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# A Role for COX Inhibition in the Prevention of Progression of Barrett's Esophagus To Esophageal Adenocarcinoma

John Speakman

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By:

John Speakman

Masters Advisor

Eric Van Hecke, MPAS, PA-C, CAQ-EM, DMSC candidate

Clinical Assistant Professor, Director of Student Affairs

Augsburg University Department of Physician Assistant Studies

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Augsburg University

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# The Role of COX Inhibition in the Prevention of Progression of Barrett's Esophagus To Esophageal Adenocarcinoma

## Abstract

**Background:** Barrett's esophagus is the most significant predictor of the development of esophageal adenocarcinoma. The current treatment recommendation is a proton pump inhibitor to control acid reflux, yet there remains a significant number of individuals who progress to cancer. More can be done to prevent this progression.

**Purpose:** To this end, this paper seeks to answer the following PICO question: P: Patients with Barrett's esophagus not yet esophageal adenocarcinoma; I: Standard PPI treatment with the addition of Aspirin; C: Standard PPI treatment only; O: Prevention of progression of Barrett's esophagus to esophageal adenocarcinoma.

**Methods:** A comprehensive literature review was conducted using PubMed, Sage Journals, and Science Direct using the search terms Barrett's esophagus treatment, Barrett's esophagus aspirin, esophageal cancer prevention aspirin, cancer prevention aspirin, and prostaglandin cancer. Inclusion criteria were peer-reviewed, scholarly journals and studies published during or after 2017. Excluded from the search were meta-analyses and reviews.

**Conclusions:** Aspirin shows promise as a possible adjunctive treatment to proton pump inhibitors. A long-term study is needed to specifically assess if adding aspirin will reduce progression to adenocarcinoma while also assessing safety. Several biomarkers and tissue pathologies are already available to risk stratify who could benefit from this add-on treatment.

**Key Words:** Barrett's esophagus, aspirin, esophageal adenocarcinoma, EAC, BE

# The Role of COX Inhibition in the Prevention of Progression of Barrett's Esophagus To Esophageal Adenocarcinoma

## Introduction

Barrett's esophagus is the metaplastic change of esophageal squamous epithelium to columnar epithelium. [1] This protective effect is in response to long-standing exposure to stomach acids, a consequence of gastroesophageal reflux disease (GERD). [2] Singh helps to explain the importance of surveillance and appropriate management of GERD and Barrett's esophagus in his 2019 article. He explains that although every case of esophageal cancer arises from Barrett's, only 90% of those with a new diagnosis of esophageal cancer had a previous diagnosis of Barrett's. [3] The more severe the symptoms of reflux, the higher the risk for the development of adenocarcinoma of the esophagus. This link between GERD, Barrett's esophagus, and esophageal cancer has not yet been fully detailed but much evidence exists describing the association between the three, along with other risk factors for adenocarcinoma such as central obesity and smoking. [1]

The NIH estimates approximately twenty percent of the US adult population has GERD, defined as symptoms associated with gastric reflux at least twice a week. [4] In a 2015 study published in Gastroenterology, S. Kroep, et. al. used modeling to predict the progression of Barrett's esophagus to esophageal adenocarcinoma. They demonstrated an annual progression rate of 0.19%. [5] The NIH can give us the numbers from estimates by the American Cancer

Society. In 2022 in the US, there will be an estimated 20,640 new cases of esophageal cancer, 16,410 deaths, and a 5-year survival rate of 20.6% after diagnosis. [6]

The incidence of Barrett's has been increasing over time and esophageal adenocarcinoma with it. [7] Esophageal adenocarcinoma represents a significant problem in the US. With the proposed chain of gastric reflux to Barrett's esophagus to cancer, new methods of prevention of the progression of Barrett's must be explored.

One of the mechanisms that may be involved in the transformation of metaplastic cells to adenocarcinoma is the overexpression of cyclooxygenase-2. Prostaglandin activity is a result of inflammation. It is synthesized by cyclooxygenases both 1 and 2. [8] Prolonged inflammation, as is seen in GERD and Barrett's, results in the overproduction of prostaglandins via COX-2 activity. This, and the other markers of inflammation, have been implicated in the formation of GI tumors. Indeed, histological examination of many tumors displays increased levels of prostaglandins. [9]

In their article Chemoprevention in Barrett's esophagus and esophageal adenocarcinoma, Alkhayyat et. al. explain the role acid reflux has in cancer, namely increased cell proliferation and decreased cell apoptosis. [10] This is why proton pump inhibitors (PPIs) have been the mainstay treatment through their mechanism of action, gastric acid suppression. The authors note that PPIs alone may not be the most effective treatment. PPIs may increase cyclooxygenase (COX)-2 expression, which as previously noted, plays a role in the development of adenocarcinoma. [10] Recent evidence points towards ASA and NSAIDS playing a role in other types of GI cancers. They act through inhibition in the COX pathway; COX-2 expression is

increased in areas of the esophagus with Barrett's and adenocarcinoma. COX is also associated with proliferation, apoptosis, and angiogenesis in cancer. [10]

Aspirin has been proposed as protective against esophageal adenocarcinoma by inhibiting COX-1 and COX-2; a longer duration of use was associated with greater protective effects, though interestingly there was no protective effect with Celecoxib. [11] This leads to the PICO question to assess trials regarding the use of aspirin in the prevention of esophageal adenocarcinoma.

