

Statins and Aspirin for Chemoprevention in Barrett's Esophagus: Results of a Cost-Effectiveness Analysis

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Abstract

Data suggest that aspirin, statins, or a combination of the two drugs may lower the progression of Barrett's esophagus to esophageal adenocarcinoma. However, aspirin is associated with potential complications such as gastrointestinal bleeding and hemorrhagic stroke, and statins are associated with myopathy. We developed a simulation disease model to study the effectiveness and cost effectiveness of aspirin and statin chemoprevention against esophageal adenocarcinoma. A decision analytic Markov model was constructed to compare four strategies for Barrett's esophagus management; all regimens included standard endoscopic surveillance regimens: (i) endoscopic surveillance alone, (ii) aspirin therapy, (iii) statin therapy, and (iv) combination therapy of aspirin and statin. Endpoints evaluated were life expectancy, quality-adjusted life years (QALY), costs, and incremental cost-effectiveness ratios (ICER). Sensitivity analysis was performed to determine the impact of model input uncertainty on results. Assuming an annual progression rate of 0.33% per year from Barrett's esophagus to esophageal adenocarcinoma, aspirin therapy was more effective and cost less than (dominated) endoscopic surveillance alone. When combination therapy was compared with aspirin therapy, the ICER was \$158,000/QALY, which was above our willingness-to-pay threshold of \$100,000/QALY. Statin therapy was dominated by combination therapy. When higher annual cancer progression rates were assumed in the model (0.5% per year), combination therapy was cost-effective compared with aspirin therapy, producing an ICER of \$96,000/QALY. In conclusion, aspirin chemoprevention was both more effective and cost less than endoscopic surveillance alone. Combination therapy using both aspirin and statin is expensive but could be cost-effective in patients at higher risk of progression to esophageal adenocarcinoma. *Cancer Prev Res*; 7(3); 341–50. ©2013 AACR.

Introduction

Although the incidence of esophageal adenocarcinoma has increased by 500% over the past 40 years (1–3), the management of Barrett's esophagus, a precursor to esophageal adenocarcinoma, has remained largely ineffective and controversial (4–7). Current strategies and practice use endoscopic surveillance with biopsy at regular intervals for early detection of esophageal adenocarcinoma and dysplastic states (8). The goal of this surveillance is to reduce mortality and morbidity from esophageal adenocarcinoma by preventing cancer through dysplasia treatment or by identifying cancer before it becomes invasive. Because of the rise of esophageal adenocarcinoma incidence in recent years, chemoprevention has received much attention as a method to reduce the progression from Barrett's esophagus to esophageal adenocarcinoma, with numerous studies

demonstrating the effectiveness of chemoprevention in Barrett's esophagus (9). The use of aspirin or other nonsteroidal antiinflammatory drugs (NSAID) and statins has been associated with reduced esophageal adenocarcinoma incidence or progression (10–12). Increased expression of the enzyme COX-2 has been detected in patients with Barrett's esophagus and esophageal adenocarcinoma, and it has been hypothesized that NSAIDs and statins both could act as COX-2 inhibitors (11, 13, 14). A recently published prospective cohort study by Kastelein and colleagues found that combination use of NSAIDs and statins as chemoprevention was associated with a 78% reduction in esophageal adenocarcinoma incidence in patients with Barrett's esophagus (15).

Our prior study used a microsimulation disease model of Barrett's esophagus to determine the effectiveness and cost effectiveness of aspirin as chemoprevention for esophageal cancer in patients with Barrett's esophagus (16). That analysis found that aspirin therapy was both effective and cost effective when compared with no therapy, either alone or when combined with endoscopic surveillance. Although cost-effectiveness analyses have been performed for aspirin as an esophageal chemoprevention agent, to our knowledge, no analysis has investigated the effectiveness and cost effectiveness of statins, or aspirin and statin combination therapy.

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In an attempt to address the need for recommendations about the use of chemopreventive agents in patients with Barrett's esophagus, our study aimed to analyze the effectiveness and cost effectiveness of aspirin, statin, and combination chemoprevention for Barrett's esophagus management.

Materials and Methods

Model design

A decision analytic Markov state transition model was constructed in TreeAge Pro 2012 (TreeAge Software). Four different strategies for the management of Barrett's esophagus initially without dysplasia were implemented in the model. All strategies included endoscopic surveillance with esophagectomy performed when cancer was detected and included: (i) endoscopic surveillance alone, (ii) aspirin chemoprevention, (iii) statin chemoprevention, and (iv) combination of aspirin and statin chemoprevention.

Health states in the model included Barrett's esophagus (no dysplasia, ND), low-grade dysplasia (LGD), high-grade dysplasia (HGD), post successful esophagectomy for cancer, inoperable or incomplete resection of cancer, and death. Possible causes of death included age-related mortality, surgical mortality, esophageal adenocarcinoma, and complications. The Markov cycle length or time between state transitions was 1 month. The simulation began with a hypothetical cohort of 50-year-old individuals who were followed until age of 80 years or death. In each cycle, the simulated patient could stay in the same state, progress to the next state of cancer, or die from age-related all-cause mortality. For model simplicity and transparency, all patients were assumed to have the correct diagnosis of Barrett's esophagus at the start of the model simulation (17, 18).

