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Nonsteroidal Anti-Inflammatory Drugs and the Risk of Barrett's Esophagus

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Abstract

Objectives—Nonsteroidal anti-inflammatory drugs (NSAIDs) have been suggested to protect against esophageal adenocarcinoma (EAC). This study examined the effect of NSAIDs on the risk of developing Barrett's esophagus (BE), the precursor lesion to EAC.

Methods—We conducted a case-control study among eligible patients scheduled for either elective esophagogastroduodenoscopy (EGD) or recruited from primary care clinics to undergo a study EGD. We compared 323 patients with BE (296 nondysplastic and 27 dysplastic) with 2 separate control groups: 1347 patients from the elective EGD group ("endoscopy controls") and 502 patients from the primary care group ("primary care controls") with no endoscopic or histopathologic BE. Use of aspirin products and 23 nonaspirin NSAIDs was ascertained from detailed, self-reported questionnaires. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable logistic-regression models.

Results—There were no significant differences in self-reported NSAID use between all BE cases and all controls (58.2% vs. 54.6%, $P=0.33$); this was seen for aspirin products (43.0% vs. 37.4%, $P=0.08$) and nonaspirin NSAIDs (7.7% vs. 8.9%, $P=0.46$). These findings persisted in the multivariable model for any NSAIDs (adjusted OR 0.89; 95% CI 0.75–1.28), aspirin (adjusted OR 1.16; 95% CI 0.90–1.51), and nonaspirin NSAIDs (adjusted OR 0.88; 95% CI 0.55–1.39). Use of a combination of aspirin and nonaspirin NSAIDs was reported in 7.4% cases and 8.3% controls,

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Conflict of Interest

Potential competing interests: None

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and a non-significant inverse association with BE was seen (adjusted OR 0.70; 95% CI 0.44–1.11). There was no significant association between BE and daily NSAID use (adjusted OR 1.03; 95% CI 0.78–1.37). Similar findings were observed for comparisons involving nondysplastic or dysplastic BE cases, and endoscopy or primary care control groups separately or combined.

Conclusion—The use of NSAIDs was not associated with a reduced risk of BE. It is likely that the protective mechanism of NSAIDs on EAC occurs subsequent to the development of BE.

Introduction

Barrett's esophagus (BE) is an acquired, premalignant condition of the distal esophagus, characterized by the replacement of normal squamous epithelium by metaplastic columnar cells (1). Individuals with BE are at a considerable increased risk of developing esophageal adenocarcinoma (EAC), with an estimated 0.25%–6% annual risk of progression to EAC depending on presence and degree of dysplasia (2–5). Given the overall high morbidity and mortality of EAC, preventive efforts have focused on early detection and surveillance in BE patients, as well as chemoprevention in BE (6).

Aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown in experimental and epidemiological studies to be associated with a significant reduction in the risk of developing several cancer types, including EAC (7–12). Chronic inflammation is a risk factor for BE and EAC (13–18); and NSAIDs exert their anti-inflammatory properties by blocking cyclooxygenase isoenzymes (COX-1 or COX-2) and thus, prostaglandin and thromboxane synthesis (19,20). NSAIDs are also suggested to induce apoptosis and inhibit angiogenesis and the cell-cycle, resulting in suppression of tumor growth (21–23). Most NSAIDs block both COX-1 and COX-2; whereas aspirin selectively inhibits COX-1 only. While COX-2 is low or absent in normal esophageal mucosa, it is overexpressed in esophageal cancer, as well as in BE tissue (24–29).

Several epidemiological studies suggest that NSAID use is associated with a decreased risk of progression from BE to EAC (30–32), however, whether these medications affect the transformation of normal esophageal cells to the intestinal metaplasia that defines BE remains unknown. Prior studies have yielded conflicting results on NSAID use and the risk of developing BE with few showing lower risk of BE in aspirin (33) and nonaspirin NSAID users (34), and one reporting no association between NSAID use and risk of BE (35). Therefore, we investigated the effects of aspirin and nonaspirin NSAIDs on the risk of nondysplastic as well as dysplastic BE, using data from a large case-control study among US veterans.

Methods

Study Population and Design

This is a case-control study performed at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) in Houston, Texas. Study participants were recruited from ambulatory patients aged 40 to 80 who were scheduled for an elective esophagogastroduodenoscopy (EGD) for upper gastrointestinal (GI) symptoms or signs at the MEDVAMC from February 15, 2008, to June 28, 2013. We also recruited patients, aged 50–80, from 7 primary care

clinics at the MEDVAMC who were eligible for screening colonoscopy from September 1, 2008, to May 8, 2012. These patients underwent an EGD at the time of their screening colonoscopy, and none were primarily referred for EGD. The elective endoscopy control group was comprised of participants from the elective EGD group without endoscopic or histologic BE, and the primary care control group was comprised of participants recruited from primary care clinics without endoscopic or histologic BE. The combined elective endoscopy and primary care groups represent the source population for BE, meaning all patients who would be diagnosed with BE at the MEDVAMC, independent of symptoms. We excluded patients with a history of esophageal or gastric surgery or cancer; history of lung, colon, or breast cancer; significant liver disease, as indicated by platelet count <70,000, ascites or gastroesophageal varices; history of major stroke or mental disorder; or current use of anticoagulants.