P: Patients with Barrett's esophagus not yet esophageal adenocarcinoma

I: Standard PPI treatment with the addition of Aspirin

C: Standard PPI treatment only

O: Prevention of progression of Barrett's esophagus to esophageal adenocarcinoma

To answer this question, literature will be reviewed demonstrating prostaglandins' role in cancer. Next, this review will focus prostaglandin's specific role in Barrett's Esophagus. Also include are studies investigating aspirin as a possible preventative for certain types of cancers then, specifically, its use in Barrett's. Finally, this review will discuss the adverse effects aspirin has demonstrated and why patients must be risk stratified when considering adding aspirin to standard Barrett's esophagus treatment. It is important to find a more effective strategy than proton pump inhibitors alone to prevent the transformation of Barrett's esophagus to high-grade dysplasia or esophageal adenocarcinoma. To that aim, this review will examine the current literature to establish whether aspirin should be added as an adjunct to PPIs in the presence of Barrett's esophagus.

## Methods

A literature review was conducted through the databases PubMed, Sage Journals, and Science Direct. The search terms were Barrett's esophagus treatment, Barrett's esophagus aspirin, esophageal cancer prevention aspirin, cancer prevention aspirin, and prostaglandin cancer. Inclusion criteria were peer-reviewed, scholarly journals and studies published during or after 2017. Excluded from the search were meta-analyses and reviews. Articles were obtained from Augsburg's Lindell Library.

## Review of Literature

Prostaglandins play an important role in the human immune inflammatory response, their production increasing during any inflammatory response to injury or illness. Their generation is governed by two synthases known as cyclooxygenase or COX-1 and COX-2. [8] An overactive or prolonged inflammatory response, and therefore prostaglandins, have been implicated in the genesis of cancer. [12] This led to investigating what, if any, role prostaglandins play in cancer.

### COX/prostaglandin in cancer

The first study reviewed was published in 2019 by Wong et al in *Theranostics*. The authors sought to if prostaglandins play a role in the development of gastric carcinoma via DNA hypermethylation. In this randomized and controlled trial, Gastric cancer cells were exposed to either prostaglandin E2 (PGE2) or control for 48 hours to assess DNA methylation, histone methylation, demethylation, acetylation, and deacetylation changes associated with epigenetic changes. They then used genomic sequencing to assess for promotor hypermethylation patterns seen in cancer in PGE2 treated cells. COX2 transgenic mice were used to assess for the same epigenetic and DNA methylation patterns observed in vitro. Finally, they retrospectively

analyzed 21 human tissue samples from patients who had undergone a placebo-controlled trial with a COX2 inhibitor and who had gastric intestinal metaplasia, comparing them to 21 tissue samples from the placebo group. [13]

Wong et al found that DNA methylation was upregulated with PGE2 vs control in such a way that indicates PGE2 can begin the DNA methylation process seen in other cancers. They also found the activity of PGE2 was dose-dependent. PGE2 treated cells did demonstrate increased promoter hypermethylation as seen in other cancer cells. Transgenic mice displayed the same DNA methylation patterns found in cancer as compared to wild-type mice that did not. The retrospectively assessed tissue samples showed the COX2 inhibitor treatment group did not show DNA methylation patterns as did those in the placebo group. [13]

While this study did not include human subjects it provides an important basis for the mechanism prostaglandins play in the development of cancer cells. The sample size of retrospectively assessed tissues was also very small but this does help to indicate further study on the subject. It also leads to the next area of study, the role cyclooxygenases play in Barrett's esophagus itself.

**COX in Barrett's**

I reviewed two studies regarding the role of cyclooxygenase-2 (COX-2) in Barrett's esophagus. The first was published in 2020 by Majka et al in the *American Journal of Physiology-Gastrointestinal and Liver Physiology.* The authors investigated the interaction between COX-2 and epidermal growth factors in the development of Barrett's esophagus. They used mice with a surgically created esophageal gastric duodenal anastomosis to introduce