Endoscopic surveillance alone

In the endoscopic surveillance alone strategy (see Fig. 1 for simplified schematic), patients would undergo upper

endoscopies with biopsies at intervals recommended by the American Gastroenterological Association guidelines (8). For Barrett's esophagus without dysplasia, patients were followed by endoscopic surveillance every 3 years. If patients were found to have LGD, the surveillance continued at 6-month intervals for the first year from diagnosis of LGD and at 12-month intervals thereafter. For patients with HGD, endoscopic surveillance continued at 3-month intervals. Esophageal cancers that would undergo surgery were modeled to be either surgically resectable or unresectable based on published rates (16, 19). After surgical esophagectomy was performed on eligible patients, annual endoscopic surveillance was continued.

Aspirin strategy with endoscopic surveillance

The aspirin with endoscopic surveillance strategy was similar to endoscopic surveillance alone strategy, except that patients were simulated to take a 325-mg enteric-coated aspirin daily (see Fig. 2 for simplified schematic). Patients who took aspirin daily were modeled to have a 53% reduction in the incidence of esophageal adenocarcinoma based on results from a prospective cohort study of patients with Barrett's esophagus, which served as our main chemoprevention source as the analysis examined both aspirin and statins in their cohort (15). These patients could have aspirin-associated complications, such as gastrointestinal or genitourinary bleeds or hemorrhagic strokes. When patients developed aspirin-associated complications and survived, they were modeled to discontinue the aspirin and return to the endoscopic surveillance alone strategy with standard cancer progression rate. Patients were not modeled to receive any other benefit from the aspirin, such as a cardiac benefit or chemoprevention of other cancers. Adherence to treatment was assumed to be 100% in the absence of complications.

Statin strategy with endoscopic surveillance

The statin with endoscopic surveillance strategy was similar to the endoscopic surveillance alone strategy, except

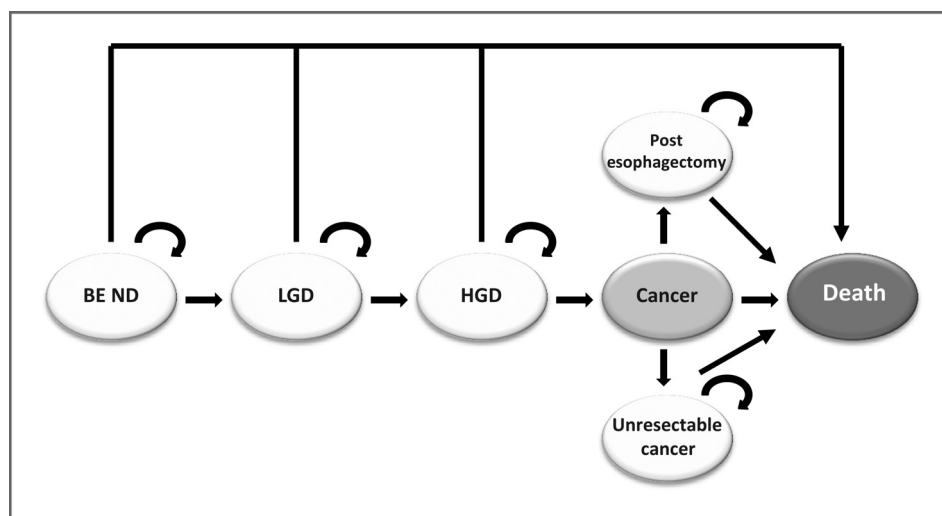


Figure 1. Endoscopic surveillance alone strategy. A cohort of patients with Barrett's esophagus spends time in a Markov state every cycle until death or age of 80 years. If the patients are found to have cancer, surgery is performed for patients eligible for resection. BE, Barrett's esophagus.

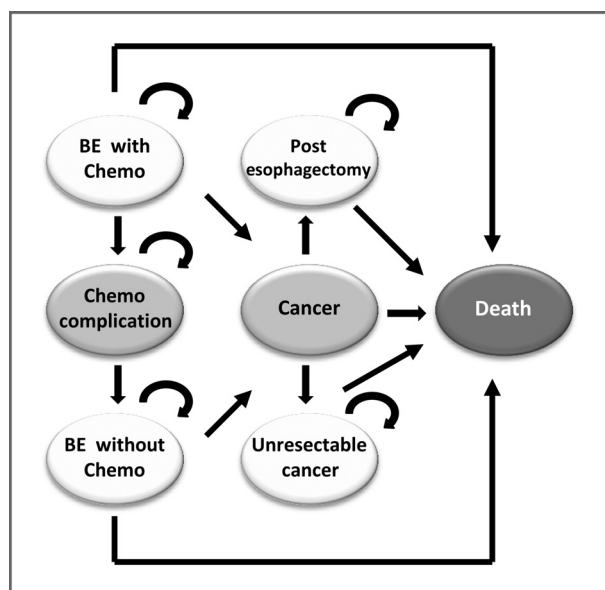


Figure 2. Chemoprevention strategy. BE, Barrett's esophagus; Chemo, chemoprevention.

that the patients would take a statin daily (see Fig. 2 for simplified schematic). Patients who took a statin daily were modeled to have a 54% reduction in the incidence of esophageal adenocarcinoma based on results from a cohort study (15). However, these patients could have statin-associated complications, such as myopathy or elevation in transaminases. When patients developed statin-associated adverse effects and survived, they were modeled to discontinue the statin and continue with the endoscopic surveillance alone strategy with the standard cancer progression rate. Patients were not modeled to receive any other benefit from the statin, and adherence to treatment was assumed to be 100% in the absence of previously described adverse events.

