated with a greater reduction in EAC risk than that with filled NSAID/aspirin prescriptions for less than 12 month or with no such prescription, but the duration-response relationship trend was not statistically significant ($p=0.3$ for trend test).

Having any filled statin prescription was associated with 45% lower risks of EAC. These significant inverse associations were observed in both unadjusted analysis (incidence density ratio, 0.58; 95% CI, 0.38–0.87), and in analysis that adjusted for race, outpatient encounters, disease comorbidity index, VA priority level, and filled prescriptions for PPI and NSAID/aspirin (incidence density ratio, 0.55; 95% CI, 0.36–0.86). Forty one (35.3%) cases had at least one filled statin prescription between the BE diagnosis date and 3 months before EAC diagnosis, of whom 18 (15.5%) had filled prescriptions for at least one year compared to 336 (48.3%) controls with at least one filled statin prescription during the same time period, of whom 161 (23.2%) controls had filled prescriptions for at least one year. Patients with a cumulative filled statin prescription for >12 months have a reduced risk of EAC compared to those with ≤ 12 month or those with no statin prescription. There was a significant linear trend for the duration-response relationship between filled statin prescriptions and the development of EAC ($p=0.02$ for trend test); however most of the risk reduction was observed between 0 and 1–12 months with a smaller reduction doe >12 months.

Discussion

In this nested matched case-control study of patients with and without EAC in BE, we found that most (>90%) patients had at least one filled prescription for PPI. In this setting of almost universal PPI use among patients with BE, filled statin and NSAID/aspirin prescriptions were associated with a significant reduction in the risk of EAC. Each of these associations were independent of race, outpatient encounters, disease comorbidity index, NSAID/aspirin, socio-economic status, or the use of the other category of medications, i.e., statins.

Reduction of intraesophageal acid exposure decreases cellular proliferation and increases cellular differentiation in BE. Previous retrospective studies from the United States and Australia indicate a significant reduction in the risk of dysplasia associated with PPI use among patients with BE.^{11–14} We could not evaluate the association between PPI use and development of cancer due to the small number of cases and controls with no PPI use. However, the high PPI use allowed for possible elimination of confounding effect when examining association of NSAID/aspirin or statin use.

Our study showed a significant association of statin use and the risk of EAC in patients with BE in the setting of high prevalence of PPI use. Statin use clearly preceded EAC development. There was also a significant duration-response relationship, which supports a causal association argument; however, the strong inverse associations with even short periods of use raise concerns of uncontrolled confounding. Experimental data showed that one possible mechanism responsible for the effect of statins in reducing the risk of EAC may be the inhibit proliferation and induce apoptosis in esophageal adenocarcinoma cells via inhibition of Ras farnesylation and inhibition of the ERK and Akt signaling pathways.⁸ Observational data suggest that statins may have protective effects against the development of cancer in general; however, our previous study which analyzed data from 344 BE patients with follow-up of 2,620 patient-years from 1982–2005, did not find a significant association between statin use and the risk of high grade dysplasia or EAC. In that cohort, 25% of BE patients had at least one filled statin prescriptions and only 6 of these patients developed high grade dysplasia or EAC.¹⁴ In the

current nested case control study of 116 EAC cases and 696 BE controls without EAC identified during 2000–2005, 35.3% of cases and 48.3% of controls had at least one filled statin prescription. Therefore, given the considerably smaller sample size, lower number of events, and lower prevalence of exposure to statins, the previously published study may not have enough power to detect a significant association. In addition, the two studies were conducted in mostly different study subjects; we cannot rule out some overlap in some of the 6 patients with cancer and few controls. Clearly, more observational studies are required before statin use is considered for testing in clinical trials.

NSAIDs taken with PPIs may reduce cyclooxygenase-2 level in esophageal tissue, which is believed to play an important role in cell proliferation and inhibition of apoptosis.¹⁷ Our study showed that filled NSAID/aspirin prescriptions were associated with reduced risk of EAC in patients with BE in the presence of high PPI usage. This is consistent with two previous studies that examined risk of EAC in relation to NSAID use in patients with BE. Vaughan *et al.* demonstrated in a prospective cohort of 350 patients with BE, of whom 37 developed EAC, that current NSAID users had an 80% reduced risk of EAC (hazard ratio: 0.20; 95% CI, 0.1–0.41), compared with never user of NSAID.¹⁵ Tsibouris *et al.* in a case control study of 382 BE patients without EAC and 114 patients with EAC, also showed that NSAID use of any type or frequency was more common in BE patients without EAC (38%) compared to patients with EAC (26%).¹⁸ Neither study examined concomitant PPI use. Since NSAID/aspirin are available over the counter, patients with higher socio-economic status may be less likely to receive NSAID/aspirin prescription at the VA pharmacy. High socio-economic status is associated with increased risk of developing EAC in non-veterans.¹⁹ The VA co-payment for 1 month supply of NSAID/aspirin during 2000–2005 varied between \$0 for those with low income (priority level 1) to \$7 for patient with higher income (priority level >6). In order to minimize the potential confounding effects of socio-economic status on filled NSAID/aspirin prescription at the VA pharmacy and the risk of EAC, our multivariate analysis adjusted for these priority levels.

