

The Role of Secondary Versus Tertiary Prevention in Decreasing the Incidence of
Esophageal Adenocarcinoma in Patients with Barrett's Esophagus.

Submitted by

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A project presented to the Department of
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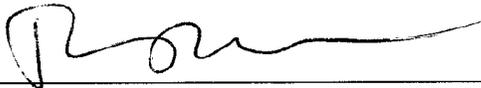
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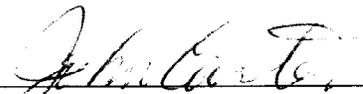
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We hereby recommend that the research project prepared under our supervision by Lindsay West entitled The Role of Secondary Versus Tertiary Prevention in Decreasing the Incidence of Esophageal Adenocarcinoma in Patients with Barrett's Esophagus will be accepted as partial fulfillment for the degree of Master of Physician Assistant.

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Abstract

Objective: The rapidly increasing incidence and high mortality of esophageal adenocarcinoma necessitate the need for research to determine the most effective method of prevention. Barrett's Esophagus is a premalignant condition of esophageal adenocarcinoma. The objective of this study is to determine if secondary or tertiary prevention is more effective in decreasing the incidence and mortality in Barrett's esophagus and esophageal adenocarcinoma. Methods: This study is an evidence based literature review. Key words used included gastroesophageal reflux disease, Barrett's esophagus, esophageal neoplasm, and treatment. Results: The literature revealed that the main method of secondary prevention is through screening and surveillance with much controversy regarding the use of these methods. Controversial issues include the success of early detection in modification of the course of the disease, guidelines for surveillance, and cost-effectiveness. Forms of tertiary prevention include proton pump inhibitors, COX II inhibitors, endoscopic procedures and open antireflux surgeries. There is evidence for and against all secondary and tertiary prevention methods resulting in controversy regarding the effectiveness of all therapies in preventing incidence and mortality of the disease. Conclusions: Research on prevention of Barrett's esophagus and esophageal adenocarcinoma is highly debated and provides varied results. There is no clear answer on which method of prevention will decrease the overall incidence or mortality of the disease, though some of the therapies with supporting evidence should not be withheld due to the high mortality involved. This subject requires additional research including prospective randomized trials.

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Introduction

Esophageal Adenocarcinoma (EA) is a predominate and deadly malignancy of the esophagus. The incidence of EA has risen dramatically in the last three decades, more than 100%, making it the most rapidly increasing malignancy in the United States.¹ The unexplained increase in incidence of EA along with its dismal 5-year survival rate of less than 10% has made it a topic of great and recent interest.²

Esophageal adenocarcinoma arises from metaplastic glandular epithelium and must be differentiated from squamous cell cancer of the esophagus, which arises from squamous cell epithelium. Many risk factors have been identified for EA including obesity, male sex, age, diet, smoking, Caucasian ethnicity, family history, gastroesophageal reflux disease (GERD), and Barrett's esophagus (BE).^{3,4} The population at highest risk for EA is Caucasian males in their mid to late sixties.³ Of these risk factors the strongest are GERD and BE.⁵ Gastroesophageal reflux disease is a condition in which acid from the stomach is refluxed into the esophagus, often described as heartburn, a symptom resulting from the exposure of the mucosal lining of the esophagus to stomach acid. GERD is a prevalent and costly condition in modern health care comprising 2-4% of primary care provider visits.⁶ Symptoms of GERD affect 7% of the general population on a daily basis.⁷ If left untreated, among other complications, GERD can lead to Barrett's esophagus.⁶ Barrett's esophagus is a premalignant condition preceding EA in which the healthy squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium due to repeated insult by gastric acid. Barrett's

esophagus is almost always due to chronic GERD and is associated with a 50 to 100-fold increase in EA.⁸

Current research on esophageal adenocarcinoma is aimed at identification of risk factors and mechanisms for primary, secondary and tertiary prevention. The most recent research on risk factors for EA is focused on identification of genetic markers so that molecular profiling could be used as a guide in risk stratification and endoscopic surveillance.⁹ Primary prevention consists of patient education on risk factors for developing GERD and BE including obesity, diet and smoking. Secondary prevention is focused on endoscopic surveillance. Tertiary prevention involves the use of medical and surgical treatments of GERD and BE to prevent the transition to EA and treatment of EA after diagnosis.