Combination strategy with endoscopic surveillance

In the combination strategy with endoscopic surveillance, patients were modeled to take both aspirin and a statin daily and to follow the endoscopic surveillance regimen described above in the prior strategies (see Fig. 2 for simplified schematic). Patients who took both medications were modeled to have a 78% reduction in the incidence of esophageal adenocarcinoma based on results from the cohort study (15). However, these patients could have either statin or aspirin-associated complications as described above. When patients developed statin or aspirin-associated adverse effects and survived, they were modeled to discontinue combination therapy and continue with endoscopic surveillance alone strategy with the standard cancer progression rate. Patients were not modeled to receive any other benefit from both drugs, and adherence to treatment was assumed to be 100% in the absence of previously described complications.

Parameter estimates

Model parameters or inputs were estimated from the published literature. Base-case values and ranges used in sensitivity analyses are summarized in Table 1. When published estimates were not available, an expert in the field was consulted to provide an estimate for the parameter. The base-case estimates for the effects of aspirin, statin, or both on cancer progression rates were based on a prospective cohort study of 570 patients with Barrett's esophagus in the Netherlands (15).

Model transition probabilities and calibration

The transition probabilities between the various Barrett's esophagus states are critical to the model's validity. However, there is a wide range of estimates and uncertainty about transition rates between specific Barrett's esophagus substates (e.g., from ND to LGD or LGD to HGD). The best quality and amount of data exist for the overall transition rate from Barrett's esophagus to esophageal adenocarcinoma. Because of the pivotal nature of the Barrett's esophagus to esophageal adenocarcinoma progression rate and the newly published estimates, the transition probabilities between the Barrett's esophagus substates were, therefore, calibrated to generate overall Barrett's esophagus to esophageal adenocarcinoma transition rates of 0.12%, 0.33%, and 0.5% per year, which encompass a wide range of values (i.e., low, intermediate, and high values; refs. 20–22). The progression rate of 0.33% was used as our base-case estimate. A published rate from HGD to esophageal adenocarcinoma was used in conjunction with other transition estimates to generate the overall Barrett's esophagus to esophageal adenocarcinoma rate (23). The transition rate from HGD to cancer was calculated to be 2.4% on the basis of the published 7.3-year probability of 16% (23). As an additional check, the transition rates derived from the calibration were compared with the ranges of transition probabilities that were used for a previously validated U.S. population simulation model of esophageal adenocarcinoma (24) that was calibrated to National Cancer Institute Surveillance, Epidemiology and End Results (SEER) data.

Costs and utilities

Base-case costs and ranges used in sensitivity analyses are summarized in Table 1. Medicare reimbursement rates were used to estimate direct costs (25). Drug costs were obtained from the 2003 Red Book average wholesale prices (26). The statin cost used in our base-case analysis was obtained by averaging the Red Book prices of simvastatin and lovastatin. Published estimates of costs from prior years were converted to 2011-year dollars using the Consumer Price Index (U.S. Bureau of Labor Statistics).

Quality-of-life measures for various states in the model were adjusted to utility scores for the specific health states: cancer = 0.5 and postesophagectomy = 0.97 (27–30). For the base-case analysis, all cost and expected life years were discounted at an annual rate of 3% to adjust for the relative value of present dollars or a present year of life (31).

Table 1. Model inputs

Parameters	Estimate, base-case	Source
Risk of neoplastic progression (HR)		
NSAID only	0.47	(15)
Statin only	0.46	(15)
NSAID and Statin	0.22	(15)
Aspirin characteristics		
Annual risk of complication (per 100,000)		
Noncerebral bleeds		
Major bleeds	40	(16, 34)
Intermediate bleeds	180	(16, 34)
Mortality from noncerebral bleeds	4.4	(16, 35)
Hemorrhagic CVA		
Disabling	11	(16, 36, 37)
Nondisabling	9	(16, 36, 37)
Mortality from CVA	6	(16, 35)
Statin characteristics		
Annual risk of complication (per 100,000)		
Myopathy		
Without rhabdomyolysis	95	(38, 39)
With rhabdomyolysis	1.6	(38, 39)
Mortality from myopathy	0.16	(39, 40)
Hepatitis		
Without liver failure	1.74	(38, 39)
With liver failure	0.5	(38, 39)
Mortality from liver failure	0	(39, 40)
Procedure characteristics		
Operative candidate, cancer	0.80	(30)
Surgical resectability rate		
Surveillance	0.80	(16, 23, 30, 41–46)
No surveillance	0.33	(16, 19)
Complications		
Complication rate from EGD	0.00013	(16, 47, 48)
Mortality from EGD complication	0.0016	(16, 47, 48)
Mortality from esophagectomy	0.05	(30, 46)
Discount rate	0.03	(32, 49)
Transition probabilities		
HGD to cancer	0.024	(23)
LGD to HGD		See Materials and Methods;
LGD to cancer		calibrated to overall
ND BE to LGD		progression rate from
ND BE to cancer		BE to EAC
Costs (2011 USD)		
Cost of cancer (annual)	49,385	(13, 50–52)
Cost surveillance EGD	930	(30, 53–56)
Cost of post surgery state (annual)	1,496	(30, 53, 54)
Cost of esophagectomy	25,882	(30, 53, 54, 56)
Aspirin related		
Aspirin drug cost (annual)	19.56	(26)
CVA complication	51,822	(16, 57)
Major bleed	6,958	(16, 58)
Intermediate bleed	1,332	(16, 51)