BE cases comprised participants found to have specialized small-intestinal epithelium (confirmed by alcian-periodic acid-Schiff stain) in the histopathological examination of at least 1 biopsy obtained from endoscopically suspected areas of BE. Two expert pathologists reviewed all slides for endoscopically suspected BE to determine the presence of specialized intestinal epithelium. Patients with endoscopically suspected BE but without histological evidence on biopsy were not included in this analysis. Presence and length of BE were recorded during the study EGD, with long-segment BE defined as length >3cm from the gastroesophageal junction. The study was approved by the Institutional Review Boards for MEDVAMC and Baylor College of Medicine.

Data Collection

All study participants completed a detailed, computer-assisted questionnaire with guidance from a trained research assistant. The questionnaire surveyed individuals on demographic data, frequency and severity of gastroesophageal reflux disorder (GERD) symptoms; alcohol and tobacco use; and use of medications, including aspirin, nonaspirin NSAIDs, and acetaminophen. The following were listed by generic and brand names to aid in recall: aspirin (Bayer Aspirin®, DurAsp®, Bufferin®, Ecotrin®, Ascriptin®), aspirin/caffeine (Anacin®), acetaminophen/aspirin/caffeine (Excedrin®), aspirin/phenylephrine (Alka-Seltzer®), ibuprofen (Advil®, Motrin®, Nuprin®, Nurofen®, Actiprofen®), naproxen (Aleve®, Naprosyn®, Anaprox®), sulindac (Clinoril®), diflunisal (Dolobid®), indomethacin (Indocin®, Arthrexin®), piroxicam (Feldene®), diclofenac (Arthrotec®, Voltaren®), meloxicam (Mobic®), celecoxib (Celebrex®), rofecoxib (Vioxx®), ketoprofen (Orudis®), etodolac (Lodine®), nabumetone (Relafen®), oxaprozin (Daypro®), and flurbiprofen (Ansaid®). We also collected self-reported use of acetaminophen (Tylenol®, Excedrin®, Tylenol #2®, Tylenol #3®, Tylenol #4®), an analgesic that does not use the COX pathway, as an internal control exposure. For each of these medications, we elicited start and stop dates, frequency and duration of use. Use of bisphosphonates was obtained from manual review of the electronic Veterans Affairs pharmacy records within 10 years of the study date.

Participants who smoked <100 cigarettes over their entire life were classified as nonsmokers. Participants were classified as *Helicobacter pylori* infection positive if

organisms were found on any of the study's gastric biopsies or if previously positive biopsies, serum antibodies, or prior treatment were revealed through review of medical records. Body mass index (BMI) and waist-to-hip ratio (WHR) values were measured for each participant.

Statistical Analysis

We calculated and compared the proportions of cases and controls with self-reported use of aspirin and nonaspirin NSAIDs, as well as the frequency and duration of use. We analyzed frequency of NSAID use by categorical variables (never, monthly, weekly, more than weekly but less than daily, and daily), as well as a continuous variable (average use per month). We analyzed cumulative duration of NSAID use as a continuous variable and categorical variables (never, <1 year, 1–3 years, and >3 years). Aspirin use was further classified as high dose (>150mg) and low dose (<150mg).

In multivariate logistic regression, we evaluated use of the following between cases and controls: use of any NSAIDs (either aspirin or nonaspirin), aspirin (further classified by high and low dose), nonaspirin NSAIDs, combination of aspirin and nonaspirin NSAIDs, and acetaminophen. Our primary analyses compared all cases with all controls but we also conducted analyses restricted to nondysplastic BE cases and dysplastic BE cases compared with all controls, endoscopy controls and primary care controls.

We calculated odds ratios (ORs) and 95% confidence intervals (CIs), using unconditional logistic-regression models. Missing data were not included in the analyses. Forward stepwise selection was used to construct multiple regression models, using variables with a P -value < 0.1 in the unadjusted analysis. These variables included age at study recruitment, race (white, black, other), gender (male, female), GERD symptom duration, high WHR (>0.85 for women and >0.9 for men), and use of PPIs. We planned several stratified analyses: white men only, long-segment (>3 cm) BE, GERD symptoms or PPI use, no GERD symptoms or PPI use, GERD symptoms, no GERD symptoms, PPI use, no PPI use, WHR tertiles, being normal weight (BMI <25), overweight (BMI 25–29), or obese (BMI ≥30), bisphosphonate use, and no bisphosphonate use. All tests for statistical significance were 2-sided, with statistical significance determined at $\alpha = 0.05$. Statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC).