Currently, primary prevention is not seen as an option in decreasing the incidence of esophageal adenocarcinoma. In order for primary prevention to be successful, the initial formation of BE would have to be prevented. The metaplastic changes associated with BE often occur early in the “reflux career” before symptoms of reflux are noted by the patient and before the patient consults a physician for treatment. Therefore, the prevention of BE by primary prevention through acid control is not an realistic option.¹⁰

The remaining forms of prevention for decreasing the incidence of EA are secondary and tertiary. Due to the rapid increase in incidence of EA and the poor 5-year survival rate there is much information about this topic in recent literature. Although, there is research being done in this field, there is substantial conflict in the literature regarding which type of prevention is the best in ultimately decreasing the incidence and

mortality of EA. This conflict necessitates research that will analyze the current literature with the goal of identifying the most effective form of prevention.

The purpose of this study is to establish the role of secondary versus tertiary prevention of esophageal adenocarcinoma in patients with Barrett's esophagus and to reveal which form of prevention is most effective in decreasing the incidence and mortality of esophageal adenocarcinoma.

Methods

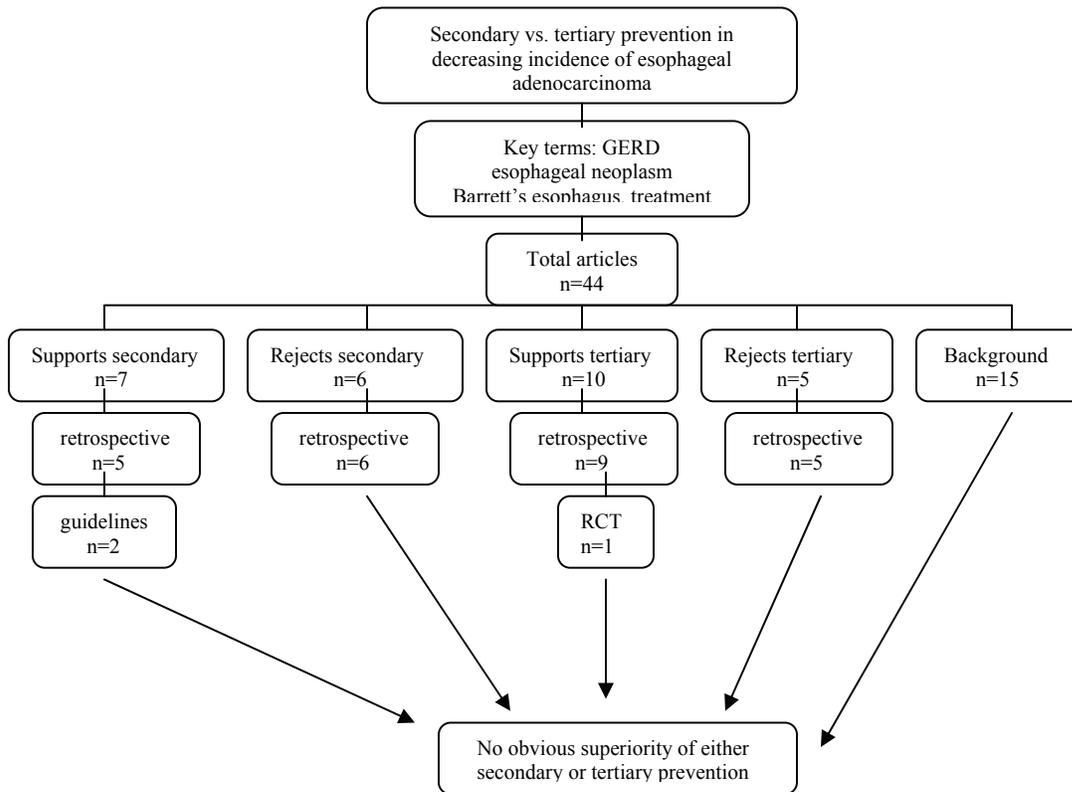
This study was a systematic review of the literature using an evidence-based technique. Research was conducted beginning September 2004 and continued through December 2005. Literature searches were performed using Pubmed and Medline with no consideration of literature published prior to 1990. The search was conducted using the key words esophageal neoplasm, gastroesophageal reflux, Barrett's esophagus, and treatment. Articles obtained were reviewed for relevant information regarding the epidemiology of esophageal adenocarcinoma and methods of primary, secondary and tertiary prevention and their success or failure in preventing EA. Selected articles were further reviewed and categorized according to the type of study and topics covered by the study. All literature was reviewed with the intent of discerning the most effective way of preventing esophageal adenocarcinoma.

Results

Fifty-five articles were obtained, and after review, forty-three were selected for use, all dating after 1990. The studies were categorized by prevention method and were summarized in this manner, though many studies addressed more than one of the topics.

