Chemoprevention of Colorectal Cancer by Aspirin: A Cost-effectiveness Analysis

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See editorial on page 230.

Background & Aims: The aim of the study is to compare the cost-effectiveness of aspirin and colonoscopy in the prevention of colorectal cancer. Methods: A Markov process is used to follow a hypothetical cohort of 100,000 subjects aged 50 years until death. Four strategies are compared: (1) no intervention, (2) colonoscopy once per 10 years and every 3 years in subjects with polyps, (3) chemoprevention with 325 mg of daily aspirin, and (4) combination of the second and third strategies. The various strategies are compared calculating incremental cost-effectiveness ratios (ICERs). Results: The expected number of colorectal cancers is 5904 per 100,000 subjects. Colonoscopy prevents 4428 colorectal cancers and saves 7951 life-years at an ICER of $10,983 per life-year saved compared with no intervention. Aspirin prevents 2952 colorectal cancers and saves 5301 life-years at an ICER of $47,249 per life-year saved compared with no intervention. The cost of aspirin therapy plus management of aspirin-related complications was reported to be $172 per year per patient. Varying the annual aspirin-related costs between $50 and $200 results in ICER changes between $4617 and $57,080, with the 2 strategies breaking even at $70. Applying aspirin chemoprevention plus colonoscopy screening concomitantly yields an ICER of $227,607 per life-year saved compared with screening colonoscopy alone. Conclusion: As compared with colonoscopy once per 10 years, the use of aspirin to prevent colorectal cancer saves fewer lives at higher costs. The high complication cost and the lower efficacy of aspirin render screening colonoscopy a more cost-effective strategy to prevent colorectal cancer.

Colorectal cancer ranks second among the causes of cancer death in the United States. More than 95% of colorectal cancer arises from adenomatous polyps. Colonoscopy by way of polypectomy reduces colorectal cancer, and this modality has been established as a cost-effective method for the prevention of colorectal cancer. Because colonoscopy is an expensive and invasive diagnostic test, alternative strategies to prevent colorectal cancer have been sought. Regular intake of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, was found to cause regression of colonic polyps and reduce the risk for developing colorectal cancer by 40%–50%. Chemoprevention of colorectal cancer by means of regular intake of aspirin or other NSAIDs may represent a viable option to reduce morbidity and mortality from colorectal cancer. NSAIDs are associated with multiple side effects, involving predominantly hemostasis and the gastrointestinal (GI) tract, which can lead to excessive consumption health care resources. Before introducing a strategy of cancer prevention through NSAIDs, one has to weigh the benefits of chemoprevention against their costly side effects. The aim of the present study is to compare the cost-effectiveness of regular aspirin intake with colonoscopy once per 10 years for the prevention of colorectal cancer. Aspirin is chosen as a representative medication for the class of NSAIDs because it is the most widely used and the least expensive.

Methods

The cost-effectiveness of 3 cancer prevention strategies are compared with a strategy of nonprevention. A previously published model of a Markov process is used to follow a hypothetical cohort of 100,000 persons aged 50 years until death. A cohort of 50-year-old persons is subjected to the following 4 prevention strategies: (1) no intervention; (2) 1 colonoscopy every 10 years or, in case of adenomatous polyps, every 3 years until polyps are no longer found; (3) no colonoscopy but chemoprevention with 325 mg of daily aspirin; and (4) combination of the second and third strategy, that is, colonoscopy every 10 or 3 years plus daily aspirin. As in the previous model, the time frame of the analysis is divided into equal increments of 1 year, during which the subjects transi-
tion from one state of health to another. The Markov chains underlying the preventive strategies are depicted in Figure 1. In the colonoscopy model, all subjects start with a colonoscopy at age 50. Subjects can then transition among 4 different states, that is, (1) a state after a negative colonoscopy without polyps, (2) a state after colonoscopy plus polypectomy, (3) a state after developing colorectal cancer, and (4) death from colorectal cancer or other causes. In case of aspirin prophylaxis, all subjects are started on a daily dose of aspirin. Subsequently, they can transition among 3 different states, that is, (1) remain disease-free on aspirin prophylaxis, (2) develop a colorectal cancer, or (3) die from colorectal cancer or other causes. The various Markov models of the 4 strategies for cancer prevention are simulated on Excel spreadsheets (Microsoft, Redmond, WA).