stomach acids to the esophagus to induce the damage seen in reflux. The rats were randomized into several treatment groups to evaluate epidermal growth factors and several medications including celecoxib and pantoprazole. After 3 months of treatment, rats were anesthetized and their abdomens surgically opened. One of the samples collected and measured was esophageal mucosal PGE2 generation. Esophageal mucosal damage was also measured macroscopically and microscopically with blinded examiners. They graded the esophagus according to the degree of lesions present and development of Barrett's, development of dysplasia of squamous cells, and development of esophageal adenocarcinoma. The primary outcome showed that epidermal growth factor decreased blood flow to the esophagus. These rats also expressed significantly higher levels of COX-2. Rats treated with celecoxib (a COX-2 inhibitor), ranitidine, or pantoprazole had significantly more blood flow. Combining celecoxib with other medications significantly reduced dysplasia and mucosal damage compared to using the other medications alone. [14] This study also used rat models instead of humans and had a relatively low number of subjects. It also used celecoxib instead of aspirin but these medications both inhibit COX-2. Using the rat models did allow researchers to dissect and thoroughly examine the esophagus for the specific chemical markers this paper is investigating. It also reinforces the effectiveness of proton pump inhibitors (PPIs) in the treatment of Barrett's but also suggests there is a need for an adjunct. The authors also demonstrated more severe esophageal mucosal damage led to more COX-2 and prostaglandin expression, suggesting an avenue for adjunctive treatment.

I also reviewed an article from 2011 in *Alimentary Pharmacology & Therapeutics*. De Bortoli et al. used a randomized clinical trial to compare two different PPIs in treating Barrett's esophagus. The researchers used three biochemical markers in their study, Ki67, COX-2, and cell apoptosis, all associated with cancer. [15] They used 77 humans for this one-year trial, a small

number but their study design was limited by both cost and finding enough participants that met inclusion criteria at a single institution. The study found increased COX-2 expression in esophageal samples of those that also had decreased cell apoptosis and increased Ki67, markers of cancer the authors had previously established. [15] This is an older study, with a small and homogenous sample size, occurring over a very short time. It also lacked in a control group receiving a placebo. This study did use objective markers though and was able to demonstrate significantly increased COX-2 in humans with Barrett's esophagus. Now that prostaglandin and COX-2 have been shown to have a role in the development of cancer, I will move on to exploring the role for aspirin, a COX inhibitor, has in preventing cancer.

**Aspirin in Cancer**

Aspirin, acetylsalicylic acid, has been used by humans in its natural form, salicylic acid from myrtle and willow, for nearly 4000 years to treat pain. [16] Aspirin acts through the nonselective inhibition of COX enzymes thereby decreasing the formation of the inflammatory messenger prostaglandin. [17] Now researchers are exploring new uses for aspirin beyond its traditional uses. Joseph Sung et al. explored the use of aspirin, metformin, or a combination of the two medications in delaying cancer onset in a retrospective cohort study. They assessed 120,971 aspirin users compared to 241, 942 nonusers from medical records in Hong Kong public hospitals. Users had to have been prescribed aspirin for at least 6 months. They found during their 7.5-year follow-up time that aspirin users were significantly less likely to develop esophageal cancer. [18] This retrospective study lacked controls beyond age and sex and the authors had no way of assessing over-the-counter use of aspirin but this data suggests further study into aspirin as a cancer preventative is warranted.

Two more studies assessed the use of aspirin for gastrointestinal-related metaplasia and dysplasia. The first, by Hideki Ishikawa et al., sought to assess the effectiveness of aspirin, mesalazine, or a combination of the two in repressing either the recurrence of polyps or colorectal adenocarcinoma in patients with familial adenomatous polyposis. The authors conducted a randomized, double-blinded, placebo-controlled study at 11 hospitals and outpatient clinics in Japan. They found the aspirin treatment group had significantly reduced numbers of polyps and exerted a protective effect against the development of atypia. [19] This study was unfortunately very short-term, only 8 months, and only included a total of 104 patients, with 26 in the aspirin treatment group, limiting the power of generalizability. This study did use effective controls and could be developed into a much larger and longer study to improve its prognostic effects.

The next study takes place over 10 years and included 861 participants, overcoming the weaknesses of the previously reviewed study. John Burn et al. conducted a 10-year follow-up of a double-blinded, placebo-controlled study attempting to determine whether taking aspirin exerts a protective effect against colorectal cancer in those with Lynch syndrome. They found those in the aspirin treatment group were at a significantly reduced risk for the development of colorectal cancer but no difference for other types of cancer outside of the gastrointestinal tract. [20] While Lynch syndrome is an inherited condition rather than acquired, as is Barrett's, this follow-up study provides evidence aspirin may protect against adenocarcinomas of the gastrointestinal tract over a prolonged period. Next, this paper will focus more specifically on adenocarcinoma of the esophagus as it relates to Barrett's and the use of aspirin.