Results

In total, 323 BE cases (296 nondysplastic and 27 dysplastic) and 1849 combined controls (1347 endoscopy controls and 502 primary care controls) were analyzed. The characteristics of study participants are described in Table 1. BE cases were more likely to be older, white and male, and to have higher average WHRs than controls. BE cases were also more likely to self-report GERD symptoms (61.9% vs. 46.9% of controls) and PPI use (68.8% vs. 51.7% of controls) but less likely to have *H. pylori* infection than controls. These significant findings were largely consistent among endoscopy controls and primary care controls in separate analyses (Table 1).

More than half (58.4%) of all participants reported NSAIDs use. NSAID users were more likely to be older than 60 years ($P<0.001$) and white than nonusers ($P=0.009$). Nonaspirin NSAID users were more likely to be female ($P<0.001$), under the age of 50 years ($P=0.010$) and to use PPIs than nonusers ($P=0.015$). There was no significant difference in GERD symptoms among NSAID users and nonusers.

There were no significant differences in self-reported NSAID use between all BE cases and all controls (58.2% vs. 54.6%, $P=0.33$); this was similarly seen for aspirin (43.0% vs. 37.4%, $P=0.08$) as well as nonaspirin NSAIDs (7.7% vs. 8.9%, $P=0.46$). A combination of both aspirin and nonaspirin NSAID use was reported in 7.5% cases and 8.3% controls ($P=0.54$). Information on aspirin dosage was available for 139 cases and 691 controls, of whom 607 were low dose aspirin users (30.3% of all BE cases vs. 27.5% of all controls) and 152 were high dose aspirin users (9.3% of all BE cases vs. 6.6% of all controls); none of the differences between cases and controls were significant.

In the multivariable model, there was no significant association between BE risk and use of any NSAIDs (adjusted OR 0.89; 95% CI 0.75–1.28), aspirin (adjusted OR 1.16; 95% CI 0.90–1.51), or nonaspirin NSAIDs (adjusted OR 0.88; 95% CI 0.55–1.39). The combination of aspirin and nonaspirin NSAID use was inversely associated with BE; however, it did not reach statistical significance (adjusted OR 0.70; 95% CI 0.44–1.11). Similarly, we found no association between acetaminophen use and BE (adjusted OR 0.98; 95% CI 0.68–1.41). These findings were not significantly different for nondysplastic or dysplastic BE cases compared with all controls or endoscopy and primary care control groups examined separately.

Of the 8 aspirin and 23 nonaspirin NSAID products for which information was elicited in the study questionnaire, there were no differences in the distribution of any of these individual medications between cases and controls. Only 6 participants in total reported celecoxib use, (3 cases and 3 controls, 1% vs. 0.2%, respectively; $P=0.048$); however, the small sample size limits the significance of this finding.

Among those who reported NSAID use, most were daily users with BE cases having a mean monthly frequency of 28.4 (SD 6.1) times compared with 28.0 (SD 6.3) times per month among all controls ($P=0.47$). There was also no significant association between daily NSAID use (adjusted OR 1.03; 95% CI 0.78–1.37) and BE (Table 2). The average frequency of NSAID use did not differ significantly when nondysplastic or dysplastic BE cases were compared separately with controls. Although participants with dysplastic BE appeared more likely than controls to take high dose aspirin daily ($P<0.001$), this finding was limited by a sample size of only 10 dysplastic BE cases. There were no significant differences between cases and controls in the proportions of patients with never, daily, and less than daily NSAID use (Table 2).

With regards to duration of NSAID use as shown in Table 3, 19.2% of all BE cases reported using NSAIDs for over 3 years, not significantly different from 18.4% in the combined controls with an adjusted OR of 0.91 (95% CI 0.64–1.30). Our analyses also did not reveal

any significant association between duration of nonaspirin NSAID use and risk of nondysplastic or dysplastic BE (Table 3).

We also examined the association between NSAID use and BE in several stratified analyses. There was no significant association between NSAID use and BE in white men or in those with long segment BE. In the event BE patients were more likely to avoid NSAIDs due to concern for possible GI side-effects, we performed a stratified analysis to account for GERD symptoms and use of PPIs. We found no association between BE and NSAID use in those with GERD symptoms or PPI use, GERD symptoms only, or PPI use only. There were no significant associations with BE and NSAID use across several BMI and WHR categories. Though we found an inverse association between NSAID use and BE within the subset of bisphosphonate users, this association did not reach statistical significance (OR 0.33; 95% CI 0.08–1.32) (supplementary material; Table 4).