The majority of the articles used for data collection were level two studies, leading to a grade B recommendation of evidence. The articles used in this study are outlined in Figure 1 below.

Figure 1: Literature Flow Sheet



Many recent studies on BE and EA have covered secondary prevention through screening and surveillance. Screening is defined as the examination of a large sample of the population to detect a specific disease or disorder.¹¹ In the case of BE this refers to the initial endoscopy used to diagnose the condition.³ Screening endoscopy has been recommended for patients with a history of GERD, ranging from five to fifteen years.¹² Surveillance is defined as continued observation for the purpose of detecting newly

developed disease in a population at risk with the intent of improving the outcome of the situation. The current guidelines on endoscopic surveillance in BE state that patients should only undergo endoscopic surveillance if the potential benefits outweigh the risks for that patient. Endoscopy with biopsy can be performed at one to three year intervals in BE patients with no dysplasia. If dysplasia is detected on endoscopic biopsy the patient must be treated according to the stage of dysplasia with possible esophagectomy for cancer and high-grade dysplasia. If intermediate dysplasia is detected the patient should be treated with proton pump inhibitors for 4-8 weeks to rule out false diagnosis due to inflammatory changes. The endoscopy should then be repeated to confirm or reverse the diagnosis. If low-grade dysplasia is diagnosed the patient should have repeat endoscopies at six and twelve months. If both repeat endoscopies are normal the patient may return to the regular surveillance intervals, and if low-grade dysplasia persists surveillance should continue at one-year intervals.^{13, 14} There is conflict over current recommendations regarding intervals for surveillance and the course of action to be taken for different diagnoses following detection.

Some studies agree that GERD cannot be used as the only criteria for screening to detect BE for a number of reasons. As much as 20% of the U.S. population suffers from GERD, 7% on a daily basis.^{7, 15} It is questionable whether it is cost-effective to screen this number of people. Also, many patients have been diagnosed with BE without ever having experienced symptoms of GERD. In one study 961 patients scheduled for screening colonoscopy also underwent a screening endoscopy after filling out a symptom questionnaire. Barrett's esophagus was present in 65 patients total, with 5.6% in patients

with no history of heartburn and 8.3% in patients with a history of heartburn, confirming the common presence of BE in the absence of symptoms of GERD.¹⁶ In a similar study, 110 patients undergoing screening sigmoidoscopy with no symptoms of GERD were invited to undergo endoscopy. Barrett's esophagus was detected in 27 (about 25%) of the asymptomatic patients.¹⁷ Other issues concerning BE that make screening questionable are the low incidence of progression to cancer, the number of patients with BE that go undiagnosed, and the number of patients with BE who actually die because of the condition. Only 0.5%-1% of patients with BE progress to cancer annually in the United States with studies in other countries showing even lower percentages.¹⁸ A retrospective study in Finland showed an increased incidence of EA, with 11 cases detected in the study area and time, but estimated the annual conversion rate of BE to EA to be only 0.17%. Of the total people that died of all causes in this time period only 0.05% of them actually died as a direct result of EA, and it was concluded that surveillance is not recommended due to the low annual risk of EA among BE patients.¹⁹ Though the incidence is rising, the incidence of AC in the general population is only 5%, with only 5% of deaths in patients with BE actually due to EA.²⁰ A comparison study in Olmstead County, Minnesota estimated the predicted incidence of BE in 266 autopsies to be 0.19 with an actual incidence of 7 cases, 5 diagnosed for the first time by autopsy. This indicates that BE goes highly undetected in the general population with many dying without ever knowing or experiencing serious complications of the condition; therefore, screening appears to be ineffective in these individuals.²¹ One study screening 51,311 patients estimated a mean time of length between formation of BE and diagnosis to be

>20 years. Of the patients diagnosed with EA, 95% were diagnosed with BE at the same time of the diagnosis of EA. It is estimated that only one in twenty people with the diagnosis of BE would benefit from surveillance.¹⁰ A retrospective study done at Leicester General Hospital in England included 143 patients that had been diagnosed with BE. The patients were in a surveillance program where they underwent endoscopy annually. Of the 143 patients, only four developed cancer over the time period of the study. Of the four that did develop cancer only one of them was diagnosed by the annual endoscopy. The other three were diagnosed during endoscopies that were recommended because of symptoms of dysphagia. The one patient that was diagnosed by the annual surveillance died one month after diagnosis, supporting the belief that surveillance programs do not decrease cancer mortality in patients with BE.²²