**Aspirin in Barrett's**

The authors of the next study attempted to find the mechanism for how COX-1, COX-2, and thromboxane A2 (TXA2) function in the development of Barrett's and esophageal adenocarcinoma. Tianshun Zhang et al. used mice with surgically created esophagoduodenostomy anastomosis to introduce stomach acids to the esophagus in a predictable manner creating 3 treatment groups, aspirin-treated, aspirin placebo-treated, surgical placebo, and aspirin placebo-treated. Aspirin was given 100mg/kg once per day for 16 weeks. Necropsy was performed at 52 weeks to obtain blood and esophageal tissue samples. Of the surgically treated placebo group 40% developed Barrett's, 20% developed esophageal adenocarcinoma, and plasma showed significantly increased levels of TXA2. In the aspirin treatment group, 31% developed Barrett's while none developed adenocarcinoma; aspirin-treated blood plasma showed significantly less TXA2 compared to the placebo-treated group. The control group developed no Barrett's and no esophageal adenocarcinoma (EAC). [21] In the same study, the authors assessed human esophageal tissue samples from a 2012 study, *Esomeprazole and 325 mg/d Aspirin Reduce Tissue Concentrations of Prostaglandin E2 in Patients with Barrett's Esophagus,* by Gary Falk et al. where Barrett's esophagus patients were given various doses of aspirin with a PPI vs placebo with a PPI. [22] Zhang et al. chose 20 random samples from each arm of the study, 49 of the 60 samples were analyzed; 11 were not sufficiently preserved. They found TXA2 levels were higher than the other 4 PGs measured, any dose of aspirin + PPI significantly reduced the presence of TXA2, and Placebo +PPI did not significantly reduce TXA2 levels. [21] This study used objective and measurable chemical markers instead of subjective data and combined data from both mice and humans although the cells were in vitro

rather than in vivo. This fact study lacks external validity for treatment but does point towards future trials exploring the protective mechanism of aspirin.

A study from 2018 by Galipeau et al. used genomic sequencing of esophageal cancer cells to help find a genetic mechanism for the development of EAC in Barrett's and how aspirin affects this process. All the participants were part of a larger ongoing trial called The Seattle Barrett's Esophagus Study. The authors chose 41 participants, from the larger trial, who had been diagnosed with Barrett's esophagus and met the necessary inclusion criteria. These 41 participants were called users, defined as having used an NSAID at least once per week for at least 6 months. The 41 were matched against 41 nonusers of NSAIDS controlling for sex, smoking status, and age within 10 years. A sample was taken from each of the participant's esophagus in the BE segment via endoscopy. DNA was extracted and assessed for single nucleotide variance to determine somatic mutations associated with adenocarcinoma. Data were analyzed using a linear regression model with 6 participants (4 users and 2 non-users) assigned a value of 0 mutations chosen based on fewer than 50 single nucleotide variances (SNVs). The values were log-transformed. 96 somatic base substitutions were identified within the context of nucleotide pairing while 46 of the 96 somatic SNVs had a lower mutation count in the users compared to the nonusers. [23] 3 of the 96 had a higher mutation count in users compared to nonusers. [23] The difference in mutation load in the 96 substitutions was statistically significant with ($p<3x10-16$). [23] Users were also noted to have significantly fewer mutations to the p53 gene, a tumor suppressor gene, when compared to non-users. [23] Their data suggests NSAID use significantly reduces the mutations associated with the transformation of Barrett's to esophageal adenocarcinoma. The cross-section allowed for direct comparison between users and nonusers of NSAIDs. This study was limited in the number of participants and data may be skewed due to

participants already enrolled in another trial. The NSAID use was also self-reported rather than controlled but they did assess objective measures in the form of SNV associated with cancers. Unfortunately, this was also a very short duration study but follow-up is certainly available in the future as this is an ongoing trial.

Finally, Janus Jankowski et al. published the results of their *Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomized factorial trial* in 2018 in The Lancet. The authors sought to discover if the combination of aspirin with esomeprazole did decrease mortality associated with esophageal adenocarcinoma in Barrett's. This study was conducted over 8 years with 2557 participants, all of whom had been diagnosed with Barrett's without EAC, high-grade dysplasia, or taking any NSAIDs at baseline. Participants were randomized 1:1:1:1 to receive esomeprazole at a high dose or low dose with or without ASA. Minimization factors for randomization were the length of dysplasia, age, and presence or absence of intestinal dysplasia. This study was not blinded. Participants received either 40mg esomeprazole or 20mg esomeprazole. Each group also received 300mg of aspirin per day or no aspirin. The primary outcomes studied were all-cause death, esophageal adenocarcinoma, or high-grade dysplasia. They found high dose PPI by itself significantly increased time to the predetermined outcome as compared to the sole use of low dose PPI. Aspirin compared to no aspirin showed no significant difference but PPI with aspirin in combination showed the most difference. [24] This trial establishes that combining high dose PPI with aspirin reduces all-cause mortality in the patient Barrett's esophagus during the time of the trial. Aspirin alone had no statistically significant effect, must be in combination with PPI to show benefit. Using high dose PPI with aspirin was better than using high dose PPI alone.