(Continued on the following page)

Table 1. Model inputs (Cont'd)

Parameters	Estimate, base-case	Source
Statin related		
Statin drug cost (annual)	872	(26)
Myopathy without rhabdomyolysis	30	(38, 50)
Myopathy with rhabdomyolysis	12,343	(38, 52)
Hepatitis without liver failure	38	(38, 50)
Hepatitis with liver failure	16,529	(38, 52)

Abbreviations: BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy.

Outcomes

The primary outcome of the analysis was the incremental cost-effectiveness ratio (ICER) per quality-adjusted life years (QALY) between competing treatment strategies. The analysis is based on standard cost-effectiveness methods using a societal perspective, which uses Medicare reimbursement costs (32). A willingness to pay (WTP) of less than \$100,000/QALY was used as a threshold to determine cost effectiveness. This threshold was derived from an analysis that estimated the ICER of hemodialysis, which was inflation-adjusted to 2011-year dollars (33). A WTP of less than \$150,000/QALY was also considered in a probabilistic sensitivity analysis. Other outcomes assessed included cost, QALYs, and unadjusted life years (life expectancy).

Analyses performed

A base-case analysis using best estimates for all model parameters and transition probabilities was performed. One-way sensitivity analyses were performed to investigate the effects of changes in model parameters on outcomes across a wide range of values, including nondysplastic Barrett's esophagus to esophageal adenocarcinoma progression rate, aspirin and statin chemoprevention efficacy, complication rates, and the cost of statins. The ranges were based on published data. In addition, probabilistic sensitivity analysis was performed. Distributions for specific

parameters or model input variables were assigned and 1,000 iterations were performed to gain further insight into the optimal strategy under uncertain conditions within our defined WTP threshold.

Results

Base-case results

In the base-case analysis (Table 2 and Fig. 3), the aspirin strategy dominated the endoscopic surveillance alone strategy, with the former strategy resulting in 0.167 more QALYs and costing \$6,900 less. When the statin and combination strategies were compared with the endoscopic surveillance alone strategy, these strategies seemed to be cost effective with ICERs of \$37,600 per QALY and \$16,300 per QALY, respectively.

Assuming a WTP threshold of \$100,000 per QALY, the combination strategy of aspirin and statin was not cost effective when compared with the aspirin strategy, as the ICER was \$158,300 per QALY, or above our WTP. Comparing the statin strategy with aspirin strategy, the ICER was \$863,200, which was well above our WTP. However, when the statin strategy was compared with endoscopic surveillance alone, the ICER was \$37,640 per QALY; this ICER may be relevant in a hypothetical group of patients who cannot tolerate aspirin therapy. The statin strategy was dominated by the combination strategy.

Table 2. Base-case results

Outcome	Endoscopic surveillance alone	Aspirin with surveillance	Statin with surveillance	Combination with surveillance
Outcomes from the strategies				
Cost (USD)	19,315	12,392	26,203	23,159
QALYs	16.873	17.040	17.056	17.108
Unadjusted life years	24.411	24.714	24.741	24.833
Comparison among strategies using ICER values (USD)				
Reference strategy				
Endoscopic surveillance alone	—	Dominates	37,640	16,350
Aspirin with surveillance	—	—	863,200	158,300
Statin with surveillance	—	—	—	Dominates

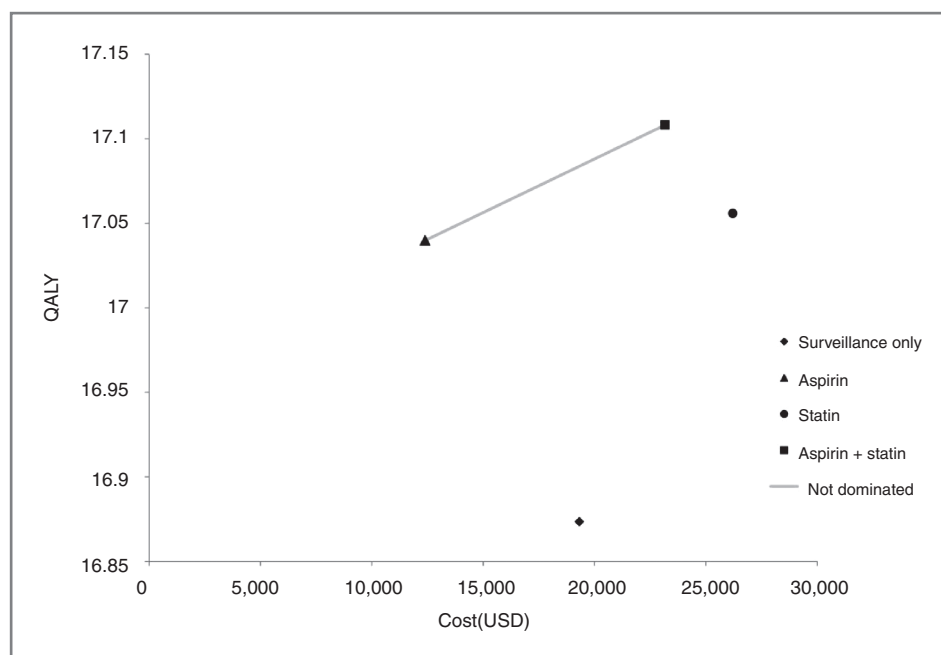


Figure 3. Cost-effectiveness analysis.