Many studies support surveillance despite the low incidence because of the poor outcome of EA, and the evidence that surveillance improves the outcome, especially in surgical patients.^{23, 24} There is evidence supporting the claim that cancers detected by endoscopic surveillance are detected at an earlier stage rather than cancers detected by endoscopies performed due to symptom presentation, and that earlier surgical referral has been widely proven to produce better post-surgical results.^{2, 23} EA detected through surveillance have an 80-90% 5-year survival rate compared to 35-45% in those detected outside of surveillance programs.⁹ One population-based study used a group of 589 patients under surveillance with either esophageal or gastric adenocarcinoma. Out of the 589 patients, 139 with EA had been diagnosed with BE, and 23 of those patients had been diagnosed with BE prior to being diagnosed with EA. This cohort of 23 patients was

used to study the effectiveness of surveillance. Seventy-three percent of the patients under surveillance were alive at the end of follow up compared with none of the patients with non-surveillance detected EA. All of the patients in the cohort had low stage cancers and none of them died as a direct result of EA. The weakness of this study is the small number of patients whose BE was diagnosed prior to EA.²⁰ In a retrospective study of 17 patients from a BE surveillance program 13 of the patients were eventually diagnosed with EA. Survival was significantly higher in this group of patients when compared with a non-surveillance group of patients diagnosed with EA.²⁵ Another study examined the effect of endoscopic surveillance on the stage of EA at the time of diagnosis. Of 77 patients with EA, 19 were under surveillance, and all but one of the patients underwent esophagectomy when severe dysplasia or adenocarcinoma was detected. The surveillance group had 58% in stage 0 or I, 21% in stage III, and a 62% 5-year survival rate. The non-surveillance group had 17%, 47%, and 20% 5-year survival rate respectively.²⁶ These results support the idea that surveillance allows for earlier detection and improves outcome in EA.

Another issue involved in the controversy regarding screening and surveillance is whether or not it is cost effective. In one study Medicare reimbursement data was used to evaluate the cost effectiveness of screening in BE. Compared with no screening, the study showed that screening endoscopy cost \$24,700 per life year saved. The study stated that it might be possible for screening to be cost effective with favorable conditions, including drastically narrowed criteria for screening, but at this time these conditions are not feasible. The study noted that effectiveness of screening is also

reduced due to the frequent reduction in quality of life following detection and treatment of EA.¹⁵ Another cost analysis used a group of 149 patients with benign BE under surveillance for 510 patient years. Seven patients developed adenocarcinoma. The cost of detecting one case of EA was compared to the cost of detecting one case of breast cancer by commonly performed surveillance mammography with the costs being \$37,928 and \$54,513 respectively. The cost per life year saved with EA was \$4,151 and \$57,926 for breast cancer. This study showed that BE compared favorably with breast cancer concerning cost, but points out that there is a much higher incidence of breast cancer in the community.²⁷ Others agree that it is not cost effective to screen because GERD is so common and EA is so rare and that the benefits must outweigh the cost and inconvenience.²⁸

The current literature regarding tertiary prevention of BE and EA includes methods of preventing the progression of BE to EA and methods to promote regression of BE. These types of prevention include chemoprevention with proton pump inhibitors (PPIs), H2 blockers, COX II inhibitors and procedures including endoscopic procedures, photodynamic therapy (PDT) and EMR.

Proton pump inhibitors and histamine receptor blockers are chemotherapies used in acid suppression in GERD and BE. The literature widely supports the superiority of PPIs over H2 blockers. In a randomized double blind study comparing omeprazole, a PPI, to ranitidine, an H2 blocker, it was found that the PPI caused slight regression in BE and there was no change with ranitidine.⁸ Proton pump inhibitors are said to be the drug of choice in GERD. In a study testing the effectiveness of PPIs in treatment of erosive

esophagitis it was found that PPIs healed 75% after four weeks and 90% after 8 weeks.²⁹ While it has been shown that PPIs provide symptom relief in GERD and BE, and have been successful in treating erosive esophagitis, it is still in doubt whether or not PPIs can cause regression of BE and prevent the formation of dysplasia and EA. A study with 350 patients with BE on PPIs found that patients who delayed the use of PPIs two years or more after diagnosis of BE were 5.6 times more likely to develop low grade dysplasia than those who started PPI therapy in the first year after diagnosis; however, there is no evidence that PPI therapy completely reverses the condition.³⁰ The study mentioned previously by Peters et al, using PPIs and H2s found that PPIs cause slight, but statistically significant regression in length and area of BE.⁸ Another study showed the rate of regression of BE with PPIs to be no more than 10-15%, and this observation agreed with other studies that it is likely that there are more factors that just acid suppression in preventing the formation of dysplasia and cancer.⁴ In a retrospective analysis of a large cohort of patients with BE, the length of BE in those who received PPIs prior to diagnosis was compared to those who did not. The average length of BE at time of diagnosis was 4.4 cm, with an average of 3.1 cm in the group who used PPIs before diagnosis, and 4.8 cm in the other group, suggesting a decreased rate of progression of BE with PPI treatment.³¹ Another analysis regarding the development of dysplasia in BE with and without PPI/H2 therapy showed that the incidence of dysplasia was significantly reduced in patients on PPIs and suggests a relationship between the duration of PPI therapy and decreased dysplasia, though it is stated that more research is needed to confirm the results of this study.³² Another issue with PPIs is that it has been