Discussion

In this large case-control study we did not find significant or consistent associations between risk of having BE and prior use of aspirin, nonaspirin NSAIDs, or a combination of both. These findings were demonstrated in separate comparisons between all BE cases and 2 distinct control groups (endoscopy controls and primary care controls), as well as between a small group of dysplastic BE and all controls. There were also no significant trends related to the type, dose, frequency or duration of aspirin or nonaspirin NSAID use and risk of BE. There may be a threshold effect for these medications below a certain cumulative dose/duration but our results do not support such contention. The findings were not changed in analyses adjusting for race, gender, GERD symptoms, PPI use, *H. pylori* infection, and markers of obesity (i.e., WHR and BMI), as well as in stratified analyses based on these variables.

An Australian case-control study by Thrift et al. found similar results to our study when they investigated the use of aspirin and nonaspirin NSAIDs in 393 BE cases (285 nondysplastic and 108 dysplastic) compared with 2 separate control groups (313 controls with GERD and 644 population controls). There was no significant difference in aspirin use among nondysplastic BE cases and both control groups (GERD controls: adjusted OR 1.16; 95% CI 0.80–1.68; and population controls: adjusted OR 1.01; 95% CI 0.71–1.43) (35). On the other hand, Thrift et al. noted an inverse association between use of nonaspirin NSAIDs and risk of nondysplastic BE when compared with population controls (adjusted OR 0.69; 95% CI 0.49–0.97) that was not seen with GERD controls (adjusted OR 0.82; 95% CI 0.57–1.18). However, this finding was present only among nonaspirin NSAID users with less than once weekly use and was not significant among more frequent nonaspirin NSAID users. Overall, the findings of our study and that of Thrift et al. do not support a protective effect of NSAIDs, including aspirin, on the development of BE (35).

In contrast to our study, a few prior studies have suggested that NSAIDs may be protective against the development of BE (33,34). A US case-control study of 434 incident BE cases compared with 434 controls who underwent elective endoscopy reported a lower likelihood of BE in aspirin users compared with nonusers (adjusted OR 0.56; 95% CI 0.39–0.80). Only

high-dose aspirin (325mg) was significantly associated with a decreased risk of BE (adjusted OR 0.36; 95% CI 0.20–0.64) (33). However, the study did not include an asymptomatic control group, and it is possible that those with upper GI symptoms such as GERD would avoid certain medications like NSAIDs that increase the risk of GI symptoms. In the FINBAR, the all-Ireland, population-based case-control study (34), Anderson et al. compared 230 participants with reflux esophagitis, 224 participants with long-segment BE (dysplastic cases excluded), and 227 participants with EAC to 260 population controls. Nonaspirin NSAID use (adjusted OR 0.40; 95% CI 0.19–0.81) and at least weekly aspirin use (adjusted OR 0.53; 95% CI 0.31–0.90) were associated with reduced risk of long segment BE. They found reduced risk of EAC in aspirin and nonaspirin NSAID users compared with controls, ORs 0.57 and 0.58, respectively. The authors suggested that, if NSAIDs are indeed protective against EAC, they likely act early on in the esophageal inflammation-metaplasia-carcinoma sequence (34). However, as acknowledged by the authors, recall bias might have been present and could have explained the findings because the interviews took place after the case and control status was known to the study participants. Conversely, in our study the study questionnaires were administered before the study endoscopy.

We found an inverse but non-significant association between NSAID use and BE within the subset of bisphosphonate users (OR 0.33; 95% CI 0.08–1.32). In a prior work published from our case-control study, oral bisphosphonate use was associated with increased risk of BE (adjusted OR 2.33; 95% CI 1.11–4.88); however, among participants who reported NSAID use within the year prior to study EGD, the positive association between bisphosphonate use and risk of BE was not seen (OR 1.23, 95% CI 0.38–3.95) (36). In our current study, which included an additional 38 BE cases and 231 controls, BE cases were still more likely to have history of bisphosphonate use. Perhaps NSAIDs are not protective against BE in average-risk individuals but exert a more notable effect in populations exposed to more esophageal inflammation, such as bisphosphonate users.

Our study was unique in that we looked at 23 nonaspirin NSAIDs individually to see whether particular formulations were more likely than others to influence the development of nondysplastic or dysplastic BE. Only 6 participants reported use of celecoxib (1% of BE cases vs. 0.2% of controls; $P=0.048$), limiting our ability to draw conclusions from this finding. Other than this, we did not find significant associations in the analysis; however, the small number of participants taking each individual medication limited the statistical power to find differences. Therefore, we may have missed associations, leaving the question of whether COX-2-selective medications have a more chemoprotective effect than nonselective NSAIDs open for future studies.

Our study has important limitations. Most participants were white men in their 7th decade of life; thus, our findings may not be generalizable to other populations. In addition, though our sample size (323 BE cases, 1849 controls, of whom 1197 self-reported use of any NSAIDs) was adequate to find associations of potential clinical significance, the small number of 27 dysplastic BE cases limited statistical power to find differences in NSAID use for this subgroup compared with controls. Furthermore, our ability to detect differences in BE rates among individual brands of NSAIDs was limited by few cases exposed to each of the

NSAID formulations. We also were not able to verify self-reported NSAID use, given the over-the-counter nature of most NSAIDs.