Sensitivity analysis

The results of the key sensitivity analyses are summarized in Table 3. The ICERs calculated in the table compare the combination strategy of aspirin and statin with the aspirin strategy. When the Barrett's esophagus to esophageal adenocarcinoma cancer progression rate of 0.33% per year was assumed in the base-case, the combination strategy did not seem to be the preferred strategy over the aspirin strategy. However, sensitivity analysis on the overall annual progression rate found that the combination strategy may be cost effective at a higher progression rate of 0.5% per year with the resulting ICER, \$96,000 per QALY.

The results of the model were not substantially affected by varying the complication rates of aspirin or statins. If the reduction in cancer progression for combined therapy of aspirin and statin is greater than 90%, then the combination strategy may become cost effective (ICER < \$100K/QALY). Lower statin cost (<70% of base-case estimate, \$872 per year) could also make the combination strategy cost effective. When the statin is reduced by more than 20%, the combination strategy dominates the aspirin strategy.

A two-dimensional sensitivity analysis of aspirin efficacy (based on HRs) and the transition probability between Barrett's esophagus and cancer (see Fig. 4) found that the combination strategy becomes more desirable as the transitional probability and aspirin efficacy decreases. When the transition probability is less than 0.35 and the aspirin efficacy is low, endoscopic surveillance may be the preferred strategy. Changing the efficacy rates of the statin strategy and the combination strategy showed little change.

Probabilistic sensitivity analyses (see results in Fig. 5) using a WTP threshold of \$150,000 per QALY found that

although the probability of being cost effective decreased with increasing WTP, the aspirin strategy was the preferred strategy when the WTP was between \$0 and \$100,000 per QALY. At a WTP of \$100,000, the aspirin strategy was optimal in the majority of 51% of trials, whereas the combination strategy was optimal in 47.6%, and the statin strategy in 1.4%. Above a WTP of \$100,000 per QALY, the combination strategy becomes more cost effective. At a WTP of \$150,000, the combination strategy was optimal in the majority of 55.9% of trials, whereas the aspirin strategy was optimal in 42% and the statin strategy in 2.1%. Endoscopic surveillance alone was never a preferred strategy at any WTP value.

Discussion

Our analysis finds that aspirin therapy with endoscopic surveillance may be the most cost-effective strategy. Endoscopic surveillance alone and statin therapy were both dominated by aspirin and combination strategies, respectively.

When compared with the aspirin strategy, the combination strategy was not cost effective, with an ICER above the WTP threshold of \$100,000 per QALY. However, if progression rates to cancer were increased (0.5% per year), combination therapy was cost effective, suggesting that combination therapy could be appropriate for the patients at high risk of esophageal adenocarcinoma. In a probabilistic sensitivity analysis, the combination strategy becomes the cost-effective strategy when the WTP threshold is above \$100,000.

In addition, although the statin therapy was dominated by the combination therapy, when statins were compared with the endoscopic surveillance alone, they seemed cost effective, suggesting that the addition of statin as a

Table 3. Sensitivity analyses: ICERs for combination versus aspirin

Parameter	Combination vs. aspirin only (USD)	Results change (WTP \$100,000)
BEND to cancer progression		
0.12%	441,400	—
0.33%	158,300	—
0.5%	96,000	Combination cost effective
Aspirin complication (of base rate)		
25%	166,400	—
50%	163,400	—
200%	147,100	—
400%	129,100	—
Statin complication (of base rate)		
25%	148,200	—
50%	151,280	—
200%	172,080	—
400%	209,400	—
Aspirin + statin reduction in progression		
95%	82,700	Combination cost effective
90%	97,800	Combination cost effective
85%	117,500	—
80%	144,200	—
75%	182,200	—
Statin cost (of base-case cost)		
20%	Dominates	Combination dominates
30%	11,180	Combination cost effective
40%	32,100	Combination cost effective
50%	53,040	Combination cost effective
60%	73,970	Combination cost effective
70%	94,900	Combination cost effective
80%	115,830	—

Abbreviation: BEND, Barrett's esophagus no dysplasia.

chemoprevention agent may be beneficial for patients who are unable or unwilling to take aspirin.