The transitions among the various states are governed by chance, the annual transition rates being shown in Table 1. To facilitate comparison with other strategies of cancer prevention, the same transition probabilities as in previous models of colorectal cancer are used.\(^5\)\(^{24}\) The Markov model uses an annual 1% incidence polyp rate to calculate the number of polypectomies and repeat colonoscopies after polypectomy.\(^25\) The annual age-specific incidence rate of colorectal cancer is taken from published statistics of the Surveillance, Epidemiology, and End Results Program.\(^26\) The population in each state is also subjected to natural attrition by the annual age-specific death rate of the US population.\(^27\)

Colonoscopy, polypectomy, or aspirin prevent colorectal cancer by reducing its incidence. In addition, early detection of colorectal cancer through colonoscopy lowers cancer-related mortality. The National Polyp Study\(^3\) showed an efficacy of colonoscopy in reducing the incidence of colorectal cancer ranging between 76% and 90%. As other studies have suggested an efficacy of only 49% to 59%,\(^4\)\(^{28}\)\(^{29}\) a median value of 75% is chosen as a baseline rate for the present analysis with a range of 50%–75% used in a subsequent sensitivity analysis. The 50% efficacy of aspirin has been reported in preventing colorectal cancer.\(^5\)\(^{–}\)\(^{10}\) In the sensitivity analysis, this efficacy value is varied between 25% to 75%.

Individual transitions between different states are associated with costs, the costs being estimated from the perspective of a third party payer. The costs of colorectal cancer therapy, colonoscopy, polypectomy, and their related complications rely on published cost data and Medicare reimbursements in the year 2000.\(^3\) Published cost estimates for the medical care of subjects with colorectal cancer range between $25,000 and $45,000.\(^7\)\(^{30}–32\) These costs include expenditures for diagnosis, surgery, radiation, and chemotherapy. We use the most recent data available from Lee et al.\(^32\) Smallley et al.\(^22\) published data on the excess costs from GI disease associated with NSAIDs, comparing a cohort of 46,000 nonusers with 5,000 regular users. Assuming a 3% interest rate, their 1989 costs data were updated to an average net present value of $154 per patient per year. Adding the annual drug cost of $18 spent on 325 mg of aspirin per day, the total cost of chemoprevention amounts to $172 per patient per year. These estimates were used as baseline cost. Similar cost data are also available from other sources. Based on 527 Medicaid patients treated over 786 treatment quarters with NSAIDs, Bloom\(^21\) estimated that in 1982, $66 was spent per quarter on adverse GI drug reactions. These numbers translate to $449 per patient per year in 2000. Lastly, in a Canadian population of 5,268 NSAID users, GI adverse events during a 2-year follow-up cost $134 (1995 Canadian dollars), resulting in a current estimate of $78 per year.\(^23\) Although the absolute Canadian price levels for all medical interventions were lower than in the United States, the percentage of GI-related costs of NSAID therapy was found to be similar in both countries.\(^21\)\(^–\)\(^23\) In a sensitivity

![Figure 1. (Left) A Markov state diagram of screening for colorectal cancer (CRC) by repeat colonoscopy every 10 years in case of normal colonoscopy or every 3 years after polypectomy. (Right) A Markov state diagram for CRC prophylaxis using daily aspirin. The arrows symbolize transitions between the various states. s/p, status post.](image)

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<thead>
<tr>
<th>Table 1. Transitions and Costs Used in the Markov Model</th>
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<td><strong>Variable</strong></td>
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<td>Types and efficacy of CRC prevention</td>
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<td>Surveillance interval for colonoscopy</td>
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<td>Efficacy of colonoscopy + aspirin</td>
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<td>Perforation rate of sigmoidoscopy</td>
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NOTE. Expenditures include professional fees and facility costs. CRC, colorectal cancer.
analysis, the baseline cost of chemoprevention is varied between $20 and $200.

Effectiveness of screening is measured in terms of life-years saved through prevention of colorectal cancer and improved survival of earlier cancer stages. The amount of life-years saved through prevention corresponds to the difference in life-years lost from cancer-related deaths between each 2 Markov models, 1 with and 1 without a preventive strategy. All costs arising from screening colonoscopy, chemoprevention, and the care of colorectal cancer and all future life-years saved are discounted at an annual rate of 3%.