shown that even with symptom control with PPI therapy, acid reflux can still be occurring. Two studies using 24 hour pH monitoring in asymptomatic patients on PPIs found that 15 of 32 patients in one study and 56.5% of patients with GERD and 50% of patients with BE in the other study still had acid reflux despite symptom control.^{33, 34}

The role of COX II inhibition in BE and EA is a concept that has recently become more popular. COX II expression has been reported to play an important role in carcinogenesis, including EA.³⁵ COX II catalyzes the synthesis of prostaglandins, which play a role in cancer formation involving modulation of cell proliferation and apoptosis.³⁶ Multiple studies have shown promising results with the inhibition of COX II. Two separate studies used biopsy samples of Barrett's epithelium from patients with BE to evaluate the expression of COX II. In one study COX II expression was present in 71% of the samples along with elevation of proliferating cell nuclear index and suppression of apoptosis.³⁵ The other study found COX II expression in 91% of the samples without dysplasia, 94% with dysplasia, and 97% of samples with adenocarcinoma. This study confirmed the elevation of COX II in BE and EA, but also showed that COX II expression does not significantly increase with the level of dysplasia or cancer, concluding that the elevation of COX II is an early event in BE that may contribute to cancer formation and could potentially be used as a marker for neoplastic progression.³⁷

There are many new endoscopic and surgical therapies emerging in the treatment of BE and EA. Though most of these only have preliminary results of effectiveness, require further research, and are mainly only useful in treatment once dysplasia or adenocarcinoma has already developed, it is necessary to at least mention these therapies.

Thermal, photodynamic and chemical endoscopic injury techniques reinjure the epithelium to stimulate cells to differentiate and heal as normal squamous cell epithelium.³⁸ For this process to occur it is necessary for the healing process to proceed in a normal environment. Therefore, ablative endoscopic therapies must be coupled with PPI therapy in order to correct the acidic environment. There are concerns with the effectiveness of these therapies regarding their high cost, morbidity and mortality involved, the possibility of the treatments unknowingly failing to penetrate the entire depth of dysplasia, and that these treatments do not yet have enough supportive evidence to validate them.³⁰ Other sources support the combination of endoscopic therapy and PPIs. A study conducted with BE patients found that the combination of omeprazole therapy and multipolar electrocoagulation, a reinjury technique, reversed Barrett's epithelium back to normal squamous epithelium.³⁸ Due to the possibility of ablation not penetrating the depth of dysplasia, some literature declares that ablation is only of use in early dysplasia or in patients who are not surgical candidates. One study used photodynamic therapy (PDT) in 33 BE patients with high-grade dysplasia or intramucosal carcinoma and found that cancer and high-grade dysplasia remained buried under normal epithelium in 9 patients, and columnar epithelium was hidden in 17 patients.³⁹ Some investigators are using endoscopic mucosal resection (EMR) to improve the efficacy of photodynamic therapy. Endoscopic mucosal resection utilizes an extensive biopsy in order to more accurately stage dysplasia and cancer to ensure when PDT is used it can fully ablate the dysplasia. In a study using EMR in BE patients EMR upstaged the diagnosis of cancer in three patients who were then able to be more

effectively treated with PDT to ablate remaining glandular mucosa.⁴⁰ Another treatment option is open antireflux surgery. One study showed that 50% of patients still required acid suppressive therapy even after surgery and most experienced an increase of other symptoms including dysphagia, flatus, bloating, belching and vomiting.⁴¹ Along with these findings, there is a higher morbidity and mortality risk involved and little evidence exists to support a decrease in incidence of EA with surgery, leading to support of pharmacological treatment over surgery.^{4,41} Still, other studies support that surgery is superior to PPI therapy. In a study that analyzed 179 matched patients it was concluded that the patients who underwent surgery suffered significantly fewer symptoms than those who only used PPIs, and that there was no difference in the quality of life between the groups.⁴² Another advantage of surgery is that it also controls bile acid production and PPIs do not. A study with a patients with a combination of GERD, BE, esophagitis and early adenocarcinoma found that fundoscopy completely suppressed bile acid production while acid suppressive medication did not.⁴³

Discussion

Evidence in the literature

The literature regarding Barrett's Esophagus and esophageal adenocarcinoma is controversial. There is evidence to support and also to reject almost all mechanisms of secondary and tertiary prevention.