We performed sensitivity analyses acknowledging the uncertainty of model inputs, including the benefit of chemoprevention and the progression rate from Barrett's esophagus to esophageal adenocarcinoma. The ICER comparing combination therapy to aspirin therapy decreased as the effect of combination therapy on esophageal adenocarcinoma progression improved, and was below our WTP at a reduction of 90% or more. The combination therapy also

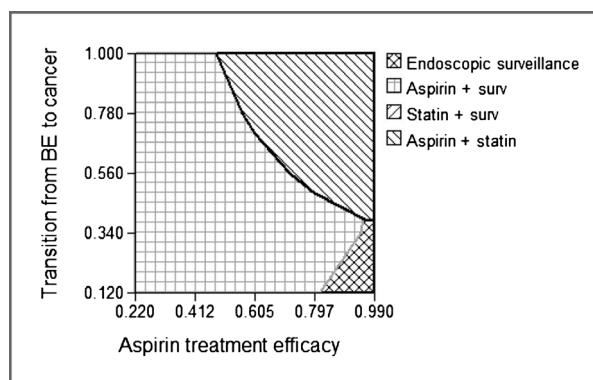


Figure 4. Two-dimensional sensitivity analysis. BE, Barrett's esophagus.

had an ICER below the threshold when statins made up <70% of the base cost, and dominated the aspirin strategy when the cost was 20% of the base cost.

We previously published a model to determine the effectiveness and cost effectiveness of aspirin as chemoprevention for esophageal cancer in patients with Barrett's esophagus. In our prior analysis, we demonstrated that aspirin therapy was both effective and cost effective when compared with no therapy, either alone or when combined with endoscopic surveillance. Our current analysis confirms and adds to our previous work by adding statins as a possible therapy, either alone or combined with aspirin. In addition, we updated our parameters with new data to reflect current trends and 2011 costs.

Our results have several implications for clinical care and health policy. The overall 5-year survival rate for esophageal cancer remains low, at 17%, but can increase to more than 30% in patients with the earliest stages of disease (1). A patient's greatest benefit to improving survival is early diagnosis; however, the cancer often spreads before symptoms are detected. Barrett's esophagus is a precursor to cancer, yet an ideal management strategy remains elusive, and the utility of current endoscopic surveillance is controversial and costly. Several published studies have suggested that aspirin and statin may help prevent esophageal cancer (10–12). Furthermore, although we did not incorporate these factors into our model and analysis, both drugs have benefits that go beyond esophageal cancer, such as the prevention of cardiac disease and other cancers. Our analysis suggests that the benefits of adding aspirin to an endoscopic surveillance program outweighs potential risks and can provide a cost-effective management strategy even when limited to esophageal adenocarcinoma. For patients at risk of cardiac disease, taking aspirin or statins may be even more compelling.

Our analysis has several limitations. The primary study we referenced to estimate the additive protective effect of combination therapy in reducing esophageal adenocarcinoma progression rate used statins and NSAIDs, not just aspirin. The additive protective effects of statins and just aspirin were not available, but prior studies and our

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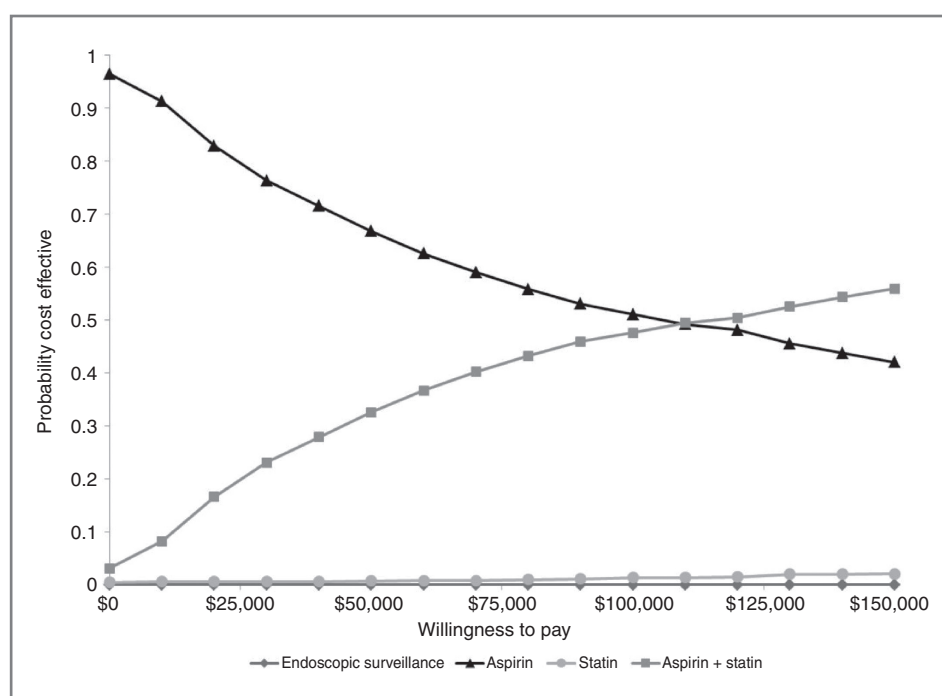


Figure 5. Probabilistic sensitivity analysis.