**Adverse effects of aspirin**

Although aspirin has a history nearly as old as human civilization, it is not benign. Its use in gastrointestinal cancer prevention has inherent dangers as indicated by the following. Louise Bowman et al. studied whether giving diabetic patients aspirin 100mg per day could lead to decreased incidence of vascular events. The primary safety outcome they also measured was the first major bleeding event defined as intracranial hemorrhage, sight-threatening, or gastrointestinal bleeding. They found participants in the aspirin treatment group had a 29% greater chance of developing a major bleed, this was a significantly greater risk with the majority of bleeds occurring in the upper GI system. [25] PPIs were used by less than 25% of participants which may have skewed the results towards the greater incidence of GI bleeding. Further study regarding the efficacy and safety of aspirin should include a PPI.

Joharatnam-Hogan et al. look further into the safety of aspirin in their 2019 study *Aspirin as an adjuvant treatment for cancer: feasibility results from the Add-Aspirin randomized trial,* in patients who had undergone radical treatment for gastro-esophageal cancer. This blinded, randomized trial included 2253 participants who had been diagnosed with cancer of the esophagus, colorectal, breast, or prostate. All received 100mg of aspirin per day for 8 weeks during a run-in period for a larger trial. 25 of the 2253 participants needed to stop the trial due to toxicities which include esophageal pain, tinnitus, allergy, dyspepsia, bowel obstruction, thrombocytopenia, hypertension, nausea, gastrointestinal bleed, and dizziness. [26] Although only 1% of participants reacted badly enough to remove them from the trial, aspirin can cause harm. This is why patients must be risk stratified when considering adding aspirin as a part of Barrett's treatment.

**Identifying potential candidates for adding aspirin**

Medication therapy is not the sole methodology in the treatment of Barrett's esophagus. Zhanwei Zhao et al. conducted a systematic review in 2021 of 250,157 patients with Barrett's. They found lifestyle changes that can reduce the risk of Barrett's progressing to EAC include reducing alcohol intake, weight loss, quitting smoking, and dietary changes such as increased fiber intake. [27] Unfortunately, many patients have difficulty adhering to recommended lifestyle modifications regardless of the risks. Xiaotao Zhang et al. conducted a prospective cohort study with 106 recently diagnosed Barrett's esophagus patients. The patients, recruited from the offices of 4 different gastroenterologists, were told to stop smoking, avoid alcohol, achieve a healthy weight, and what foods to avoid but were provided no training on how to achieve these goals. They completed follow-up surveys at 3 and 6 months assessing lifestyle risk factors such as weight, dietary intake, and smoking status. They also inquired about adherence determinants, perceived benefits of therapy, perceived severity of Barrett's, perceived risk of EAC, and perceived barriers, to assess how likely to adhere to lifestyle changes. They found that 91% of respondents did not meet the counseled dietary guidelines at 6 months, nor was there a statistically significant change in any of the risk factors by 6 months even though all respondents, in the initial survey, had high perceived benefits to lifestyle changes and risks of EAC. [28] This was a small cohort assessed, and of the initial 106 participants, only 81 completed the 6-month survey. This study's authors also relied on self-reporting rather than a more controlled environment but this helps to show real-world results with patients increasing the externalizable power. This study suggests another avenue of treatment though, patients could have daily coaching and support groups. Respondents reported wanting to learn more about acid control

and wanting to learn in a group atmosphere. This also suggests medication therapy is warranted in those who struggle with lifestyle changes, 91% of patients in this study.

Patients should be risk stratified when deciding who could benefit from adding aspirin given the aforementioned adverse effects of aspirin, especially to the gastrointestinal system which is already compromised in Barrett's. A 2021 study from *Gastrointestinal Endoscopy* sought to identify clinical risk factors for neoplastic progression of Barrett's in a multicenter retrospective cohort study at Cambridge University in the UK and the Mayo Clinic in the US. Data was collected over 10 years and included 465 patients. The authors found that the biggest predictor for progression was the length of the segment of metaplasia with an odds ratio of 1.21 for every 1 cm of the affected esophageal segment. [29]

To refine stratification, specific biomarkers and histological criteria are available and should be used. T Kauttu et al. at Helsinki University compared cell lines from several healthy esophagi, Barrett's esophagi, and EAC patients to demonstrate increased expression of ADAM9 (a disintegrin and metalloproteinases). In both Barrett's and EAC samples, compared to controls, there with a rising trend in ADAM9 as Barrett's progressed to EAC. [30] Likewise, Dr. Edward Tsoi at St. Vincent's Hospital in Melbourne was able to isolate 4 histological markers from esophageal tissue samples from 38 Barrett's patients who had progressed to EAC versus 17 Barrett's patients who had not. They found that "loss of surface maturation, mucin depletion, nuclear enlargement, and increase of mitosis" significantly predicted who would progress to EAC if all 4 markers were present in Barrett's esophagus histology samples. [31] Finally, Prassad Iyer et al. assessed the use of a commercial product called TissueCypher™ in predicting the progression of Barrett's to EAC versus clinical variables alone. The authors pooled data from 4