However, the study also had several strengths including accurate classification of cases and controls, and the systematic standardized collection of information on medication use and several important potential confounders and effect modifiers before the case/control status became recognized to the study subjects or investigators. We also attempted to limit biases inherent to case-control studies by having 2 separate control groups, one representing symptomatic patients and the other representing asymptomatic patients, all of whom underwent study EGD. It is also important to note that the internal validity of the study was high, as we were able to show the previously established BE risk factors of white race, male gender, and GERD (37).

In conclusion, our findings do not support a protective effect for aspirin or nonaspirin NSAIDs against the development of BE. Currently, there are not enough data to support the use of NSAIDs to reduce the risk of BE. More studies are needed to better elucidate the role NSAIDs may play in reducing the risk of BE in those at high risk, such as bisphosphonate users.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Sharma P. Clinical practice. Barrett's esophagus. *N Engl J Med*. 2009; 361:2548–2556. [PubMed: 20032324]
2. Murray L, Watson P, Johnston B, Sloan J, Mainie IM, Gavin A. Risk of adenocarcinoma in Barrett's oesophagus: population based study. *BMJ*. 2003; 327:534–535. [PubMed: 12958113]
3. Sikkema M, de Jonge PJ, Steyerberg EW, et al. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2010; 8:235–244. [PubMed: 19850156]
4. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. *JAMA*. 2013; 310(6):627–636. [PubMed: 23942681]
5. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc*. 2008; 67:394–398. [PubMed: 18045592]
6. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology*. 2011; 140:1084–1091. [PubMed: 21376940]
7. Gonzalez-Perez A, Garcia Rodriguez LA, Lopez-Ridaura R. Effects of nonsteroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. *BMC Cancer*. 2003; 3:28. [PubMed: 14588079]

8. Harris RE, Beebe-Donk J, Doss H, et al. Aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade (review). *Oncol Rep.* 2005; 13:559–583. [PubMed: 15756426]
9. Rothwell PM, Wilson M, Elwin C-E, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet.* 2010; 376:1741–1750. [PubMed: 20970847]
10. Duan L, Wu AH, Sullivan-Halley J, et al. Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric adenocarcinomas in Los Angeles County. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:126–134. [PubMed: 18187391]
11. Sadeghi S, Bain CJ, Pandeya N, et al. Aspirin, nonsteroidal anti-inflammatory drugs, and the risks of cancers of the esophagus. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:1169–1178. [PubMed: 18483339]
12. Corley DA, Kerlikowske K, Verma R, et al. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology.* 2003; 124:47–56. [PubMed: 12512029]
13. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer.* 2004; 4:579–591. [PubMed: 15286738]
14. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet.* 2001; 357:539–545. [PubMed: 11229684]
15. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002; 420:860–867. [PubMed: 12490959]
16. Schottenfeld D, Beebe-Dimmer J. Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. *CA Cancer J Clin.* 2006; 56:69–83. [PubMed: 16514135]
17. Garcia JM, Splenser AE, Kramer J, et al. Circulating Inflammatory Cytokines and Adipokines are Associated With Barrett's Esophagus: a Case-Control Study. *Clin Gastroenterol Hepatol.* Available online 2013 Aug 15 [Epub ahead of print].
18. Kramer JR, Fischbach LA, Richardson P, Alsarraj A, Fitzgerald S, Shaib Y, Abraham NS, Velez M, Cole R, Anand B, Verstovsek G, Rugge M, Parente P, Graham DY, El-Serag HB. Waist-to-hip ratio, but not body mass index, is associated with an increased risk of Barrett's esophagus in white men. *Clin Gastroenterol Hepatol.* 2013; 11:373–381. [PubMed: 23220167]
19. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol.* 1971; 231:232–235. [PubMed: 5284360]
20. Vane JR, Botting RM. The mechanism of action of aspirin. *Thromb Res.* 2003; 110:255–258. [PubMed: 14592543]
21. Husain SS, Szabo IL, Tarnawski AS. NSAID inhibition of GI cancer growth: clinical implications and molecular mechanisms of action. *Am J Gastroenterol.* 2002; 97:542–553. [PubMed: 11922545]
22. Williams CS, Mann M, DuBois RN. The role of cyclooxygenases in inflammation, cancer, and development. *Oncogene.* 1999; 18:7908–7916. [PubMed: 10630643]
23. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst.* 2002; 94:252–266. [PubMed: 11854387]
24. Lagorce C, Paraf F, Vidaud D, et al. Cyclooxygenase-2 is expressed frequently and early in Barrett's oesophagus and associated adenocarcinoma. *Histopathology.* 2003; 42:457–465. [PubMed: 12713622]
25. Shirvani VN, Ouatu-Lascar R, Kaur BS, et al. Cyclooxygenase 2 expression in Barrett's esophagus and adenocarcinoma: Ex vivo induction by bile salts and acid exposure. *Gastroenterology.* 2000; 118:487–496. [PubMed: 10702199]
26. Morris CD, Armstrong GR, Bigley G, et al. Cyclooxygenase-2 expression in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. *Am J Gastroenterol.* 2001; 96:990–996. [PubMed: 11316217]
27. Kandil HM, Tanner G, Smalley W, et al. Cyclooxygenase-2 expression in Barrett's esophagus. *Dig Dis Sci.* 2001; 46:785–789. [PubMed: 11330414]