The study only included veterans who received care at the VA Healthcare System; these patients are more likely to be male and relatively older than other patients with BE. This may limit the generalizability of the finding. In addition, this study has limitations related to the use of administrative databases in defining the study groups and exposures (e.g. classification of exposure to medications, choice of cut-offs, and timing of the exposure in relation to esophageal cancer development) may affect the validity of the study. We defined exposure to medications based on filled or dispensed prescriptions. This is a more valid method for identifying medication intake than dealing with prescribed medications. The validity of identifying prescribed medications in VA databases is virtually identical to that of detailed review of medical records.²⁰ The appropriate classification of exposure to medications is unclear; we used several classifications (at least one prescription, cumulative prescriptions <12 and >12 months) within the constraints of the data. It is possible that exposure to medications within the study period is different from long term exposure patterns not captured by the study. Similarly the timing of exposure to medication in the course of BE cannot be examined since the exact onset of BE is unknown.

We purposefully used a nested case control design (as opposed to a traditional cohort study design) to minimize the effect of lost outcomes and to give us confidence about the case definition and to large extent the control definition (as we required being alive for 30 days following the index date of the case and absence of EAC diagnosis). This design also allows us to examine the exposures of interest (filled or dispensed outpatient prescriptions for PPI, NSAID/aspirin, or statin) following BE diagnosis and ending 3 months before EAC diagnosis (or corresponding dates in controls), so we can be confident that the exposure of interest occurred prior to EAC development but after BE diagnosis.

Since the information on prescriptions was abstracted from Pharmacy Benefit Management (PBM) database, prescriptions for patients who used non-VA pharmacies would have escaped capture. Morgan *et al.* has shown that approximately 64% of veterans with Medicare drug coverage still received their medications from the VA pharmacy, and factors that favor VA pharmacy use included young age, high priority level (surrogate for lower socio-economic status), male sex, and poor overall health status.²¹ Since PPI, H2RA, statins, and most NSAIDs are considerably less expensive in the VA pharmacy compared to non-VA pharmacies, we were less likely to have missed prescription data filled at non-VA pharmacies. To account for care received outside of the VA system, the multivariable models adjusted for the frequency of outpatient visits as well as priority level (surrogate for socioeconomic status) in cases and controls.

The definition of BE was based on the presence of ICD9 code 530.2. We have previously shown that using an algorithm that included this diagnostic code combined with EGD within one year of diagnosis is highly predictive of the presence of BE confirmed by endoscopy or pathology.²²

We did not have information on factors that may affect filled prescriptions of interest (e.g. lifestyle habits that linked with the use of preventive medications NSAID/aspirin and statins) as well as the risk of EAC, including length of BE segment, or the presence/grade of dysplasia. We attempted to correct for confounding by adjusting for non cancer disease comorbidity index that captures several common diseases such as myocardial infarction, cerebrovascular disease, chronic pulmonary disease, peptic ulcer disease, liver disease, diabetes, and renal disease and socio-economic status. However, we did not have specific information on obesity, diet, tobacco smoking, alcohol use, or *H. pylori* status. The magnitude and direction of such residual confounding is unclear.

This study had several strengths related to its large sample size of patients with BE that allowed the identification of an adequate number of EAC cases and tightly matched controls. The efficiency of the nested case-control design (rather than a cohort design) was high in defining relevant duration of medications. This made analyzing for a duration-response relationship of filled medication prescriptions possible. Lastly, we were able to match the controls to cases on age and date of entry into the BE cohort.

In summary, this matched nested case-control study suggests that filled statin and NSAID/aspirin prescriptions were associated with a significant reduction in the risk of EAC in patients with BE in the setting of high prevalence of PPI use. Given the observational nature of this study and the limitations discussed above, these findings need to be evaluated in other studies.