There is literature for and against screening and surveillance of BE. The current recommendation guidelines for screening and surveillance in GERD and BE are highly debated, with most investigators declaring that the presence of GERD cannot be a

guideline because of the high prevalence of GERD in the general population. Using GERD as a screening guideline is also controversial due to extensive evidence that acid production persists in medically treated asymptomatic patients, and BE has been found to be prevalent in a population of individuals with no history of symptoms of GERD. Though screening is widely practiced and proven to improve the outcome of EA and allow for diagnosis at an earlier stage, many believe the benefits do not outweigh the drawbacks. The overall incidence of EA is rapidly increasing, yet still remains low, with a low incidence of progression from BE to EA, leading to the question of the cost effectiveness of screening for EA. There are studies both supporting and rejecting the cost-effectiveness of screening. There is evidence that screening and surveillance programs significantly reduce mortality in EA due to earlier detection of dysplasia and EA compared to those detected by endoscopy performed due to symptoms and better treatment outcome with earlier detection. It has been proven that morbidity and mortality in BE and EA could be reduced if all patients with GERD were screened by endoscopy, but evidence also shows that it is not cost effective to screen the number of individuals with this disease. There is research being conducted involving genetic markers in BE and EA that could be used to narrow surveillance guidelines and therefore increase the cost effectiveness of surveillance, but more research must be done before this technique can be utilized. The literature widely supports the need for more specific criteria to improve overall effectiveness.

Research on the effectiveness of tertiary prevention techniques in BE and EA also shows varied results. The superiority of PPIs over H2 blockers and the effectiveness of

PPIs in healing esophageal ulcers and esophagitis has been confirmed. However, there is little evidence confirming the role of PPIs in inducing course changing regression of BE or reducing mortality in BE and EA. There are also concerns with symptom control in PPI therapy in the presence of persistent acid reflux. There is optimism regarding the future role of COX II inhibitors in the treatment and prevention of BE and EA, but more research is warranted on this topic before it can be a widely used option. There are many endoscopic therapies that have supporting and rejecting evidence. There are still many questions on the efficacy and cost effectiveness of these therapies and determining if the risks outweigh the benefits of the procedures. It has been shown that combinations of these therapies, for example PDT with EMR or PDT followed by PPIs, could be more effective than monotherapy. Open antireflux surgeries have been proven to be effective in removal of dysplasia, but they have also been shown to carry risks and may result in no increase, or even a decrease in quality of life. In addition, many patients experience persistent acid production after the procedures are performed.

Weaknesses in the literature

A significant consideration in reviewing the literature on esophageal adenocarcinoma and BE is the overall lack of research with high levels of evidence. Most studies on these topics are retrospective. Prospective randomized studies are currently not feasible due to the necessity of a large sample size, extended length requirements, and the high risk to patients.¹⁹ The reliability of the literature is limited by the lack of high-level studies.

Validity of the review

Articles were selected in a systematic manner. Original articles were collected using PubMed and Medline using the key terms outlined above. The articles were reviewed for relevant information and only articles meeting required criteria were chosen. The articles were then organized by topic and outcome as seen in Figure 1. Ten articles were eliminated because they did not meet inclusion criteria. Discarded articles are listed in appendix B.

Weaknesses in the review

In this review process, the author names, institutions and journals were not blinded for the author or the advisor. Therefore, the process was not protected against bias. There was also no internal validity, forcing the reader to rely on the author's interpretation of which research and data is valid.