Table 2 shows the outcomes of modeling 4 different strategies to prevent colorectal cancer. Without any prevention, the expected number of colorectal cancers in a cohort of 100,000 subjects is 5,904, and the only costs incurred relate to the care of colorectal cancer. Colonoscopy once per 10 years at 75% efficacy prevents 4,428 colorectal cancers and saves 7,951 life-years. The cost of colonoscopy screening in this cohort amounts to $189,667,598. This includes facility fees, physician fees, and the costs incurred for the care of associated complications. The ACER is $28,143 per life-year saved. The ICER is calculated at $10,983 per life-year saved compared with no intervention. Chemoprevention at 50% efficacy prevents 2,952 colorectal cancers and saves 5,301 life-years. The ACERs and ICERS are both larger than those of colonoscopy. Chemoprevention as an added measure to colonoscopy is assumed to prevent an additional 50% of all cancers failed to prevent through colonoscopy alone. The ACERs and ICERS are smaller than those of chemoprevention alone, but much larger than those of colonoscopy alone. The ICER of combined chemoprevention plus colonoscopy, compared with colonoscopy alone, exceeds $200,000 per life-year saved (Table 2). On the other hand, if aspirin prevention was already implemented in the general population, the addition of 1 colonoscopy per 10 years to prevent even more deaths from colorectal cancers would result in a relatively low ICER of $34,836 compared with chemoprevention alone. In other words, chemoprevention on top of screening colonoscopy is not cost-effective, whereas screening colonoscopy on top of chemoprevention still represents a cost-effective addition.

Figure 2 shows the results of a sensitivity analysis varying the cost of chemoprevention and the preventive efficacy of both colonoscopy and daily aspirin. Under baseline conditions, the costs of chemoprevention need to fall below $70 to become more cost-effective than colonoscopy. Even under the assumption of highly efficacious (75%) chemoprevention and a comparatively inefficacious (50%) colonoscopy, the threshold is only $150. This value still lies below the actual costs of $172 associated with chemoprevention.

Under baseline assumptions, colonoscopy combined with chemoprevention prevents 87.5% of all colorectal cancers. In a second sensitivity analysis, the combined
efficacy is varied between 50% and 100%. The lower value corresponds to the efficacy of colonoscopy alone with a 0% contribution of chemoprevention, whereas 100% corresponds to a 25% or 50% efficacy of chemoprevention added to a 75% or 50% baseline efficacy of colonoscopy alone. On the x-axis of Figure 3, the additional efficacy of chemoprevention (beyond the baseline efficacy of colonoscopy) is varied between 0% and 50%. The 2 curves represent 2 baseline efficacy rates of colonoscopy. The lower curve representing 75% baseline efficacy of colonoscopy ends at 25% efficacy of chemoprevention, because otherwise the joint efficacy would rise beyond 100%. As the figure shows, a higher added efficacy of chemoprevention makes it a more cost-effective option. If endoscopy and aspirin combined were able to prevent all cancers, the incremental cost-effectiveness of aspirin would vary between $50,000 and $100,000, dependent on the preventive efficacy of colonoscopy alone. Such expectations seem unrealistic, and with more moderate success of chemoprevention, its cost-effectiveness ratio (as compared with colonoscopy alone) is more likely to fall into the $100,000 to $200,000 range. This holds true even if due to the reduced incidence rate of polyps under chemoprevention, the interval of surveillance colonoscopy after polypectomy is increased to 5 years.

**Discussion**

The notion is quite appealing that by taking a daily aspirin pill, one could reduce the risk of colorectal cancer and avoid unpleasant, repeated, and costly colonoscopy. As the present analysis shows, unfortunately, chemoprevention of colorectal cancer may represent a conceptually interesting but presently not cost-effective strategy. The relatively large costs associated with the adverse effects of NSAIDs render 1 colonoscopy every 10 years a more cost-effective alternative. A combined prevention strategy using both colonoscopy plus daily aspirin could increase the overall effectiveness of a cancer prevention program. However, the incremental cost-effectiveness of chemoprevention combined with colonoscopy alone would be rather high, costing more than $100,000 per additional life-year saved as compared with colonoscopy alone.

In the assessment of cost-effectiveness, our analysis was based on the comparison of 4 management options, that is, no prevention, colonoscopy alone, aspirin alone, and combination of colonoscopy plus aspirin. The arguments against or in favor of a particular strategy are based on the comparison of 2 ICERs rather than their absolute values. In terms of absolute values, however, all ICERs fall within a range that is still considered economically feasible. To put values of ICERs in perspective, it has become customary to compare the cost-effectiveness of various health care interventions by “league tables.” Different types of medical procedures and therapies are ranked in a league table by their cost-effectiveness. For instance, it has been estimated that endoscopic surveillance of Barrett’s esophagus would cost $98,000 per quality adjusted life-year gained. Cervical cancer screening may cost as much as $250,000 per life saved.