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Reference List

1. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005 January 19;97(2):142–6. [PubMed: 15657344]
2. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 2005 December;129(6):1825–31. [PubMed: 16344051]
3. Phillips RW, Wong RK. Barrett's esophagus. Natural history, incidence, etiology, and complications. *Gastroenterol Clin North Am* 1991 December;20(4):791–816. [PubMed: 1787014]
4. Spechler SJ. The columnar-lined esophagus. History, terminology, and clinical issues. *Gastroenterol Clin North Am* 1997 September;26(3):455–66. [PubMed: 9309397]

5. Pera M. Trends in incidence and prevalence of specialized intestinal metaplasia, barrett's esophagus, and adenocarcinoma of the gastroesophageal junction. *World J Surg* 2003 September;27(9):999–1008. [PubMed: 12917764]
6. Blais L, Desgagne A, Leloir J. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. *Arch Intern Med* 2000 August 14;160(15):2363–8. [PubMed: 10927735]
7. Karp I, Behloul H, Leloir J, Pilote L. Statins and cancer risk. *Am J Med* 2008 April;121(4):302–9. [PubMed: 18374689]
8. Ogunwobi OO, Beales IL. Statins inhibit proliferation and induce apoptosis in Barrett's esophageal adenocarcinoma cells. *Am J Gastroenterol* 2008 April;103(4):825–37. [PubMed: 18371146]
9. Garcia Rodriguez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. *Gut* 2006 November;55(11):1538–44. [PubMed: 16785284]
10. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology* 2003 January;124(1):47–56. [PubMed: 12512029]
11. El-Serag HB, Aguirre TV, Davis S, Kuebel M, Bhattacharyya A, Sampliner RE. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. *Am J Gastroenterol* 2004 October;99(10):1877–83. [PubMed: 15447744]
12. Hillman LC, Chiragakis L, Shadbolt B, Kaye GL, Clarke AC. Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus. *Med J Aust* 2004 April 19;180(8):387–91. [PubMed: 15089728]
13. Hillman LC, Chiragakis L, Shadbolt B, Kaye GL, Clarke AC. Effect of proton pump inhibitors on markers of risk for high-grade dysplasia and oesophageal cancer in Barrett's oesophagus. *Aliment Pharmacol Ther* 2008 February 15;27(4):321–6. [PubMed: 18047565]
14. Nguyen DM, El-Serag HB, Henderson L, Stein D, Bhattacharyya A, Sampliner RE. Medication Usage and the Risk of Neoplasia in Patients With Barrett's Esophagus. *Clin Gastroenterol Hepatol*. 2009 June 10;
15. Vaughan TL, Dong LM, Blount PL, et al. Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's esophagus: a prospective study. *Lancet Oncol* 2005 December;6(12):945–52. [PubMed: 16321762]
16. Prentice R, Brestlow N. Retrospective Studies and Failure Time Models. *Biometrika* 1978 April;65(1):153–8.
17. Morris CD, Armstrong GR, Bigley G, Green H, Attwood SE. Cyclooxygenase-2 expression in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. *Am J Gastroenterol* 2001 April;96(4):990–6. [PubMed: 11316217]
18. Tsibouris P, Hendrickse MT, Isaacs PE. Daily use of non-steroidal anti-inflammatory drugs is less frequent in patients with Barrett's oesophagus who develop an oesophageal adenocarcinoma. *Aliment Pharmacol Ther* 2004 September 15;20(6):645–55. [PubMed: 15352913]
19. van Vliet EP, Eijkemans MJ, Steyerberg EW, et al. The role of socio-economic status in the decision making on diagnosis and treatment of oesophageal cancer in The Netherlands. *Br J Cancer* 2006 November 6;95(9):1180–5. [PubMed: 17031405]
20. El-Serag HB, Johnson ML, Hachem C, Morgana RO. Statins are associated with a reduced risk of hepatocellular carcinoma in a large cohort of patients with diabetes. *Gastroenterology* 2009 May;136(5):1601–8. [PubMed: 19208359]
21. Morgan RO, Petersen LA, Hasche JC, et al. VHA pharmacy use in veterans with Medicare drug coverage. *Am J Manag Care* 2009 March;15(3):e1–e8. [PubMed: 19298095]
22. El-Serag HB, Wieman M, Richardson P. The use of acid-decreasing medication in veteran patients with gastro-oesophageal reflux disorder with and without Barrett's oesophagus. *Aliment Pharmacol Ther* 2008 June;27(12):1293–9. [PubMed: 18363892]

Table 1

Comparisons of demographic features between cases (BE with EAC) and matched controls (BE and no EAC).