Conclusion

The purpose of this study was to establish the role of secondary versus tertiary prevention of EA in patients with BE and to possibly reveal which form of prevention is most effective in decreasing the incidence and mortality of EA. After a thorough review of the literature on these topics it is apparent that there is no clear answer to the proposed question. The studies show varying results leaving no mechanism of prevention without questions and concerns. It is unclear whether any form of prevention in BE and EA can ultimately lead to a decrease in incidence and mortality. Secondary and tertiary prevention both have a promising future, but due to an overall lack of research in some of the more recent therapies and also a lack of prospective randomized studies, no

conclusion can be made regarding the superiority of either secondary or tertiary prevention in decreasing the incidence or mortality of EA. However, with the five-year survival rate and the current rapidly increasing incidence of EA, it is necessary to utilize any treatment options with evidence of success where the benefits currently appear to outweigh the risks. These options include using PPIs in patients with GERD and BE for symptom control, possible regression, and possible deceleration of progression of BE to EA, and closely monitoring patients with a history of these conditions. Monitoring should be performed using endoscopic surveillance after analyzing risk/benefit in individual patients due to the improved outcome of disease with early detection. Current controversy over treatment and prevention of GERD, BE and EA leaves health providers with the responsibility of staying current on the literature and making treatment decisions on a patient by patient basis. Further research on all forms of prevention in BE and EA is necessary including surveillance guidelines, the use of genetic markers, PPIs, COX II inhibitors, endoscopic therapies and combinations of the preceding therapies.

It is currently impossible to declare the superiority of either secondary or tertiary prevention in decreasing the incidence and mortality of BE and EA. It appears that PPI therapy and early detection through endoscopic surveillance have the most supporting evidence to change the course of BE and EA. Therefore, due to lack of high level evidence of the effectiveness of other therapies, at this time utilization of a combination of both secondary and tertiary prevention is the best option in decreasing the incidence and mortality of BE and EA.

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Appendix A
Raw Data

<u>Study Year and Author</u>	<u>Research Addresses</u> 1.secd prevtn 2.tert prevtn 3.background	<u>Level of Evidence</u> 1.random control 2.retrospective 3.background	<u>Demographics</u> Main data	<u>Findings</u>	<u>Supports/Rejects</u> 1.supp secd 2.rej secd 3.supp tert 4.rej tert 5.background
Hillman et al 2004	2	2	350 pts with BE treated with ppi	Ppi therapy delays development of dysplasia in BE	3
Hebbard and Sanjay 2004	3	3	n/a	background	5
Peters et al 1999	2	1	68 pts w/ gerd and be treated with ppi or H2 blocker	Ppi superior to H2 Both relieve symptoms Small, but significant regression of be w/ omeprazole in length and area	3
Freston 2004	2	2	n/a	Background	3
Sharma 2004	3	3	n/a	Def of BE, forms of prevention	5
Ban et al 2004	2	2	33 pts w/ HGD or IMC arising in BE treated with PDT	In 9 pts post PDT CA/dysplasia was buried underneath normal epithelium, and in 17 pts columnar epithelium was still buried	4
Sarela et al 2004	2	2	32 pts w/ long segment BE and asymptomatic on PPI	Abnormal acid reflux persisted in 15, bile reflux in 11 and both in 8 pts	4
Gerson et al 2004	2	2	110 pts w/ gerd and/or be on ppi and asymptomatic	Only 58% w/ gerd and 50% w/ BE had acid normalization w/ ppi	4
Sharma 2005	3	3	N/a	Is s/s worthwhile	5
Lagergren 2005	3	3	N/a	Who is at risk for AC	5
Amano et al 2004	2	2	466 biopsy samples of BE from 358 pts	COX II detected in 71% of samples, so possible to decrease risk with COX II inhibition	3
Wolfsen et al 2004	2	2	Pts w/ BE and HGD evaluated with CT and endosonography then EMR followed by PDT	In 3 pts emr upstaged diagnosis to mucosal AC and PDT ablated remaining glandular mucosa. Some pts had chest discomfort and odynophagia	3
Lagorce et al 2003	2	2	66 specimens of resected AC from BE pts	COX II in 91% of BE, 94% of BE w/ dysplasia, and 97% of AC	3
asser et al 2004	2	3	N/a	Background on COX II	5
El-Serag et al 2004	2	2	340 pts w/ BE. 139 on PPI, H2 or both and 201 w/ no acid sup med	Length if BE at dx was significantly shorter in those on acid suppressive etx prior to dx	3