studies, defining progression as Barrett's transforming to EAC greater than or equal to one year after the initial diagnosis of Barrett's esophagus. They found that 28% of samples were progressors, the median time to progression was 38.1 months, and 79% of progression was within 5 years of diagnosis. [32] They found TissueCypher™ to have a sensitivity of 0.38 and specificity of 0.94 meaning this test is good at ruling out patients who will probably not progress to EAC but may have many false negatives. [32] Interestingly, they also found that Barrett's length was a strong clinical predictor for transformation to EAC. This commercial test needs refining to increase the sensitivity but, the data from this study suggests combining clinical factors with histological tests could strongly help to risk stratify who would qualify for treatment beyond the standard PPI, such as with aspirin.

## Discussion

Although a small minority of patients will progress from Barrett's to EAC, the survival 5-year survival rate of EAC is an abysmal 20.6%, which will lead to an estimated 16,410 deaths this year. [6] Clearly there is room for treatment modalities beyond lifestyle changes and PPIs. De Bertoli et al. established COX inhibition may play a role in the treatment of Barrett's by looking at specific biomarkers, namely Ki67, cell apoptosis, and COX-2. The study was open-label, randomized, and contained a parallel group. They evaluated 77 patients via endoscopy and laboratory tissue analysis. Samples were taken from the esophageal-gastric junction from patients who had a previous diagnosis of Barrett's esophagus but no dysplasia. The two treatment groups received either esomeprazole 40 mg bid (n=39) or pantoprazole 40 mg bid (n=38) for 1 year. Results demonstrated a statically significant decrease in Ki67 and COX-2 expression and an increase in apoptosis for the esomeprazole group while the pantoprazole group

showed no significant difference between baseline and trial completion. [15] While the PPI group did demonstrate decreased COX-2 activity, there was still activity present. This study did not involve a large number of participants, but the prospective study effectively demonstrated COX expression plays a role in Barrett's.

A mechanism for COX inhibition via aspirin must be explained before aspirin can be considered. Zhang et al. provide this mechanism in their paper *Targeting the COX1/2-Driven thromboxane A2 pathway suppresses Barrett's esophagus and esophageal adenocarcinoma development.* This study used mice with surgically induced Barrett's and COX-1, COX-2, and TXA2 antibodies to show an increase in the expression of TXA2, COX-1, and COX-2. They also showed When COX1 and COX2 were knocked out of Barrett's and EAC cells, this resulted in reduced cell proliferation. [21] This answers the chemical component of the PICO question but not the treatment portion. It proposes the mechanism for how aspirin will work, the thromboxane A2 pathway, in preventing Barrett's esophagus from converting to EAC. It also demonstrated providers can measure plasma levels of TXA2 to use as a marker for who might be a candidate for ASA treatment in the presence of Barrett's.

Jankowski et al. continued this line of research with their *AspECT* trial. In light of the role COX plays in Barrett's, they sought to answer if combining a PPI with aspirin would lead to decreased mortality associated with EAC. This large study was conducted over 8 years. They concluded aspirin by itself did not affect the progression of Barrett's to EAC but aspirin in combination with a high dose PPI regimen was more effective than high dose PPI alone in delaying transformation and also resulted in a lower rate of all-cause mortality. The number needed to treat with high dose PPI and aspirin was 43 in regards to preventing high-grade

dysplasia, adenocarcinoma, or death. [24] This study suggests there is an interplay between aspirin and a PPI that is worth at the very least further study and possibly as an adjunct to treatment.

Finally, a risk stratification strategy must be employed when considering adding aspirin to standard PPI treatment. Several biomarkers and tissue pathologies are available, including the commercially available TissueCypher™. Tsoi et al. continued the work of Ten et al. in verifying 4 histological criteria in predicting who will progress from Barrett's to EAC, an important tool given the relatively low Barrett's to EAC progression rate. [31, 5]. Iyer et al. went beyond their assessment of TissueCypher™ to create a 5-year risk assessment tool for progression to EAC using TissueCypher™ in combination with several clinical factors such as age, sex, Barrett's segment length, and presence of a hiatal hernia. [32] This tool could help identify participants for a much larger study investigating the power of aspirin combined with a proton pump inhibitor to not only arrest the transformation of Barrett's to esophageal adenocarcinoma but possibly reverse the dysplastic changes seen in Barrett's.

We suggest some further studies may be needed to clarify the benefits of adding aspirin in the chemoprevention of EAC in the presence of Barrett's esophagus. We propose a 5-year study with two goals. The first is to assess the effectiveness of the Iyer et. risk assessment tool. [32] The second is to specifically assess the effectiveness of aspirin in preventing the progression of Barrett's esophagus, and the potential dose that would be most effective. We propose a randomized, double-blinded, placebo-controlled study over a 5-year period wherein participants with Barrett's esophagus are given both PPI and either placebo or aspirin at various doses. Participants will receive follow-up endoscopies at years 1, 3, and 5 of the trial to assess for

progression in each of the groups. This study could further demonstrate the potential role for aspirin in Barrett's esophagus.