	Cases	Controls	Incidence Density Ratio (95 % CI)
Number of patients	116	696	
Age, mean years (SD)	65.0 (10.3)	64.7 (10.3)	
Gender			
Male	113 (97.4%)	678 (97.4%)	Reference
Female	3 (2.6%)	18 (2.6%)	1.00 (0.29–3.46)
Race			
White	90 (77.6%)	508 (73.0%)	Reference
Non-white	14 (12.1%)	66 (9.5%)	1.60 (0.73–3.51)
Unreported	12 (10.3%)	122 (17.5%)	0.54 (0.29–1.03)
Exposure time [*] , mean days (SD)	691 (386)	691 (351)	
Outpatient encounters ^{**} , mean (SD)	40 (52)	33(41)	1.00 (1.00–1.01)
Priority level			
high			Reference
1	19 (16.4%)	129 (18.5%)	
2	8 (6.9%)	41 (5.9%)	
3	12 (10.3%)	73 (10.5%)	
4	12 (10.3%)	22 (3.2%)	
5	47 (40.5%)	272 (39.1%)	
6	1 (0.9%)	11 (1.6%)	
low			0.61 (0.35–1.08)
7	6 (5.2%)	42 (6.0%)	
8	10 (8.6%)	101 (14.5%)	
unreported	1 (0.9%)	5 (0.7%)	1.17 (0.14–10.05)
Non-cancer comorbidity index			
0	49 (42.2%)	348 (50.0%)	Reference
1	33 (28.5%)	185 (26.6%)	1.29 (0.82–2.10)
2	14 (12.1%)	71 (10.2%)	1.42 (0.74–2.74)

	Cases	Controls	Incidence Density Ratio (95 % CI)
3+	20 (17.2)	92 (13.2%)	1.57 (0.89–2.80)

* Duration between BE index date and EAC diagnosis date (or corresponding date in controls)

** Outpatient encounters are number of clinic visits within the exposure time.

SD: standard deviation

Table 2

The use of selected medications compared between cases (BE with EAC) and matched controls (BE and no EAC). Conditional logistic regression analyses were used to calculate incidence density ratio, 95% CI, and p-values. Medication use was defined by filled prescriptions following BE diagnosis and ending 3 months before EAC diagnosis (or corresponding dates in controls).

	Cases	Controls	p-value	Incidence Density Ratio (95% CI)	
				Unadjusted	Adjusted*
Number of patients	116	696			
PPI Prescriptions					
patients with at least one prescription	110 (94.8%)	653 (93.8%)	0.67	1.21 (0.50–2.90)	1.50 (0.61–3.66)
duration, mean in days (SD)	377 (308)	407 (303)	0.69	0.98 (0.86–1.11)	
H2RA Prescriptions					
patients with at least one prescription	48 (34.5%)	282 (33.8%)	0.45	1.17 (0.78–1.76)	
duration, mean in days (SD)	72 (167)	67 (161)	0.52	1.03 (0.95–1.12)	
NSAID (includes Aspirin) Prescriptions					
patients with at least one prescription	57 (49.1%)	411 (59.1%)	0.04	0.66 (0.44–0.99)	0.60 (0.40–0.92)
duration, mean in days (SD)	147 (257)	164 (226)	0.05	0.93 (0.86–1.00)	
Statin prescriptions					
patients with at least one prescription	41 (35.3%)	336 (48.3%)	<0.01	0.58 (0.38–0.87)	0.56 (0.36–0.87)
duration, mean in days (SD)	131 (255)	197 (277)	<0.01	0.90 (0.84–0.97)	

* adjusted for race, outpatient encounters, non cancer disease comorbidity index, VA priority level, and filled prescriptions of the other two medication categories.
SD: standard deviation

Table 3

The association between duration of filled prescriptions and the risk of EAC. Cases were patients with BE and EAC, and controls were patients with BE and no EAC at the time of diagnosis or corresponding case.

Duration of filled prescriptions (months)	Cases n (%)	Controls n (%)	Incidence Density Ratio (95% CI)	Cochrane-Armitage trend test p-value
Number of patients	116	696		
PPI				
0	6 (5.2)	43 (6.2)	Reference	
>0 to 12	62 (53.5)	328 (47.1)	1.39 (0.33–3.41)	
>12 to 24	31 (26.7)	219 (31.5)	0.89 (0.33–2.36)	
>24	17 (14.7)	106 (15.2)	1.00 (0.33–3.00)	
NSAIDs/aspirin *				0.30
0	59 (50.9)	285 (41.0)	Reference	
>0 to 12	43 (37.1)	295 (42.4)	0.70 (0.46–1.07)	
>12	14 (12.1)	116 (16.6)	0.55 (0.29–1.06)	
Statins *				0.02
0	75 (64.7)	360 (51.7)	Reference	
>0 to 12	23 (19.8)	175 (25.1)	0.63 (0.38–1.06)	
>12	18 (15.5)	161 (23.2)	0.52 (0.30–0.91)	

* >24 months was not examined because <5% of patients were in this category.