28. Wilson KT, Fu S, Ramanujam KS, et al. Increased expression of inducible nitric oxide synthase and cyclooxygenase-2 in Barrett's esophagus and associated adenocarcinomas. *Cancer Res.* 1998; 58:2929–2934. [PubMed: 9679948]
29. Zimmermann KC, Sarbia M, Weber AA, et al. Cyclooxygenase-2 expression in human esophageal carcinoma. *Cancer Res.* 1999; 59:198–204. [PubMed: 9892207]
30. Kastelein F, Spaander MC, Biermann K, Steyerberg EW, Kuipers EJ, Bruno MJ. Probar-study Group. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett's esophagus. *Gastroenterology.* 2011; 141:2000–2008. [PubMed: 21878200]
31. Nguyen DM, Richardson P, El-Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. *Gastroenterology.* 2010; 138:2260–2266. [PubMed: 20188100]
32. Vaughan TL, Dong LM, Blount PL, et al. Nonsteroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. *Lancet Oncol.* 2005; 6:945–952. [PubMed: 16321762]
33. Omer ZB, Ananthakrishnan AN, Nattinger KJ, et al. Aspirin protects against Barrett's esophagus in a multivariate logistic regression analysis. *Clin Gastroenterol Hepatol.* 2012; 10:722–727. [PubMed: 22426086]
34. Anderson LA, Johnston BT, Watson RGP, et al. Nonsteroidal anti-inflammatory drugs and the esophageal inflammation-metaplasia-adenocarcinoma sequence. *Cancer Res.* 2006; 66:4975–4982. [PubMed: 16651456]
35. Thrift AP, Pandeya N, Smith KJ, Green AC, Webb PM, Whiteman DC. The Use of Nonsteroidal Anti-inflammatory Drugs and the Risk of Barrett's Oesophagus. *Aliment Pharmacol Ther.* 2011; 34:1235–1244. [PubMed: 21967506]
36. Lin D, Kramer JR, Ramsey D, et al. Oral bisphosphonates and the risk of Barrett's esophagus: case-control analysis of US veterans. *Am J Gastroenterol.* 2013; 108:1576–1583. [PubMed: 23857477]
37. Anderson LA, Watson RG, Murphy SJ, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. *World J Gastroenterol.* 2007; 13:1585–1594. [PubMed: 17461453]

Table 1

Demographic and life style characteristics of Barrett's esophagus cases and controls.

Variable	BE cases (N=323)	All controls (N=1849)	Endoscopy controls (N=1347)	Primary care controls (N=502)
	n (%)	n (%)	n (%)	n (%)
Age				
Mean, (SD)	61.6 (7.44)	60.1 (8.22)	59.5 (8.64)	61.7 (6.7)
		.001	<.001	.95
Race				
White	283 (87.5)	1129 (61.1)	852 (63.2)	277 (55.2)
		<.001	<.001	<.001
Black	36 (11.1)	666 (36.0)	451 (33.5)	215 (42.8)
Other	4 (1.2)	54 (2.9)	44 (3.3)	10 (2.0)
Gender				
Male	316 (97.8)	1681 (90.9)	1195 (88.7)	486 (96.8)
		<.001	<.001	.39
Female	7 (2.2)	168 (9.1)	152 (11.3)	16 (3.2)
GERD				
No symptoms	118 (36.5)	927 (50.1)	580 (43.1)	347 (69.1)
		<.001	.02	<.001
< 5 years	6 (1.9)	29 (1.6)	26 (1.9)	3 (0.6)
5-9 years	7 (2.2)	57 (3.1)	52 (3.9)	5 (1.0)
10 years	179 (55.4)	733 (39.6)	620 (46.0)	113 (22.5)
Missing*	13 (4.0)	103 (5.6)	69 (5.1)	34 (6.8)
BMI				
BMI <25	55 (17.0)	343 (18.6)	266 (19.7)	77 (15.3)
		.58	.29	.81
BMI 25-29	113 (35.0)	675 (36.5)	496 (36.8)	179 (35.7)
BMI >30	155 (48.0)	831 (44.9)	585 (43.4)	246 (49.0)
Waist-to-hip ratio				
Low (<0.85 or 0.9)	25 (7.7)	269 (14.5)	205 (15.2)	64 (12.7)
		.001	<.001	.02
High (>0.85 or 0.9)	297 (92.1)	1519 (82.2)	1093 (81.1)	426 (84.9)
Missing*	1 (0.2)	61 (3.3)	49 (3.6)	12 (2.4)
Tobacco smoking				
Never smoker	82 (25.4)	543 (29.4)	408 (30.3)	135 (26.9)
		.16	.16	.07