The present decision analysis uses a previously published model of a Markov process to assess the impact of various screening strategies on the prevention of colorectal cancer.
tal cancer. As compared with colonoscopy, the previous model showed screening by annual fecal occult blood testing to cost less, but also save fewer life-years. A screening strategy based on flexible sigmoidoscopy every 5 or 10 years was not cost-effective compared with the other 2 screening methods. Because under baseline assumptions, screening through fecal occult blood testing and decennial colonoscopy were comparable, fecal occult blood testing was not again included in this study. The incidence rates of colon polyps and the length of the time intervals between each 2 endoscopic examinations had already been shown to exert a lesser influence on the outcome of the analysis. The present analysis also relies on other results of the foregoing cost-effectiveness study. Because low compliance of colonoscopy, for instance, reduces both the overall number of cancers prevented and the total costs in a linear fashion, it does not affect the cost-effectiveness ratio of colonoscopy. A low compliance rate of aspirin intake would reduce its efficacy and render it even less cost-effective than the other means of cancer prevention.

Chemoprevention alone is not cost-effective compared with colonoscopy alone for 2 reasons. The first reason relates to the overall high annual costs associated with regular intake of nonsteroidals. The common occurrence of adverse effects during the treatment with NSAIDs renders this drug class costly, even if the expenses for the drug itself may appear relatively cheap. The annual costs of chemoprevention, including the expenditures for the NSAIDs and their side effects, would need to fall below a threshold that seems by today’s standards unrealistically low. The second influence to determine the outcome of chemoprevention relates to its efficacy in preventing colorectal cancer. Even if chemoprevention alone were as efficacious as colonoscopy and averted, for instance, 75% of all colorectal cancers, its overall annual costs would need to be less than $100 to $150 to become a cost-effective alternative. Again, such assumptions seem overly optimistic. Chemoprevention represents only a viable, yet expensive means to reduce the occurrence of colorectal cancer if added to an endoscopic screening program. Rather than estimate the possible occurrence of various GI adverse events and the health care expenditures associated with individual complications, the present model relies on actual average cost data. The cost data from several large patient populations treated with NSAIDs fall within the same order of magnitude and support the contention that similar costs could be expected if chemoprevention were to be implemented in the general population.

To reduce the side effects of NSAIDs, new specific cyclooxygenase-2 inhibitors have been developed. Results from laboratory studies suggest that, like conventional NSAIDs, these newer compounds with a lesser GI toxicity may also protect against colorectal cancer. The cost saved by the drugs’ safer profile and lesser side effects, however, becomes spent on the drug itself. A year’s supply of daily 100 mg celecoxib (Celebrex; Searle, Skokie, IL) costs about $600. These costs exceed by far the threshold for chemoprevention to become a cost-effective alternative. It is conceivable, however, that in the future other and cheaper drugs with few or no adverse effects on the GI tract will make chemoprevention of colorectal cancer a cost-effective option.

Several economic analyses have dealt with the use of aspirin in the secondary prevention of recurrent myocardial infarction, transient ischemic attack, or stroke. In addition to being clinically efficacious, these studies suggest that aspirin therapy also represents a cost-effective management option. In patients who are already put on aspirin to prevent recurrent cardiovascular disease, therefore, the prevention of colorectal cancer adds to the overall cost-effectiveness of the preventive strategy. Three large randomized clinical trials have shown that aspirin is efficacious in the primary prevention of cardiovascular disease. It reduces the overall occurrence of cardiovascular death, nonfatal myocardial infarction, and stroke by 15%–30%. These results were achieved in populations of hypertensive patients or patients who presented with an increased risk for cardiovascular disease. Chemoprevention in the general population would be associated with a lesser benefit, but excess GI bleeding and hemorrhagic cerebrovascular events. It is currently being debated among cardiologists and public health researchers whether, in the general population as well, the benefit of aspirin outweighs its adverse effects.

Data derived through meta-analysis and modeling suggest that primary prevention of cardiovascular disease may be cost-effective only in subpopulations with an increased risk. Because cardiovascular disease is much more frequent than colorectal cancer, the issue of cancer prevention becomes completely overwhelmed by the cardiovascular side. From a strictly cancer-related perspective, however, chemoprevention alone does not represent a cost-effective alternative to colonoscopy. If primary cardiovascular prevention with aspirin were already used in the general population, the added screening through colonoscopy would still represent a cost-effective strategy, because it would save many more lives at relatively low additional costs.
We conclude that in the prevention of colorectal cancer, colonoscopy once per 10 years saves more lives at lower overall costs than daily aspirin. The high cost of chemoprevention and its relatively low efficacy render screening colonoscopy the more cost-effective option to reduce morbidity and mortality related to colorectal cancer. Chemoprevention used in addition to endoscopic screening provides a viable strategy to save more lives than through colonoscopy screening alone, although this benefit is associated with an ICER that may be prohibitively high for most health-care systems.

References

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