referenced study provided comparable benefits of NSAIDs and aspirin in esophageal adenocarcinoma prevention (9–12, 15). Radiofrequency ablation (RFA) was not incorporated into our model as a treatment strategy because the model parameter estimates used in our analysis were based on results from a cohort study where RFA was not a treatment option (15). Also, as described above, our model did not incorporate any additional potential benefits from aspirin and statins beyond the chemoprevention of esophageal cancer. Our analysis focused solely on a comparison of aspirin and statins benefits in the prevention of esophageal adenocarcinoma. In addition, death from cardiac diseases accounts for a large percentage of mortality in older adults. To model this without long-term aspirin and statin data would result in an oversimplification of all-cause mortality rates, leading to significant inaccuracies in the model. Because of the lack of randomized clinical trials on the use of statins and aspirin among patients with Barrett's esophagus for the prevention of esophageal cancer, our model used parameters primarily from prospective cohort studies. A study centered in the United Kingdom, AspECT [<http://www.octo-oxford.org.uk/alltrials/infollowup/aspect.html>], is evaluating the impact of low and high-dose aspirin on Barrett's esophagus progression rates to cancer; however, a similar trial that evaluates the impact of statins and the combination of a statin and aspirin is not currently ongoing. When data from this trial become available in the future, we will be able to incorporate any changes in the impact of aspirin on progression rates into our model and analysis. In addition, as with any disease model that incorporates natural history, the limited amount of data available increases the uncertainty in the model and raises concerns about validity, particularly as future projections are made. Although the team of investigators that participated in this

analysis has extensive experience with disease models, including more complex versions, we chose to construct a model that was as simple as possible to maintain a high level of model transparency and minimize the "black box" phenomenon. We performed extensive sensitivity analyses and despite these uncertainties, our results were robust.

In summary, our results suggest that among the four treatment strategies analyzed, aspirin therapy is the cost-effective chemoprevention strategy for patients with Barrett's esophagus. A combination of aspirin and statins could potentially be cost effective in the patients with Barrett's esophagus at a higher risk of progression to esophageal adenocarcinoma. Although the benefits of aspirin generally outweigh the risks in this patient population, statin therapy may be potentially cost effective in patients who are unable or unwilling to take aspirin. Although the \$100,000–150,000 QALY figure may seem high, emerging technologies, medications, and screening can provide future improvements to Barrett's esophagus management and improve the cost effectiveness of care. Future clinical trials studying the long-term use of aspirin and statins in patients with Barrett's esophagus would be beneficial to confirm our model results.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.E. Choi, C.Y. Kong, C. Hur

Development of methodology: S.E. Choi, C.Y. Kong, C. Hur

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.E. Choi, C. Hur

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.E. Choi, A.C. Tramontano, C.Y. Kong, C. Hur

Writing, review, and/or revision of the manuscript: S.E. Choi, K.E. Perzan, A.C. Tramontano, C.Y. Kong

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.E. Choi
Study supervision: C. Hur

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References

- American Cancer Society. Cancer facts & figures 2013. Atlanta, GA: American Cancer Society; 2013.
- Bollschweiler E, Wolfgarten E, Gutschow C, Holscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. *Cancer* 2001;92:549–55.
- Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, et al. Trends in esophageal adenocarcinoma incidence and mortality. *Cancer* 2013;119:1149–58.
- Bulsiewicz WJ, Shaheen NJ. The role of radiofrequency ablation in the management of Barrett's esophagus. *Gastrointest Endosc Clin N Am* 2011;21:95–109.
- Lyday WD, Corbett FS, Kuperman DA, Kalvaria I, Mavrelis PG, Shughoury AB, et al. Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry. *Endoscopy* 2010;42:272–8.
- Pouw RE, Wirths K, Eisendrath P, Sondermeijer CM, Ten Kate FJ, Fockens P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. *Clin Gastroenterol Hepatol* 2010;8:23–9.
- Shaheen NJ, Frantz DJ. When to consider endoscopic ablation therapy for Barrett's esophagus. *Current Opinion in Gastroenterol* 2010;26:361–6.
- Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterology* 2011;140:e18–52.
- Mehta S, Johnson IT, Rhodes M. Systematic review: the chemoprevention of oesophageal adenocarcinoma. *Aliment Pharmacol Ther* 2005;22:759–68.
- 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;138:2260–6.
- Ogunwobi OO, Beales IL. Statins inhibit proliferation and induce apoptosis in Barrett's esophageal adenocarcinoma cells. *Am J Gastroenterol* 2008;103:825–37.
- Vaughan TL, Dong LM, Blount PL, Ayub K, Odze RD, Sanchez CA, et al. Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. *Lancet Oncol* 2005;6:945–52.
- Morris CD, Armstrong GR, Bigley G, Green H, Attwood SE. Cyclooxygenase-2 expression in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. *Am J Gastroenterol* 2001;96:990–6.
- Shirvani VN, Ouatu-Lascar R, Kaur BS, Omary MB, Triadafilopoulos G. Cyclooxygenase 2 expression in Barrett's esophagus and adenocarcinoma: *Ex vivo* induction by bile salts and acid exposure. *Gastroenterology* 2000;118:487–96.
- Kastelein F, Spaander MC, Biermann K, Steyerberg EW, Kuipers EJ, Bruno MJ. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett's esophagus. *Gastroenterology* 2011;141:2000–8.
- Hur C, Nishioka NS, Gazelle GS. Cost-effectiveness of aspirin chemoprevention for Barrett's esophagus. *J Natl Cancer Inst* 2004;96:316–25.
- Fleischer DE, Overholt BF, Sharma VK, Reymunde A, Kimmey MB, Chuttani R, et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy* 2010;42:781–9.
- Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009;360:2277–88.
- Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002;347:1662–9.
- Desai TK, Krishnan K, Samala N, Singh J, Cluley J, Perla S, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. *Gut* 2012;61:970–6.
- Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011;365:1375–83.
- Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* 2000;119:333–8.
- Schnell TG, Sontag SJ, Chejfec G, Aranha G, Metz A, O'Connell S, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 2001;120:1607–19.
- Hur C, Hayeck TJ, Yeh JM, Richards EM, Spechler SJ, Gazelle GS, et al. Development, calibration, and validation of a U.S. white male population-based simulation model of esophageal adenocarcinoma. *PLoS ONE*. 2010;5:e9483.
- Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 1996;276:1172–7.
- Medical Economics Company. Red Book for Windows Version 5.0. Montvale, NJ: Medical Economics Company; 2003.
- de Boer AG, Stalmeier PF, Sprangers MA, de Haes JC, van Sandick JW, Hulscher JB, et al. Transhiatal vs extended transthoracic resection in oesophageal carcinoma: patients' utilities and treatment preferences. *Br J Cancer* 2002;86:851–7.
- Fisher D, Jeffreys A, Bosworth H, Wang J, Lipscomb J, Provenzale D. Quality of life in patients with Barrett's esophagus undergoing surveillance. *Am J Gastroenterol* 2002;97:2193–200.
- Gerson LB, Ullah N, Hastie T, Triadafilopoulos G, Goldstein M. Patient-derived health state utilities for gastroesophageal reflux disease. *Am J Gastroenterol* 2005;100:524–33.
- Inadomi JM, Somsouk M, Madanick RD, Thomas JP, Shaheen NJ. A cost-utility analysis of ablative therapy for Barrett's esophagus. *Gastroenterology* 2009;136:2101–14.
- Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA* 1996;276:1253–8.
- Gold M. Panel on cost-effectiveness in health and medicine. *Med Care* 1996;34:DS197–9.
- Winkelmayer WC, Weinstein MC, Mittleman MA, Glynn RJ, Pliskin JS. Health economic evaluations: the special case of end-stage renal disease treatment. *Med Decis Making* 2002;22:417–30.
- Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* 2001;85:265–71.
- Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med* 1989;321:129–35.
- Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136:161–72.
- Wolf PA, D'Agostino RB. Secular trends in stroke in the Framingham Study. *Ann Epidemiol* 1993;3:471–5.