Variable	BE cases (N=323)		All controls (N=1849)		Endoscopy controls (N=1347)		Primary care controls (N=502)	
	n (%)		n (%)	P-value*	n (%)	P-value*	n (%)	P-value*
<30 pack-years	103 (31.9)		584 (31.6)		403 (29.9)		181 (36.1)	
30 pack-years	125 (38.7)		617 (33.3)		466 (34.6)		151 (30.1)	
Missing*	13 (4.0)		105 (5.7)		70 (5.2)		35 (7.0)	
Helicobacter pylori status								
Negative	262 (81.1)		1264 (68.4)	<.001	949 (70.5)	<.001	315 (62.7)	<.001
Positive	61 (18.9)		581 (31.4)		395 (29.3)		186 (37.1)	
Missing*	0 (0)		4 (0.2)		3 (0.2)		1 (0.2)	
PPI use								
No	96 (29.7)		837 (45.3)	<.001	474 (35.2)	.04	363 (72.3)	<.001
Yes	212 (65.6)		897 (48.5)		794 (58.9)		103 (20.5)	
Missing*	15 (4.6)		115 (6.2)		79 (5.9)		36 (7.2)	
H2RA use								
No	275 (85.1)		1556 (84.1)	.91	1117 (82.9)	.49	439 (87.4)	.02
Yes	32 (9.9)		177 (9.6)		150 (11.1)		27 (5.4)	
Missing*	16 (5.0)		116 (6.3)		80 (6.0)		36 (7.2)	
PPI or H2RA use								
No	84 (26.0)		756 (40.9)	<.001	417 (31.0)	.06	339 (67.5)	<.001
Yes	224 (69.4)		978 (52.9)		851 (63.2)		127 (25.3)	
Missing*	15(4.6)		115 (6.2)		79 (5.8)		36 (7.2)	
Bisphosphonate use								
No	303 (93.8)		1797 (97.2)	.002	1299 (96.4)	.03	498 (99.2)	<.001
Yes	20 (6.2)		52 (2.8)		48 (3.6)		4 (0.8%)	

BE, Barrett's esophagus; SD, standard deviation; GERD, gastroesophageal reflux disease; BMI, body mass index; PPI, proton pump inhibitor; H2RA, histamine 2 receptor antagonist.

* Missing values not included in analyses.

Table 2

Univariate and Multivariate Analyses: Frequency of NSAID use in all cases of Barrett's esophagus (BE) and in dysplastic BE compared to all controls. Multivariate models adjusted for age, sex, race, GERD symptoms, PPI use, waist-to-hip ratio, and *H. pylori* infection.

	All Controls N= 1849	All BE cases N= 323			Dysplastic BE cases N= 27		
		n	P- value *	Multivariate OR (95% CI)	n	P- value *	Multivariate OR (95% CI)
Any NSAIDs		273	.26			.89	
None	728 (47.0%)	120 (44.0%)		Ref.	12 (52.2%)		Ref.
Less than daily	86 (5.5%)	11 (4.0%)		0.78 (0.40–1.55)	1 (4.3%)		0.72 (0.09–5.71)
Daily	737 (47.5%)	142 (52.0%)		1.03 (0.78–1.37)	10 (43.5%)		0.58 (0.24–1.38)
ASA use only			.08			.63	
None	1046 (65.8%)	169 (59.1%)		Ref.	16 (64.0%)		Ref.
Less than daily	25 (1.6%)	4 (1.4%)		1.05 (0.35–3.19)	1 (4.0%)		2.24 (0.27–18.32)
Daily	519 (32.6%)	113 (39.5%)		1.26 (0.95–1.66)	8 (32.0%)		0.81 (0.34–1.94)
Low-dose ASA use only			.84			.39	
None	182 (30.8%)	41 (32.5%)		Ref.	5 (50.0%)		Ref.
Less than daily	19 (3.2%)	3 (2.4%)		0.78 (0.21–2.88)	0		---
Daily	390 (66.0%)	82 (65.1%)		0.91 (0.59–1.40)	5 (50.0%)		0.46 (0.13–1.64)
High-dose ASA use only			.24			<.001	
None	569 (84.8%)	109 (79.0%)		Ref.	6 (60.0%)		Ref.
Less than daily	3 (0.4%)	1 (0.7%)		1.88 (0.18–20.27)	1 (10.0%)		35.39 (2.34–534.42)
Daily	99 (14.8%)	28 (20.3%)		1.35 (0.83–2.20)	3 (30.0%)		1.04 (0.93–1.15)
Non-ASA NSAID use	1703		.36			.68	
None	1573 (92.4%)	283 (94.6%)		Ref.	23 (95.8%)		Ref.
Less than daily	52 (3.0%)	7 (2.4%)		0.79 (0.34–1.83)	0		---
Daily	78 (4.6%)	9 (3.0%)		0.66 (0.32–1.37)	1 (4.2%)		1.01 (0.13–7.77)
Combination of aspirin and nonaspirin NSAID use			.30			.68	
None	1583 (91.4%)	284 (93.4%)		Ref.	25 (96.2%)		Ref.
Less than daily	9 (0.5%)	0		---	0		---