Kyrgidis et al 2005	3	3	N/a	Information of genetic components	5
Peters et al 1994	1	2	17 pts w/ BE and HGD or CA from surv program and 35 pts w/ newly dx BE not in surv program	13 of the 17 ended up with CA, 12 detected at early stage and survival was significantly better than nonsurv group	1
El-Serag et al 2004	2	2	Data on 236 VA pts w/ BE some on PPI or H2 and some not	Incidence of dysplasia decreased in pts who used ppi than those with H2 or none. Longer use of ppi=decreased dysplasia also	3
Soni et al 2000	1	2	Data from medicare reimbursement records	May be cost effective under favorable conditions, but these conditions prob not possible	2
Sampliner 2002	3	3	N/a	Guidelines for dx, surv, and tx of BE	5
Cameron and Lomboy 1992	3	2	Data on 51,311 pts under upper GI endoscopy	BE prevalence increases with age. Mean age of dx of BE is 63, and 64 with CA. Length didn't increase with age. BE may develop > 20 yrs before mean age of clinical recognition or devel of EAC	5
Blot et al 1991	3	2	Data from Nat CA Inst	Steadily rising rates of EAC. 4-10% per yr, more than any other CA. Higher inc in white men, topic needs investigation	5
Sampliner et al 1996	2	2	Pts w/ at least 2cm BE and tx w/ ppi, then a section tx with MPEC	Combo of acid control and reinjury techniques reversed BE to normal squamous epithelium	3
Vakil et al 2003	2	2	Pts who underwent laproscopic fundoplication	43 satisfied; 26 on med for heart burn; 9 underwent dilation for dysphagia; 6 had to have repeat surg; 64 with new symptoms of gas, bloating, dysphagia etc	4
Olberg et al 2005	2	2	373 pts w/ gerd treated surgically matched w/ control treated medically	Surg had signif fewer reflux symptoms than med tx group. Surg group had more indigestion. No diff in QOL btwn grps	3
Conio et al 2005	2	3	N/a	Background on endoscopic treatments	5
Macdonald et al 1998	1	2	143 pts dx w/ BE by endoscopy for various reasons, had annual endoscopy	4 developed LGD, 4 developed CA, w/ one dx at annual endoscopy and other by endoscopy ordered due to symptoms	2
Corley et al 2002	1	2	589 gastric and esophageal AC pts w/ BE, 23 dx > 6mo before CA dx	Among 23, 73% of surveillance detected alive at end of f/u compared with none of the non-surv group. Surv detected CA had lower stage and none died directly from CA	1
Streitz et al 1998	1	2	Cost analysis comparison with mammography for breast CA	Cost of endoscopic surv of pts w/ BE compares favorably w/ mammography	1
Sharma 1998	3	3	N/a	Surv guidelines	1

Amer. Soc. For GI endscopy 1998	3	3	N/a	Surv guidelines	1
Streitz et al 1993	1	2	Evaluation of resected segments from 77 EAC pts, with 19 having been under endoscopic surv	Resected CA signif lower stage in surv grp. 62% compared to 20% 5-year survival rate	1
Voutilainen and Juhola 2005	1	2	Data collected on all pts dx w/ EAC in referral area between 1996 and 2001	Incidence of EAC increased since the 70's. EAC was seldom detected by surveillance. 2 dx with BE, one at the same time as CA dx.	2
Sandler et al 2002	3	3	Data from national databases	Burden of digestive diseases	5
Locke et al 1997	3	2	2200 olmsted county residents btwn 25-74 yrs old	19.8% had gerd symptoms weekly, of those 1% had an episode of hematemesis and 1.3% had esophageal dilation	5
Rex et al 2003	1	2	961 pts scheduled for colonoscopy w/ no prior egd underwent endoscopy	65 w/ BE, 56% w/ no symptoms had BE, 8.3% w/ heartburn sx had BE	2
Gerson et al 2002	1	2	Pts >50 yrs undergoing screening sigmoidoscopy asked to undergo endoscopy	Of 110 pts, 27 has intestinal metaplasia, 8 has LSBE, and 19 had SSBE. So 25% of asymptomatic pts had BE	2
Cameron et al 1990	3	2	Compared data from 2 studies. One used autopsy data and another on detection of BE	BE goes highly undetected in the general pop w/ many dying of other conditions without BE ever being detected	5
Stein et al 1998	2	2	20 asymt, 19 w/ gerd, 45 w/ gerd and esophagitis, 33 w/ gerd and BE and 14 w/ early AC	Fundoscopy completely suppressed bile acid and medication does not.	4
Anderson et al 1994	3	3	N/a	background	5
Farrow and Vaughan 1996	3	2	Data from nat ca inst	Determinants of survival, 5 yr surv rate <10%	5
Shaheen et al 2000	3	2	N/a	CA risk may be overestimated in BE	5
Wright et al 1996	1	2	166 pts under annual endoscopic surv	6 developed CA. Screened pts has earlier stage ca than control group. Cost may be justified due to high mortality	1

Appendix B
Discarded Articles

1. Savarion V, Dulbecco P. Optimizing symptom relief and preventing complications in adults with gastro-oesophageal reflux disease. *Digestion*. 2004;69:9-16.
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