38. Galper BZ, Moran A, Coxson PG, Pletcher MJ, Heidenreich P, Lazar LD, et al. Using stress testing to guide primary prevention of coronary heart disease among intermediate-risk patients: a cost-effectiveness analysis. *Circulation* 2012;125:260–70.
39. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;97:52C–60C.
40. Pletcher MJ, Lazar L, Bibbins-Domingo K, Moran A, Rodondi N, Coxson P, et al. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. *Ann Intern Med* 2009;150:243–54.
41. Corley DA, Levin TR, Habel LA, Weiss NS, Buffler PA. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. *Gastroenterology* 2002;122:633–40.
42. Pera M, Trastek VF, Carpenter HA, Allen MS, Deschamps C, Pairolero PC. Barrett's esophagus with high-grade dysplasia: an indication for esophagectomy? *Ann Thorac Surg* 1992;54:199–204.
43. van Sandick JW, van Lanschot JJ, Kuiken BW, Tytgat GN, Offerhaus GJ, Obertop H. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. *Gut* 1998;43:216–22.
44. Peters JH, Clark GW, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. *J Thorac Cardiovasc Surg* 1994;108:813–21.
45. Streitz JM Jr, Andrews CW Jr, Ellis FH Jr. Endoscopic surveillance of Barrett's esophagus. Does it help? *J Thorac Cardiovasc Surg* 1993;105:383–7.
46. Nguyen NT, Schauer P, Luketich JD. Minimally invasive esophagectomy for Barrett's esophagus with high-grade dysplasia. *Surgery* 2000;127:284–90.
47. Falk GW, Chittajallu R, Goldblum JR, Biscotti CV, Geisinger KR, Petras RE, et al. Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. *Gastroenterology* 1997;112:1787–97.
48. Silvis SE, Nebel O, Rogers G, Sugawa C, Mandelstam P. Endoscopic complications. Results of the 1974 American Society for Gastrointestinal Endoscopy Survey. *JAMA* 1976;235:928–30.
49. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 1996;276:1339–41.
50. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–60.
51. Edelson JT, Tosteson AN, Sax P. Cost-effectiveness of misoprostol for prophylaxis against nonsteroidal anti-inflammatory drug-induced gastrointestinal tract bleeding. *JAMA* 1990;264:41–7.
52. Illingworth DR, Tobert JA. A review of clinical trials comparing HMG-CoA reductase inhibitors. *Clin Ther* 1994;16:366–85.
53. Provenzale D, Kemp JA, Arora S, Wong JB. A guide for surveillance of patients with Barrett's esophagus. *Am J Gastroenterol* 1994;89:670–80.
54. Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. *Am J Gastroenterol* 1999;94:2043–53.
55. Gorelick AB, Inadomi JM, Barnett JL. Unsedated small-caliber esophagogastroduodenoscopy (EGD): less expensive and less time-consuming than conventional EGD. *J Clin Gastroenterol* 2001;33:210–4.
56. Soni A, Sampliner RE, Sonnenberg A. Screening for high-grade dysplasia in gastroesophageal reflux disease: is it cost-effective? *Am J Gastroenterol* 2000;95:2086–93.
57. Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. *Stroke* 1996;27:1459–66.
58. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;120:594–606.