## Conclusion

This analysis sought to clarify the use of aspirin as adjunctive therapy in the treatment of Barrett's esophagus. It began with the PICO question

P: Patients with Barrett's esophagus not yet esophageal adenocarcinoma

I: Standard PPI treatment with the addition of Aspirin

C: Standard PPI treatment only

O: Prevention of progression of Barrett's esophagus to esophageal adenocarcinoma

To do this we investigated how prostaglandins and COX are associated with cancer development and how a COX inhibitor, such as aspirin, may be of therapeutic use.

COX has been demonstrated to be a factor in the transformation of Barrett's to EAC. While PPI treatment alone is effective for some, many patients progress to adenocarcinoma placing a burden on an already taxed medical system. Aspirin is an inexpensive and readily available medication with notable but relatively few adverse effects when used appropriately with the appropriate patient population. There are several methods available to determine which Barrett's patients are likely to progress to EAC. Using clinical factors, histological criteria, plasma markers, or commercial devices can help risk stratify who would most benefit from adding aspirin to PPI treatment. Further, longer-term prospective human trials investigating the PPI aspirin combination are certainly warranted. This combination could be the stopgap needed to prevent EAC for many patients.

**References**


1. Spechler MD SJ. *Barrett's Esophagus: Epidemiology, Clinical Manifestations, and Diagnosis - UpToDate*.; 2021. Accessed July 3, 2022. https://www-uptodate-com.ezproxy.augsburg.edu/contents/barretts-esophagus-epidemiology-clinical-manifestations-and-diagnosis?search=barrett%20esophagus&source=search_result&selectedTitle=1~120&usage_type=default&display_rank=1

2. Kahrilas MD PJ. *Complications of Gastroesophageal Reflux in Adults - UpToDate*. Jan 14, 2022 Accessed July 3, 2022. https://www-uptodate-com.ezproxy.augsburg.edu/contents/complications-of-gastroesophageal-reflux-in-adults?search=barrett%27s%20esopphagus%20GERD&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

3. SINGH T, SANGHI V, THOTA PN. Current management of Barrett esophagus and esophageal adenocarcinoma. *Cleve Clin J Med*. 2019;86(11):724-732. doi:10.3949/ccjm.86a.18106

4. Digestive Diseases Statistics for the United States | NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed July 3, 2022. https://www.niddk.nih.gov/health-information/health-statistics/digestive-diseases

5. Kroep S, Lansdorp-Vogelaar I, Rubenstein JH, et al. AN ACCURATE CANCER INCIDENCE IN BARRETT'S ESOPHAGUS: A BEST ESTIMATE USING PUBLISHED DATA AND MODELING. *Gastroenterology*. 2015;149(3):577-585.e4. doi:10.1053/j.gastro.2015.04.045

6. Cancer of the Esophagus - Cancer Stat Facts. SEER. Accessed March 25, 2022. https://seer.cancer.gov/statfacts/html/esoph.html

7. Kuipers EJ. Barrett Esophagus and Life Expectancy: Implications for Screening? *Gastroenterol Hepatol (N Y)*. 2011;7(10):689-691.

8. Ricciotti E, FitzGerald GA. Prostaglandins and Inflammation. *Arterioscler Thromb Vasc Biol*. 2011;31(5):986-1000. doi:10.1161/ATVBAHA.110.207449

9. Wang X, Baek SJ, Eling T. COX inhibitors directly alter gene expression: role in cancer prevention? *Cancer Metastasis Rev*. 2011;30(0):641-657. doi:10.1007/s10555-011-9301-4

10. Alkhayyat M, Kumar P, Sanaka KO, Thota PN. Chemoprevention in Barrett's esophagus and esophageal adenocarcinoma. *Therap Adv Gastroenterol*. 2021;14:17562848211033730. doi:10.1177/17562848211033730

11. Falk GW. Barrett's oesophagus: Frequency and prediction of dysplasia and cancer. *Best Practice & Research Clinical Gastroenterology*. 2015;29(1):125-138. doi:10.1016/j.bpg.2015.01.001

12. Nathan C. Points of control in inflammation. *Nature*. 2002;420(6917):846-852. doi:10.1038/nature01320

13. Wong CC, Kang W, Xu J, et al. Prostaglandin E2 induces DNA hypermethylation in gastric cancer in vitro and in vivo. *Theranostics*. 2019;9(21):6256-6268. doi:10.7150/thno.35766

14. Majka J, Wierdak M, Szlachcic A, et al. Interaction of epidermal growth factor with COX-2 products and peroxisome proliferator-activated receptor-γ system in experimental rat Barrett's esophagus. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2020;318(3):G375-G389. doi:10.1152/ajpgi.00410.2018