	All Controls N= 1849	All BE cases N= 323			Dysplastic BE cases N= 27		
		n	P-value*	Multivariate OR (95% CI)	n	P-value*	Multivariate OR (95% CI)
Daily	140 (8.1%)	20 (6.6%)		0.63 (0.38–1.04)	1 (3.8%)		0.34 (0.05–2.53)
Acetaminophen use			.91			.10	
None	1506 (88.2%)	265 (87.5%)		Ref.	21 (84.0%)		Ref.
Less than daily	88 (5.2%)	16 (5.3%)		0.98 (0.55–1.75)	0		---
Daily	113 (6.6%)	22 (7.2%)		0.99 (0.60–1.62)	4 (16.0%)		2.77 (0.91–8.48)

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease.

* P-value provided for univariate modeling. Missing values or medication use of unknown frequency not included in analyses.

Table 3

Comparison of the mean duration of NSAID use in all Barrett's esophagus (BE) cases compared to all controls. Multivariate models adjusted for age, sex, race, GERD symptoms, PPI use, waist-to-hip ratio, and *H. pylori* infection.

	All Controls N=1849	All BE cases N=323		
		n	P-value *	Multivariate OR (95% CI)
Any NSAIDs			.84	
No	728 (53.2%)	120 (52.9%)		Ref.
<1 year	82 (6.0%)	12 (5.3%)		0.80 (0.41–1.56)
1–3 years	217 (15.9%)	33 (14.5%)		0.823 (0.54–1.28)
>3 years	341 (24.9%)	62 (27.3%)		0.91 (0.64–1.30)
ASA use only			.25	
No	1046 (67.8%)	169 (61.9%)		Ref.
<1 year	46 (3.0%)	10 (3.7%)		1.35 (0.64–2.83)
1–3 years	154 (10.0%)	29 (10.6%)		1.19 (0.76–1.87)
>3 years	297 (19.2%)	65 (23.8%)		1.18 (0.85–1.66)
Low-dose ASA use only			.93	
No	182 (32.3%)	41 (35.1%)		Ref.
<1 year	40 (7.1)	8 (6.8%)		0.95 (0.40–2.28)
1–3 years	128 (22.7%)	24 (20.5%)		0.85 (0.48–1.50)
>3 years	214 (37.9%)	44 (37.6%)		0.80 (0.49–1.31)
High-dose ASA use only		133	.54	
No	569 (86.3%)	109 (82.0%)		Ref.
<1 year	5 (0.8%)	2 (1.5%)		2.37 (0.39–14.34)
1–3 years	18 (2.7%)	4 (3.0%)		1.06 (0.33–3.34)
>3 years	67 (10.2%)	18 (13.5%)		1.25 (0.70–2.25)
Non-ASA NSAID use			.92	
No	1573 (94.4%)	283 (95.3%)		Ref.
<1 year	24 (1.4%)	3 (1.0%)		0.82 (0.24–2.85)
1–3 years	43 (2.6%)	7 (2.4%)		0.88 (0.38–2.05)
>3 years	26 (1.6%)	4 (1.3%)		0.93 (0.31–2.83)
Combination aspirin and nonaspirin NSAID use		303	.71	
No	1583 (92.6%)	284 (93.7%)		Ref.
<1 year	14 (0.8%)	1 (0.3%)		0.27 (0.03–2.11)
1–3 years	33 (2.0%)	4 (1.3%)		0.59 (0.20–2.11)
>3 years	79 (4.6%)	14 (4.7%)		0.81 (0.44–1.47)
Acetaminophen use			.29	
No	1506 (91.6%)	265 (89.5%)		Ref.
<1 year	55 (3.3%)	9 (3.0%)		0.93 (0.44–1.97)

	All Controls N=1849	All BE cases N=323		
		n	P-value*	Multivariate OR (95% CI)
1—3 years	36 (2.2%)	7 (2.4%)		1.04 (0.44–2.45)
>3 years	48 (2.9%)	15 (5.1%)		1.75 (0.93–3.28)

* P-value provided for univariate modeling. Missing values or medication use of unknown duration not included in analyses.