15. de Bortoli N, Martinucci I, Piaggi P, et al. Randomised clinical trial: twice daily esomeprazole 40 mg vs. pantoprazole 40 mg in Barrett's oesophagus for 1 year. *Alimentary Pharmacology & Therapeutics*. 2011;33(9):1019-1027. doi:10.1111/j.1365-2036.2011.04616.x

16. The Story of Aspirin | The International Aspirin Foundation. Aspirin Foundation. Accessed July 20, 2022. https://www.aspirin-foundation.com/history/the-aspirin-story/

17. Aspirin: Drug information - UpToDate. Accessed July 20, 2022. https://www-uptodate-com.ezproxy.augsburg.edu/contents/aspirin-drug-information?search=aspirin&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F137053

18. Sung JJ, Ho JM, Lam AS, Yau ST, Tsoi KK. Use of metformin and aspirin is associated with delayed cancer incidence. *Cancer Epidemiology*. 2020;69:101808. doi:10.1016/j.canep.2020.101808

19. Ishikawa H, Mutoh M, Sato Y, et al. Chemoprevention with low-dose aspirin, mesalazine, or both in patients with familial adenomatous polyposis without previous colectomy (J-FAPP Study IV): a multicentre, double-blind, randomised, two-by-two factorial design trial. *Lancet Gastroenterol Hepatol*. 2021;6(6):474-481. doi:10.1016/S2468-1253(21)00018-2

20. Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. *Lancet*. 2020;395(10240):1855-1863. doi:10.1016/S0140-6736(20)30366-4

21. Zhang T, Wang Q, Ma WY, et al. Targeting the COX1/2-Driven thromboxane A2 pathway suppresses Barrett's esophagus and esophageal adenocarcinoma development. *EBioMedicine*. 2019;49:145-156. doi:10.1016/j.ebiom.2019.10.038

22. Falk GW, Buttar NS, Foster NR, et al. Esomeprazole and 325 mg/d Aspirin Reduce Tissue Concentrations of Prostaglandin E2 in Patients with Barrett's Esophagus. *Gastroenterology*. 2012;143(4):917-926.e1. doi:10.1053/j.gastro.2012.06.044

23. Galipeau PC, Oman KM, Paulson TG, et al. NSAID use and somatic exomic mutations in Barrett's esophagus. *Genome Medicine*. 2018;10:1-1. doi:10.1186/s13073-018-0520-y

24. Jankowski JAZ, de Caestecker J, Love SB, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. *Lancet*. 2018;392(10145):400-408. doi:10.1016/S0140-6736(18)31388-6

25. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med*. 2018;379(16):1529-1539. doi:10.1056/NEJMoa1804988

26. Joharatnam-Hogan N, Cafferty F, Hubner R, et al. Aspirin as an adjuvant treatment for cancer: feasibility results from the Add-Aspirin randomised trial. *Lancet Gastroenterol Hepatol*. 2019;4(11):854-862. doi:10.1016/S2468-1253(19)30289-4

27. Zhao Z, Yin Z, Zhang C. Lifestyle interventions can reduce the risk of Barrett's esophagus: a systematic review and meta-analysis of 62 studies involving 250,157 participants. *Cancer Med*. 2021;10(15):5297-5320. doi:10.1002/cam4.4061

28. Zhang X, Anandasabapathy S, Abrams J, Othman M, Badr HJ. Lifestyle Risk Factors, Quality of Life, and Intervention Preferences of Barrett's Esophagus Patients: A Prospective Cohort Study. *Glob Adv Health Med*. 2021;10:21649561211001344. doi:10.1177/21649561211001346

29. Phillips R, Januszewicz W, Pilonis ND, et al. The risk of neoplasia in patients with Barrett's esophagus indefinite for dysplasia: a multicenter cohort study. *Gastrointestinal Endoscopy*. 2021;94(2):263-270.e2. doi:10.1016/j.gie.2021.01.042

30. Kauttu T, Mustonen H, Vainionpää S, et al. Disintegrin and metalloproteinases (ADAMs) expression in gastroesophageal reflux disease and in esophageal adenocarcinoma. *Clin Transl Oncol*. 2017;19(1):58-66. doi:10.1007/s12094-016-1503-3

31. Tsoi EH, Williams RA, Christie M, et al. Not all low grade dysplasia in Barrett's oesophagus is the same: using specific histological criteria in predicting progression to neoplasia. *Pathology*. 2021;53(6):700-704. doi:10.1016/j.pathol.2021.06.116

32. Iyer PG, Codipilly DC, Chandar AK, et al. Prediction of Progression in Barrett's Esophagus Using a Tissue Systems Pathology Test: A Pooled Analysis of International Multicenter Studies. *Clinical Gastroenterology and Hepatology*. Published online February 22, 2022. doi:10.1016/j.cgh.2022.02.033

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